

REVIEW ARTICLES

Long QT syndrome and anaesthesia

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Long QT syndrome (LQTS) is an arrhythmogenic cardiovascular disorder resulting from mutations in cardiac ion channels. LQTS is characterized by prolonged ventricular repolarization and frequently manifests itself as QT interval prolongation on the electrocardiogram (ECG). The age at presentation varies from *in utero* to adulthood. The majority of symptomatic events are related to physical activity and emotional stress. Although LQTS is characterized by recurrent syncope, cardiac arrest, and seizure-like episodes, only about 60% of patients are symptomatic at the time of diagnosis.³

The clinical features of LQTS result from a peculiar episodic ventricular tachyarrhythmia called 'torsade de pointes'. 'Twisting of the points' describes the typical sinusoidal twisting of the QRS axis around the isoelectric line of the ECG. Usually torsade de pointes start with a premature ventricular depolarization, followed by a compensatory pause. The next sinus beat often has a markedly prolonged QT interval and abnormal T wave. This is followed by a ventricular tachycardia that is characterized by variation in the QRS morphology, and a constantly changing R-R interval (Fig. 1). The 'short-long-short' cycle length sequence heralding torsade de pointes is a hallmark of LQTS. Commonly, the episode of torsade de pointes is self-terminating, producing a syncopal episode or pseudo-seizure, secondary to the abrupt decrease in cerebral blood flow. The majority of episodes of sudden death in LQTS result from ventricular fibrillation triggered by torsade de pointes, although the mechanism of this deterioration is unknown.

Traditionally, LQTS has been classified as either familial (inherited) or acquired. However, it is likely that many patients with previously labelled acquired LQTS carry a silent mutation in one of the genes responsible for

congenital LQTS.^{22 119} The evidence for this hypothesis has been gradually emerging over the past few years. It is important for anaesthetists to be aware of this concept, as it means that a much higher proportion of the general population may be affected by asymptomatic mutations in genes encoding cardiac ion channels than was thought previously. The prevalence of LQTS in developed countries may be as high as 1 per 1100–3000 of the population.^{32 119}

About 30% of congenital LQTS carriers have an apparently normal phenotype, and thus a normal QT interval, and remain undiagnosed until an initiating event.¹⁰⁵ Fatal arrhythmias associated with primary electrical disease of the heart such as the Brugada and LQTS, probably account for 19% of sudden deaths in children between 1 and 13 yr of age, and 30% of sudden deaths that occur between 14 and 21 yr of age.¹⁰ Furthermore, there is a strong association between prolonged corrected QT interval (QTc) in the first week of life and risk of sudden infant death syndrome.⁸⁶

Diagnosis

The QT interval normally varies with heart rate, lengthening with bradycardia and shortening at increased rates. The measured QT interval is therefore corrected for heart rate according to the formula of Bazette:¹⁵

$QTc = \text{Measured QT} / \sqrt{\text{RR interval}}$ (all measured in seconds).

A QTc interval of >440 ms is considered prolonged, although about 6% of patients with symptomatic LQTS have a normal QTc interval.³⁵ As the QT interval on the ECG represents the total duration of both the depolarization and repolarization phases of the ventricular action potential, a lengthening of the QT interval occurring because of a

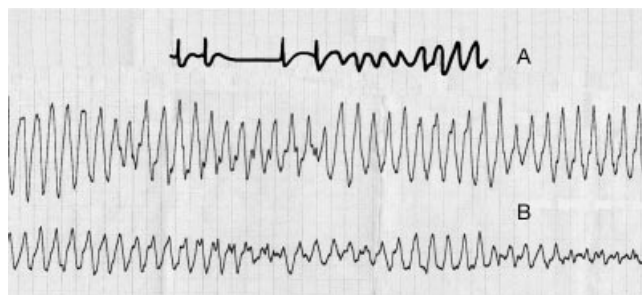


Fig 1 Part of a Holter ECG recording, which was originally recorded at 5 mm s⁻¹ but now expanded to 25 mm s⁻¹, showing a torsade de pointes arrhythmia. (A) A sinus tachycardia followed by a pause. The next RS complex is not preceded by a P wave, has a markedly prolonged QT interval and an abnormal T wave. This is followed by an R-on-T and then a typical torsade de pointes ventricular tachycardia, continued on in (B), which shows simultaneous recordings in leads I and II.

prolongation in QRS complex duration does not constitute LQTS. Hence, measurement of the JT interval, which avoids incorporation of the QRS duration, has been advocated as a more accurate reflection of ventricular repolarization.¹⁷

The QT interval is generally measured in lead II, as the T-wave ending is usually discrete, and the QT interval in lead II has a good correlation with the maximal QT measurement from the whole 12-lead ECG. In many LQTS patients, the QT interval is not only prolonged but also has increased variability in length as measured in the individual leads of the 12-lead ECG. QT dispersion (QTD) is an index of this variation and is the difference between the longest and shortest QT interval measured from all 12 leads of the standard surface ECG. QTD is significantly increased in symptomatic LQTS patients, but may not be significantly different to control values in asymptomatic LQTS patients.⁹⁵

T wave and U wave abnormalities are common in LQTS. T waves may be larger, prolonged, or have a notched, bifid or biphasic appearance.³² A pathognomonic feature of LQTS is so-called T wave alternans, where there is beat-to-beat variation in T wave amplitude. This sign of enhanced electrical instability is a highly specific but very insensitive marker for LQTS.⁴² Exercise testing of patients with LQTS may provoke prolongation of the QTc. Patients with LQTS also have reduced heart rates at maximal exercise, although there is considerable overlap with the normal distribution.⁹⁶ A notched T wave during the recovery phase of exercise is highly suggestive of LQTS. Holter recordings may be helpful in establishing the diagnosis by revealing abnormal QT prolongation during bradycardias, and ventricular arrhythmias. Head up tilt testing may also provoke abnormal QT prolongation and arrhythmias.

Schwartz and colleagues first proposed formal criteria to help the clinical diagnosis of LQTS in 1985;⁸⁰ these were revised in 1993.⁸³ The current criteria are based on clinical history, family history, and ECG findings (Table 1).

Table 1 Diagnostic Criteria in LQTS.⁸³ The ECG findings, clinical history and family history are all individually scored as detailed below. If the total score is <1 point, the patient has a low probability of having the syndrome, whereas if the total score is 2–3 points, there is an intermediate probability, and a score of >4 points implies a high probability. ^aIn the absence of medications or disorders known to affect these ECG features. ^bQTc calculated from Bazette's formula, where QTc = QT/√RR. ^cMutually exclusive. ^dResting heart rate below the second percentile for age. ^eThe same family member cannot be counted twice. ^fDefinite LQTS is defined by a LQTS score >4

	Points
ECG findings^a	
QTc ^b	
≥480 ms	3
460–470 ms	2
450 ms (in males)	1
Torsades de pointes ^c	2
T wave alternans	1
Notched T wave in three leads	1
Low heart rate for age ^d	0.5
Clinical history	
Syncope ^e	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history^e	
Family members with definite LQTS ^f	1
Unexplained sudden cardiac death before age 30 in immediate family members	0.5

The different subtypes of LQTS may display specific ECG phenotypes. Thus, LQT1 typically has a prolonged T wave duration, the LQT2 subtype has lower amplitude T waves in the limb leads and, characteristically, LQT3 patients have a late appearing T wave preceded by a long isoelectric ST segment.¹²⁰ There is, however, considerable variation between patients, and the morphology varies with age. These patterns are useful in directing the search for a mutation by genetic testing, but cannot be relied upon in isolation in directing genotype-specific treatment without confirmation.

Diagnosing LQTS in patients is difficult, because of variable penetrance and genetic heterogeneity. Examination of clinical and ECG features cannot always accurately identify gene carriers in affected families and genetic testing is usually recommended.⁴² However, only 60% of families diagnosed with LQTS can be genotyped to one of the known mutations. Moreover, sporadic cases occur because of spontaneous new mutations, so at present negative genetic screening cannot rule out the disease. In addition, as several mutations have been discovered in each of the known LQTS genes, diagnostic genotyping is extremely expensive, laborious, and equivalent to searching a haystack for the proverbial needle. Currently, diagnostic genotyping within a realistic time frame is not routinely available in the UK, so such a policy of perfection is not practicable, even in patients with a suggestive family history. Examination of clinical and ECG features therefore remains the mainstay of diagnosing LQTS in this country.

Screening

ECGs should be obtained in all first-degree relatives of a patient with LQTS. The identification of QTc interval prolongation and T wave abnormalities in family members of a victim of sudden cardiac death is suggestive of a LQTS gene in the family. Routine genetic screening is not yet feasible, however, for all the reasons outlined above; automated analysis is required before routine screening becomes a possibility.

Ion channel physiology

In order to understand the underlying pathophysiology of LQTS, it is necessary to appreciate the current concepts of ion channel function in human myocardial cells.

The cardiac action potential, which represents variation in the transmembrane potential of the myocyte during one cardiac cycle, is traditionally divided into five phases. These phases reflect the variation in the composition of ionic currents flowing during this time period. Ionic currents arise mainly from passive movements of ions through ion channels, which are composed of transmembrane proteins. The ionic basis of the 'fast' response action potential, seen in atrial and ventricular muscle cells and Purkinje fibres, is different from that of the 'slow' response action potential, seen in sinoatrial and atrioventricular nodal cells. However, as nodal cell function is not relevant to this review, it is not discussed further.

In the resting myocyte, the potential of the cell interior is about 90 mV less than that of extracellular fluid. When the myocyte is stimulated, the cell membrane rapidly depolarizes. During depolarization, the potential difference reverses such that the potential of the cell interior exceeds that of the exterior by about 20 mV. This rapid change in potential difference is reflected by the upstroke of the action potential and is designated phase 0. The upstroke is followed immediately by a brief period of partial early repolarization (phase 1), and then by a plateau (phase 2) that persists for about 0.1–0.2 s. The membrane then further repolarizes (phase 3), until the final resting state of repolarization (phase 4) is again attained.

Ionic basis of the fast response action potential

Phase 0; the upstroke

Any stimulus that abruptly changes the resting membrane potential to a critical 'threshold' value results in an action potential; human ventricular myocytes have a threshold value of about –65 mV. At this potential, there is a sudden increase in sodium conductance because of opening of fast Na⁺ channels; the resultant influx of Na⁺ into the myocyte causes rapid depolarization (phase 0). The opening and closing of fast Na⁺ channels is controlled by voltage-dependent gating; Na⁺ channels, like all other ion channels, are dynamic molecules that change their structural con-

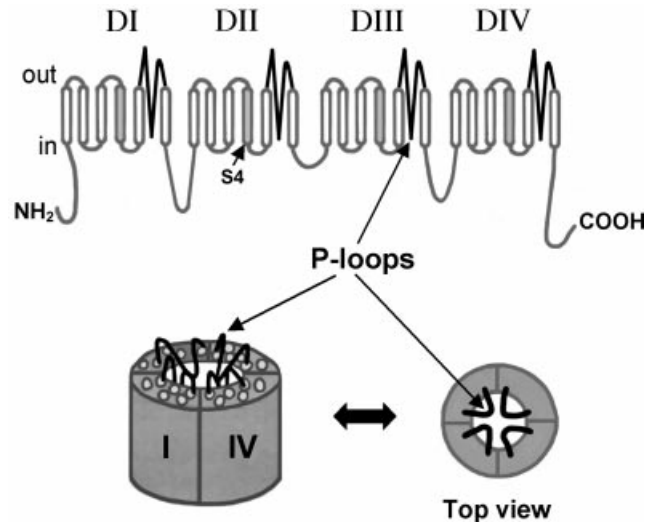


Fig 2 Schematic depiction of Na⁺ channel topology. The four domains of the channel fold around a central ion-conducting pore. Each of the four homologous domains contains six membrane-spanning segments of amino acid residue sequences; the S4 segment, which is affected by changes in membrane potential and is responsible for activation gating, is coloured grey. The interdomain linkages and the N- and C-terminal ends of the channel protein are all located at the cytoplasmic end of the molecule. The central pore is lined by the S5–S6 linker or P-loop from each domain. Each of the four P-loops, which are shown in bold, has a unique structure, and that specific structure defines the ion selectivity of the channel. (Modified from Balser,¹³ with permission.)

formation in response to changes in transmembrane potential. The Na⁺ channel consists of a principal α -subunit, the pore-forming component, and one or more smaller, regulatory β -subunits. There are at least three different types of β -subunit genes widely expressed in mammalian cardiac Na⁺ channels; they may affect the rate of channel activation and inactivation, although their precise function is uncertain.^{18 30 36}

The α -subunit is composed of four homologous domains, each containing six transmembrane segments (S1–S6). Cytoplasmic chains of amino acids link the four domains to each other. Links between the fifth and sixth segments line the transmembrane pore, hence the term 'P-loop' (Fig. 2). The P-loops for each domain are different and their specific structure defines the permeation characteristics of the ion channel. Na⁺ channels permit selective flux of Na⁺ over other monovalent cations by a factor of 10:1 or more, and are not normally conductive to divalent cations such as Ca²⁺. However, a change in one amino acid in the domain III P-loop can convert a Na⁺ channel into a Ca²⁺ selective channel.¹³

Cell membrane depolarization triggers activation (opening) of the Na⁺ channels, but if the depolarization is maintained, the channels become inactivated and non-conducting. Subsequent to complete repolarization, the channels return to a closed state capable of being activated once again. All these processes are the result of complex

interactions among the structural domains of the channel protein. The fourth transmembrane segment (S4 in Fig. 2) in each domain is affected by changes in membrane potential, and is responsible for activation gating. Depolarization causes these helical segments to rotate outwards, leading to opening of the channel pore.³⁶

Inactivation has an initial rapid component and one with a slower recovery time constant. The cytoplasmic linker between the third and fourth domains (DIII and DIV) mediates fast inactivation. A portion of this linker acts as a hinged lid, that docks against receptor sites surrounding the inner vestibule of the pore, thereby occluding it (Fig. 3). These receptor sites become available only when the channel is activated. Slow inactivation involves conformational changes in the outer pore that probably involve the P-loops.¹⁸

Inactivation is coupled to activation; the rate of inactivation increases as a consequence of conformational changes in the channel protein associated with activation. This is because movement of the S4 segments that initiate activation of the channel, changes both the position of the DIII–DIV cytoplasmic linker relative to its docking sites, and the orientation of the docking sites themselves (Fig. 3).

At the resting transmembrane potential of -90 mV the activation gates are all closed, the inactivation gates are open, and the conductance of the resting cell to Na^+ is very low. As the transmembrane potential becomes less negative, activation gates start to open. The precise potential required to open activation gates varies from one channel to another in the cell membrane. As the transmembrane potential becomes progressively less negative, more and more gates open, and the influx of Na^+ accelerates. The entry of Na^+ into the cell neutralizes some of the negative charges within the cell and thereby makes the transmembrane potential still less negative, which in turn results in more gates opening and the Na^+ current increasing. As the transmembrane potential approaches about -65 mV, virtually all the activation gates are open.

Although Na^+ ions that enter the cell during one action potential alter the transmembrane potential by more than 100 mV, the actual quantity of Na^+ that enters the cell is so small that the resultant change in its intracellular concentration is tiny. Hence, the chemical force (concentration gradient) remains virtually constant, and only the electrostatic force changes throughout the action potential. As Na^+ enters the cardiac cell during phase 0, the negative charges inside the cell are neutralized, and the transmembrane potential becomes progressively less negative until it reaches zero, at which point there is no electrostatic force attracting Na^+ into the cell. As long as Na^+ channels are open, however, Na^+ continues to enter the cell because of the large concentration gradient. This continuation of the inward Na^+ current causes the inside of the cell to become positively charged with respect to the exterior, resulting in the 'overshoot' of the cardiac action potential. As the Nernst potential equilibrium for Na^+ is approached, the electro-

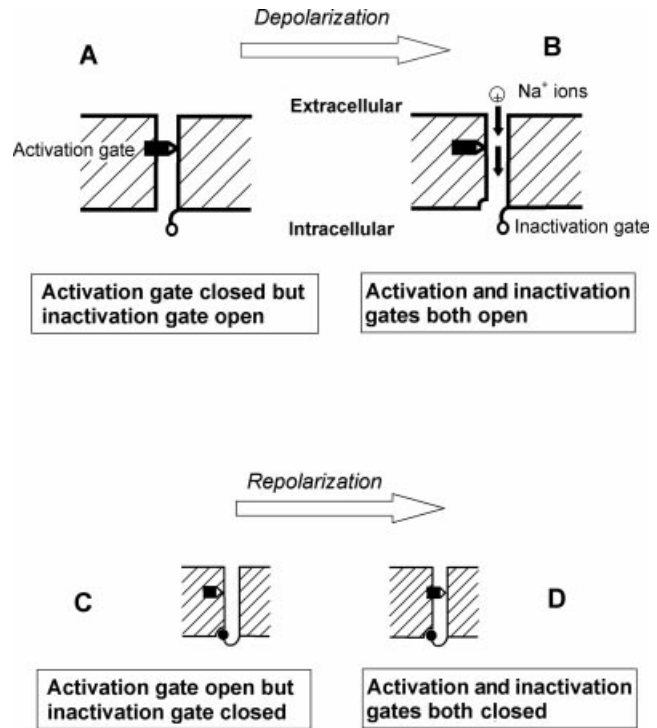


Fig 3 Model of Na^+ channel gating. The Na^+ channel is represented as a pore spanning the cell membrane. In the resting state, the inactivation (inner) gate is open but the (midpore) activation gate is closed (A). After depolarization, the activation gate assumes the open position, and with both gates open, Na^+ ions move into the cell (B). Activation changes both the position of the inactivation gate relative to its docking site, and the orientation of the docking site itself, such that the inactivation gate moves into the closed position, blocking ion movement (C). Inactivation gates remain closed while activation gates are open. Once the cell has partially repolarized (phase 3), the change in transmembrane potential triggers closure of the activation gates, a process called deactivation (D). The closure of the activation gates results, after a variable interval, in opening of the inactivation gates; the cell is then ready to react to further stimuli.

static force opposing Na^+ influx starts to counter the chemical force generated by the concentration gradient across the cell membrane, and the rate of net inward Na^+ flux starts to decrease. Nevertheless, this inward Na^+ current persists during phase 1 and 2, and only finally ceases when all the inactivation gates have closed.

Inactivation gates are not directly affected by the value of the transmembrane potential, and derive most of their voltage dependence from being coupled to activation. Whereas activation gates take about 0.1 ms to open, inactivation gate closure, which can occur only after activation has occurred, takes a few milliseconds. This relative delay in pore closure provides sufficient time for the Na^+ influx seen in phase 0, which is terminated when all the inactivation gates have closed. Inactivation gates remain closed while activation gates are open. Once the cell has partially repolarized (phase 3), the change in transmembrane potential triggers closure of the activation gates by

reversal of the conformational changes in the S4 segments, a process called deactivation. Deactivation results, after a variable interval, in reversal of the inactivation mechanism and hence, opening of the inactivation gates (Fig. 3).

Phase 1; early repolarization

This phase constitutes an early brief period of limited repolarization, consequent upon activation of various types of K^+ channels. K^+ channel opening results in a substantial efflux of K^+ from the cell, because the interior of the cell is positively charged and because the concentration of K^+ inside the cell greatly exceeds that in the exterior. Phase 1 produces a notch in the action potential between the end of the upstroke and the beginning of the plateau. It is particularly prominent in Purkinje fibres and in myocytes in the epicardial and mid-myocardial regions; in endocardial myocytes it is almost undetectable.

The configuration and rate of repolarization of action potentials are controlled by many types of K^+ channel currents that differ with respect to their kinetics and density in the cell membrane. There are at least 20 different K^+ channel proteins in the human myocardium, although all can be assigned to one of four categories based on function: transient outward, delayed rectifier, inward rectifier, and leak channels. The delayed rectifier 'current' is actually a composite of at least three distinct currents: the ultra-rapid (I_{Kur}), the rapid (I_{Kr}), and the slow (I_{Ks}) delayed rectifier currents. These vary in their speed of activation and in their pharmacological properties.¹⁰¹ Cloning and analysis of the secondary structure of voltage-dependent Ca^{2+} and K^+ channels have revealed that the relationship between structure and gating function is similar to that described above for Na^+ channels.¹¹⁸ Recent reviews of the molecular basis of cardiac K^+ currents are recommended for interested readers.^{60 101}

The rapid partial repolarization of phase 1 is the result of the transient outward (I_{Kto}), the I_{Kur} and leak currents.¹⁰¹ K^+ channels carrying I_{Kto} activate very rapidly in response to the rapid depolarization of phase 0. A membrane-spanning helical portion of one of the K^+ channel protein domains senses membrane depolarization; it is coupled to other regions of the protein that form the activation gate. When the activation gate is open, the channel conducts K^+ in a direction that depends on the electrochemical gradient across the cell membrane. Within 10–500 ms after depolarization, the channels close and this state of inactivation continues until such time as the membrane is repolarized to the resting potential. Only then do these channels recover from their inactivated state and again become capable of opening in response to membrane depolarization.

Channels carrying I_{Kur} activate during depolarization and stay open for most of the duration of the action potential; the magnitude of this current progressively decreases during repolarization because of the progressive decrease in electrostatic driving force (Fig. 4). Most cardiac cells also

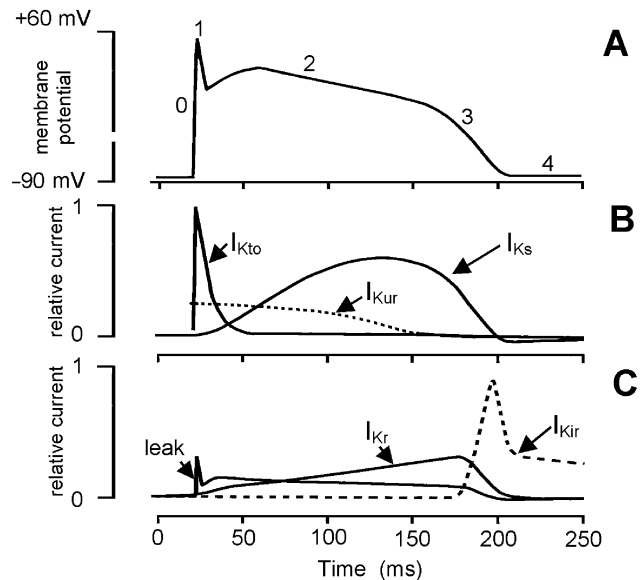


Fig 4 K^+ currents responsible for repolarization. The top diagram (A) shows the phases of a typical ventricular action potential (AP). The rapid repolarization of phase 1 is the result of the contribution of the transient outward (I_{Kto}), the ultra-rapid delayed rectifier (I_{Kur}), and the leak currents (diagrams B and C). During the plateau of phase 2, the I_{Kur} , rapid (I_{Kr}), and slow (I_{Ks}) delayed rectifier K^+ currents, counter the depolarizing influence of the L-type Ca^{2+} current (not shown). I_{Kr} and inward rectifier (I_{Kir}) currents provide repolarizing current during the terminal phase of the AP. (Modified from Tristani-Firouzi and colleagues,¹⁰¹ with permission.)

have a very small background K^+ conductance through so-called leak K^+ channels, which are open at all voltages; they contribute to the maintenance of the resting potential and repolarization of the action potential.

Phase 2; the plateau

The efflux of positively charged K^+ ions during phase 1 results only in a brief, partial repolarization because it rapidly becomes counterbalanced by an influx of Ca^{2+} ions during phase 2. The voltage-regulated Ca^{2+} channels are activated as the transmembrane potential becomes progressively less negative during the upstroke of the action potential. But because the predominant type of Ca^{2+} channel, the L-type, activates and inactivates much more slowly than do the fast Na^+ channels, Ca^{2+} conductance does not increase until after most of the Na^+ channels have closed. Ca^{2+} ions move across the cell membrane down their concentration gradient to cause a significant increase in intracellular Ca^{2+} concentration, although the amount of Ca^{2+} that enters the cell from the interstitium is not sufficient in itself to induce myofibril contraction; rather it acts as a trigger to release Ca^{2+} from the sarcoplasmic reticulum. Hence, peak force development does not occur until repolarization is complete. Inactivation of L-type Ca^{2+} channels occurs in two phases: an initial fast phase that is dependent upon a Ca^{2+} -calmodulin complex binding to the cytoplasmic side of the channel protein, and a slower phase

that is voltage-dependent.^{5 94} Both mechanisms act to induce a conformational change in the channel protein, so resulting in pore closure; the inward Ca^{2+} current (I_{Ca}) is insignificant at potentials more negative than about -50 mV.¹⁴

During the plateau of the action potential, the concentration gradient for K^+ across the cell membrane is virtually the same as that during the resting state, but the transmembrane potential is positive. Therefore, both chemical and electrostatic forces favour efflux of K^+ from the cell. The activation of the I_{Ks} channels by depolarization proceeds very slowly and tends to increase K^+ conductance only very gradually during phase 2. In addition, I_{Kur} channels and leak channels continue to allow K^+ efflux out of the cell. Towards the end of the plateau phase, as the transmembrane potential starts to become slightly more negative, I_{Kr} starts to assume significance. The amplitude of I_{Kr} increases during repolarization, reaching a peak at about -30 mV, before decreasing again as the membrane potential reaches its resting level. This increase in current occurs in spite of a decrease in electrostatic driving force, because channels recover from inactivation to an open state in a voltage-dependent manner. The action potential plateau persists as long as efflux of charge carried mainly by K^+ is balanced by the influx of charge carried mainly by Ca^{2+} , together with a small amount carried by Na^+ . Hence, administration of either calcium or potassium channel blockers can substantially diminish or prolong the duration of the plateau.

Action potential duration, which relates to the duration of phase 2, shows considerable heterogeneity within the heart. The action potential duration is longer in mid-myocardial (M) cells than in epicardial or endocardial cells, because of a smaller I_{Ks} , and larger I_{Na} and $\text{Na}^+/\text{Ca}^{2+}$ exchange ($I_{\text{Na-Ca}}$) currents. It is the transmural differences in the time course of repolarization of the three types of myocyte that are largely responsible for T wave morphology on the ECG, and it is the duration of the M cell action potential that determines the QT interval.¹¹

Phase 3; final repolarization

The process of final repolarization, phase 3, begins when the efflux of K^+ significantly exceeds the influx of Ca^{2+} and Na^+ . I_{Kto} takes no part in this phase, and I_{Kur} and leak currents are relatively insignificant (Fig. 4). I_{Ks} and I_{Kr} are the largest contributors during initial repolarization, although both decrease substantially as the membrane potential approaches its resting level. The inward rectified K^+ current (I_{Kir}) does not participate in the initiation of repolarization because the conductance of these channels is low at the transmembrane potential that prevails during phase 2. However, once phase 3 has started and the net efflux of cations causes the membrane potential to become increasingly negative, the conductance of I_{Kir} channels increases dramatically; it is these particular K^+ channels that contribute the most to the rate of repolarization.⁴⁷

Phase 4; restoration of resting state

In most myocytes, I_{Kir} largely determines the resting membrane potential, as the conductance through these channels at potentials between -50 and -90 mV is much higher than that of any other K^+ channel, with the exception of certain inward rectifier channels that are inhibited by cytosolic ATP; these so-called I_{KATP} channels are only activated under conditions where intracellular concentrations of ATP are low.⁴⁷ Multiple types of I_{Kir} channels are present in most myocytes, and I_{Kir} channel density is higher in ventricular cells than in atrial or Purkinje cells.

The excess Na^+ that enters the cell rapidly during phase 0 and more slowly throughout the cardiac cycle is eliminated by the action of the enzyme Na^+/K^+ -ATPase. This enzyme expels three Na^+ ions in exchange for entry of two K^+ ions, the latter being ions that had left the cell during phases 2 and 3. Although an ATP-driven Ca^{2+} pump eliminates some Ca^{2+} ions, a $\text{Na}^+/\text{Ca}^{2+}$ exchanger eliminates most of the Ca^{2+} ions that enter the cell during phase 2. As three Na^+ ions are exchanged for each Ca^{2+} ion, an inward current is generated when Ca^{2+} is extruded from the cell, and an outward current is generated when Ca^{2+} enters via this transporter. The direction and magnitude of this $\text{Na}^+/\text{Ca}^{2+}$ exchange are dependent on the membrane potential and on the intracellular and extracellular concentrations of the ions in the direct vicinity of the exchanger protein. Under normal conditions, the exchanger functions predominantly to generate inward current during most of the repolarization phase, lengthening action potential duration.

Congenital LQTS

The syndrome of familial QT interval prolongation, polymorphic ventricular tachycardia, and sudden death, has been linked to inherited defects of membrane ion channels or their regulatory subunits. Congenital LQTS can be inherited as an autosomal dominant (Romano-Ward syndrome), or recessive (Jervell and Lange-Nielsen syndrome) condition. Seven ion channel genes are known to cause LQTS, with over 300 mutations so far identified.^{57 93} Mutations of genes coding for ion channel proteins can cause channel protein dysfunction by a variety of mechanisms. Single amino acid substitutions often cause dysfunctional, abnormally folded channels that undergo rapid degeneration, reducing the number of functional channels by more than 50%. Sometimes the amino acid substitution may not affect folding of the protein channel complex, but because of its critical position may prevent normal ion flow through the narrowest region of the pore. Alternatively, mutations may result in subunits that co-assemble with normal subunits to produce a channel with altered properties, such as a shift in voltage activation or inactivation. In some individuals the mutated gene does not encode for the channel protein itself, the α -subunit, but for an associated regulatory protein (β -subunit).

The different forms of LQTS are commonly referred to by their original loci assignment. Hence, mutations in *KCNQ1*, *HERG*, *SCN5A*, *KCNE1*, *KCNE2*, and *KCNJ2* cause LQT1, LQT2, LQT3, LQT5, LQT6, and LQT7 forms of LQTS, respectively. The very rare LQT4 phenotype has not yet had a specific gene or functional current identified, and will not be discussed further.⁷³ Over 90% of individuals with the Romano–Ward phenotype (i.e. no deafness) are heterozygous for a mutation in one of these genes. Some individuals with the autosomal recessive Jervell and Lange-Nielsen (JLN) phenotype are homozygous for mutations in *KCNQ1* (JLN 1) or *KCNE1* (JLN 2). Some families with congenital LQTS do not have one of the identified gene mutations, implying that ascertainment of these remains incomplete.¹⁰⁵

The complexity of LQTS genotypes and phenotypes has increased recently with the discovery of mutations that generate only mildly dysfunctional protein products. Heterozygotes with such mutations are phenotypically normal, although genotypically they have autosomal dominant LQTS with low penetrance. The discovery of a patient with phenotypical Romano-Ward syndrome who was found to be homozygous for a *KCNQ1* mutation,⁷⁰ suggests that the function of the gene product is so little reduced from the wild type that a ‘double dose’ is needed to generate a phenotype. The clinical significance of mutations with very low penetrance is that there may be a much larger reservoir of heterozygous LQTS gene carriers in the population than suspected previously, who are completely phenotypically normal, but who nevertheless have a reduced functional reserve with respect to their affected ion channel. Evidence is accumulating that individuals with ‘acquired’ LQTS may in fact be ‘decompensating’ when exposed to exogenous influences, such as drugs or electrolyte imbalances, which affect repolarization mechanisms.

LQT1

Patients with this form of LQTS, who account for about 42% of all patients with congenital LQTS,⁹³ usually present before the age of 10 yr.⁸⁵ They are heterozygous for a mutation in the *KCNQ1* gene, which encodes subunits that form the K^+ channel that carries I_{Ks} . When co-expressed with normal subunits, they combine to form dysfunctional channel proteins that are abnormally folded, and which usually undergo rapid degradation. The ensuing significant reduction of I_{Ks} during the plateau phase of the action potential results in prolonged ventricular repolarization.¹⁰¹

Homozygotes for mutations in *KCNQ1* express only the mutant subunits, which do not form functional channels. This generates the rare and severe Jervell and Lange-Nielsen phenotype (JLN 1), which is associated with sensorineural deafness. Deafness results from dysfunctional potassium channel function in the cochlea.⁷³

Physical exercise and sympathetic stimulation are known to precipitate syncope and sudden death in patients with

LQT1.⁸⁵ β -Adrenoreceptor stimulation in normal individuals augments a number of currents, including I_{Ks} and I_{Na-Ca} , secondary to its activation of various protein kinases. A net increase in the outward (repolarizing) current, because of a relatively larger increase in I_{Ks} than in I_{Na-Ca} , results in the reduction in action potential duration and QT interval shortening seen in normal individuals in response to β -adrenoreceptor stimulation. This does not occur in LQT1 patients, firstly because of their deficiency in channels conducting I_{Ks} , and secondly, because mutant channels cannot respond normally to protein kinase-activated messenger protein complexes.⁴⁸ Instead, sympathetic stimulation causes an increase in both transmural and spatial dispersion of repolarization, and hence an increased susceptibility to arrhythmogenesis.^{90 97}

This heterogeneity of cellular response to β -adrenoreceptor stimulation in LQT1 patients relates to the anatomical distribution of potassium channels. The relative density of the different potassium channels normally varies both intramurally (between endo-, mid-, and epicardial myocytes) and between each cell type in different regions of the ventricle. M cells have a longer action potential duration, greater prolongation of action potential duration with slowing of rate, and a higher susceptibility to the development of arrhythmogenic early after-depolarizations (EADs) than surrounding epicardial or endocardial cells, because they have a lower density of channels conducting I_{Ks} than other cells in the vicinity.¹⁰⁹ β -Adrenoreceptor stimulation therefore disproportionately prolongs the action potential duration of M cells in LQT1 patients, as stimulation of Na^+/Ca^{2+} exchange and the consequent increase in inward Na^+ current is relatively unopposed by a smaller increase in the outward K^+ current during phase 2, owing to the low density of channels carrying I_{Ks} in M cells.⁹⁰ β -Adrenoreceptor block in these patients is usually very effective at preventing arrhythmia generation.

LQT2

Patients with this form of LQTS account for about 45% of all patients with congenital LQTS.⁹³ The median age of presentation, because of a cardiac event, is 12 yr.⁸⁵ These patients have a mutation in the *HERG* gene, which encodes subunits that form the K^+ channel that carries I_{Kr} . The reduced I_{Kr} seen in patients with *HERG* mutations is due either to mutant subunits that do not co-assemble with normal subunits, or the formation of dysfunctional channels, in either case resulting in a greater than 50% reduction in functional channels.⁵⁹ LQT2 patients with dysfunctional channels have a higher risk of arrhythmias than do patients that form reduced numbers of normal channels.⁵⁹

Experimental studies have demonstrated that suppression of I_{Kr} does not necessarily prolong the mean action potential duration, though it does increase dispersion of repolarization,³⁹ as M cells exhibit a longer prolongation of action potential duration following suppression of I_{Kr} than other

cells. At rest, the transmural and spatial dispersion of repolarization in LQT2 patients is similar to that seen in LQT1 patients, but the increased heterogeneity of repolarization seen after sympathetic stimulation is less marked in LQT2 patients than LQT1 patients.⁹⁷ β -Adrenoreceptor stimulation only transiently prolongs the action potential duration of M cells in LQT2 patients,⁹⁰ so transmural dispersion of repolarization is increased above normal but not by as much as in LQT1 patients. This may explain why, in contrast to LQT1 patients, exercise only rarely triggers a cardiac event in LQT2 patients, and why β -adrenoreceptor block is less successful at preventing arrhythmias. Sudden auditory stimuli, and emotional stress are relatively common initiators of arrhythmias in LQT2 patients;⁸⁵ that this is because of a sudden adrenergic stimulation is mechanistically plausible, but speculative.

LQT3

This subtype accounts for about 5% of all LQTS. It is caused by mutations in the gene that encodes the cardiac sodium channel (SCN5A); nine distinct mutations, usually involving amino acid substitutions or deletions in segments located in domains III and IV, have been reported to date.¹⁸ All these mutations cause a significant alteration in the properties of the Na^+ channel protein resulting, either directly or indirectly, in a prolongation of ventricular repolarization. Most of the mutations produce Na^+ channels that either re-open after inactivation at a later time during depolarization or fail to inactivate altogether, causing the Na^+ channel to open repetitively.³⁶ These late components of Na^+ current potentiate an otherwise very small inward (depolarizing) Na^+ current (I_{Na}) that normally occurs during phase 2; this inward plateau current is sufficient to delay repolarization in affected patients and increase the vulnerability of the heart to arrhythmogenesis.¹⁸

One particular Na^+ channel mutation is not associated with a persistent inward Na^+ current, but instead appears to disrupt α - β_1 subunit interaction, causing a reduction in Na^+ channel availability at the resting transmembrane potential, and an increase in the speed of onset of inactivation.⁸ Affected patients have a reduced inward Na^+ channel current during phase 0 of the action potential, resulting in a slower upstroke and a less positive overshoot. The reduction of action potential overshoot is thought to reduce the electrostatic force tending to oppose the concentration gradient driving Ca^{2+} entry into the cell once the Ca^{2+} channels open.¹¹¹ The resulting increase in Ca^{2+} influx during phases 1 and 2 of the action potential both increases the activity of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, and reduces I_{Ks} (as a consequence of the change in transmembrane potential); the ensuing net increase in inward plateau current causes an increase in action potential duration.

Patients with LQT3 mutations are at particularly high risk of developing an arrhythmia during a bradycardia, and a relatively high percentage die when asleep.⁸⁵ Conversely,

and in contrast to patients with LQT1 mutations, LQT3 patients are at relatively low risk during exercise. This is because at rapid heart rates Na^+ accumulates in the cell, lowering the Na^+ gradient across the membrane and consequently the magnitude of the inward Na^+ current. The effect of such a reduction is negligible during the upstroke (phase 0) of the action potential, but becomes much more significant during the plateau phase, and acts to reduce the potential enhancement of the inward Na^+ current that occurs in LQT3 patients during this critical period.

LQT5

Patients with this form of LQTS, who account for about 3% of all patients with congenital LQTS,⁹³ have a mutation in the KCNE1 gene, which encodes a regulatory β -subunit that associates with the KCNQ1 α -subunit to form the I_{Ks} channel protein. The association of the wild type KCNE1 β -subunit with the KCNQ1 α -subunit alters the activation kinetics of I_{Ks} channels, which activate much more slowly than homomultimer KCNQ1 channels (i.e. those expressed without regulatory β -subunits), and they require more depolarized voltages for their activation.^{73 104}

Two different mutations in KCNE1 have been shown to cause an increase in the rate of I_{Ks} channel deactivation and a reduction in current magnitude. Other mutations, that are located in the cytoplasmic region of the protein, cause a shift in the voltage dependence of current activation to more positive potentials, and also increase the rate of deactivation. In all cases, these mutations result in a decrease in the magnitude of I_{Ks} during repolarization, leading to a significant prolongation of action potential duration and QT interval.^{39 101}

LQT6

Patients with this form of LQTS, who account for about 2% of all patients with congenital LQTS,⁹³ have a mutation in the KCNE2 gene, which encodes a regulatory β -subunit that can co-assemble either with HERG α -subunits to form channels that conduct I_{Kr} , or with the KCNQ1 subunit to form channels that conduct I_{Ks} . The association of wild type KCNE2 with the KCNQ1 subunit results in a transformation of the voltage-dependent channel into a voltage-independent channel so that the KCNQ1 channel is permanently open.⁹⁹ Hence, it would appear that KCNQ1-KCNE2 channels normally provide a background current that may have a role in the maintenance of the resting membrane potential, and influence the length of the refractory period. KCNE2 mutations may modify the effects of this normal interaction, resulting in a reduction in the speed of activation and a shift in the voltage dependence of current activation to more positive potentials, reducing I_{Ks} . In addition, when mutant KCNE2 β -subunits assemble with HERG they cause the channels to open more slowly and close more rapidly than normal, thereby diminishing I_{Kr} .²

Hence, KCNE2 mutations may prolong repolarization by reducing both I_{Ks} and I_{Kr} .

The KCNE family of β -subunits produce similar effects on many different α -subunits. Furthermore, there is a general correlation between location of the mutation and alteration of function: mutations in the extracellular region of subunits alter voltage-dependent activation and drug block, whereas mutations in the transmembrane and cytoplasmic segments influence gating kinetics and ion conduction.¹

LQT7

This rare form of LQTS, also known as Andersen Syndrome, produces a combination of both a skeletal and a cardiac muscle phenotype. The disorder can be inherited in an autosomal dominant fashion, but sporadic cases also occur; penetrance is extremely variable. Clinical manifestations include periodic paralysis, prolongation of the QT interval and ventricular arrhythmias, and characteristic physical features that include micrognathia, low set ears and clinodactyly. These patients have mutations in the KCNJ2 gene, which encodes the inward rectifier K^+ channel, expressed in both skeletal and cardiac muscle.¹⁰⁰ All known KCNJ2 mutations cause loss of I_{Kir} channel function, resulting in prolongation of phase 3 of the action potential. Computer simulations suggest that after-depolarizations and spontaneous action potentials are dependent upon depolarizing current through the Na^+/Ca^{2+} exchanger.¹⁰⁰ Hypokalaemia is one trigger known to induce delayed after-depolarizations and spontaneous arrhythmias in affected individuals. However, although episodes of ventricular tachycardia are seen commonly in affected patients, torsade de pointes is rare and sudden death has never been reported.

Prolongation of repolarization vs propagation of ventricular arrhythmias

The precise relationship between genetically determined alterations of cellular repolarization, QT interval prolongation, and torsade de pointes remains unclear. It is increasingly apparent that QT prolongation *per se* is not the problem in LQTS; rather it is transmural heterogeneity of action potential duration that provides the substrate for torsade de pointes.⁹² Experimental studies have confirmed that abnormally prolonged repolarization can abruptly and markedly exaggerate transmural dispersion of repolarization.⁷ Islands of M cells (which vary in spatial extent and location across the heart), with their relatively low I_{Ks} channel density, can form regions of increased relative refractoriness in LQTS patients, and produce intramural gradients of repolarization that result in areas of conduction block and the potential for self-sustaining intramural re-entrant circuits.

Prolongation of repolarization in myocytes favours the generation of EADs.⁷ EADs are transient retardations or reversals of repolarization during phases 2 and 3 of the action potential that can trigger new action potentials, depending on the level of the membrane potential at which they are generated. EADs and triggered action potentials can exacerbate and perpetuate electrical heterogeneity via re-entrant circuits between areas that are still inexcitable and those that have already recovered from refractoriness.¹¹⁰ EADs arising in spatially discrete areas of the myocardium may result in triggered activity in competing ventricular foci. Hence, EADs provide the trigger (premature ectopic beats) and exacerbate the substrate (electrical heterogeneity with non-uniform repolarization and refractoriness) for the initiation and perpetuation of torsade de pointes. EADs have been recorded during phase 3 of the action potentials in patients with LQT2 and LQT3, and in LQT1 patients in the presence of adrenergic stimulation.

The ionic basis for the generation of EADs in LQTS patients is multifactorial, but probably relates to increased Ca^{2+} entry into the cell during an abnormally prolonged phase 2, subsequently leading to an inward Na^+ current through the Na^+/Ca^{2+} exchanger during phase 3, a process that is particularly evident in M cells.¹¹⁰ This increased Ca^{2+} influx may relate to slowed inactivation or reactivation of L-type Ca^{2+} channels. The magnitude of the inward Na^+ current relates to the cytoplasmic Ca^{2+} concentration, and so is likely to be exacerbated by β -adrenoreceptor stimulation.

The concept of transmural dispersion of repolarization helps explain why prolongation of action potential duration is not necessarily pro-arrhythmogenic. As the M cell action potential duration is physiologically longer than that of epicardial and endocardial cells, drugs which preferentially lengthen the latter will lengthen the overall action potential duration (and hence the QT interval), but will reduce transmural dispersion of repolarization. Such drugs do not predispose to torsade de pointes. Conversely, drugs which preferentially lengthen the M cell action potential duration increase transmural dispersion of repolarization and hence the risk of torsade de pointes.

'Acquired' LQTS

A variety of commonly prescribed drugs belonging to many different therapeutic classes, including anti-arrhythmic, antibiotic, antihistamine, and prokinetic drugs, possess the adverse property of prolonging cardiac repolarization. However, arrhythmias related to drug-induced QT prolongation do not occur in every patient treated with such drugs, but only in 'susceptible' patients. It is surmised that these individuals may be silent LQTS gene carriers, as up to 70% have a normal QTc interval until exposed to a provoking drug.²⁹⁻⁸⁷ The most common type of DNA sequence variation, single nucleotide polymorphisms (SNPs), are observed at a frequency of >1:1000 nucleotides.²⁴ Several SNPs result in variant products from genes

coding for cardiac ion channel protein components. One example of a SNP produces a KCNE2 variant found in 1.6% of the population.⁸⁷ These patients have a normal QT interval at rest, but when exposed to sulphamethoxazole, which has no significant effect on wild type channels, they exhibit a 50% reduction in I_{Kr} , because of an increase in the channel deactivation time constant, and subsequent prolonged repolarization. The great genotypic and phenotypic heterogeneity of the disease, and the significant age-related attenuation of its severity in males,⁴⁵ means that an unknown but potentially significant number of genetically affected patients will remain undiagnosed until an initiating event unmasks their reduced repolarization reserve and precipitates a malignant arrhythmia.

There are many different types of drugs that prolong the QT interval, and which should be avoided by patients with LQTS (Table 2).^{103 117} Many drugs, such as amitriptyline, prolong the QT interval by blocking I_{Kr} , which is conducted by HERG channel proteins.²⁹ Some drugs partially block I_{Kto} or rarely, activate an increase in I_{Kir} . Anti-arrhythmic drugs that belong to class IA (e.g. quinidine) or class III (e.g. amiodarone) of the Vaughan-Williams classification are used to intentionally prolong cardiac repolarization, (which can represent both a pro- and anti-arrhythmic mechanism), although they can induce torsade de pointes even after months of uncomplicated treatment in 'susceptible' patients.

Long-term treatment of LQTS

The objectives of long-term treatment of patients with LQTS are the prevention of torsade de pointes and sudden death. The estimated mortality in untreated, symptomatic LQTS exceeds 20% in the first year after diagnosis and approaches 50% within 10 yr; with effective therapy, the 10-yr mortality risk can be reduced to 3–4%.³⁵

β-Blocking drugs

The mainstay of treatment of congenital LQTS since 1975 has been β -block. Schwarz reported a decrease in mortality from 71% in untreated historical controls to 6% in those treated.⁸¹ However, 32% of patients on β -blockers for symptomatic LQTS will have another cardiac event within 5 yr, and of those who present with aborted cardiac arrest, 14% will have further episodes of aborted sudden death or die in the next 5 yr, in spite of β -blocker therapy.⁵⁸

The dose of β -blocker is determined by ensuring a reduction in maximal heart rate on treadmill exercise testing to 130 beats min^{-1} or less; further reduction in symptomatic events does not occur if the dose is increased.⁵⁸ Propranolol is the most widely used drug at a daily dose of 2–3 mg kg^{-1} , although β -blockers with longer half-lives may increase compliance. Patients who develop marked bradycardia or prolonged sinus arrest on treatment may require back up permanent pacing. The QTc is unchanged despite efficacy

Table 2 Non-anaesthetic drugs that affect repolarization.^{103 117} All listed drugs prolong the QT interval. ^aRisk of precipitating torsade de pointes. ^bDocumented cases of torsade de pointes

Type of drug	Examples
Class Ia anti-arrhythmic agents	Quinidine ^a Disopyramide ^a Procainamide ^a
Class Ic anti-arrhythmic agents	Flecainide ^a
Class III anti-arrhythmic agents	Sotalol ^a Amiodarone ^a
Butyrophenone antipsychotics	Droperidol ^{a b} Haloperidol ^a
Phenothiazine antipsychotics	Thioridazine ^a
'Atypical' antipsychotics	Pimozide ^b Quetiapine Risperidone Zotepine
Selective serotonin re-uptake inhibitors	Fluoxetine ^a Paroxetine ^a Sertraline ^a
Macrolide antibiotics	Erythromycin ^a Clarithromycin ^b Azithromycin
5-HT ₁ agonists	Zolmitriptan Naratriptan
Antimalarial agents	Halofantrine ^a
Antihistamines	Terfenadine ^a
Prokinetic agents	Cisapride ^a

of treatment, although QTD is higher in patients who do not respond to β -block.⁶⁸

Anti-bradycardia pacing

Permanent cardiac pacing prevents bradycardia and pauses, which are known to provoke arrhythmia in LQTS. Patients in whom bradycardia is a prominent feature and patients who remain symptomatic despite β -block should have a pacemaker implanted to maintain heart rate, while β -blockers are continued.¹⁰⁷ Patients with the LQT3 subtype are particularly likely to benefit from pacing as they show slow sinus rates at baseline, which are often exacerbated by β -block.

Implantable automatic cardioverter-defibrillator

There has been a progressive reduction in the size of implantable cardioverter-defibrillators (ICD), first introduced over 15 yr ago, such that they can now be implanted in infants. Currently, ICDs are implanted when syncope or documented torsade de pointes continue despite β -block and pacing, or when the initial event is a resuscitated cardiac arrest. ICD insertion is also advised in patients with a QTc duration of >550–600 ms, a group where the risk of sudden death does not correlate with symptoms.³⁵ ICDs do not prevent torsade de pointes; they reduce (but do not eliminate) the incidence of sudden death when the episode of torsade de pointes is prolonged or deteriorates to ventricular fibrillation.¹¹³ Treatment with β -blockers has

to continue after ICD implantation, as many ICD algorithms result in defibrillation when a pre-programmed ventricular rate is exceeded. However, more sophisticated dual chamber ICDs are now available that have anti-tachycardia pacing and sensing capability.

Left cervicothoracic sympathectomy

Historically, left cervical sympathetic denervation was recommended when episodes of torsade de pointes persisted despite β -block. Adequate cardiac sympathetic denervation requires removal of the first 4–5 left thoracic ganglia and the lower half of the left stellate ganglion. Schwarz and colleagues used this technique in 123 patients who were either unresponsive to or intolerant of β -block, and reported significant reductions in symptoms and cardiac events.^{27 82} However, the efficacy of this technique has not been reproduced in other centres, and it is now reserved for patients refractory to drugs, pacing and ICD therapy.

Genotype-directed therapy

Although experimental evidence exists to support genotype-directed therapy, clinical trials have not yet corroborated the benefits of this potential change in management. Experimental models indicate that β -adrenergic block confers maximum protection in patients with LQT1 and LQT5, but confers much less protection in those with LQT2 and LQT6, and may actually increase the risk of torsade de pointes in LQT3 patients. Such observations are entirely compatible with data available on several hundred genotyped patients that indicate the existence of gene-specific triggers for cardiac events.⁸⁵ These differences in manifestations according to mutation suggest the feasibility of gene-specific therapy.¹⁰⁸

Sodium channel blockers such as mexiletine can reduce dispersion of repolarization and prevent torsade de pointes in experimental LQT3 models.⁸⁸ Moreover, preliminary clinical studies have demonstrated that mexiletine can normalize ventricular repolarization in LQT3 patients.^{84 116} However, as flecainide may induce ST elevation in some LQT3 patients, chronic sodium channel blocker therapy may not be entirely risk free.⁶⁹ Anti-bradycardia pacing has a particularly important role in LQT3 patients, in whom events are usually bradycardia mediated. Whether β -block therapy is effective in LQT3 patients in preventing arrhythmias remains unproven. In contrast, β -adrenergic block appears to be most effective for LQT1 patients, whose symptomatic episodes are almost always adrenergically mediated, in whom paradoxical increases in QTc can be induced by epinephrine, and in whom therapy reduces QT hysteresis during exercise.^{4 85 89} In the absence of any contradictory evidence from long-term trials, β -block remains the first line treatment for all patients at the present time.

Anaesthesia and LQTS

The age at which LQTS becomes clinically manifest is gene specific, but is usually before the age of 40 yr, and chiefly in childhood and adolescence.⁸⁵ Genotypically susceptible individuals may be completely asymptomatic, have a normal QTc interval, and may present for the first time during the intra-operative period with torsade de pointes. Alternatively, preoperative assessment of the patient may reveal historical or ECG features compatible with a diagnosis of LQTS; such patients can be presumptively diagnosed on the basis of published probability criteria (Table 1), and require full electrophysiological investigation before surgery. The patient may be aware of their diagnosis, allowing perioperative management to be optimized. LQTS patients refractory to conventional therapy may present for permanent pacing, insertion of ICD, or left cervical ganglionectomy.

Anaesthesia in patients with untreated LQTS carries a very high risk of intra-operative malignant ventricular arrhythmias,^{6 19 26 31 38 66 67 71} which may prove refractory to treatment.¹¹⁴ However, as discussed above, β -block is not completely protective and treated patients remain at risk of life-threatening episodes of torsade de pointes in the perioperative period. The practical considerations of anaesthesia for patients with LQTS therefore include immediate management of torsade de pointes, and, in known cases, avoidance of factors that increase the risk of precipitating torsade de pointes.

Patients with known LQTS

Preoperatively, all patients with known LQTS should be on maintenance β -blocker therapy, which must be continued up to and including the day of surgery. Preoperative assessment of its adequacy should determine that the heart rate does not exceed 130 min^{-1} during exercise; where exercise testing is impractical, there should ideally be no change in the QT interval in response to a Valsalva manoeuvre in a fully β -blocked individual.⁵⁶ In all patients with LQTS, serum electrolytes must be normal, as hypokalaemia, hypomagnesaemia, and hypocalcaemia all predispose to delayed ventricular repolarization. Drug therapy that unintentionally prolongs the QT interval should be avoided. The effect of anaesthetic drugs on the QTc is discussed below. A preoperative 12-lead ECG is mandatory and the QTc should be calculated as a baseline, although the presence and magnitude of any prolongation is not itself predictive of arrhythmia.¹⁰⁶ The presence and settings of any pacemaker device or ICD should be sought and checked. Time and effort should be expended in alleviating patient anxiety to minimize sympathetic activation, and premedication, where appropriate, should aim to produce a calm patient.

Intra-operative management should continue to focus on prevention of excessive sympathetic activity and avoidance of factors that can prolong the QT interval. Non-invasive

monitoring should commence before the induction of anaesthesia and ideally should include ECG monitoring of more than one lead, as short bursts of torsade de pointes may be difficult to distinguish from monomorphic ventricular tachycardia, when only one lead is available for analysis. A low threshold for intra-arterial monitoring is justified, as it is for central venous access, which facilitates rapid institution of trans-venous pacing. Potent stimuli, such as laryngoscopy, intubation, and extubation may be covered with boluses of esmolol or a potent, short-acting opioid; topical anaesthesia to the vocal cords before intubation is appropriate, whilst extubation should be achieved in a surgical plane of anaesthesia whenever feasible. Normoxaemia, normocarbica, and normoglycaemia will help prevent unnecessary sympathetic activity. Volume status must be carefully monitored and judicious fluid replacement maintained, as β -blocked patients tolerate hypovolaemia poorly. Positive pressure ventilation strategies should ensure that sustained high intrathoracic pressures are avoided, as this mimics a Valsalva manoeuvre, which can prolong the QT interval in patients who are not completely β -blocked;⁵⁶ such strategies include high peak and end expiratory pressures, end inspiratory pauses, and prolonged inspiratory times with low or reversed I:E ratios. During major surgery, hypokalaemia, hypomagnesaemia, and hypocalcaemia should be sought regularly and corrected promptly. Hypothermia prolongs the QT interval, so core temperature should be monitored and maintained. Trans-venous or external pacing apparatus, a defibrillator, and all the necessary drugs for management of cardiac arrhythmias must be immediately available. In patients with permanent pacemakers or ICD, the usual intraoperative precautions should be taken to avoid disruption of function.

Throughout the recovery period, a calm and quiet atmosphere must be strived for, as sudden auditory stimuli can provoke onset of torsade de pointes, especially in patients with LQT2 phenotype.⁸⁵ ECG monitoring in the postoperative period is mandatory, including during any transfer from the operating theatre to the recovery area, and should probably continue for at least 24 h postoperatively in a high dependency or intensive care environment. Adequate analgesia is essential. Postoperatively, β -block should be maintained i.v. until resumption of oral maintenance therapy is possible.

Although these are generic perioperative management principles, ensuring adequate perioperative β -adrenergic block and avoiding excessive sympathetic activity are perioperative goals most likely to benefit patients with LQT1 or LQT5. The anaesthetist should be far less reassured by the likely protection offered by effective β -block to patients with LQT2 or LQT6. In addition, the I_{Kr} channel is the most commonly affected by (non-anaesthetic) drugs that are known to prolong the QT interval (Table 2); such drugs are best avoided in all patients with LQTS, but particularly LQT2 or LQT6. I_{Kr} channel block is also particularly augmented by hypokalaemia. Experimental

models have suggested that potassium channel opening drugs such as nicorandil may be beneficial in LQT2,^{23 91} and patients presenting on such medication as part of a therapeutic trial should be maintained on it perioperatively.

For patients with LQT3, the emphasis during perioperative care must be to avoid physiological, pharmacological, and surgical factors that cause bradycardia. At a molecular level, the delayed inactivation of the channel conducting the I_{Na} current shows steep rate-dependence, being much greater at slow heart rates. The onset of torsade de pointes in experimental models of LQT3 is highly pause-dependent and both pacing and β -adrenergic stimulation are protective, whilst β -adrenergic block provokes torsade de pointes.⁹⁰ It must seem counterintuitive to ensure that such patients are adequately β -blocked, but it must be remembered that most patients with known LQTS will not have been genotyped, and are statistically likely to benefit from β -block. Even if a patient is known to have the LQT3 genotype, clinical trials are lacking to corroborate the experimental model evidence of increased risk from β -block. Given that LQT3 only accounts for 5% of genotyped LQTS, itself a small population, it is unlikely that such clinical evidence will be obtained easily and, in recognition of the experimental model evidence, patients with genotypic LQT3 or phenotypic features suggestive of LQT3 should have anti-bradycardia pacing in addition to β -block. Patients with LQT3 who are taking mexiletine or flecainide should have their therapy maintained.

Management of torsade de pointes

Episodes of torsade de pointes may be short-lived and self-terminating, but long bursts cause severe haemodynamic compromise and may degenerate into ventricular fibrillation. Such episodes should be treated with cardioversion/defibrillation. The arrhythmia may be preceded or succeeded by beats of sinus bradycardia that alternate with ventricular ectopics, to produce ventricular bigeminy. Short-term control of recurrence can be achieved with magnesium sulphate or temporary pacing.

Magnesium sulphate is the treatment of choice for torsade de pointes, even if the serum level is normal: an initial bolus of 30 mg kg⁻¹ over 2–3 min is usually effective, and should be followed by an infusion at 2–4 mg min⁻¹.¹⁰² The bolus can be repeated after 15 min if bursts of torsade de pointes persist. Although the mechanism by which magnesium suppresses torsade de pointes is unknown, it may block inward Na⁺ or Ca²⁺ currents involved in generating EADs.¹² Magnesium does not shorten the QT interval. Serum levels of magnesium should be monitored during the infusion to avoid toxicity, and the augmentation of neuromuscular block must be borne in mind. Serum potassium should be checked and high normal levels of 4.5–5 mmol litre⁻¹ maintained, if necessary by a potassium infusion.

Temporary trans-venous pacing is an effective way of controlling torsade de pointes if i.v. magnesium is ineffect-

ive.²⁸ Pacing is particularly effective in controlling torsade de pointes that is pause-dependent or bradycardia-dependent (LQT3, some LQT2 and most drug-induced QT prolongation). If central venous access is available, transvenous pacing of the right atrium is recommended, at a rate of 90–110 beats min⁻¹. Ventricular pacing can be used if atrioventricular block preceded the onset of torsade de pointes. Pacing eliminates pauses that may predispose to onset of torsade de pointes and enhances repolarizing currents, thus reducing the likelihood of EADs reaching threshold and inducing action potentials.²⁵ There are no reports of the use of temporary cardiac pacing to control torsade de pointes during anaesthesia.

Anaesthetic drugs and ventricular repolarization

The effect on the QT interval of various drugs used during the conduct of anaesthesia has been investigated *in vivo*, but conclusions from these studies are difficult to draw because of co-administration of several drugs. Moreover, some drugs with documented effects on the QT interval in healthy subjects appear to have different effects in patients with LQTS. Animal studies can examine the effect of a single drug on the QT interval and electrophysiological studies on isolated cardiac myocytes provide insight into the influence of anaesthetics on the ionic currents involved in generating cardiac action potentials. Many studies of anaesthetic drugs were conducted before the significance of M cells and transmural dispersion of repolarization were known. Thus, although information on the effects of some anaesthetic drugs on the QT interval is available, the clinical significance is often unclear, and it remains difficult to advise with authority on which are the safest anaesthetic agents to use in patients with LQTS. Our summary of anaesthetic management (Table 3) should, therefore, be treated with a degree of circumspection.

Inhalation agents

Halothane, enflurane, isoflurane, and sevoflurane, when administered as the sole agent for induction and maintenance, all prolong the QT interval in unpremedicated healthy humans, and can extend the QTc to beyond the upper limit of the normal range.^{44–79} Sevoflurane depresses I_K currents in isolated guinea-pig cardiac myocytes, which would account for observed prolongation of action potential duration.⁶⁴ Similarly, depressed I_K currents occur with equipotent doses of halothane and isoflurane, albeit in different species.^{37–63} Halothane increases transmural dispersion of repolarization in dogs.¹¹² A direct effect upon repolarization is supported by the observation that QT prolongation by these volatile anaesthetics is independent of autonomic tone in chronically instrumented dogs.⁷²

All four volatile agents have been used as a component of uneventful anaesthesia in known LQTS patients who were β -blocked,^{21–34–61–62} although sevoflurane further prolonged the QTc. However, enflurane and isoflurane have also been

administered to β -blocked LQTS patients whose anaesthetics were complicated by ventricular bigeminy,¹⁹ and torsade de pointes respectively,⁴⁰ whilst halothane was the volatile agent in use in six reported cases of malignant intraoperative arrhythmia that subsequently proved to be attributable to undiagnosed LQTS.^{6–38–40–50–71–114} None of these patients were β -blocked.

Conflicting reports, in healthy adults and children, of the effect of halothane on the QT interval in the presence of other drugs include suggestions that it has no significant effect or shortens the QT interval.^{33–41–46–52–53} In some of these studies, halothane has been compared with isoflurane, although not in equianaesthetic doses; these investigations have consistently reported prolongation of the QT interval by isoflurane.^{41–52–53} However, in the only two studies to serially monitor intra-operative QTc in LQTS patients, isoflurane actually shortened the QT interval towards normal in two β -blocked individuals.^{50–115}

Hence, no inhalation agent is known to be completely safe in LQTS patients. Uneventful anaesthesia with all of these agents has been reported with perioperative β -block in patients with LQTS whose subtype at the time was unknown and unknowable. Halothane increases transmural dispersion of repolarization in dogs, and should probably be avoided. Isoflurane and sevoflurane reduce I_K currents but their effect on transmural dispersion of repolarization awaits investigation. Sevoflurane seems to have a consistent propensity to prolong the QTc, but all four volatile agents discussed should probably be added to the list of drugs that can prolong the QT interval. The effect of desflurane is unreported.

Intravenous induction agents

Thiopental prolongs the QTc in healthy, premedicated adults and children,^{49–75–77} but its effect has only been studied in one patient with LQTS, whose QTc of 0.49 s was unaffected by thiopental induction.¹¹⁵ Sodium pentobarbital has the ability in *in vivo* animal models to inhibit the spontaneous or stimulated onset of torsade de pointes in controls, and in the presence of inhibitors of ion channels that mimic LQT2 and LQT3. The drug prolongs the overall action potential duration (and hence the QT interval), but reduces transmural dispersion of repolarization through a relatively greater prolongation of the epicardial and endocardial cell action potential durations compared to M cells.¹¹

Propofol appears to be potentially beneficial with respect to the QTc interval and QTD in individuals at high risk of torsade de pointes; its use in two patients with LQTS undergoing insertion of ICD after midazolam premedication suggests that it is worthy of further study.⁵¹ There are no reports of its effect on the QTc interval when used as the sole anaesthetic agent in unpremedicated patients with or without LQTS. Propofol may prolong the QT interval in healthy, premedicated adults,⁷⁶ and children⁷⁴ (although by a lesser magnitude than thiopental),⁴⁹ but other investigators

Table 3 Anaesthetic management of patients with known LQTS

Preoperative	<p>Ensure therapeutic β-block continues</p> <p>Ensure normal K^+, Ca^{2+}, Mg^{2+}</p> <p>Avoid drugs that further prolong QT interval</p> <p>Continue genotype-directed therapy</p> <p>Prescribe anxiolytic premedication</p> <p>If symptomatic, consider pacing—liaise with cardiologist</p> <p>If pacemaker/ICD <i>in situ</i>, check settings</p>
Perioperative	<p>Pre-induction monitoring of >1 ECG lead</p> <p>Low threshold for intra-arterial monitoring</p> <p>Establish central venous access:</p> <ul style="list-style-type: none"> to facilitate emergency pacing to ensure adequate filling in face of β-block <p>Thiopental or propofol for induction</p> <p>Consider propofol maintenance</p> <p>Avoid halothane; all volatiles prolong QTc</p> <p>Vecuronium probably safe</p> <p>Cisatracurium theoretically attractive but no clinical experience</p> <p>Avoid reversal if possible</p> <p>Minimize sympathetic stimulation:</p> <ul style="list-style-type: none"> topical LA/esmolol during laryngoscopy and intubation regional techniques where appropriate extubation during surgical anaesthesia/esmolol cover <p>Maintain normoxia, normocarbica, normothermia, and normoglycaemia</p> <p>Maintain normal serum K^+, Ca^{2+}, and Mg^{2+}</p>
Postoperative	<p>Continuous ECG monitoring</p> <p>Recovery in quiet environment</p> <p>Ensure maintenance of therapeutic β-block</p> <p>High dependency/intensive care unit monitoring</p> <p>Good analgesia</p>
Management of torsades de pointes	
(i)	<p>Treatment of sustained torsades de pointes</p> <p>DC cardioversion</p>
(ii)	<p>Treatment/prevention of short bursts of torsades de pointes</p> <p>Mg^{2+} 30 mg kg^{-1} i.v. bolus over 2–3 min, followed by infusion of 2–4 mg h^{-1}</p> <p>Repeat bolus after 15 min if bursts of torsades de pointes not suppressed</p> <p>Trans-venous pacing at 90–110 beats min^{-1}</p>

have found no effect on the QTc interval.^{43 44 54 65} Propofol reduces QTc at induction in patients with subarachnoid haemorrhage.⁹⁸ Midazolam alone has no effect on the QTc in healthy adults.^{54 55} The effect of other benzodiazepines is unknown. Methohexital prolongs the QTc in healthy adults,⁷⁶ but apparently not children (despite atropine premedication).⁷⁴ The effect of ketamine on the QT interval is unreported, but it should probably be avoided because of its sympathomimetic properties.

In summary, very limited clinical experience suggests that propofol may be a useful agent in patients with LQTS, particularly as it can be used for maintenance of anaesthesia; electrophysiological evidence of a beneficial effect on transmural dispersion of repolarization would be very helpful in confirming propofol's suitability. Such evidence exists for pentobarbital, making thiopental a good choice in theory; the prolongation of QTc in clinical studies would be acceptable if a reduction in transmural dispersion of repolarization were to be confirmed. Midazolam appears safe, although no information is available on its effect on transmural dispersion of repolarization and the studies examining QTc were small.

Neuromuscular blocking drugs

Among the modern agents in common use, only succinylcholine consistently prolongs the QTc.^{54 77} Inevitably, study

of the isolated effects of these agents is impossible in the clinical setting. Succinylcholine and pancuronium have featured as components of eventful and uneventful case reports in LQTS patients; in retrospect, it is again usually the presence or absence of β -block that distinguishes the two types of report. Vecuronium has been used in several LQTS patients, the rationale being its lack of autonomic effects. It is impossible, on the basis of the published evidence, to identify agents that are definitely safe, but vecuronium at least has been used without reported event in LQTS patients. Although relevant experience with atracurium and cisatracurium is lacking, the latter is a theoretically attractive choice, combining excellent haemodynamic stability (*vs* atracurium) with greater ability to omit reversal (*vide infra*) after a suitable period of time (*vs* vecuronium). Further study into the electrophysiological effects of neuromuscular blocking drugs on the relevant cardiac ion channels is urgently needed.

Anticholinesterases and anticholinergic agents

Atropine and glycopyrrolate prolong the QT interval in healthy individuals.^{9 78} This is perhaps surprising given that they increase heart rate, and should therefore shorten the QT interval. However, it has long been known that unopposed sympathetic tone can prolong the QT interval and this observation is compatible with the *in vitro* prolongation of

action potential duration by β -adrenergic stimulation. Diabetics who gradually develop vagal denervation also exhibit prolongation of the QTc and have an increased incidence of arrhythmias during anaesthesia.²⁰ Administration of atropine has been reported to precipitate torsade de pointes in a patient with LQTS.¹⁶ As neostigmine is never given in isolation to reverse neuromuscular block, its true effect is unknown, but one would predict that the inevitable resultant bradycardia would be undesirable, given the pause dependency of some forms of LQTS. Overall, until further information is available, reversal of neuromuscular block in known LQTS patients is probably best avoided whenever possible.

Conclusions

LQTS represents a group of cardiac ion channelopathies. Although relatively rare, its importance lies in the significant morbidity and mortality associated with failure to recognize and treat symptomatic patients, and the potential for anaesthesia to induce malignant arrhythmias in asymptomatic carriers with reduced repolarization reserve. The perioperative period is a time of high risk for patients with LQTS. The anaesthetist is faced with difficult decisions about the best way to conduct anaesthesia, and has scant information or evidence on which to base them. LQTS pathophysiology illustrates the clinical relevance of basic science research into the effects of anaesthetic agents at molecular and cellular levels; in order to improve scientific rationale in the anaesthetic management of LQTS patients, future investigations should focus on perioperative physiological and pharmacological influences on transmural dispersion of repolarization.

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