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Review Article

Long QT Syndrome and Perioperative Torsades de Pointes: What the Anesthesiologist Should Know

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TORSADES DE pointes (TdP or "twisting of the points") is a rare but potentially fatal polymorphic ventricular tachycardia characterized by rapid, wide QRS complexes of gradually varying amplitude that appear to "twist" around the isoelectric baseline on the electrocardiogram (ECG) (Fig. 1). Although TdP frequently terminates spontaneously, it has the potential to degenerate into ventricular fibrillation and lead to cardiac arrest. Due to the transient nature of TdP, its incidence is largely unknown, but it has been reported to occur with a frequency of anywhere from 0.004% to 0.343% per year.[1-3] It is widely accepted that TdP is associated with lengthening of the corrected QT interval (QTc). QTc prolongation may be congenital (ie, inherited channelopathies) or acquired as in the setting of drug administration, electrolyte disturbances, hypothermia, cardiac disease, cerebrovascular injury, thyroid dysfunction, and other factors.

The perioperative period is a unique time frame during which patients are exposed to a number of factors that are known to induce QTc prolongation. Surgical stress can trigger proinflammatory responses, fluid shifts, and electrolyte abnormalities, as well as myocardial injury. In addition, the patient is exposed to a number of drugs, including anesthetics, many of which may cause QTc prolongation. In one study, roughly 80% of patients undergoing noncardiac surgery under general anesthesia developed postoperative QTc prolongation.[4] It is, therefore, critical that anesthesia providers understand the factors that contribute to this potentially fatal arrhythmia and its specific treatment strategies. In this review, the authors present the current knowledge of perioperative TdP, as well as its known mechanisms and risk factors, including an overview of the numerous medications commonly used in the perioperative period.

Pathophysiology of TdP

The cardiac conduction system is comprised of specialized "pacemaker" cells that spontaneously generate electric activity and conduction pathways that propagate it throughout the heart in a coordinated fashion, generating action potentials (APs) in individual cardiac myocytes.[5] The AP relies on a number of ion channels within the sarcolemma and is divided into five phases—Phase 0 to Phase 4 (Fig. 2).

Phase 0 (rapid depolarization), corresponding to the start of systole, is triggered by the depolarization of neighboring cells via current leakage through gap junctions. Once a threshold potential is reached, the cardiac myocyte rapidly depolarizes due to an influx of sodium (I_{Na}) via fast, time-dependent sodium channels.[6] This depolarization initiates the opening of a long-opening (L-type) calcium channel, allowing calcium to begin to flow into the cell.[6]

Phase 1 is the transient repolarization phase. This brief repolarization is associated with inactivation of the sodium channels and activation of transient outward potassium current, IKto.[6]

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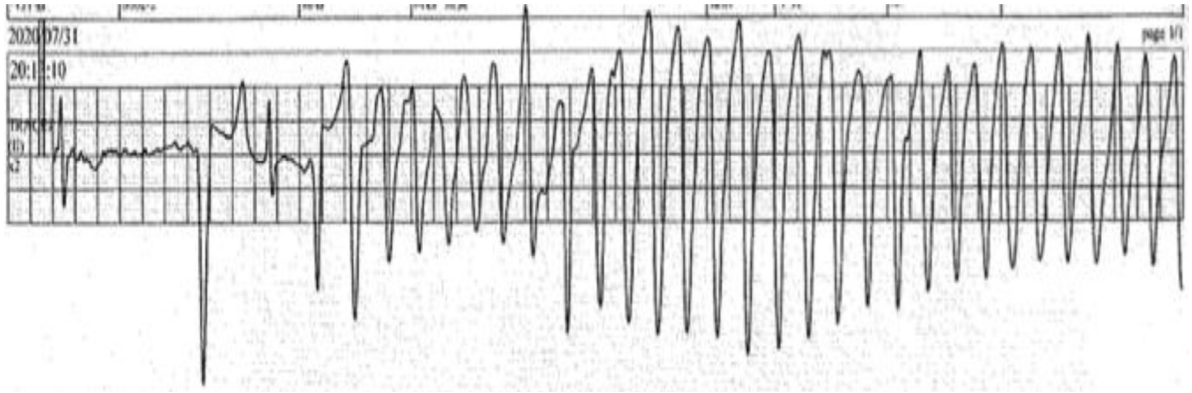

Fig. 1. Electrocardiogram tracing characteristic of Torsades de Pointes. A wide complex tachcardia with the QRS complex varying in amplitude around the isoelectric line is shown.

Phase 2 (plateau phase) is characterized by a constant, small inward current of calcium ($I_{Ca,L}$) that is electrically balanced by an outward potassium current through three delayed rectifier potassium channels (I_{Kur}, I_{Kr}, and I_{Ks}).[5,6] It is during this phase that excitation-contraction coupling occurs.

Repolarization occurs in Phase 3 wherein calcium channels are inactivated and increased conductance of rapid potassium current (I_{Kr}) completes repolarization, together with contributions from slow potassium current (I_{Ks}) and inward rectifying current (I_{K1}).[5,6] When there is a decrease in the outward potassium current or an increase in the inward calcium or sodium currents during this phase, QT prolongation may occur.

Finally, Phase 4 represents the cell's resting potential.[6]

Quantitative or qualitative defects in ion channels lead to the generation of abnormal APs and have the potential to result in arrhythmias.[5] TdP has been associated with the occurrence of delayed repolarization with early afterdepolarization, delayed afterdepolarization, and functional re-entry in the setting of unidirectional conduction block and increased transmural dispersion of repolarization (TDR, a measure of the intrinsic electrical heterogeneity of the ventricular myocardium).[7-13] Afterdepolarization is an inappropriate secondary depolarization during Phase 2 or 3 of the AP. The decrease in outward potassium current causes an increase in calcium uptake by the voltage-dependent calcium channel and subsequent calcium release from the sarcoplasmic reticulum. This increase in cytosolic calcium level then translates into new sodium inward current via calcium-sodium exchanger for afterdepolarization,[14] which leads to the generation of a premature ventricular complex.

The Measurement of QTc Interval and TDR

On ECG, the QT interval represents the sum of ventricular depolarization and repolarization.[15] It is measured from the

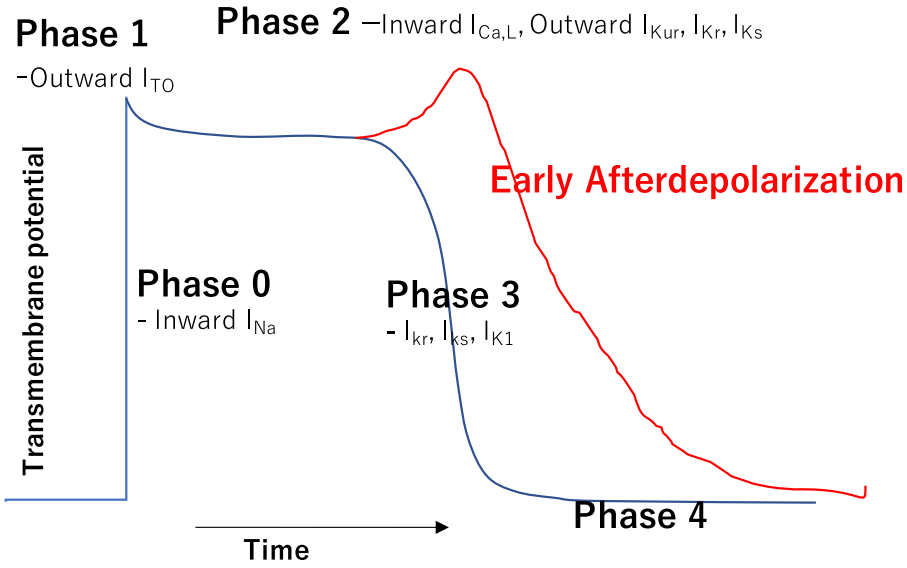

Fig. 2. Cardiac action potential and responsible ion channels. Cardiac action potential consists of five phases (Phase 0-4). In Phase 0 (rapid depolarization phase), inward sodium current (I_{Na}) is involved. In Phase 1 (transient repolarization phase), inactivation of I_{Na} and activation of I_{TO} occur. Phase 2 (plateau phase) is made by electrical balance between inward current (I_{Na}) and outward current (I_{Kur}, I_{Kr}, I_{Ks}). Phase 3 (repolarization phase) occurs when $I_{Ca,L}$ is inactivated and I_{Kur}, I_{Kr}, and I_{K1} are increased. Phase 4 corresponds to the resting potential. Early afterdepolarization (EAD, shown in red) occurs during Phase 2 or 3 because of a decrease in the outward K current or and an increase in the inward Ca or Na current. As in the manuscript, I_{Kr} is the major target for torsadogenic drugs. I_{Ks} is the main target of volatile anesthetics.

start of the earliest Q wave to the end of the latest in the lead showing the longest interval[16] (Fig. 3). Although some authors recommend that the measurement should include large, fused U waves (when present), the most recent American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (AHA/ACCF/HRS) Recommendations for the Standardization and Interpretation of the Electrocardiogram recommend that when fused U waves are present, the QT interval should be measured in a lead without U waves or that the end of the T wave should be determined by drawing a tangent to the steepest proportion of the downslope until it crosses the TP segment[17,18] (Fig. 3).

The QT interval is inversely proportional to heart rate, and as such is often corrected to a standardized heart rate of 60 beats/min in order to improve diagnostic utility. The most common method of calculating QTc is the Bazett formula[19]:

$$QTc = QT/(RR)^{1/2}$$

where QT is the measured QT interval and RR is the RR interval. Other formulae for calculation for QTc are listed in Table 1. What constitutes a normal QT value depends on both age and sex.[20,21] According to the AHA/ACCF/HRS recommendations, QTc prolongation is defined as ≥450 ms in men, and ≥460 ms in women.[18] A QTc greater than 470 ms generally is considered to be prolonged regardless of age and sex; however, in an otherwise asymptomatic individual without any family history, QTc >500 ms is needed to demonstrate a meaningful predictability of Long QT Syndrome (LQTS). Normal QTc values are depicted in Table 2.

Although QT prolongation is a risk factor for TdP, the QT interval is not its sole electrophysiologic marker of risk.[22-25] In fact, in studies of drug-induced QT prolongation, QT prolongation in the absence of increased TDR has been shown not to provoke TdP.[13,26-28] On ECG, the morphology of the T wave is representative of the intrinsic differential time course of regional repolarization (ie, TDR) across the myocardium.[10] TDR can be measured as the interval from the peak of the T wave to the end of the T wave (TPE) (Fig. 3).[26-28] Patients with LQTS have been found to have abnormal T-wave morphology (eg, biphasic or notched T waves, T wave alternans, U waves) as well as greater median and maximum TPE, indicating abnormal TDR.[29-31] The cut-off value of TPE associated with increased arrhythmogenicity has yet to be conclusively defined. A meta-analysis by Tse et al. concluded that the cut-off point of TPE prolongation for a significant elevation in arrhythmic risk in the general population is 113.6 ms, with lower values in certain disease states such as Brugada syndrome (95.8 ms) or heart failure (106.3 ms), but cautioned that the TPE alone should not be used to estimate arrhythmia risk.[32] QTc is automatically calculated in some of the currently available intraoperative monitoring devices, and TPE is not. Availability of automatic TPE calculation might be helpful as an adjunct to intraoperative monitoring.

Table 1
Formula for QTc Calculation

Name	Formula
Bazett Formula	$QTc = QT/(RR)^{1/2}$
Fredericia Formula	$QTc = QT/(RR)^{1/3}$
Framingham Formula	QTc = QT+0.154(1-RR)
Hodges Formula	QTc = QT+1.75(heart rate-60)
Rautaharju Formula	QTc = QT−0.185(RR−1)+k (k = +0.006 for men and +0 for women)

Abbreviations: QTc, corrected QT interval; RR, .

Table 2
Normal QTc Values

QTc (ms)	1-12 y	Women (>12 y)	Men (>12 y)
Short		<390	<390
Normal		390-460	390-450
Prolonged	≧450	≧460	≧450

Abbreviation: QTc, corrected QT interval.

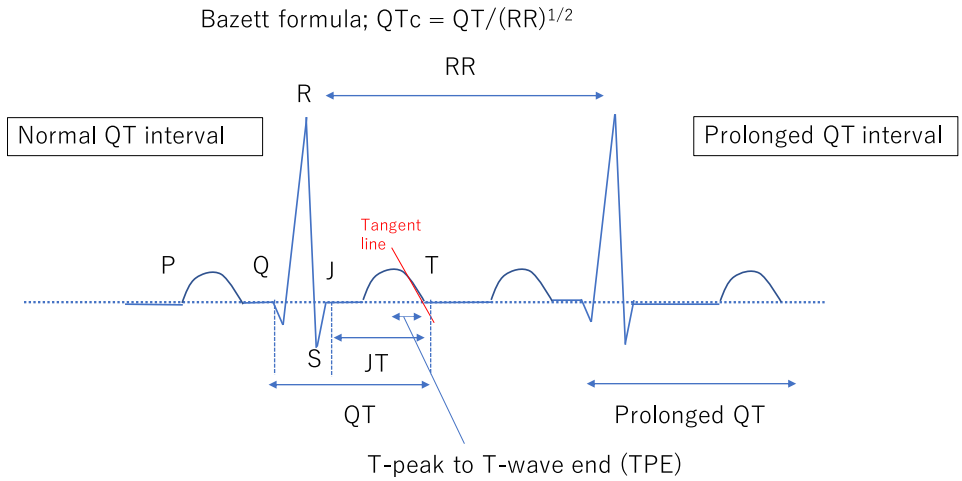

Fig. 3. Schematic representation of electrocardiogram. QT intervral and JT interval are indicated in the scheme. The end of the T wave should be determined by drawing a tangent line at the steepest proportion of the downslope until it crosses the isoelectric line. In patients with QRS >=120 msec, JT interval should be considered instead of QT interval. The peak of T wave to the end of T wave interval (TPE), which is associated with transmural dispersion of repolarization, also is shown.[53,54]

In patients with a prolonged QRS interval (QRS ≧120 ms), the JT interval (QTc − QRS) (Fig. 3) may be more indicative of a mortality risk than the QTc interval. Zulqarnain et al. (Third National Health and Nutrition Examination Survey) demonstrated that a prolonged JT interval (>362 ms) was a stronger risk factor for all-cause mortality than a prolonged QT interval in patients with QRS≧120 ms; however, Crow et al. (Atherosclerosis Risk In Communities Study) found this only to be true in men.[33,34] The AHA/ACCF/HRS guidelines make no specific recommendations of the use of JT interval over QTc interval, but note that if used, normal standards specific to the JT interval should be used.[18]

Congenital LQTS (LQTS)

In 1957, Anton Jervell and Fred Lang-Nielsen described a syndrome in four siblings consisting of prolonged QT interval, congenital deafness, functional heart disease, and sudden death.[35] Since that time, several other named syndromes (Romano-Ward, Timothy, Andersen-Tawil) involving QT prolongation have been described and enormous strides have been made in the understanding of the genetics and molecular biology underpinning inherited channelopathies. LQTS is the most common genetic arrhythmogenic disease , with an estimated prevalence of 1/2,000.[36] To date, 17 LQTS susceptibility genes have been identified with varying levels of evidence to support disease causation[37] (Table 3). LQTS1, LQTS2, and LQTS3 are the common genotypes of LQTS, accounting for 40%-55%, 30%-45%, and 5%-10% of LQTS, respectively.[38] LQTS may lead to recurrent syncope, seizure, cardiac arrest, or sudden death. The mortality of LQTS is 0.6% to 2.9% per year due to fatal arrhythmia. In patients with untreated, symptomatic LQTS, there is a 21% mortality rate within one year after first syncope and 50% within ten years.[39,40] Treated patients with the most common types on LQTS in the modern era have markedly improved outcomes, with estimated cardiac events and mortality rates of 1.3%/year and 0.05%/year, respectively.[41] Patients with malignant variants, including the Jervell and Lange-Nielsen Syndrome and Timothy Syndrome (LQTS8), continue to be difficult to manage and carry a high risk of mortality.[38]

According to the HRS/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society consensus statement (2013) on the diagnosis and management of patients with inherited primary arrhythmia syndromes, LQTS is diagnosed in the presence of a LQTS (Schwartz) risk score ≧3.5 in the absence of a secondary cause for QT prolongation and/or in the presence of an unequivocally pathogenic mutation in one of the LQTS genes or in the presence of a corrected QT interval for heart rate using Bazett's formula (QTc) ≧500 ms in repeated 12-lead ECGs and in the absence of a secondary cause for QT prolongation.[41] In a patient with unexplained syncope and without a secondary cause for QT prolongation or a pathogenic mutation, LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms in repeated 12-lead ECGs.[42]

The Schwartz score (Table 4) is a set of diagnostic criteria that is widely used to estimate the probability of LQTS.[43] This

Table 3
Type of cLQTS

Type	Gene Mutation	Prevalence(%)	Clinical Features
LQTS1	KCNQ1	40-55	ECG shows a broad-based and symmetrical T wave.[235] Arrhythmic events are often triggered by exercise, especially swimming. Tends to have cardiac events in younger age. High b-blocker effectiveness. Mutations can cause Jervell-Lange-Nielsen syndrome.
LQTS2	KCNH2	30-45	ECG shows bifid or notched T wave that is asymmetrical and low amplitude.[235] Arrhythmic events are often triggered by auditory stimuli (eg, an alarm clock) from sleep or periods of rest. Tends to have higher risk of cardiac events in first 9 months of postpartum women.
LQTS3	SCN5A		ECG shows delayed pointed T wave.[235] Cardiac events tend to occur later in life and be more lethal. Cardiac events are associated with bradycardia (eg, at rest and during sleep). Least responsive to b-blockers.
LQTS4	ANK2	<1	Produces wide spectrum of arrhythmias (ie, catecholaminergic polymorphic ventricular tachycardia, atrial fibrillation, intraventricular conduction alteration, sinus node dysfunction, and bradycardia).
LQTS5	KCNE1	<1	Mutations can cause Jervell-Lange-Nielsen syndrome. High b-blocker effectiveness.[236]
LQTS6	KCNE2	<1	Sulfa drugs may lead the carriers to diLQTS.
LQTS7	KCNJ2	<1	Known as Andersen-Tawil syndrome. Characterized by periodic paralysis, dysmorphic anatomical features, ventricular arrhythmia, and particular susceptibility to develop ventricular fibrillation, particularly in women.[46,235] Lower risk of sudden cardiac death compared with others.
LQTS8	CACNA1C	<0.5%	Known as Timothy Syndrome, characterized by cardiac malformations, intermittent immunological deficiency, hypoglycemia,

(*continued*)

Table 3 (*continued*)

Type	Gene Mutation	Prevalence(%)	Clinical Features
			cognitive alterations including autism, interdigital fusion, and prolonged QT.[46,235]
LQTS9	CAV3	<1	Alter the biophysical properties of sodium channel similar to LQTS3.[46]
LQTS10	SCN4B	<1	Very severe case with QTc >600 ms, fetal bradycardia, and 2:1 atrioventricular block.[46]
LQTS11	AKAP9	<1	
LQTS12	SNTA1	<1	
LQTS13	KCNJ5	<1	
LQTS14	CALM1	<1	
LQTS15	CALM2	<1	
LQTS16	CALM3	<1	
LQTS17	TRDN	<1	

Abbreviations: diLQTS, drug-induced long QT syndrome; ECG, electrocardiogram; LQTS, Long QT Syndrome.

scoring system takes family history, clinical history, and electrocardiographic findings into consideration. Scoring is as follows: ≦1.0 point = low probability of LQTS, 1.5-3.0 points = intermediate probability of LQTS, ≧3.5 points = high probability of LQTS.[43] Measures of TDR (eg, TPE, JT interval, and QRS duration) are not included in this scoring system, as it pre-dates the overwhelming majority of the work investigating the impact of TDR on cardiovascular risk profiles.

LQTS1

LQTS1 is caused by a loss of function KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) gene mutation that causes a decrease in outward potassium current during Phase 2, which leads to a delay in ventricular depolarization and a prolongation of QT interval on ECG. KCNQ1 is the α-subunit of the voltage-dependent potassium channel responsible for the slow component of the delayed rectifier current I_{Ks}.[44] I_{Ks} amplitude is low at baseline, but enhanced in the setting of α-adrenergic stimulation and increased heart rate, leading to a shortening of both the AP and QT interval. AP shortening is essential to ensure an appropriate myocardial contraction-relaxation period. Patients with LQTS1 cannot appropriately shorten their AP and QT intervals.[45] Adrenergic stimulation, such as exercise, particularly swimming, is the trigger of arrhythmogenic events in patients with LQTS1.[45] Therefore, exercise is used as a diagnostic test in individuals with suspected LQTS1. Patients with LQTS1 often show significantly lower maximal heart rate during exercise testing, which is associated with sinus node dysfunction.[46,47] Patients with LQTS1 tend to have cardiac events in younger ages compared with other genotypes.[48]

Table 4
Schwartz Risk Score

Electrocardiographic Findings	Score
QTc ≥480 ms	+3
QTc 460-479 ms	+2
QTc 450-459 ms in males	+1
QTc ≥480 ms in 4th minute of recovery from exercise	+1
Torsade de pointes (mutually exclusive from syncope)	+2
Notched T-wave in 3 leads	+1
T-wave alternans	+1
Bradycardia (<2nd percentile for age)	+0.5
Clinical history	
Syncope (with stress)	+2
Syncope (without stress)	+1
Congenital deafness	+0.5
Family history	
Family member with definite LQTS	+1
Unexplained sudden death in a 1st degree family member <age 30	+0.5

Abbreviations: LQTS, Long QT Syndrome; QTc, corrected QT interval.

LQTS2

LQTS2 is caused by a loss of function mutation in the KCNH2 gene (potassium voltage-gated channel, subfamily H, member 2, also known as the human Ether-à-go-go-Related Gene) that encodes the pore-forming α-subunit of the I_{Kr} channel.[49] The I_{Kr} current, which occurs during low-frequency stimulation, increases in amplitude during Phase 3 of the AP and represents the rapid component of the delayed rectifier current. The I_{kr} current is delayed in LQTS2, leading to longer AP duration. Arrhythmogenic events typically occur in the setting of arousal due to auditory stimuli, most commonly from sleep or during periods of rest.[45] LQTS2 tends to have a higher risk of cardiac events in postpartum women.[48]

LQTS3

LQTS3 is caused by a gain of function mutation in the SCN5A (sodium voltage-gated channel, type V, α-subunit) gene, which encodes the $Nav_{1.5}$ Na^+ channel α-subunit, and leads to excessive late inward Na^+ current (I_{Na}) during the plateau phase (Phase 2) of the AP, leading to its prolongation.[50] Compared with LQTS1 and LQTS2, cardiac events in patients with LQTS3 tend to occur later in life and be more lethal.[22,51] No specific arrhythmogenic triggers are identified in patients with LQTS3, but they are also more likely to occur at rest or during sleep rather than triggered by exercise or emotion.[45]

Acquired QT Prolongation

Acquired long QT syndrome (aLQTS) is characterized by QT prolongation that is secondary to exogenous stressors such as drug administration, electrolyte disturbances (eg, hypokalemia, hypomagnesemia, hypochloremia, and hyponatremia), hypothermia, cardiac disease (eg, hypertension, congestive heart failure, ischemic cardiomyopathy, left ventricular hypertrophy, and after cardiopulmonary bypass after cardiac

surgery[52-54]), cerebrovascular injury, renal failure, cirrhosis, and endocrine dysfunction (eg, diabetes mellitus, thyroid disease, testosterone deficiency). Advancing age, female sex, and elevated body mass index are known risk factors for aLQTS.[55,56] Drug-induced long QT syndrome (diLQTS) often is regarded as the most common type of aLQTS; however, its incidence is challenging to estimate given that patients at risk for diLQTS often have multiple other nondrug risk factors.

diLQTS

Considerable progress has been made with regard to understanding the pathogenic and pharmacogenetic mechanisms underlying diLQTS and drug-induced TdP. Numerous classes of drugs are known to cause diLQTS (Table 5). Antiarrhythmic drugs, especially Vaughan Williams class III drugs, are the most well-known class of QT prolonging agents.[57] A comprehensive list of QT-prolonging drugs can be referenced at crediblemeds.org.[58] Most of the drugs previously identified as torsadogenic have been shown to inhibit the KCNH2-encoded I_{Kr} current channel, causing a phenocopy of LQTS2.[59] Silico drug screening trials have suggested that other ion channels including $Nav_{1.5}$ and $Cav_{1.2}$ also are involved.[60] Importantly, not all QTc-prolonging drugs are torsadogenic. As noted previously, QT prolongation in the absence of increased TDR has been shown not to provoke TdP.[13,26-28] For example, amiodarone blocks I_{Kr} but reduces TDR due to a differential effect on AP duration in endocardial and mid-myocardial cells.[61] Its use is associated with a very low incidence of TdP (<1%).[62,63] diLQTS is associated with a number of environmental, epigenetic, and genetic risk factors including highdrug concentrations, rapid intravenous administration, hypokalemia, hypomagnesemia, female sex, ethnicity, bradycardia, recent conversion from atrial fibrillation, left ventricular hypertrophy, heart failure, subclinical/unrecognized LQTS, polymorphisms in the LQTS genes, and other polymorphisms, such as those involving the CYP enzymes involved in the metabolism of culprit drugs.[59] Almost 70% of patients with latent or "silent" LQTS (ie, undiagnosed LQTS in a patient with a normal QTc at baseline) have normal QTc until they are first exposed to drugs that induce QT prolongation.[64] Latent LQTS may be responsible for up to 19% of diLQTS.[65] In patients without LQTS, it is possible that genetic polymorphisms in the LQTS genes underlie an additional portion of aLQTS/diLQTS. In one cross-sectional study, polymorphisms in the KvLQT1 and human Ether-à-go-go-Related genes were identified in 10% to 15% of subjects with aLQTS.[66] Polymorphisms associated with diLQTS are estimated to be present in anywhere from 1.6% to 13.2% of the population, depending on ethnicity.[67-71]

Although Tisdale et al. published a quantitative multivariate risk index for the prediction of TdP in a hospital-based population, there is currently no such index of diLQTS.[72] According to the American Heart Association and the American College of Cardiology Foundation's scientific statement on the prevention of TdP in hospital settings, after the initiation of a drug associated with TdP providers should be alert to ECG signs that are indicative of the risk for arrhythmia, including a 60-ms increase in QTc from predrug baseline, QTc interval prolongation >500 ms, T-U wave distortion that is exaggerated in the beat after a pause, macroscopic T-wave alternans, new onset ventricular ectopy, couplets, and nonsustained polymorphic ventricular tachycardia initiated in the beat after a pause.[73]

Table 5
The List of Torsadogenic Drugs

Class	Example
Antiarrhythmics (class IA and class III)	Disopyramide, quinidine, procainamide, sotalol, ibutilide, dofetilide
Antibiotic	Macrolide, fluoroquinolone
Antifungal	Fluconazole, ketoconazole, itraconazole
Antimalarial	Choloroquinine, halofantrine, quinidine
Antineoplastic	Lapatinib, nilotinib, sunitinib, tamoxifen
Antidepressant	Amytriptyline, imipramine, paroxetine, fluoxetine, doxepin, desipramine, trimipramine
Antipsychotic	Risperidone, quetiapine, haloperidol, drioperidol, phenothiazines, amisulpride, chlorpromazine
Antihistamine	Diphenhydramine, terfenadine, astemizole
H2 receptor antagonist	Famotidine
Dopaminergic	Amantadine
Bronchodilator	Ephedrine, salmeterol, metaproterenol, albuterol
Intravenous anesthetic agents	Methadone, ketamine
Volatile anesthetics	Almost all the volatile anesthetics
Neuromuscular relaxants and reversals	Depolarizing neuromuscular relaxants, Anticholinesterase/ anticholinergic drugs (glycopyrrolate, atropine, neostigmine)
Vasopressor agents	Dopamine, dobutamine, epinephrine, norepinephrine
Antiemetics	Ondansetron, droperidol
Local anesthetic	Cocaine

Perioperative TdP and QTc Prolongation

Due to the lack of large epidemiologic studies, the actual prevalence of perioperative TdP largely is unknown and what is known with regard to potential risk factors is limited to case reports and small studies, as are summarized in Table 6. Johnston et al. performed a systemic review and meta-analysis of the 46 perioperative TdP cases reported from 1978 to 2011.[74] They found that female sex (67%), surgery type (cardiac 27%, craniotomy 13%), QT prolongating drugs (30%), hypokalemia (28%), and bradycardia (16%) were the most frequent risk factors and that the majority of events occurred during the maintenance of anesthesia (49%) or within three postoperative days (42%), with a case fatality rate of 4%.[74] In 90% of the patients, the QTc interval increased by >100 ms; the mean QTc intervals at baseline and at the time of TdP manifestation were 457 ms and 647 ms, respectively, representing an average QTc increase of 118 ms (99% confidence interval 70-160 ms; $p < 0.001$).[74]

Table 6
Perioperative TdP Study

Authors	Aim	Sample size	Data extraction	Comment/outcome
Johnston et al.[72]	To perform a systematic review and identify the risk factors of perioperative TdP.	46 case reports of perioperative TdP published in 1978-2011.	Age, sex, timing of the TdP event, heart rates at baseline and at the event, electrolytes, administered drugs, pre-/post-event QTc, treatments, and outcome (fatal/nonfatal).	Identified female sex (67%), cardiac surgery (27%), craniotomy (13%), hypokalemia (26%), and bradycardia (15%) as the risk factors of TdP. On average, the mean QTc at TdP increased by +118 ms compared with baseline.
Nagele et al.[4]	To investigate the effects of drugs and conditions on perioperative QTc prolongation.	469 adult patients (average age of 65 y) with or at risk for coronary artery diseases undergoing major noncardiac surgery under general anesthesia.	QTc from preoperative to postoperative day 2, administered drugs, electrolytes, and temperature.	80% of the patients showed significantly prolonged QTc. 39% of the patients had QTc prolongation >30 ms, 8% had >60 ms, 0,5% had >100 ms. Epinephrine (80%), isoflurane (54%), methadone (53%), ketorolac (58%), ephedrine (49%) and several antibiotics were associated with QTc prolongation. Incidence rate of postoperative TdP was 0.4%.
Duma et al.[73]	To identify whether the type of anesthesia (general, spinal, and local) influence the QTc interval.	300 patients undergoing general anesthesia (n = 101), spinal anesthesia (n = 99), and local anesthesia (n = 100).	Preoperative, intraoperative, and postoperative QTc.	Significant QTc prolongation occurred during general anesthesia and spinal anesthesia (median increase of 33 ms and 22 ms, respectively), but not in local anesthesia. Substantial QTc prolongation ($\geqq$60 ms) was observed only in patients under general anesthesia (5% preoperatively, 27% intraoperatively, and 14% postoperatively).
Nuttall et al.[74]	To determine whether low-dose droperidol administration increase the incidence of TdP in the general surgical population.	Retrospective study of patients who underwent surgery with general anesthesia or central neuraxial blockade in 1998-2001 (before black box warning, n = 139,932) and 2002-2005 (after black box warning, n = 151,256).	Occurrence of TdP within 2 days after surgery, pre-/postoperative QTc, and droperidol administration	The incidence of patients who died within 48 h after surgery, experienced TdP, or exhibited QT interval prolongation was 1.66% (1998-2001) and 1.46% (2002-2005), respectively. Only 2 patients experienced documented TdP and neither of them received droperidol. They found no change in the incidence of TdP with the commonly used low-dose droperidol in the perioperative period.
Pickham et al.[75]	To test the value of QT interval measurement in hospitalized patients.	Prospective, observational study of all adult patients in critical care unit (n = 154).	Continuous QT/QTc monitoring.	The incidence of QT prolongation was 24%. Out of 16 cardiac arrests, TdP represent 6% (1/16) of in-hospital cardiac arrests. Acutely ill patients with QT prolongation had 3-times the odds for mortality rate compared with those without QT prolongation.

Abbreviations: QTc, corrected QT interval; TdP, Torsades de Pointes.

Perioperative QTc prolongation is a common occurrence. In a study of 429 adult patients undergoing general anesthesia for noncardiac surgery, Nagele et al. found the incidence of immediate postoperative QTc prolongation to be 80%, with a mean QTc increase of 23 ± 26ms; 51% of patients had a QTc >440 ms and 4% had a QTc >500 ms.[4] The patients enrolled in this study were adult patients (average age of 65 years) with or at risk for coronary artery diseases. One patient, with a QTc increase of 29 ms, developed TdP. In another study of a similar cohort (n = 300) by Duma et al., the intraoperative QTc interval was compared with the preoperative value and found to be prolonged under both general and spinal anesthesia, but not under local anesthesia, with a median increase of 33 ms and 22 ms, respectively.[75] The occurrence of TdP was not reported in this study. The clinical relevance of perioperative QTc prolongation is unknown. Although the larger increases in QTc duration seen in those patients with reported perioperative TdP compared with the smaller median increases seen in perioperative patients without TdP suggested that there is an association between magnitude of QTc prolongation and the risk of TdP, further studies are needed.

When compared with QTc prolongation, perioperative TdP is rare. The transient nature of TdP and the historic use of less robust perioperative monitoring systems have contributed to under-reporting, contributing to the divergence in reported estimates and complicating the determination of a true incidence. Nagele et al. and Nuttall et al. reported perioperative TdP incidences of 0.4% (1/242),[4] and 0.001% (2/291,000),[76] respectively. Outside of the perioperative settings, the incidence of TdP has been shown to be 1/1,500 (0.07%) among acutely ill adult patients, with TdP contributing to 6% of in-hospital cardiac arrests.[77]

Perioperative Management

During the perioperative period, patients are exposed to a number of pharmacologic agents and physiologic perturbations that are known to prolong the QTc interval, be torsadogenic, or both. Although the incidences of LQTS and perioperative TdP are low, it is imperative that clinicians understand the underlying risk factors and take the necessary precautions in order to prevent any resultant morbidity or mortality. Given the centrality of drug administration to the practice of anesthesiology, the authors will first review those medications germane to perioperative practice after which they will discuss other aspects of perioperative management. A summary of drugs to be avoided in the patient with LQTS and those that are considered safe for administration are summarized in Tables 5 and Table 7, respectively. An extensive review of all anesthetic agents is beyond the scope of this review, but can be found elsewhere.[78]

Intravenous Anesthetic Agents

Intravenous anesthetic agents are known to block repolarizing cardiac ion currents in vitro, decreasing $I_{Ca,L}$ and, to a lesser extent, I_K.[79] In healthy humans, midazolam generally has been shown not to prolong QTc or TDR at either premedication or induction doses up to 0.4 mg/kg and is regarded as safe for use in patients with LQTS.[80-83] It should be noted, however, that midazolam does not effectively blunt the sympathetic response to intubation or the QTc prolongation that this response causes.[83]

Studies reporting the effects of propofol on QTc are conflicting, with most studies of healthy patients undergoing anesthesia reporting either no change[84-89] or a decrease[90-92] in QTc with induction boluses of 1-to -2.5 mg/kg, but others reporting a statistically significant, albeit clinically insignificant, increase in QTc.[82,93-96] The effects of maintenance anesthesia infusions of propofol on QTc interval are likewise divergent, with either no significant change[84,91,97] or a decrease (in the setting of sevoflurane-associated QTc prolongation)[98] demonstrated. At clinically relevant doses in healthy patients, propofol does not lengthen QTc dispersion (QTcd; defined as the difference between longest and shortest QTc values on a 12 lead-ECG)[92] or TDR.[97,99,100] There is ex vivo animal data to suggest that propofol may be effective in the mitigation of diLQTS and TdP through its favorable effects on QTc duration and dispersion.[101] Although propofol generally is considered to be nontorsadogenic, its administration more recently has been associated with TdP in animal models of LQTS2,[102] and with clinically significant QTc prolongation[103,104] and/or TdP[105,106] in critically ill patients with comorbidities (trauma/latent LQTS, severe hypoalbuminemia).

Etomidate's effects on QTc have been less well-studied than those of midazolam or propofol, but generally are considered to be negligible. In premedicated adults undergoing elective cardiac surgery, etomidate was shown to have no significant effect on QTc.[89] In patients with major depression undergoing electroconvulsive shock therapy, propofol (1 mg/kg), but not etomidate (0.2 mg/kg), was able to blunt the QTc prolongation associated with the induced seizure.[107] During the intubation period, patients with coronary artery disease who were induced with etomidate (0.2-0.3 mg/kg) experienced an increase in QTcd of unknown clinical significance, whereas patients without coronary artery disease did not.[108]

Methohexital has been shown to have varying effects on QTc when used as an induction agent at a dose of 2 mg/kg—in children, there was no effect on QTc,[95] and in adults the effect was dependent on the baseline QTc, with an increase seen in those with a normal baseline, but a decrease seen in those with a prolonged baseline.[82] Dexmedetomidine, when administered to pediatric patients undergoing electrophysiology studies at a bolus dose of 1 μg/kg administered over ten minutes followed by an infusion of 0.7 μg/kg/hr for ten minutes, caused a

Table 7
List of Intraoperative Drugs Used Safely

Intravenous anesthetic agents	Fentanyl, remifentanil, morphine, midazolam, propofol, etomidate
Neuromuscular relaxants and reversals	Nondepolarizing neuromuscular relaxants, sugammadex
Vasopressor agents	Phenylephrine
Antiemetics	Dexamethasone, Metoclopramide

statistically significant, but clinically insignificant increase in QTc from 394 ± 9 ms to 424 ± 9 and decreases in sinus and AV node conduction.[109] The effects of ketamine on QTc in humans has not been well-studied. In a small observational study of pediatric patients undergoing procedural sedation (1.5 mg/kg) for emergency room procedures, there was no difference in QTc or QTcd.[110] Despite this finding, ketamine generally is avoided in patients with LQTS due to its sympathomimetic properties.

Inhaled Anesthetic Agents

Almost all volatile anesthetics prolong QTc through the inhibition of potassium membrane currents, primarily I_{Ks} (as opposed to I_{Kr} as in most diLQTS). The effect of sevoflurane on QTc has been the subject of numerous studies, many of which found increases in QTc[84-88,90,97,111-117] and QTcd[111,117] of varying degrees of clinical significance, and others found no significant changes.[96,99,118-123] Sevoflurane-associated QTc prolongation may be attenuated by the addition of IV agents,[123] reversed by conversion to propofol,[98] and influenced by the speed of concentration change, favoring gradual over one-breath induction techniques.[85,117-120] Elderly patients may be at a higher risk of QTc prolongation than younger patients.[113] Importantly, despite any QTc prolongation associated with its use, sevoflurane uniformly has been shown to not increase TDR/TPE, perhaps suggesting low torsadogenicity.[97,113,115,116,123] In a case series of pediatric patients undergoing left cardiac sympathetic denervation, both sevoflurane and isoflurane were used without incident in patients with LQTS; however, those patients with profound QTc prolongation deemed to be at the highest risk for arrhythmia also were managed with intraoperative esmolol infusions.[124] There are several case reports of TdP in patients with LQTS undergoing sevoflurane anesthesia.[125-127] Although the theoretic risk of sevoflurane-associated TdP is low, care should be taken when using sevoflurane in the setting of LQTS with profound baseline QTc prolongation or the concomitant administration of other QTc-prolongating agents.

Desflurane has been shown consistently to cause QTc prolongation,[111,122,123,128] with either an increase[99,111] or no change[122] in QTcd. In patients induced with propofol and administered 6% desflurane during intubation, there was no change in TPE when compared with controls.[129] Desflurane is a known airway irritant. A rapid increase in desflurane concentration has been shown to cause greater increases in plasma catecholamine and vasopressin concentrations than a rapid increase in isoflurane concentration.[130] Although QTc prolongation secondary to increased autonomic tone may be attenuated with midazolam premedication[122] or propofol induction,[131] it may be best to avoid desflurane in patients with LQTS. Isoflurane unvaryingly causes significant QTc[4,111,118,121,132-135] and QTcd[112] prolongation when used for induction or maintenance. Its effect on TPE is unknown.

Opioids

Opioids have an inhibitory effect on I_{Kr} in vitro.[136,137] With the exception of methadone, which has been shown to cause QTc prolongation[138-146] and is strongly associated with TdP (at doses as low as 40 mg/day),[138-140] most opioids used in the perioperative setting have no effect on QTc when used at clinically relevant doses. This is true for fentanyl,[147,148] alfentanil,[149] remifentanil,[147,150,151] morphine,[137] and tramadol.[137,152] Fentanyl (2 μg/kg),[148] alfentanil (25-75 μg/kg),[149,153,154] and remifentanil (bolus 1 μg/kg, infusion 0.25 μg/kg/min)[147,150] all have been shown to attenuate the QTc-prolongating effects of laryngoscopy. Additionally, an infusion of remifentanil, 0.25 μg/kg/min, during induction has been shown to decrease QTcd after intubation.[147] The effects of sufentanil and meperidine on QTc interval have not been well-studied in humans, but there are reports of TdP associated with their use.[151,156] Hydromorphone's effect on QTc largely is unknown; however, a blinded RCT is underway (NCT03893734) and a recent case report described the successful conversion of a patient from methadone to hydromorphone for QTc prolongation in the setting of methadone maintenance therapy.[157] Lastly, despite methadone's association with QTc prolongation and TdP, adverse cardiovascular events with intraoperative dosing of 0.1-to-0.3 mg/kg have not been reported.[158]

Neuromuscular Blocking and Reversal Agents

Succinylcholine has been shown to increase QTc.[81,83,95,149,154,155,159,160] Pretreatment with opioids (alfentanil 25-75 μg/kg)[149,154,155] or beta-blockers (metoprolol 20-40 μg/kg,[159] esmolol 2-3 mg/kg[149,161]) also has been shown to attenuate the sympathetic stimulation and resultant QTc prolongation caused by succinylcholine. In adult patients with normal baseline QTc, induction with either propofol (2 mg/kg) or methohexital (2 mg/kg) has been shown to abolish this increase, and in those with a prolonged baseline QTc, induction with propofol led to a significant (60 ms) decrease in QTc after succinylcholine administration, suggesting that propofol may be the induction agent of choice when succinylcholine is required.[82]

The nondepolarizing muscle relaxants vecuronium,[83,150,161] pancuronium,[162] rocuronium (0.6 mg/kg and 1.2 mg/kg),[151,163,164] and cisatracurium,[165] do not cause QTc prolongation. Anticholinesterase-anticholinergic antagonism of neuromuscular blockade with neostigmine (40 μg/kg) and glycopyrrolate (8 μg/kg) or atropine (20 μg/kg) has been shown to cause clinically significant QTc prolongation and should be avoided in patients with LQTS.[166] The cardiovascular safety profile of sugammadex has been extensively studied, with the overwhelming majority of studies demonstrating no significant effect on QTc when administered alone (supratherapeutic doses up to 96 mg/kg) or in combination with rocuronium or vecuronium.[167-173] Vanaker et al. found QTc to be prolonged mildly by sugammadex when administered to patients undergoing maintenance anesthesia with sevoflurane, but not propofol.[173]

Antiemetics

The 5-hydroxytryptamine type 3 (seratonin) receptor antagonist class of antiemetics has been shown to block both I_{Kr} and cardiac sodium channels in vitro and has the potential to cause QRS and QTc prolongation to varying degrees, especially when used

intravenously, at high-doses, or in high-risk patients.[174-180] When used at standard perioperative doses, ondansetron (4 mg, 0.15 mg/kg)[175,177,178] and, to a lesser extent , granisetron[178] and dolasetron,[175,179] cause QTc prolongation. Only ondansetron is known to lengthen the JT interval.[176] The Federal Drug Administration suggests that ondansetron should be avoided in patients with LQTS, that electrolyte abnormalities should be corrected before its administration, and that ECG monitoring should be conducted in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmia, or the concurrent administration of other QTc-prolongating agents.[181] Droperidol also inhibits I_{Kr} and causes QTc prolongation.[175,177,182-185] Computer modeling has suggested that low-dose "antiemetic" droperidol (0.625-1.25 mg) would be unlikely to produce clinically significant (>30 ms) QTc prolongation.[186] In men without cardiovascular disease undergoing elective orthopedic surgery, low-dose droperidol (and ondansetron, 8 mg) were shown not to lengthen TPE.[184] Droperidol is contraindicated in patients with known or suspected QT prolongation and should be administered with extreme caution in patients at risk of QT prolongation.[187] Low-dose haloperidol (mean dose 1.34 mg) administered for postoperative vomiting has a similar odds ratio of QTc prolongation to 5-hydroxytryptamine type 3 receptor antagonists.[188]

Metoclopramide increases QT dynamicity (QT variance),[189] suggesting potential arrhythmogenicity; however, case reports of TdP attributed to its administration are rare.[190] Promethazine significantly lengthens QTc, but has no effect on TDR.[81] Although this suggests low teratogenicity, phenothiazines, such as promethazine, should be used with caution, if at all, in patients with LQTS or those at risk of TdP. Dexamethasone has the potential to suppress the LQTS phenotype and can be safely and, perhaps beneficially, used as a perioperative antiemetic.[191,192] Scopolamine has no known effects on QTc and also can be used safely as an antiemetic.

Perioperative Management Considerations

At present, there are no evidence-based consensus clinical guidelines for the anesthetic management of patients with LQTS. Patients with known LQTS should be considered high risk for TdP throughout the entirety of the perioperative period and be closely monitored for worsening QTc prolongation and arrhythmias. Exposure to torsadogenic factors should be minimized. The key points of perioperative management are summarized in Table 8.

Preoperative management begins with a thorough medical history (including family history of acute cardiac events and sudden death), physical examination, and review of available diagnostic cardiac testing including a recent ECG. Knowing which type of LQTS the patient has, the known triggering factors associated with that type, and the patient's history of cardiac events and any inciting factors is important, as it will dictate perioperative management goals. β-blockers are a routine part of the management of LQTS, as they have been shown to decrease the incidence of cardiac events in patients with LQTS and should be continued for those patients who are preoperatively managed on them.[193,194] A subset of LQTS patients experiences bradycardia-dependent QTprolongation and the absence of complex ventricular ectopy.[195] These patients may benefit from emergency back-up pacing.[195] Electrolyte and endocrine abnormalities should be normalized and cardiovascular pathophysiology optimized before surgery. Implantable cardiac electronic devices should be interrogated and managed in consultation with an electrophysiologist.

Throughout the perioperative period, care should be taken in order to mitigate excessive sympathetic stimulation. Anxiolytic premedication is recommended and a calm, quiet, and warm operating room environment should be maintained. In addition to standard American Society of Anesthesiologists monitors, defibrillator pads should be placed on the patient before induction. As mentioned above, both induction and intubation are associated with hemodynamic perturbations, sympathetic stimulation, and QTc prolongation. A balanced intravenous induction incorporating lidocaine,[196] opioids,[147-150,154,155] and beta-blockers,[149,160,161] or a gradual inhalation induction[85,117-120] when this is not possible, is preferred to rapid inhalation induction. Hypoxia and hypercapnia should be avoided due to their effect on sympathetic tone and known QTc-prolongating effect, as should acute hypocapnia and its resultant hypokalemia.[197,198] Normal body temperature should be maintained because both hypothermia and hyperthermia have been associated with QTprolongation.[199-201]

With regard to blood pressure support, phenylephrine does not increase QT interval or QT dispersion and is, therefore, a good option in patients with LQTS without bradycardia-induced QT prolongation, pause-dependent TdP, or bradyarrhythmia.[202] Epinephrine has been shown to increase both QT interval and QT dispersion in patients with LQTS.[202] This response seems to be gene-dependent, with LQTS1, but not LQTS2, LQTS3, or control subjects, exhibiting QTc prolongation with epinephrine provocation testing.[203] Despite this, in case of anaphylaxis, epinephrine should be used, and inhaled beta-adrenergic agents can be used with careful, continuous monitoring.[204] Dobutamine[205,206] and isoproterenol[207,208] induce EADs, QTc prolongation, and TdP in patients with LQTS, but may be helpful in the management of LQTS with bradycardia-dependent QT prolongation when pacing is not immediately available.[209]

Table 8
Key Points of Perioperative Management of Patients With Known LQTS

Preoperatively
All the electrolytes should be normalized
Continue b-blocker (only patients who are already under medication)
Anxiolytic premedication
Prepare defibrillation pads
Maintain calm and quiet environment in the operating room
Induction and maintenance of anesthesia
Consider topical anesthesia before intubation
Total intravenous anesthesia is recommended
Avoid hypoxia, hypocapnia, hypercapnia, and hypothermia
Postoperatively
Avoid emergent agitation
Keep monitoring the patient in post-anesthesia care unit
Ensure adequate pain control

Abbreviation: LQTS, Long QT Syndrome.

Although the intravenous administration[210,211] of local anesthetics has been shown to have no significant effect on QTc, neuraxial blocks do have variable effects on QTc, likely via modulation of the autonomic nervous system. In healthy adults undergoing spinal anesthesia for nonobstetric surgeries, spinal anesthesia has a slight, dose-related lengthening effect on QTc and no change in QTc or QTcd observed when a low dose (bupivacaine 5 mg, T10 block level) is administered.[75,212-215] In women undergoing spinal anesthesia for cesarean delivery, no changes in QTc or TPE were seen with intrathecal injection of bupivacaine up to 10 mg,[216] and a significant decrease in QTc was seen in preeclamptic parturients.[217] The safety of spinal anesthesia in patients with LQTS is limited to case reports.[218,219] Oxytocin should be used with caution as it does significantly increase QTc[216,220] and TPE[216] and has been associated with ventricular tachycardia when used in patients with LQTS.[221] Thoracic, but not lumbar, epidural anesthesia may have a shortening effect on both QTc and TDR mediated through blockade of cardiac preganglionic sympathetic fibers; however, studies have been conflicting.[222,223] Epidural anesthesia and analgesia have been used safely in patients with LQTS.[219,224,225] Local and regional anesthesia techniques have no effect on QTc.[75,226] The addition of epinephrine should be avoided when possible. In case of local anesthetic toxicity, intravenous lipid emulsions should be administered.[227]

As with induction and intubation, emergence is a period of increased sympathetic stimulation that should be approached with equal thoughtfulness and caution. The patient should be monitored closely until the QTc returns to baseline. Pain should be well-controlled. Upper airway obstruction, hypo/hyperthermia, and excessive noise should be avoided. The management of postoperative nausea/vomiting and emergence delirium poses a clinical challenge in patients with LQTS. Antiemetics should be chosen carefully on the basis of QTc-prolongating effects and torsadogenecity. The first choice of treatment for delirium should be reorientation and environmental interventions. Polypharmacy should be avoided when possible as should the concomitant administration of multiple QTc-prolongating drugs. Implantable cardiac devices should be interrogated postoperatively and their baseline settings restored before discharge.

Treatment of TdP

When TdP occurs in the setting of LQTS, an intravenous (IV)/Intraosseous (IO) bolus of 25-to-50 mg/kg (max 2 g) of magnesium sulfate should be administered over two-to-three minutes (or up to ten-20 minutes if stable with pulses), followed by an additional bolus after ten-to-15 minutes and an infusion if warranted. Magnesium is thought to stabilize the myocardial membrane and decrease AEDs through its modulation of sodium, potassium, and calcium channels.[228] If TdP is bradycardia- or pause-dependent, temporary overdrive pacing or the administration of isoproterenol should be considered in consultation with an electrophysiologist. In all patients, the underlying cause of QTc prolongation should be sought out and reversed. Cardioversion is reserved for Torsades that has degenerated into ventricular fibrillation or for prolonged episodes refractory to other treatment.[229] Treatment of TdP is summarized in Table 9.

Research of Perioperative Drug Effects on QT Prolongation

The research on perioperative QT prolongation on a molecular basis is limited. Because a number of factors, such as LQTS and electrolyte abnormalities aside from drugs, can contribute to the prolongation of QTc interval, testing a large repertoire of drugs used in perioperative settings covering electrolyte abnormalities and temperature change may require significant efforts, even in laboratory settings. Regarding LQTS, for example, more than 600 mutations have been identified in the responsible genes.[13] The prevalence of congenital long QT syndrome is quite high when latent or concealed LQTS is a factor.[31] As indicated above, drug-induced LQTS may be a pharmacogenomic syndrome predisposed by rare genetic variants.[62] Because a large number of patients with LQTS have either LQT1, LTQT2, or LQT3, it is reasonable to target them for research first.

Mikuni et al. examined the effect of isoflurane on A341V mutant of KCNQ1 channel, a severe type of LQT1 mutation, using transiently transfected HEK293 and HL-1 cells.[230] They showed that the inhibitory effect of isoflurane on a KCNQ1-A341V mutant was greater than the wild type. This cell-based approach is beneficial so that experimental conditions can be tightly controlled. Iks is highly regulated by β-adrenergic stimulation.[231] HEK293 cell system has been shown to be tested for β-adrenergic stimulation as well.[232] The use of preclinical models is another approach. A zebrafish has a two-chambered heart, but its fundamental electric properties are remarkably similar to those of humans. Zebrafish have been used as models to study LQTS.[233] Mice commonly are used for research. Without exception, they also are used to study LQTS.[234] Although ion channels in humans and mice are conserved highly, there is a significant electrophysiologic difference between the two species. Mice have ten times higher heart rate than humans, requiring shorter action potentials and different repolarizing potassium currents. In humans, the major repolarizing currents are Iks and Ikr, whereas their expression is low in mice. Although there is a need to understand the underlying mechanism of perioperative TdP from clinical studies, these in vitro and in vivo tools should be used to stratify the clinical approach to mitigate its occurrence given its potential fatal outcome.

Table 9
Treatment of TdP

Defibrillation	1st choice for unstable patient
Magnesium sulfate	bolus of 25-50 mg/kg over 2-3 min followed by infusion of 2-4 mg/kg consider re-bolus after 15 min
Potassium	should be maintained high-normal levels
Pacemaker or ICD	when TdP is bradycardia or pause dependent
Left cardiac denervation	as a long-term treatment

Abbreviations: ICD, Implantable Cardioverter Defibrillator; TdP, Torsades de Pointes.

Conclusion

Perioperative TdP can lead to sudden cardiac death and fatal arrhythmias.

Although there are still no guidelines for anesthetic management, careful monitoring and accurate knowledge are required.

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