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REVIEW ARTICLE

QT interval abnormalities: risk factors and perioperative management in long QT syndromes and Torsades de Pointes

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Abstract Electrophysiological abnormalities of the QT interval of the standard electrocardiogram are not uncommon. Congenital long QT syndrome is due to mutations of several possible genes (genotype) that result in prolongation of the corrected QT interval (phenotype). Abnormalities of the QT interval can be acquired and are often drug-induced. Torsades de Pointes (TP) is an arrhythmia that is a result of aberrant repolarization/QT abnormalities. If not recognized and corrected quickly, QT interval abnormalities may precipitate potentially fatal ventricular dysrhythmias. The main mechanism responsible for the development of QT prolongation is blockade of the rapid component of the delayed rectifier potassium current (I_{kr}), encoded for by the human-ether-a-go-go-related gene (hERG). The objectives of this review were (1) to describe the electrical pathophysiology of QT interval abnormalities, (2) to differentiate congenital from acquired QT interval abnormalities, (3) to describe the currently known risk factors for QT interval abnormalities, (4) to identify current drug-induced causes of acquired QT interval abnormalities, and (5) to recommend immediate and effective management strategies to prevent unanticipated dysrhythmias and deaths from QT abnormalities in the perioperative period.

Keywords QT prolongation · Anesthetics · Torsade de Pointes

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Introduction

Electrophysiological abnormalities of the QT interval of the standard electrocardiogram (ECG) are not uncommon and may be congenital or acquired [1]. Congenital long QT syndrome (LQTS) is due to mutations of one or more of several genes (genotype) that results in prolongation of the corrected QT interval (phenotype). Abnormalities of the QT interval can be acquired and are often drug-induced. Torsades de Pointes (TP) is an arrhythmia that is a result of aberrant repolarization/QT abnormalities. If not recognized and corrected quickly, QT interval abnormalities may precipitate potentially fatal ventricular dysrhythmias [1]. Since new congenital and drug-induced causes of QT interval abnormalities continue to be reported, the objectives of this review were (1) to describe the electrical pathophysiology of QT interval abnormalities, (2) to

differentiate congenital from acquired QT interval abnormalities, (3) to describe the currently known risk factors for QT interval abnormalities, (4) to identify current drug-induced causes of acquired QT interval abnormalities, and (5) to recommend immediate and effective management strategies to prevent unanticipated dysrhythmias and deaths from QT abnormalities in the perioperative period.

Torsades de Pointes was initially observed in 1966 by Dessertenne, who described, in French, the twisting-ribbon ECG pattern as a "twisting of the points" (Fig. 1) [3]. TP is a potentially fatal form of polymorphic ventricular tachycardia (VT) and results from either congenital or acquired LQTS. Although TP is usually short-lived and self-limited, it may recur episodically and precipitate ventricular fibrillation (VF) and sudden death. TP is characterized by a ventricular rate between 160 and 250 beats per minute (bpm) with irregular RR (inter-beat) intervals and a sinusoidal, polymorphic QRS axis (Fig. 1) [4].

The exact incidences of LQTS and TP remain unknown. However, the true incidences of LQTS and TP are likely to be higher than reported for several reasons, including recently described drug-induced causes of QT interval prolongation and a failure to establish a clinical diagnosis of congenital LQTS based on baseline ECG measurements [5]. Newly approved and marketed drugs often do not show evidence of QT prolongation until post-marketing surveillance in larger populations of advancing age and co-morbidities.

The normal QT interval

The normal QT interval is an electrocardiographic representation of ventricular depolarization and repolarization. The QT interval is measured from the beginning of the QRS complex to the end of the T wave. Since measurements of QT intervals in milliseconds (ms) are not normally distributed in populations, standard measurements for normal versus prolonged QT intervals have been difficult to establish (Table 1) [4, 6]. The normal QT interval varies inversely with heart rate and should be corrected. Bazett's formula, as originally described by Henry Cuthbert Bazett [11] in 1920, corrects the QT interval to QTc by dividing the QT interval by the square root of the RR interval. There are, however, several limitations to Bazett's QTc formula, including overestimation of the QT interval at fast heart rates and underestimation at slow heart rates [11, 12]. Therefore, the QT interval should always be measured when the heart rate is within normal range and based on more than one 12-lead ECG recording [12]. In addition to its inverse variability with heart rate, the QT interval may vary throughout the day as a result of circadian rhythms, autonomic nervous system impulses, and eating and post-prandial status [12]. Other more accurate formulas for measuring QTc include the Fridericia, Framingham, and Hodges formulas, which in the near future may replace Bazett's formula for the QTc (Table 2) [1, 4, 11, 12]. Currently, a "normal" measurement parameter for a QT interval of <440 ms has been proposed based on several population-based and genetic studies; however, some of these formulas, such as Bazett's formula, were found to be gender-biased (Table 1) [4].

The prolonged QT interval

A borderline prolonged QT interval is between 440 and 460 ms for men and between 450 and 470 ms for women, and a prolonged QT interval is >460 ms in men and

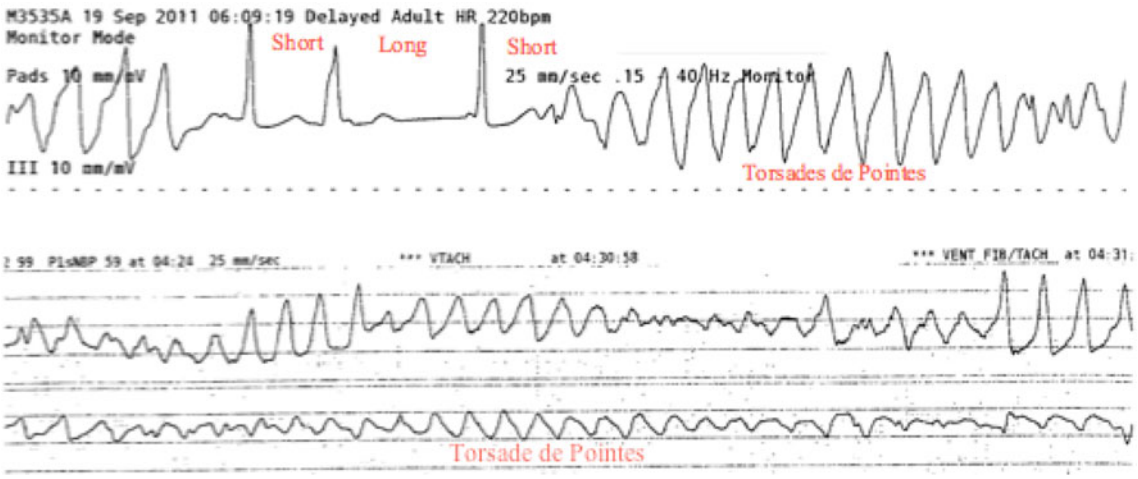

Fig. 1 Rhythm strips depicting Torsade de Pointes (TP). This figure shows the development of TP in a 68-year-old hypokalemic woman on a multi-drug regimen of citalopram, azithromycin, furosemide, and amiodarone. The patient presented with syncope and profound depression. Defibrillation was required. The *top* rhythm strip demonstrates the characteristic short-long-short cycle preceding the formation of TP. The *bottom* rhythm strip shows a strip of ongoing TP

Table 1 QT interval parameters

QT category	Males	Females
Normal QT (ms)	<440	<450
Borderline long QT (ms)	440–460	450–470
Long QT (ms)	>460	>470

According to several population-based and genetic studies, parameters for the QT interval have been proposed [4, 6, 7]. The values presented here are general QT interval parameters; however, due to the Gaussian distribution of the QT interval, there are no clear-cut boundaries for each QT category

QT Time between the start of the Q wave and the end of the T wave

Table 2 Formulas to correct the QT interval

Formulas for measuring QTc	Formula specifics
Bazett	$QT/\sqrt{RR}$
Fridericia	$QT/\sqrt[3]{RR}$
Framingham	$QT + 0.154 \times (1 - RR)$
Hodges	$QT + 1.75 \times (HR - 60)$

For a description of formulas, see [11, 12]

RR R wave to R wave interval, *QTc* corrected QT, *HR* heart rate

>470 ms in women [4]. According to data from congenital and drug-induced LQTS studies, arrhythmias are usually associated with QT intervals of >500 ms [4, 8, 9]. The American Heart Association (AHA) has now described QT intervals that have increased 60 ms from baseline as potentially arrhythmogenic [1, 4, 10]. Although frequently asymptomatic, clinical manifestations of LQTS may include palpitations, syncope, seizures, aborted sudden cardiac death (SCD), and death. The medical history may reveal an aborted SCD in a family member in addition to the mentioned manifestations. Often times, patients with congenital LQTS are diagnosed by screening of family members following aborted SCD in the index patient.

The mechanisms of QT prolongation

The mechanisms of QT prolongation are determined by the depolarization–repolarization cycle of ventricular myocardial cells. This cycle consists of five phases: depolarization (phase 0), partial repolarization (phase 1), plateau (phase 2), rapid repolarization (phase 3), and resting (phase 4), with phase 3 having the greatest impact on QT abnormalities (Fig. 2) [1, 14]. Rapid repolarization is primarily mediated by potassium efflux from the cell by the Ito channels, I_{kr} and I_{ks}. These channels determine the duration of the action potential and repolarization. When these channels are blocked, either the action potential or repolarization will be prolonged, causing an increased QT interval with potential for arrhythmogenesis [1, 15].

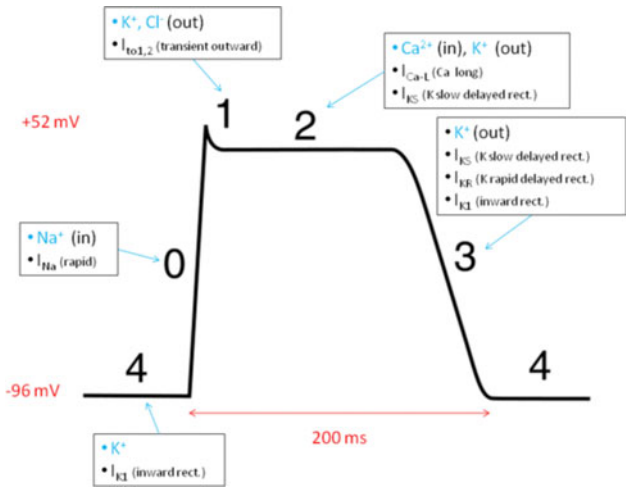

Fig. 2 Cardiac action potential. Illustration of the phases of the cardiac action potential and the ion movement at each phase. Depolarization occurs in phase 0, which results from rapid sodium (Na^+) influx. Phase 1 is partial repolarization and occurs via the movement of potassium (K^+) and chloride (Cl^-) out of the cell. In the plateau phase, phase 2, there is calcium (Ca^{2+}) influx and K^+ efflux from the slow component of the delayed (slow) rectifier K^+ channel (I_{ks}). Phase 3, rapid repolarization, is mediated by K^+ efflux from both of the delayed rectifier currents [I_{ks} and I_{kr} (rapid)]. The resting phase, phase 4, is controlled by the Na^+/K^+ ATPase, which pumps Na^+ out of the cell and K^+ into the cell. This results in the cell reaching its resting membrane potential. Reproduced with permission from Wikipedia (http://en.wikipedia.org/wiki/Cardiac_action_potential)

Whereas LQTS can occur from a mutation at one of several genes, the mechanism of drug-induced TP often involves three cascading steps: (1) increased action potential duration or prolonged repolarization, (2) early afterdepolarizations (EADs), and (3) premature ventricular contractions (PVCs). In step 1, there is an increased action potential duration or a prolonged repolarization resulting in QT prolongation [13, 14]. The increased action potential duration or the prolonged repolarization results from the net reduction in outward flow of potassium ions. This occurs most commonly from potassium outflow reduction, but can also occur from an increase in sodium and calcium inflow, or from any combination of these electrolyte movements limiting outward flow of potassium [14]. In step 2, EADs may form during a prolonged repolarization phase as either single or multiple depolarizing oscillations during phase 2 or 3 of an action potential (AP). When EADs reach threshold potentials, PVCs are generated in step 3 (Fig. 3) [14]. PVCs may trigger different action potential durations within each of the three ventricular wall cell types, resulting in dispersed repolarization [17].

Antzelevitch and co-investigators [15] have described three cell types of the ventricular wall as epicardial, midmyocardial (M cells), and endocardial cells. Of these, M cells are the most susceptible to the effects of the I_{kr} blockade which causes more severe action potential

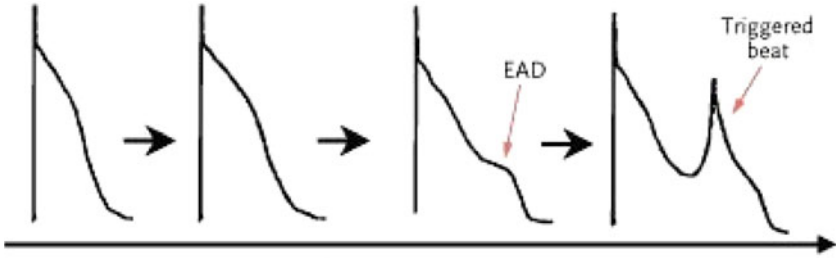

Fig. 3 Early after-depolarizations showing the progression of EADs and the formation of a triggered beat, which is thought to be one mechanism behind TP development. Reproduced with permission from the *New England Journal of Medicine* [14]

prolongation and amplified dispersion of repolarization [17]. Dispersed repolarization creates a milieu for re-entry phenomena and TP [1, 16, 17]. TP may be maintained by repeated EADs or PVCs, both of which stimulate abnormal automaticity and re-entry. In addition to their occurrence in M cells, EADs and EAD-induced TP may occur in Purkinje fibers [16, 17].

Risk factors for prolonged QT intervals

The major epidemiological risk factors for QT prolongation include gender, hormonal imbalance, bradycardia, hypokalemia, and polymorphisms or mutations in genes regulating cardiac ion channel expression and ventricular repolarization (Table 3) [18]. Female gender is a significant risk factor for QT prolongation. Baseline QTc intervals are longer in women than men, and TP occurs two- to threefold more often in women than men [18]. Although the exact electrophysiological mechanisms are unknown, hormonal imbalances have been implicated, with estrogens thought to increase susceptibility to TP in women and androgens felt to reduce TP susceptibility in men [19].

Bradycardia and hypokalemia work synergistically to enhance the effects of QT-prolonging drugs by increasing the length of delayed repolarization. In addition, enhanced I_{kr} channel blocking activity during episodes of bradycardia and hypokalemia will increase the length of delayed repolarization and promote QT prolongation.

Approximately 10–15 % of the population possess subclinical genetic polymorphisms or mutations in LQTS genes which encode for the ion channels that predispose individuals to QT prolongation [20]. In essence, these mutations can prolong the ventricular action potential and increase QT interval. Roden [21] has described these genetically modified ion channels as demonstrating "reduced repolarization reserve". Reduced repolarization reserve is characterized by a redundancy in repolarizing currents created by increased activity of outward potassium Ito currents (I_{kr}, I_{ks}) and decreased activity of inward sodium and calcium currents [22]. In most cases, the reduced repolarization reserve is insignificant, and there is sufficient redundancy to allow for normal repolarization [21, 22]. However, when a QT-prolonging drug or a predisposing risk factor is superimposed in a patient with polymorphisms or mutations in LQTS genes, repolarization redundancy may be insufficient, and both QT prolongation and TP may result [21, 22]. Low penetrance and variable expressivity of these ion channel genetic polymorphisms or mutations may have resulted in an overestimation of the actual number of drug-induced QT prolongation cases [23, 24].

Table 3 Risk factors for drug-induced long QT syndrome and Torsades de Pointes

Risk factors for drug-induced long QT syndrome and TP
Female
Advanced age
Certain electrolyte abnormalities: hypokalemia, hypomagnesia, hypocalcemia
Bradycardia
Complete AV nodal block
Structural heart disease: myocardial infarction, heart failure, cardiomyopathy, valvular abnormality
Baseline QT interval of >450 ms
Premature ventricular complexes with slow-long-slow RR intervals
T-wave lability
Recent conversion from atrial fibrillation
Subclinical congenital long-QT syndrome
Genetic polymorphisms of the genes that code for ion channels
High doses/concentrations of a QT-prolonging drug (except for quinidine)
Rapid IV infusion of a QT-prolonging drug
Concomitant use of a QT-prolonging drug and drug that inhibits its metabolism
Slow metabolizers
Impaired hepatic or renal function
Obesity (possibly; needs further investigation)

See references [1, 16, 17, 77, 78]

TP Torsades de Pointes, *AV* Atrioventricular, *IV* intravenous

Drug-induced long QT syndrome and TP

As previously described, LQTS may occur in congenital disorders of repolarization or may be induced by many drugs. The ventricular rate in TP is usually between 160

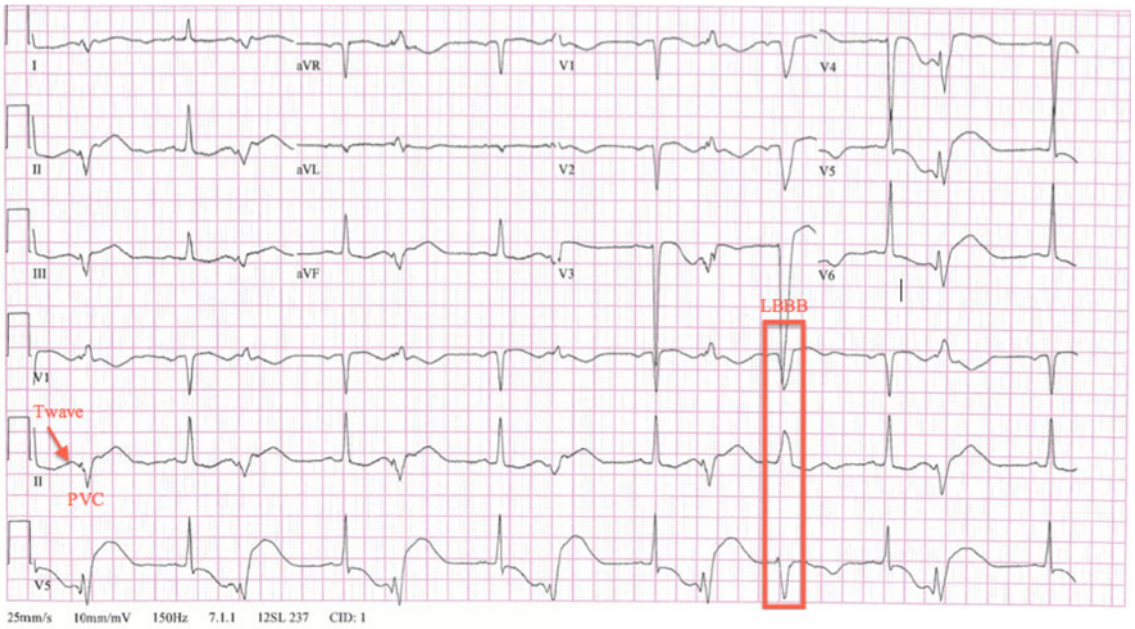

Fig. 4 Electrocardiogram (ECG) depicting premature ventricular contractions (*PVCs*) and T-wave abnormalities in a patient who developed TP. This ECG was recorded prior to the development of TP in a 68-year-old hypokalemic woman on a multidrug regimen and shows sinus rhythm with evidence of an old anterior septal myocardial infarction and drug-induced prolonged QT. Early afterdepolarizations (EADs) manifesting as PVCs are present at every T wave. Based on lead II, the QT interval is likely approximately 500 ms; however, accurate measurement is precluded by distortion of the T wave by the PVC. Note: the isolated sinus beat with a left bundle branch block (*LBBB*) showing widening of the QRS. This signifies that the patient has a functional LBBB with peeling back of refractoriness with each PVC on the T wave

and 250 bpm, with irregular RR intervals and a sinusoidal polymorphic QRS axis (Fig. 1) [5, 10]. Most TP events are preceded by a sequence of short-long-short RR intervals (Fig. 4). This sequence consists of a premature ventricular beat (short) followed by a compensatory pause with a long QT wave and a distorted T–U complex (long) [13]. Another premature ventricular beat (short) occurs, and TP is initiated (Fig. 2) [13].

Prodromal events and risk factors for TP

Although a QTc of >500 ms, as measured on preoperative baseline ECGs, may be a risk factor for TP, the following prodromal electrocardiographic events often herald TP. These ECG early warning signs may precede the onset of both drug-induced TP and LQTS and include: (1) a short–long–short RR cycle, (2) a long QT wave with an abnormal T–U complex, (3) macroscopic T-wave alternans, (4) bradycardia and frequent pauses from complete atrioventricular block, and (5) PVCs [4].

The risk factors for TP development are controversial. Many risk factors of TP have been suggested, with the length of the QT interval being the most commonly accepted risk factor. However, there is increasing evidence that other risk factors may also be useful for predicting TP. The currently accepted risk factors for TP development are listed in Table 3 [1, 4, 9, 16, 25, 26, 30].

Many drugs can cause a significant prolongation of the QT interval without causing TP [1, 16]. For example, both sotalol and amiodarone can significantly increase the QT interval, but only sotalol causes EADs and TP [27, 28]. Although, the degree of QT prolongation does not always correlate with TP risk, most antiarrhythmic drugs that can induce TP will prolong the QT interval by at least 50 ms [29]. To a lesser degree, terfenadine, an antihistamine sold under the trade name Seldane®, only increases the QT interval by 5–10 ms; this drug has been withdrawn from the market due to its association with an increased risk for TP [29].

Dispersion of repolarization is another predictor of TP via spatial, transmural, and temporal dispersion [2]. An increase in any type of dispersion leads to heterogeneity of repolarization and possible re-entry with arrhythmogenesis. Spatial dispersion results from differences in repolarization in different areas of the heart (apex vs. base or right vs. left ventricle) and is measured by the difference between the maximum and minimum QT intervals [2]. Transmural dispersion of repolarization (TDR) results from differences in action potential durations across the ventricular wall cells and is measured by the difference between the T-wave peaks and ends (Fig. 5) [15].

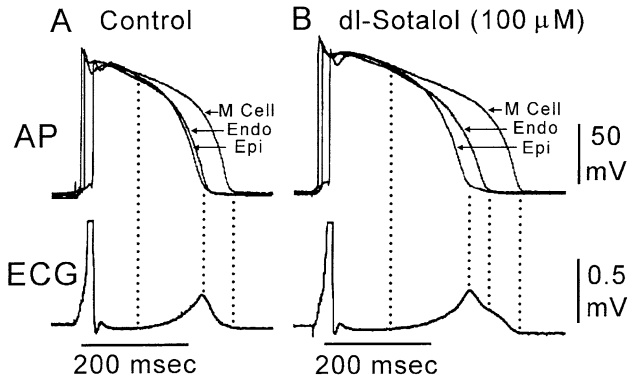

Fig. 5 Transmural dispersion among cardiac cells and its effects on the QT interval. Each panel shows a transmembrane action potential and ECG of the endocardial (*Endo*), epicardial (*Epi*), and midmyocardial (*M cell*) cells simultaneously recorded from an isolated arterially perfused canine left ventricular wedge under control conditions (**a**) and in the presence of DL-sotalol (**b**). When DL-sotalol is administered, there is a preferential prolongation of the M cell action potential, illustrating transmural dispersion of depolarization. This results in changes of the descending limb of the T wave and an increased QT interval on the ECG. Reproduced with permission from *Circulation* [15]

TDR with ventricular electrical heterogeneities may be the most important predictor of TP rather than QT prolongation [15, 16, 31, 32]. Yan et al. [33] compared DL-sotalol and azimilide for their propensity to trigger TP and found that DL-sotalol caused QT prolongation and TDR, while azimilide caused QT prolongation without TDR. Quinidine and erythromycin also cause action potential prolongation in M cells, inducing TDR and, possibly, TP [14, 32, 34]. Amiodarone and sodium pentobarbital will increase the QT interval and decrease the dispersion of repolarization, but they have little potential to induce TP and possibly provide protection from TP [16, 34].

Temporal dispersion results from the beat-to-beat variation in the action potential duration and is measured by the difference between two consecutive monophasic action potentials at 50 % repolarization [27, 30]. The larger the beat-to-beat variation, the more instability and temporal dispersion. Thomsen et al. [27] have proposed that the proarrhythmic risk of a drug is correlated to the beat-to-beat variability of repolarization rather than QT prolongation. In a study that infused guinea pig hearts with specific human-ether-a-go-go-related gene (hERG) blockers, Fossa et al. [35] demonstrated that bepridil, terfenadine, and cisapride increased the action potential beat-to-beat variability and were more likely to promote arrhythmogenesis.

Verapamil does not increase beat-to-beat variability or increase the risk of TP, and risperidone decreases beat-to-beat variability [5, 35]. Thomsen et al. [27] also demonstrated that D-sotalol increased temporal dispersion in a canine model with atrioventricular (AV)-blocked hearts, while amiodarone did not, and concluded that D-sotalol is more likely to induce TP than amiodarone.

Although most drugs that cause TP work via hERG channel blocking, all drugs that block the hERG channel do not necessarily cause TP. Milberg et al. [28] provided further support for TP induction via hERG channel blockade in a comparison study of two hERG blocking drugs, DL-sotalol and amiodarone. Both drugs prolonged the QT interval; however, DL-sotalol was more likely to induce TP [28]. This differential risk for inducing TP via hERG blockade is probably multifactorial. For example, sotalol causes the development of TDR and triggers both EADs and TP, whereas amiodarone does not cause TDR, EADs, or TP [28]. Although both sotalol and amiodarone cause increased action potential duration, the shape of the action potentials differ with each drug. Sotalol causes triangulation of the action potential by prolonging phase 3, while amiodarone causes square-shaped action potentials by prolonging phase 2 (Fig. 5). While squared-shaped action potentials are considered to be antiarrhythmic, triangulated action potentials are considered to be proarrhythmic [25, 26].

Like triangulation, EADs are a major predictor of TP development. Hondeghem and co-investigators [25, 26] have proposed that the "TRIad" surrogate markers of TP, triangulation (T), reverse-use dependence®), and instability (I), act synergistically to produce an increased risk of arrhythmia. They also suggested that increased action potential duration without instability or triangulation is actually antiarrhythmic versus proarrhythmic [25, 26]. In summary, any drug that creates a suitable condition for re-entry can cause TP.

Drug-induced QT interval abnormalities

Nearly all of the drugs that induce acquired LQTS or QT interval prolongation work via blocking the rapid component of the delayed rectifier potassium current (I_{kr}) channel, encoded for by hERG, although some of the genes related to LQTS also block sodium channels or other rectifying currents [36]. This channel allows for the outward flow of potassium and is most important for phase 3 of the action potential [36]. With most of QT-prolonging drugs, the risk of further prolongation of the QT interval increases as the dose and plasma drug concentration increase. The only exception to this dose–response effect occurs with the Class IA antiarrhythmics, which may induce QT prolongation at lower doses [4].

The number of drugs that can induce a long QT interval is expansive (Table 4), with numerous drugs already having been reported to cause QT prolongation and new drugs continuously being identified. A new drug on the market is

often not labeled as QT prolonging until years after it has been on the market. This is secondary to the small number of TP cases that occur compared to the actual number of prescriptions. Also, when the drug is being tested during clinical trials, patients with risk factors are excluded from the trials. Therefore, even if an investigational new drug exhibits no TP risk during its testing phases, it may actually prove to have a TP risk once administered to larger populations of advanced age and those with comorbidities. Table 4 lists some of the more commonly prescribed QT-prolonging drugs. Interested readers are referred to a more extensive listing of QT-prolonging drugs that pose a risk for TP at http://www.azcert.org/.

Anesthetics and neuromuscular blockers

Many of the drugs used during induction and maintenance of general anesthesia can cause prolonged QT intervals, but few have been reported to cause TP. Although TP has occurred during general anesthesia, the responsible drug has often been difficult to identify in multidrug anesthetics [37, 38]. Saarnivaara et al. [39] and Michaloudis et al. [40] showed that the combination of thiopental and succinylcholine or succinylcholine alone can increase the QT interval. The non-depolarizing muscle relaxants pancuronium, atracuronium, and alcuronium can all cause significant QT prolongation when administered alone or with atropine [41, 42]. The volatile anesthetics halothane, isoflurane, sevoflurane, enflurane, and desflurane also cause QT prolongation via inhibition of the I_k currents [41, 43]. However, each volatile anesthetic affects the I_{ks} and I_{kr} channels differently, causing varying degrees of QT prolongation [44, 46, 47]. Studies by Riley et al. [46] and Schmeling et al. [47] demonstrated that halothane, isoflurane, and enflurane could increase QTc, independent of their effects on the autonomic nervous system. To date, both desflurane and sevoflurane have been demonstrated to have effects on the QT interval and on the dispersion of repolarization [43, 48]. Since volatile anesthetics have differing effects on I_k channels and QT intervals, each anesthetic will demonstrate a different effect on the QT interval [47]. In addition, some studies report that volatile anesthetics do not significantly prolong the QT interval [45, 48]. Sevoflurane increases the QT interval in a dose-dependent manner, but does not increase the TDR [45, 48, 50]. A few cases of sevoflurane-associated TP have been reported, and in each of these cases multiple predisposing risk factors were present [51, 52]. Lastly, tizanidine, a centrally acting α_2 adrenergic agonist used in the management of chronic neuropathic pain, causes QT prolongation in animal models and was implicated in a fatal human case of TP [53]. Therefore, several risk factors often contribute to drug-induced QT prolongation and TP perioperatively, including patient comorbidities, such as bradycardia and hypokalemia, drug synergism, such as the impact of thiopental and succinylcholine on QT intervals, and changes in adrenergic tone in response to endotracheal intubation and surgical stimulation.

Propofol infusions for sedation and general anesthesia have been reported to either have little impact on QT intervals or cause QT prolongation and TP [40, 49, 54, 55]. It should be noted that propofol has been shown to rapidly reverse sevoflurane-induced QT prolongation in healthy patients and thus may be beneficial [56]. Limited data are available on benzodiazepines, with midazolam being the most studied benzodiazepine to date, and thus far these drugs appear to have no adverse affect on QT interval [56].

Antiarrhythmics

Antiarrhythmics were among the earliest drugs shown to cause drug-induced QT prolongation and TP. The combination of antiarrhythmics and diuretics may escalate the risks for the development of TP, in part due to the resulting presence of bradycardia, hypokalemia, and/or hypomagnesemia. The Class IA antiarrhythmics (quinidine, disopyramide, and procainamide) block both the inward sodium channels and the outward potassium channels (I_{ks} and I_{kr}). However, at slow heart rates and at therapeutic drug levels, I_{kr} blockade predominates and prolongs the QT interval, while at supratherapeutic/toxic Class IA drugs levels, the combination of reduced sodium inflow and reduced potassium outflow become balanced and the likelihood of QT prolongation and TP reduced. The incidence rate of quinidine-induced TP has been reported to be 0.6–1.5 % [8]. Most cases occur within 2 days of initiating therapy in the presence of at least one other risk factor [8]. *N*-acetylprocainamide, a metabolite of procainamide, blocks I_{kr} channels and can cause TP in patients with renal insufficiency or who are rapid genetic metabolizers of procainamide [1, 10, 57, 58].

The Class IIIA antiarrhythmics (sotalol, dofetilide, and ibutilide) will block the I_{kr} channel in a dose-dependent manner [1, 13]. The incidence rate of sotalol-induced TP incidence is around 2 % in men and 4 % in women [59]. Sotalol not only blocks the I_{kr}, but also increases the TDR and promotes EAD formation [2, 13, 15, 27, 28, 34]. Dofetilide caused TP when administered to patients with heart failure and myocardial infarction [60]. The incidence rate of dofetilide-induced TP has been reported to be 0.9 % in recent myocardial infarction patients and 3.3 % in heart failure patients, with TP usually occurring within 3 days of initiation of therapy [60, 61]. Since both sotalol and dofetilide are cleared by the kidneys, reduced renal dosing for patients with renal insufficiency is indicated to decrease risks of TP [10]. The incidence rate of ibutilide-induced TP

Table 4 Drugs that cause QT prolongation and/or TP

Drugs associated with a definite TP risk	Drugs associated with QT prolongation and TP but with an unclear risk
Antiarrhythmics	
Quinidine	Dronedarone
Disopyramide	Propafenone
Procainamide	Mexiletine
Amiodarone	
Ibutilide	
Sotalol	
Dofetilide	
Flecainide	
Other cardiac drugs	
Bepridil[a]	Nicardipine
	Moexipril/HCTZ
	Ranolazine
	Isradipine
Antipsychotics	
Haloperidol	Risperidone
Thioridazine	Paliperidone
Chlorpromazine	Iloperidone
Mesoridazine	Clozapine
Pimozide	Olanzapine
	Quetiapine
	Ziprasidone
	Aripiprazole
	Asenapine
	Sertindole[a]
	Sulpiride[a]
	Amisulpride[a]
Antidepressants	
	Escitalopram
	Venlafaxine
	Maprotiline
	Citalopram
	Fluoxetine
	Paroxetine
	Sertraline
	Amitriptyline
	Nortriptyline
	Protriptyline
	Clomipramine
	Desipramine
	Imipramine
	Trimipramine
	Doxepin
	Trazodone
Antibacterials	
Erythromycin	Azithromycin
Clarithromycin	Telithromycin
Moxifloxacin	Roxithromycin[a]
Sparfloxacin[a]	Levofloxacin
Grepafloxacin[a]	Ofloxacin
	Gatifloxacin
	Ciprofloxacin
	Gemifloxacin
	Norfloxacin
	Trimethoprim–sulfamethoxazole
Antifungals	
Pentamidine	Voriconazole
	Fluconazole
	Itraconazole
	Ketoconazole
Antimalarials	
Halofantrine	
Chloroquine	
Antivirals	
	Ritonavir
	Lopinavir
	Nelfinavir
	Saquinavir
	Atazanavir
	Amantadine
	Efavirenz
	Ribavirin
	Lamivudine
	Foscarnet
Opiates	
Methadone	Buprenorphine
Levomethadyl	Oxycodone
	Propoxyphene[a]
Antimigraine agents	
	Sumatriptan
	Naratriptan
	Zolmitriptan
Antiemetics	
Droperidol	Ondansetron
Domperidone[a]	Granisetron
Cisapride[a]	Dolasetron
	Famotidine
	Metoclopramide
Antihistamines	
Astemizole[a]	Diphenhydramine
Terfenadine[a]	
Antiepileptics	
	Fosphenytoin
	Felbamate
Acetylcholinesterase inhibitors	
	Galantamine

Table 4 continued

Drugs associated with a definite TP risk	Drugs associated with QT prolongation and TP but with an unclear risk
	Donepezil
	Rivastigmine
Anti-cancer agents	
Arsenic trioxide	Lapatinib
Vandetanib	Nilotinib
	Sunitinib
	Tamoxifen
Anesthetic agents/muscle relaxants	
	Halothane
	Isoflurane
	Sevoflurane
	Desflurane
	Chloral hydrate
	Tizanidine
	Pancuronium
	Atracuronium
	Alcuronium
Diuretics and other drugs that can cause hypokalemia	
	Amphotericin B
	Aminoglycosides
	β2-agonists
	Indapamide
	Insulin
	Penicillin
Herbals/dietary supplements	
	Cesium
	Licorice
	Grapefruit Juice
	Enzyte
Miscellaneous	
Clobutinol[a]	Lithium
Probucol[a]	Alfuzosin
	Octreotide
	Oxytocin
	Vardenafil
	Tacrolimus
	Solifenacin
	Sibutramine
	Atomoxetine
	Alcohol
	Cocaine

Interested readers are referred to a more extensive listing of QT-prolonging drugs that pose a risk for TP at http://www.azcert.org/

[a] Drug is not available in the USA

when administered to patients in atrial fibrillation or flutter is between 3.6 and 8.3 % and usually occurs within 4 h of initiation of therapy [62].

The complex Class III antiarrhythmic amiodarone routinely increases the QT interval to more than 500 ms, but has a reported TP incidence of <1 % [63]. If TP develops, it usually does so in a milieu of hypokalemia or concomitant use of a Class IA antiarrhythmic [63, 64]. Amiodarone blocks not only the potassium outflow at the I_{kr} channel, but also the sodium and L-type calcium inflow channels. Amiodarone will uniformly delay repolarization in all ventricular wall cell types, resulting in reduced dispersion of repolarization [64, 65]. This drug will cause significant QT prolongation, but rarely TP, probably owing to its protective ability to block sodium and calcium inflow.

Calcium channel blockers

The calcium channel blockers bepridil and verapamil both block the I_{kr} channel, but exhibit opposite TP risks. Bepridil was removed from the U.S. market in 2003 because of its TP risk. Verapamil, a potent I_{kr} and L-type calcium channel blocker, can cause QT prolongation but not TP, probably due to its protective calcium blocking effect [4]. The antianginal agent ranolazine blocks ventricular myocardial I_{kr}, I_{ks} and sodium and calcium channels and causes QT prolongation without TDR or EADs, with a low risk for TP. Ranolazine's TP protective effects are likely due to its sodium and calcium channel blocking effects [10, 66].

Antiemetics

The serotonin receptor antagonists ondansetron, granisetron, and dolasetron have been reported to cause QT prolongation by hERG channel blockade, but rarely cause TP, with only one report of dolasetron-induced TP in a patient with multiple risk factors [41, 67]. Given the extensive use of ondansetron in the perioperative setting and the lack of reported cases of ondansetron-induced TP, ondansetron has proven to exhibit a low risk of inducing TP. However, other antiemetics have significantly greater propensities to cause QT prolongation and TP than the serotonin receptor antagonists. In 2001, the Federal Drug Administration (FDA) required the manufacturer of droperidol to issue a black box warning about the risks of droperidol-induced TP at therapeutic doses [68, 69]. This warning was primarily based on reports of TP from outside the USA and followed extremely high doses (>25 mg) of droperidol in patients with other risk factors for QT abnormalities [68].

Opioids

Many opioids are hERG channel blockers, but not all can cause QT prolongation or TP [70]. Methadone blocks I_{kr} in a dose-dependent manner and prolongs the QT interval [71, 72]. In 2006, an FDA alert and black box warning were

issued concerning the risk of TP with methadone opioid substitution therapy [72]. Methadone-induced TP cases have now been reported in patients receiving high doses (>200 mg/day) or following recent dose increases [10]. Stringer et al. [72] recommended a baseline ECG and ECG monitoring throughout treatment while a patient is being treated with chronic methadone maintenance. Both buprenorphine and oxycodone block the I_{kr} channel and can prolong the QT interval without precipitating TP [41, 73]. Buprenorphine has now been recommended as a safe and effective alternative to methadone for opioid substitution therapy in heroin abusers and in patients with methadone-associated TP [73]. Levomethadyl can prolong the QT interval to a greater extent than methadone and has a greater risk of inducing TP [73, 74]. Propoxyphene was withdrawn from the U.S. market in 2010 because of its propensity to cause QT abnormalities even at therapeutic doses [70, 74, 75].

The perioperative assessment and management of QT abnormalities

The low incidence of perioperative TP is a good indicator that most drugs used during general anesthesia have minimal QT prolongation risks when used in patients without predisposing risk factors and without concomitant therapy with QT-prolonging drugs. It should noted, however, that there are various genotype-specific triggers in the congenital form of LQTS as these have specific targeted therapies, including the continuation of perioperative beta blockade. When perioperative TP does occur, many contributing factors are usually present, including comorbidities, electrolyte abnormalities, concurrent QT-prolonging medications, and other TP risk factors. Since the "safe" QT interval length is unknown, monitoring the QT interval perioperatively in all patients may not help to predict QT abnormalities. If TP does develop perioperatively, primary management should include discontinuing the offending drug, correcting electrolyte abnormalities, and administering intravenous magnesium sulfate or magnesium chloride (Table 5). If the patient still has TP after initial magnesium sulfate administration, another bolus of 2 g can be given in 15 min followed by a maintenance infusion of 3–20 mg/min [10].

Should TP recur despite magnesium sulfate therapy, there are two options to help prevent further recurrences: (1) temporary transvenous overdrive pacing or (2) pharmacological overdrive pacing with isoproterenol. Both of these treatment options prevent TP recurrence by increasing the heart rate and shortening the QT interval. Temporary overdrive pacing to a heart rate of 90–100 bpm is preferred [76, 77]. If a patient does not respond to magnesium sulfate and pacing is not yet available, administering isoproterenol titrated to a heart rate of 90–100 bpm is advised [76, 77]. Isoproterenol might need to be used temporarily in some forms of LQTS after consultation with an electrophysiologist prior to institution of electrical pacing and should be used cautiously in patients with structural heart disease [76]. Immediate synchronized cardioversion is indicated should VT with a pulse develop. Immediate defibrillation and other advanced cardiovascular life support protocols are indicated for either pulseless VT or VF.

Alkalization of the plasma with intravenous sodium bicarbonate is helpful in quinidine-induced TP because it decreases the availability of the active drug. The administration of intravenous potassium may be helpful in patients with low to low–normal potassium levels [10]. In all patients with TP, it is important to maintain the serum potassium level in the high–normal range (4.5–5 mmol/L) so as not to further predispose these patients to TP.

The long-term management of patients who have experienced QT prolongation and/or TP is based on prevention, which can be difficult for those patients with genetic polymorphisms that only manifest following

Table 5 Primary management for treating perioperative TP

Management options for treating perioperative TP
First option: Discontinue the offending agent
Second option: Stable vs. unstable patient:
Unstable: Non-synchronized cardiac defibrillation
Stable: ECG monitoring required until bradyarrhythmia has resolved or permanent pacemaker is placed. Bolus dose → 2 g 50 % magnesium sulfate IV over 1–2 min (second bolus if needed). Maintenance dose → 3–20 mg/min of 50 % magnesium sulfate IV over 15 min
Third option: Adjunctive treatment
IV potassium to maintain serum potassium levels between 4.5 and 5 mmol/L
Continuous ECG monitoring until the agent washes out and the QTc interval is decreasing
Fourth option: Prevention of recurrent TP
Transvenous overdrive pacing to a heart rate of 90–100 bpm
Fifth option: Long-term management/prevention
Avoid QT-prolonging drugs
Educate patient about culprit drugs and symptoms
Electrophysiology consult
Patient with acute neurological events: periodic QT measurement if the patient has normal QTc; frequent QT measurement if QTc >500 ms
Healthy patients who require drugs that pose little TP risk: No ECG monitoring if no risk factors and normal baseline QT

See references [1, 5, 10]

ECG Electrocardiogram

exposure to a drug. In these patients, the physician must avoid prescribing any QT-prolonging drugs and must correct any disorders that cause electrolyte abnormalities. A permanent pacemaker may be necessary in patients with chronic bradyarrhythmias, sick sinus syndrome, or AV blocks [77]. Evidence from studies on the use of pacemakers in these patients suggests the use of a pacing rate that is >70 bpm [77]. In addition, a full medical history of immediate family members of a TP patient should be obtained, together with a physical examination, including an ECG, and possibly genetic testing in order to search for the presence of congenital LQTS.

The AHA has recommended guidelines for monitoring patients at risk for TP (Table 4) [4]. When monitoring for the presence of drug-induced prolonged QT, a baseline QTc should be obtained, the QTc should be measured every 8 h, and before and after every dose of a suspected QT-prolonging medication [4]. If any one of the following conditions are met during QT interval monitoring, the patient should be admitted to the hospital for telemetry: (1) QTc >500 ms; (2) QTc increase ≥60 ms above baseline; (3) QT prolongation accompanied by syncope; (4) any evidence of ECG instability, specifically T-wave alternans, AV block, QRS widening, or ventricular ectopy. The offending drug should be discontinued, electrolyte abnormalities corrected, and a defibrillator placed at bedside [4].

If mild QT prolongation develops without syncope or TP in a patient who benefits greatly from the drug, the drug may be continued with intermittent ECG and Holter monitoring [10]. The patient should be informed about the symptoms of QT prolongation and TP and any drugs that may interact with the currently prescribed QT-prolonging drug. Patients starting diuretics or recovering from gastroenteritis may become hypokalemic and further predisposed to drug-induced QT prolongation and TP [10]. Anesthesiologists should conduct a thorough pre-operative assessment for any risk factors for QT abnormalities and TP, especially for therapy with QT-prolonging medications. QT-prolonging drugs should be discontinued, if possible, and normal serum electrolytes and a heart rate of <130 bpm should be maintained perioperatively. Recent data in patients with LQTS have indicated that there is an increased risk of adverse events during periods of enhanced sympathetic activity, especially during emergence. These risks are increased if drugs which prolong QT interval are delivered during this time, emphasizing the need for restriction of these medications in high-risk populations [78]. In this regard, a recent study in which serial postoperative 12-lead electrocardiograms were obtained from 469 adult patients undergoing major noncardiac surgery under general anesthesia demonstrated minor prolongation of the QT interval in 80 % of patients, with a 4 % incidence of marked prolongation (QTc >500 ms) and one case of TP with modest QT prolongation, emphasizing the common rate of occurrence of this type of event [79].

In summary, important factors include the identification of a pre-existing substrate (i.e., LQTS or positive family history), identification of current drug history, including current therapy for QT abnormalities, continuation of beneficial drug therapy in the perioperative period, device use if necessary, and appropriate individualized strategy for the management of TP or TP-induced ventricular tachycardia or VF.

Conclusions

The number of drugs reported to cause QT prolongation and TP continues to increase. Most of the cases of TP occur when there is a pre-existing risk factor and a QT-prolonging drug is used [78, 79]. These risks might be increased if drugs which prolong QT interval are delivered during this time, emphasizing the potential need for restriction of these medications in high-risk populations. Physicians should weigh the risks and benefits of prescribing QT-prolonging drugs. In some cases, the use of a high-risk QT-prolonging drug may decrease morbidity and/or mortality and would therefore be beneficial to the patient.

When administering QT-prolonging drugs in patients who have any risk factors for QT abnormalities, the QT interval should be monitored closely, and the patient should be informed of the common symptoms accompanying arrhythmias. Drug-induced QT prolongation and TP may occur during general anesthesia. In these cases, the clinical manifestations of QT prolongation will be unapparent, and only a preoperative medication history and risk assessment will predict the risks of QT abnormalities and TP perioperatively. More accurate prior-approval drug testing for QT abnormalities are recommended, especially for commonly prescribed medications in populations with advancing ages, such as analgesics, antiarrhythmics, antibiotics, antiemetics, antihistamines, and antihypertensives.

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