BRIEF COMMUNICATION

The QT Interval: What the Pulmonologist Needs to Know

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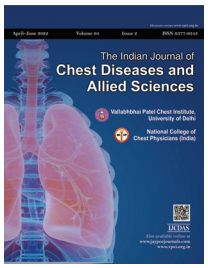

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Abstract

The QT interval is an electrocardiographical measurement that denotes the time interval between the commencement and completion of the cardiac ventricular contraction process. Alterations in its value indicate abnormal cardiac rhythm and herald the risk of *torsades de pointes*; a fatal ventricular arrhythmia. Causes leading to a prolonged QT interval encompass a heterogeneous gamut including genetic conditions, electrolyte imbalances, hormonal imbalances, and drugs. A wide range of drugs can lead to a prolonged QT interval and these include certain crucial drugs which are routinely prescribed by a pulmonologist for infectious as well as non-infectious pulmonary indications. This becomes particularly relevant in this decade which has witnessed an excrescence in drug-resistant tuberculosis cases. Certain vital drugs employed in its management prolong QT interval significantly. In these situations, the clinician faces the predicament of cautiously prescribing these drugs to eradicate the disease microbiologically whilst balancing the risk of sudden cardiac death due to *torsades de pointes*. We summarise the basics of QT interval which every pulmonologist presently needs to know.

Keywords: Drugs, QT Interval, *Torsades de points*

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Abbreviations used in this Article

TdP = Torsade de pointes; DR-TB = Drug-resistant tuberculosis; ECG = Electrocardiogram; KR = Known risk; PR = Possible risk; CR = Conditional risk; SR = Special risk; AIDS = Acquired immunodeficiency syndrome; RR interval = The time elapsed between two successive R waves of the QRS signal on the electrocardiogram; HERG = Human Ether-a-go-go Related Gene; CNS = Central nervous system; CTN = Continue; Pt = Patient

Importance of QT interval

The QT interval was first recognized with quinidine therapy in the 1950s. The QT interval is used in drug development and by clinicians as an indicator to predict the severe adverse event, syncope, or death due to *torsade de pointes* (*TdP*).[1] A wide range of drugs can lead to a prolonged QT interval and these include certain crucial drugs which are routinely prescribed by a pulmonologist for infectious as well non-infectious pulmonary indications. This becomes particularly relevant in this decade which has witnessed an excrescence in drug-resistant tuberculosis (DR-TB) cases. Certain vital drugs employed in its management prolong QT interval significantly. In these situations, the clinician faces the predicament of cautiously prescribing these drugs to eradicate the disease microbiologically whilst balancing the risk of sudden cardiac death due to *TdP*.

Normal QT Interval

The QT interval is measured on the electrocardiogram (ECG). It is measured from the start of the Q wave to the end of the T wave (Fig. 1). The value indicates the time taken by the ventricle from the beginning of a contraction to the end of relaxation.[1] The value for a normal QT interval is similar in males and females from birth till adolescence. QT interval has to be corrected for the heart rate. This can be calculated by various formulae, e.g., Bezold's formula and Fredericia's formula. As most of the drug trials evaluating newer anti-tuberculosis (anti-TB) drugs have used QT corrected by Frederica formula (QTcF), this will be explained in detail here.

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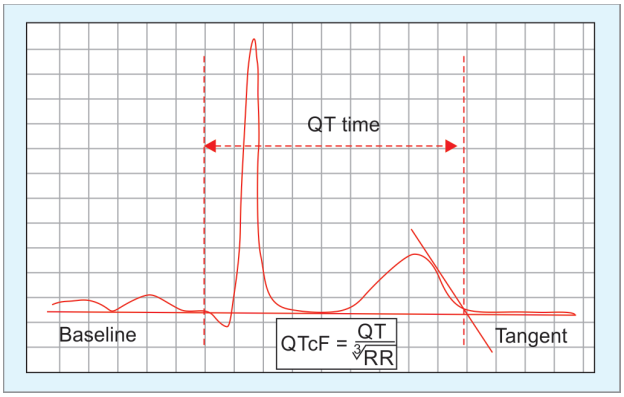


Fig. 1: The QT interval

QT Calculation by Fredericia Formula

The heart rate is an important variable in the calculation of QT interval. So, the "rate corrected" QT interval (QT at 60 heart rate) is commonly used in clinical practice. QT corrected by Frederica formula is calculated by the formula QT interval on ECG divided by the cube root of RR interval in milliseconds. Alternatively, medical calculators or medical software can be used to calculate QTcF easily. Some ECG machines are configured for automated calculation and mention the QTc on the ECG print-out. The Lead II, V5, or V6 are used to calculate QT and RR intervals. The QT interval (msec) equals (number of small squares Q-T)*(40). The heart rate (beats per min) equals 300/large squares of RR interval. The QTcF has been classified as normal (QTcF <450 msec), borderline (QTcF 450–480 msec), prolonged (QTcF 480–500 msec or increase from baseline by 60 msec), and dangerous (QTcF >500 msec).

QT Prolongation and *Torsades de Pointes*

Prolong QT interval/bradycardia causes early after-depolarization and in cases of HERG mutation (reduced repolarization reserve) leads to ventricular ectopic beats (Fig. 2).[2] This increases the predilection for polymorphic ventricular tachycardia (*TdP*). QT prolongation predicts that a given drug may carry some risk, these can neither assess nor quantify it accurately. Prolongation of QT interval is usually asymptomatic. The presence of warning symptoms, like dizziness, palpitation, fainting, syncope, and seizures, suggest recurrent TdPs which predispose to sudden death.

Torsade de pointes is a fatal arrhythmia manifesting as polymorphic ventricular tachycardia with rapid and bizarre QRS complexes. Because of the countenance of wavy and intertwining complexes, it has acquired its peculiar name which in French means "twisting of the peaks". Occurrence of a gene leading to an inherent long QT interval results in congenital long QT syndrome. The common acquired causes include *TdP* occurring as aftermath of consumption of several drugs. During an active *TdP* event, the heart rate of the patient may shoot up to dangerous levels of 200–250 beats/min, clinically manifesting as palpitation or syncope. In most circumstances, the episodes show spontaneous resolution. However, in some patients, it can progress to severe ventricular fibrillation causing sudden cardiac death. Risk factors for QT prolongation are given in Table 1.[1–3] List 1 drugs prolong the QT interval and are associated with a known risk (KR) of *TdP*, even when taken as recommended. List 2 drugs can cause QT prolongation and are associated with a possible risk (PR) of *TdP*. List 3 drugs are associated with *TdP* but only under certain conditions of their use or by creating conditions that facilitate or induce *TdP*, hence with conditional risk (CR) of *TdP*. List 4 drugs are avoided in congenital long QT syndrome (cLQTS) as these pose a high risk of *TdP* for patients with cLQTS. These include all drugs in the above three categories (KR, PR, and CR) *plus* additional drugs that do not prolong the QT interval *per se* but which have a special risk (SR) because of their other actions.

Information about any drug and its risk is available on the CredibleMeds website https://www.crediblemeds.org/index.php/drugsearch. Table 2 gives the common list 1 and list 2 drugs causing QT prolongation used in patients referred to a pulmonologist.

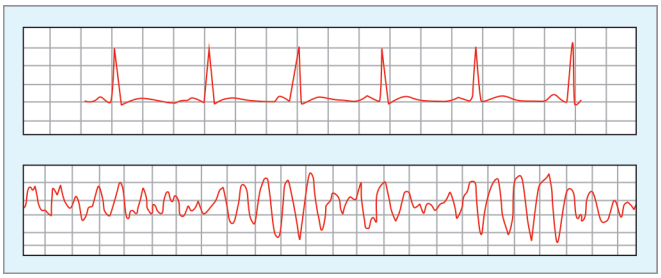


Fig. 2: *Torsades de pointes*

Therapy Initiation and Follow-up while using QT Prolonging Drugs

An algorithmic approach would save time and help the pulmonologist decide if the patient can be safely initiated on a QT-prolonging drug (Flowchart 1). The out-patient risk score

Table 1: Risk factors for QT prolongation

Risk factors	
Demographic	Female gender, age more than 65 years
Cardiac disease	Myocardial infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, arrhythmias, bradycardia, family history of sudden cardiac death at less than 50 years of age
Other comorbidities	Diabetes mellitus, thyroid, liver, renal, CNS disease, AIDS, obesity, alcohol and substance abuse, acute neurological events, autonomic neuropathy, nutritional deficits/hypoalbuminemia
Electrolyte imbalances	Hypokalemia, hypomagnesemia, hypocalcemia, hypoglycemia, diuretics, laxatives, enemas, high dose corticosteroids, vomiting, diarrhea, dehydration

Table 2: List 1 and List 2 drugs causing QT prolongation

	List 1	*List 2*
Antituberculosis therapy	Moxifloxacin, levofloxacin, macrolides	Bedaquiline, delamanid, clofazimine
Concomitant medications	Domperidone, ondansetron	Tramadol, granisetaron
Antipsychotics	Chlorpromazine, pimozide, haloperidol, droperidol	Olanzapine, quetiapine, risperidone
Antidepressants	Escitalopram	Imipramine, amitriptyline, lithium, nortriptyline
	Antiarrhythmics, anesthetic agents, chloroquine, fluconazole	

Flowchart 1: Algorithm for initiation of QT-prolonging drugs (Pt, patient; QTc, corrected QT interval)

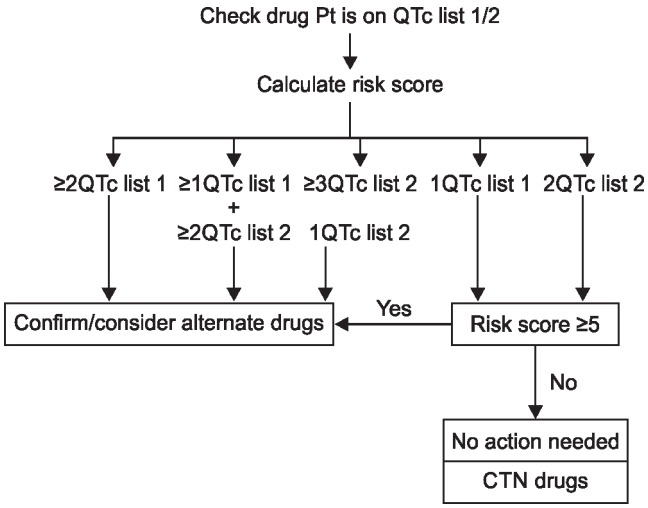


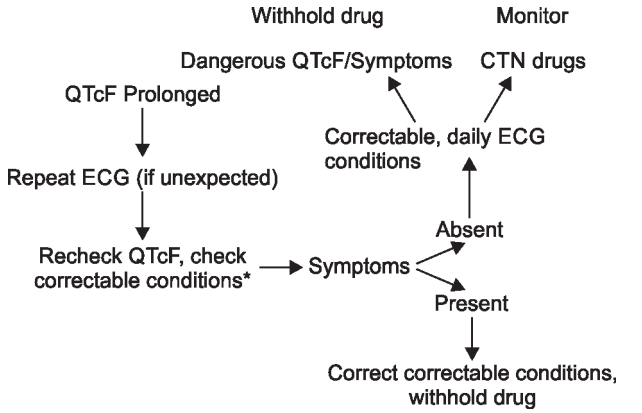
Table 3: Risk score calculation for QT prolongation

Characteristic	*Points*
Use of ≥1 potassium-lowering diuretic*	3
Use of ≥1 antiarrhythmic drug	3
Age ≥65 years	2
Female gender	2
Thyroid disturbances	2
Cardiovascular comorbidities†	1
Diabetes mellitus	1
Total risk score	14

*No points if used in combination with potassium-sparing diuretics
†Including antihypertensive drugs, beta-blocking agents, nitrates, calcium-channel blockers, agents acting on the renin-angiotensin system, and lipid-modifying agents

used for calculation (a simplified QT risk score developed by Eline Vandeal) is described in Table 3.[3] The follow-up in asymptomatic cases is clinical with ECG done at clinically relevant intervals. A similar simplified algorithmic approach could help the pulmonologist in taking the decision on the continuation of a QT-prolonging drug as shown in Flowchart 2.

Flowchart 2: Approach to a case of QT prolongation on therapy with QT-prolonging drugs



*Correctable conditions: Electrolyte (K, Ca, Mg) disturbances, bradycardia, nutritional deficit, thyroid disease, and concomitant medication

The knowledge of basic facts about QT interval is essential from a pulmonary point of view, particularly on a background of an era where the elimination of tuberculosis is being attempted. This will enable the pulmonologist to prescribe drugs/regimens, minimizing the drug toxicities.

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