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The QT Interval and Torsade de Pointes

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Abstract

The QT interval on the electrocardiogram is the time from the onset of ventricular depolarisation (the Q wave) to completion of repolarisation (the end of the T wave). It is influenced by heart rate, autonomic factors, electrolyte levels, gender and age. A prolonged QT interval indicates an increased risk of developing malignant ventricular tachyarrhythmias, particularly torsade de pointes. QT prolongation may be primary (inherited, familial, congenital, idiopathic) or caused by disease, drugs or toxins.

Drugs that have been associated with the development of torsade de pointes include antiarrhythmic, antibacterial and psychotropic agents and antihistamines. Several of these drugs depress myocardial ion channels, particularly the rapidly activating delayed rectifier (repolarising) potassium current (I_{Kr}). Overdosage of drugs that affect the delayed rectifier (repolarising) potassium currents (I_K), or coadministration of these drugs with another medication that inhibits their metabolism (e.g. an antihistamine such as terfenadine with an antifungal agent such as ketoconazole, which inhibits the cytochrome P450 3A4 hepatic enzyme), can induce torsade de pointes.

Torsade de pointes is a potentially life-threatening ventricular tachyarrhythmia and the risks of administering drugs that can induce this condition must be carefully considered.

The QT interval on the electrocardiogram is the time from the onset of ventricular depolarisation (the Q wave) to completion of repolarisation (the end of the T wave) in the axis of the lead chosen for measurement. The QT interval is of special interest to physicians and pharmaceutical companies, in view of the disease processes and medications that can influence the interval and the known association between QT prolongation and the potential for malignant ventricular arrhythmias.

The QT interval reflects a dynamic process involving the ion channels within the myocellular membranes. It is influenced by the heart rate, autonomic factors and electrolyte levels, as well as gender (it is somewhat longer in females than males) and age.

The surface-recorded QT interval reflects the complex relationship between the 3-dimensional cellular transmembrane action potentials throughout the heart. The duration of the QT interval may vary among the 12 ECG leads, because of internal cancellation of some electromotive activity, depending on the direction of the 3-dimensional cellular repolarisation vector. In many cases, the end of the T wave is somewhat indistinct, because of either a low amplitude T wave or the presence of a somewhat prominent U wave. Thus, quantification of the QT interval is compounded by the imprecision inherent in identifying the end of the T wave on the electrocardiogram.

1. Measurement of the QT Interval

The optimal approach for measuring the QT interval should utilise a multi-channel recorder to record simultaneously limb and precordial leads, preferably at a paper speed of at least 50 mm/sec. Unfortunately, most reports in the literature measure one QT interval in lead II at a paper speed of 25 mm/sec, and this compromises the accuracy of measurement.

The QT interval should be measured from the earliest onset of the QRS complex to the latest end of the T wave, where its terminal limb joins the baseline. A discrete U wave should not be included in the measurement of the QT interval. If a U wave interrupts the lower portion of the end of the T wave, then the end of the T wave should be determined from a straight line extrapolation of the terminal portion of the T wave to the point where it intersects the baseline.

For greatest precision, the QT interval and the preceding RR intervals should be measured on 3 consecutive beats, and the QT and RR intervals averaged. Because of the numerous sources of inaccuracy with regard to the QT measurement, it is difficult to evaluate the clinical and biological significance of minor QT changes, even when they are statistically significant.

2. The Corrected QT Interval

It is known that the QT interval shortens as the heart rate increases, and various regression formulae have been used to correct the QT interval for heart rate.

In 1992, Sagie et al.[1] described a new linear correction formula that adjusted the QT interval for heart rate (QTlc) based on more than 5000 individuals from the Framingham Heart Study. The linear regression model yielded the following correction formula (for a reference RR interval of 1 second):

$$QTlc = QT + 1.54\ (1–RR)$$

This formula applies to men and women. The mean QTlc (95% confidence limits) is 0.376 seconds (0.332 to 0.420 seconds) for men and 0.388 seconds (0.344 to 0.432 seconds) for women. Although this formula is quite straightforward, it has not been widely applied.

The logarithmic expressions for adjusting the QT interval for heart rate include the Bazett formula,[2] which utilises a square root adjustment for the RR cycle length, and the Fridericia formula,[3] which utilises a cube root adjustment for the RR interval.

The popularised Bazett formula is simply

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

Because of its simple algebraic form and because it is easy to memorise, the Bazett formula is the one most widely used for correcting the QT interval for heart rate. The Bazett formula actually adjusts the QT interval for an RR cycle length of 1.0 seconds, and the corrected QT (QTc) interval should be reported in the same units as the measurement of the QT interval, i.e. either in seconds or milliseconds.

Bazett's original study involved only 20 males and 19 females, and the derived mean value for the QTc was 0.37 seconds for males and 0.40 seconds for females. Several studies have quantitated the normal spectrum of the QT interval within a wide range of RR intervals. Table I summarises reported normal QTc values (Bazett formula). For simplicity, the commonly used upper limit of normal for

Table I:

Table II:

the QTc is 0.44 seconds, and gender differences are ignored. Obviously, this is an oversimplification.

During the past several years, our research group has established a digitised data file for QT and RR interval measurements on 581 healthy individuals, including children aged 1 to 15 years and adults aged 16 to 81 years. The longest QT interval on each tracing was determined from the earliest onset of the Q wave to the latest offset of the T wave. The RR interval was averaged for all normal beats during a 10-second recording. The QTc values were quite stable for children, with no gender difference. There was, however, a significant difference in QTc values for adult men and women in this healthy population. Our 3-level categorisation of QTc values is presented in table II.

3. QT Prolongation

QT prolongation is generally categorised into primary (inherited, familial, congenital, idiopathic) and secondary (disease-, drug- or toxin-related) forms. Regardless of the cause of the QT prolongation, the length of the QT interval is directly related to the risk of developing ventricular tachyarrhythmic episodes, especially torsade de pointes.[7] In our research work with the primary long QT syndrome, we evaluated the risk between the length of the QT interval and the occurrence of subsequent cardiac events, including arrhythmic syncope or arrhythmic sudden death. The risk of experiencing cardiac events was 1.052^{x}, where x is the increase in QTc per 10 msec. Thus, an individual with a QTc of 600 msec would have a 2.76-fold greater risk of experiencing a subsequent cardiac event per unit of time than an individual with a QTc of 400 msec (hazard ratio = 1.052^{20} = 2.76). The arrhythmic risk is directly related to the length of the QTc interval. Although this risk relationship was derived from patients with the primary long QT syndrome, we believe that a similar risk exists for other forms of QT prolongation, including drug-induced QTc lengthening.

The risk of cardiac events in patients with QT prolongation also bears some relationship to the distorted morphology of the repolarisation T waves that frequently accompany QT prolongation. It has been known for some time that T-wave alternans is usually associated with QT prolongation and is frequently a harbinger of torsade de pointes. Furthermore, 'humps' or 'bumps' are reflections of disordered propagation of repolarisation, and these patterns are also associated with an increased likelihood of experiencing dangerous ventricular tachyarrhythmias.

4. Ionic Mechanisms of QT Prolongation

The inscription of the cellular action potential is determined by the flow of ion currents into and out of the cell. Ion currents are regulated by ion channels that consist of complexes of proteins residing in the cell membrane. The movement of charged ions reflects the function of specific ion channel proteins. An important feature of the cardiac cell during repolarisation is that very small changes in individual ion currents can significantly alter the delicate balance between inward and outward current flow, thus prolonging or shortening the action potential duration.

Several genes that encode ion channel proteins have been identified, and remarkable progress has been made during the past few years in the molecular genetics of ventricular repolarisation.[9] In the study of primary long QT syndrome, 4 mutant genes that influence ventricular repolarisation have been identified. The mutant *KVLQT1* gene on chromosome 11 encodes an abnormal K^+ channel protein (α subunit) that, when coexpressed with a protein (minK) encoded by the *KCNE1* gene, produces a reduction (dominant-negative effect) in the

slowly activating delayed rectifier (repolarising) potassium current (I_{Ks}).[10,11] The mutant *HERG* gene on chromosome 7 encodes an abnormal K^+ channel protein that produces a reduction (dominant-negative effect) in the rapidly activating delayed rectifier (repolarising) potassium current (I_{Kr});[12] it appears that minK also acts to regulate I_{Kr} by complexing with *HERG*.[13] The mutant *SCN5A* gene on chromosome 3 encodes an abnormal Na^+ channel protein with alteration in fast inactivation (gain of function or dominant-positive effect), resulting in a continued leakage of the Na^+ current (I_{Na}) into the cell with prolongation of repolarisation.[14] The *KCNE1* gene on chromosome 21 encodes β subunits (minK) that coassemble with *KVLQT1* α subunits to form I_{Ks} and complex with *HERG* to regulate I_{Kr}.[11,13] Although there are several other genes that regulate ionic channels in the membrane of the myocyte, the 4 cardiac ion channel genes described above seem to have the greatest clinical relevance at this time.

In addition to these ion channel genes, it is now recognised that there is heterogeneity in repolarisation across the myocardium. Recently, a population of cells with distinctive repolarisation properties, called M cells, has been identified in the mid-myocardium.[15] M cells display marked prolongation of the action potential in response to stimuli such as hypokalaemia, slow heart rate, or the presence of drugs that prolong action potential. The humps and bumps on repolarisation T waves are thought to represent the inhomogeneity of repolarisation by the M cells.

5. Torsade de Pointes

The ventricular tachyarrhythmia most frequently associated with QT prolongation is torsade de pointes. In 1966, Dessertenne described an elderly female patient with recurrent syncope in association with atrial-ventricular block and accompanying bradycardia.[16] The syncope was not due to advanced degrees of heart block. Rather, the syncopal episodes were caused by runs of polymorphic ventricular tachycardia, which occurred when the heart rate slowed. Dessertenne recognised the distinctive polymorphic nature of the tachycardia, and he named this arrhythmia 'torsade de pointes', which means 'twisting of the points' (fig. 1).

The mechanism that underlies torsade de pointes is poorly understood.[9] Triggered activity arising from early afterdepolarisations that are seen in association with action potential prolongation produces many of the ECG features of torsade de pointes. Another possible mechanism relates to complex 3-dimensional re-entry within the ventricular myocardium. The heterogeneity of repolarisation might result in a relatively organised beat-to-beat re-entrant pathway along the functional barrier created by the M-cell region. Regardless of the mechanism of initiation of torsade de pointes, the QT interval is almost always prolonged prior to the onset of this tachyarrhythmia.

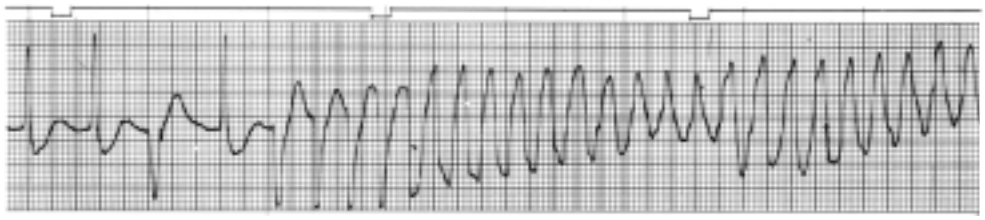

Fig. 1. ECG recording of torsade de pointes. A rapid polymorphous ventricular tachycardia begins after the third supraventricular (narrow complex) beat, with the first 4 beats of the wide-complex ventricular tachycardia having a uniform appearance during an accelerating heart rate. Thereafter, the morphology of the ventricular tachycardia has a gradually changing 'twisting of the points' configuration consistent with torsade de pointes. Of note, the polymorphous ventricular tachycardia is initiated by short-long-short interval sequence that begins with an early-cycle ventricular premature beat following the second supraventricular beat. ECG paper speed 25 mm/sec.

Table III. Drugs that can induce torsade de pointes

Medication	Mechanism of QTc prolongation
Antiarrhythmic drugs	
Class I: disopyramide, quinidine, procainamide	↓ I_K
Class III: amiodarone, *d*-sotalol, ibutilide	↓ I_{Kr}
Antibacterial/antiviral agents	
Amantadine	?
Clarithromycin, erythromycin	↓ I_{Kr}; inhibits CYP3A4
Pentamidine	?
Cotrimoxazole (trimethoprim-sulfamethoxazole)	?
Antifungal drugs[a]	
Fluconazole	Inhibits CYP3A4
Itraconazole	Inhibits CYP3A4
Ketoconazole	Inhibits CYP3A4
Miconazole	Inhibits CYP3A4
Antihistamines	
Astemizole	↓ I_{Kr}
Terfenadine	↓ I_{Kr}
Gastrointestinal drugs	
Cisapride	↓ I_{Kr}
Psychotropic drugs	
Lithium	?
Thioridazine	?
Tricyclic antidepressants	?
Other drugs	
Bepridil	? Calcium antagonist
Lidoflazine	?
Prenylamine	?

a These drugs do not induce torsade de pointes when administered alone. However, they can cause some prolongation of the QTc interval and inhibit the hepatic cytochrome P450 (CYP) 3A4 enzyme system responsible for detoxifying several drugs, whose parent form or metabolite can induce torsade de pointes.

I_K = K^+ current; **I_{Kr}** = rapidly activating delayed rectifier (repolarising) potassium current; **I_{Na}** = Na^+ current; **QTc** = corrected QT; ↓ = decrease; ↑ = increase; **?** = unknown.

6. QT Prolongation and Drug-Induced Torsade de Pointes

A number of different drugs have been associated with the development of torsade de pointes (table III). For instance, it has been known for many years that most antiarrhythmic agents prolong the QT interval and can suppress, as well as induce, tachyarrhythmic episodes. Several of the agents implicated have a negative effect on ion currents in the myocardium, particularly I_{Kr}. Drug-induced reduction in the function of the potassium channel produces QT prolongation similar to that seen in the primary long QT syndrome with mutations of the *HERG* gene. Overdosage with drugs that affect the I_{Kr} potassium channel, or excessive blood concentrations of these drugs resulting from coadministration with another medication that inhibits the hepatic cytochrome P450 (CYP) 3A4 enzyme system responsible for their detoxification (parent form or its metabolite), can induce torsade de pointes. The most common example of this adverse drug interaction is the combination of an antihistamine drug such as terfenadine, which depresses I_{Kr} function, with an antifungal agent such as ketoconazole, which inhibits the CYP3A4 detoxifying hepatic enzyme.[17]

7. Conclusions

Primary and secondary forms of QT prolongation may be associated with life-threatening torsade de pointes. The cellular and ionic channel mechanisms responsible for the associated arrhythmias are gradually being understood. The occurrence of drug-induced torsade de pointes is infrequent to rare. However, because of the potential lethality of this ventricular tachyarrhythmia, the risk of administering drugs that can induce torsade de pointes must be carefully balanced against their possible benefits.

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