QT interval variations and mortality risk: Is there any relationship?

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Abstract

Abnormal prolongation and shortening of the electrocardiographic QT interval duration, which occur in the hereditary forms of long and short QT syndromes, are associated with an increased risk of ventricular arrhythmias and sudden cardiac death. Even within the normal range, these altered durations are associated with an increased mortality risk in the general population. While extreme prolongation or reduction of the QT interval predisposes patients to malignant ventricular arrhythmias and sudden cardiac death, the precise dose-response relationship between the QT interval and cardiovascular disease mortality is still unknown. This paper describes the need for more standardized methods for measuring and reporting the QT interval and the need for more precise assessments of the risk associated with QT interval variation.
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Introduction

Prolongation of the QT interval is associated with early afterdepolarizations. Early afterdepolarizations of sufficient amplitude can generate premature action potentials that lead to cardiac arrhythmias, which can progress to ventricular fibrillation and sudden cardiac death. By contrast, shortening of the QT interval is associated with exaggerated heterogeneity of repolarization in time and space. This exaggerated heterogeneity of the action potential duration creates a substrate for functional reentry similar to that of the long QT syndrome but with hastened recovery and reduced refractoriness in the ventricle. Arrhythmias are more likely to be malignant in short, compared with long, QT syndromes (1, 2).

QT interval assessment

Frequently, reference ranges for the QT-interval in the general population are expressed in terms of QTc, a corrected form of the QT interval (3-6). Bazett's formula is the most commonly used method to calculate QTc and adjusts for the heart rate, although it tends to underestimate the duration of repolarization when the heart rate is particularly slow (or overestimate when the heart rate is fast). The electrocardiographic QTc is approximately normally distributed in the general population. Normal values for the QTc range from 350 to 450 ms for adult men and from 360 to 460 ms for adult women; however, 10%-20% of otherwise healthy persons may have QTc values outside this range. Marked prolongations in the QT interval may be caused by genetic disorders (e.g., long QT syndrome), pharmacological agents (e.g., antiarrhythmics, antipsychotics, and antibiotics), electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia), and their interactions (7). Other factors associated with QT interval length variability include age, sex, hypertension, body mass index, medication usage, low-calorie diets, serum potassium levels, and common genetic variants (7). Finally, within-person variability and measurement error are additional sources of variability in the QT interval length.

Bazett's correction is still recommended for the diagnosis of congenital long and short QT syndrome (8, 9). However, Bazett's correction has a strong residual correlation with heart rate. The 2009 recommendations for the standardization and interpretation of the QT interval from the American Heart Association Electrocardiography and Arrhythmias Committee Council on Clinical Cardiology, American College of Cardiology Foundation, and Heart Rhythm Society were to use linear regression functions (the R-R interval-adjusted QT-interval duration) for QT correction instead of Bazett's formula (10). In addition, heart rate, sex, and age should be incorporated into QT adjustments because women and elderly individuals tend to have longer QT

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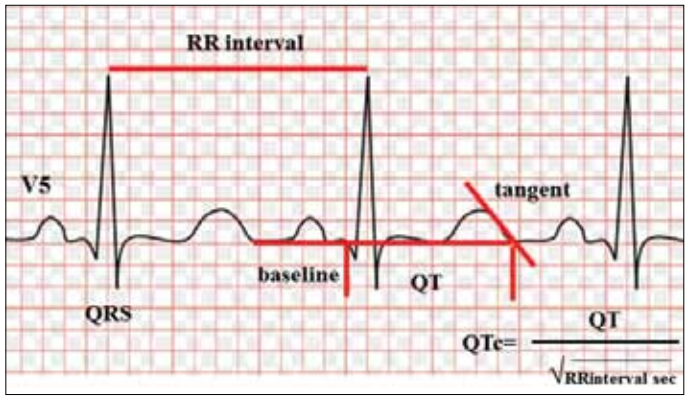

Figure 1. The QT interval starts at the onset of the Q wave and ends where the tangent line for the steepest part of the T wave intersects with the baseline of the electrocardiogram (in V5 or DII lead)

intervals. The report proposed a reference range for linear function-adjusted QT-interval durations from 390 to 450 ms for men and 390 to 460 ms for women.

Heart rate correction of the QT interval is fraught with problems. Manual measurements of the QTc interval are better than digital (with the 12SL algorithm) because the latter may lack a prolonged QTc interval diagnostic statement (11). Therefore, automated measurements should be manually confirmed (Fig. 1), both in daily clinical practice and for scientific purposes.

Mechanism of ventricular arrhythmias in QT interval variations

Prolongation of the QT interval is associated with early afterdepolarizations, in which an abnormal depolarization occurs during phase 2 or 3 of the action potential before repolarization has been completed. Early afterdepolarizations of sufficient amplitude can generate premature action potentials that lead to cardiac arrhythmias. This can progress to ventricular fibrillation and sudden cardiac death. Longer QT intervals reflect longer ventricular action potentials and a reduction in the repolarizing reserve that is associated with exaggerated spatial and temporal heterogeneity of electrical recovery of the ventricle (12). This allows for the development of functional reentry, in which still-activated regions of the ventricular myocardium re-enter and reactivate regions with shorter action potentials, producing polymorphic ventricular tachycardias (such as torsade de pointes) (7). The progressive association of QT-interval duration with mortality reflects the increased likelihood of ventricular arrhythmias associated with increasing heterogeneity in the ventricular action potential duration (7).

Similar to QT prolongation, shortening of the QT interval is not uniform in time and space in the ventricle (7), producing an exaggerated heterogeneity of repolarization. This creates a substrate for functional re-entry, similar to that of long QT syndrome but with hastened recovery and reduced refractoriness in the ventricle (13). Therefore, arrhythmias are even more likely to be malignant in short, compared with long, QT syndrome (13). However, less is known regarding shortened QT intervals, especially at the population level.

QT interval variations and mortality rate

In literature, there are many papers describing QT interval variation and mortality in patients with cardiac or non-cardiac pathologies. Increased levels of B-type natriuretic peptide are associated with prolongation of the action potential in the ventricular myocardium. It seems that a B-type natriuretic peptide augmentation in patients with heart failure is associated with an increased risk of sudden cardiac death only in patients with QTc interval prolongation (14). The paced QTc interval appears to be a more useful marker for predicting increased total mortality and cardiac mortality than the intrinsic QTc interval in patients with indications for a permanent pacemaker (15). A 50-ms increase in the QTc interval is associated with doubling in the probability for all-cause mortality in patients with rheumatoid arthritis (16). The association of QTc with C-reactive protein levels could indicate a potentially hazardous interplay between inflammation and arrhythmogenesis (16). A high prevalence of prolonged QT interval duration has been observed in hemodialysis patients. In a case series of these patients, QTc seemed to be associated with total mortality and sudden cardiac death (17). QTc prolongation is also associated with increased mortality in patients with sickle cell diseases (18). Intubation and respiratory arrest are independently associated with the QTc interval in acute methadone-intoxicated patients presenting to the emergency department; indeed, QTc could be a potential predictor for adverse outcomes related to acute methadone intoxication (19).

Short QT syndrome is a rare disease associated with hastened ventricular repolarization (QT intervals typically ≤320 ms) and an increased risk of sudden cardiac death (20, 21). However, more recent studies have shown that genetically confirmed cases of short QT syndrome may have QT interval durations of 320-360 ms (21). Two studies found no association with sudden cardiac death when comparing participants with Bazett's heart rate-corrected QT interval duration (QTc) of <400 vs. 400-440 ms (21) or with a QTc of <340 vs. 360-449 ms (7). Another study reported no association with cardiovascular mortality when comparing participants with a QTc of <397 vs. 410-422 ms (22). Unfortunately, none of these studies presented a more detailed dose-response analysis (7).

Therefore, there are consistent associations between QT interval variation and an increased risk of mortality. At the population level, these associations are substantial and comparable in magnitude to the effect of other traditional cardiovascular risk factors (23). QT interval prolongation may be associated with conditions affecting autonomic tone or left ventricular structure, including left ventricular hypertrophy or myocardial infarction (24). By contrast, the QT interval may simply be a marker for the severity of an underlying clinical or subclinical cardiac disease (25). However, most studies adjusted for blood pressure levels or the presence of hypertension and either excluded or adjusted for the presence of a pre-existing coronary heart disease (23, 24). Furthermore, a direct link has been established between genetic variations in the QT interval length and sudden cardiac death, indicating that QT prolongation could be a direct causal contributor to mortality risk (26). However, one meta-analysis study provided evidence of substantial heterogeneity in the

methodology used to study QT and mortality relationships across studies (7). All the studies reported a positive association. They found consistent increases in mortality associated with a prolonged QT interval, but there are substantial variations in the cut-offs used to present the associations between QT interval length and mortality. When combined with the genetic findings related to genetic variability in the QT-interval length and mortality, the QT-interval length is still thought to be a determinant of mortality in the general population (7).

Although the risk of mortality increases with longer and shorter QT interval durations compared with the population average, until now there is still no clear threshold for this risk. Some studies have shown progressive associations between the QT-interval duration and mortality rate (27-29), whereas others have shown either U-shaped or non-significant associations (30-32). More than 20 studies have demonstrated an association between the QTc interval and all-cause and cardiovascular mortality in large samples from the general population with dose-effect responses even within the normal QTc interval range (33). In a large study (72 subgroups from 173,529 Danish primary care patients aged 50–90 years) analyzing the 5-year risk of all-cause, cardiovascular, and non-cardiovascular mortalities based on the QTc interval, the authors found that either the prolongation or shortening of the QTc interval (defined as ≤379 ms), especially in women, is associated with a worse prognosis (34).

Another important issue related to QT interval and mortality rate in clinical practice is the proarrhythmia risk of drugs. The pharmaceutical industry has focused on developing new approaches to assess the proarrhythmia risk during the discovery phase of potential new drugs (35, 36). Recently, Fossa et al. (37) developed a methodology that could validate the sensitivity of the QT interval using drugs in early development that enhanced diagnosis of long QT syndromes by reducing the variability and allowing adequate definition of normal limits. The QT beat-to-beat methodology and electrocardiogram (ECG) restitution could be used for future analyses to potentially quantify the arrhythmogenic vulnerability from temporal irregularities (38).

From a clinical perspective, the most important aspect is how the QTc interval-based predicted risk of mortality affects patient management. The RR–QT interval trend co-variability could be a novel index for the sudden cardiac death risk stratification (39). In addition to the QTc interval itself, other resting conduction and repolarization ECG indices such as heart rate (40), P-wave duration (41), and frontal T-wave angle (42) are increasingly associated with all-cause and cardiovascular mortality and morbidity in the general population. However, these ECG indices may not be causally related to mortality; all these parameters could reflect an arrhythmogenic substrate. We should also be aware of the risk potential of cardiovascular and non-cardiovascular drugs that may further lengthen the QTc interval. Currently, recognition of acquired QTc prolongation is poor according to a study that assessed whether prescribers checked for arrhythmic risk with QT-prolonging medications (43). Finally, normal values for ECG indices may differ between individuals from different ethnic backgrounds (44); geographic factors should be taken into consideration when determining risk assessment models.

Conclusion

Shortened and prolonged QT interval durations, even when found within normal reference ranges and calculated using the most recent normative standards, are associated with an increased risk of cardiovascular disease mortality. However, there is a need for more standardized methods for measuring and reporting QT-interval measurements, population characteristics, and sudden cardiac death to more precisely estimate the magnitude of the increased risk associated with the QT interval variation. A risk model for mortality assessment based on multivariate models, including all recently reported ECG indices associated with mortality such as SCORE or other cardiovascular disease risk models that are frequently used in patient management should be developed in the future.

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