The QT interval: Too long, too short or just right

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The hallmark of the congenital long QT syndrome (LQTS) and short QT syndrome (SQTS) is an abnormality of the QT interval, which is either "too long" or "too short." Consequently, physicians struggle to define the upper and lower limits of the normal QT interval. Two different sources have helped define these limits: (1) large population-based studies reporting the distribution of QTc intervals in ostensibly healthy individuals and (2) genetic studies reporting the QTc intervals of individuals who are not genetically affected. All of those studies show that QTc has a gaussian normal distribution. Therefore, one may define the "normal QT" as any value falling within two standard deviations from the mean. However, in practice there is considerable overlap of QTc intervals between truly healthy individuals and patients affected by SQTS or LQTS. A clinical approach to coping with the absence of rigorous cutoff values is presented: at both ends of the QTc spectrum, patients with very short or very long QT are diagnosed as SQTS or LQTS, respectively, even in the absence of symptoms. For patients with lesser degrees of QT shortening or prolongation, additional tests to clarify the diagnosis are proposed.

The definition of "normal"

The congenital long QT syndrome (LQTS) and short QT syndrome (SQTS) are genetic disorders caused by mutations in specific myocardial ion channels leading to abnormal ventricular repolarization. Clinical manifestations include a tendency to develop syncope or cardiac arrest due to spontaneous polymorphic ventricular arrhythmias. Because the hallmark of these disorders is an abnormality of the QT interval, which is either "too long" or "too short," physicians have struggled to define the upper and lower limits of the normal QT interval. Two different sources have helped define these limits: (1) large population-based studies reporting the distribution of QTc intervals in ostensibly healthy individuals and (2) genetic studies reporting the

QTc intervals of individuals who are not genetically affected.

Population-based studies

Several investigators used large databases of individuals undergoing medical screening to define the normal QT.[1–8] The major strength of this source is the large number of individuals studied (>10,000 in each study). The study reported by Kobza et al[8] in this issue of *Heart Rhythm* presents data on more than 40,000 healthy males recruited to the Swiss Army[8] and is an important contribution. The large number of individuals included in these studies clearly establishes that QTc in the general population conforms to a gaussian normal distribution (Figure 1).[1–8] Therefore, one may define the "normal QT" as any value falling within a range delineated by two standard deviations from the mean. This definition categorizes 95% of all values as "normal" and labels the remaining 5% as abnormal, such that QTc values shorter than the 2.5th percentile are "too short" and those longer than the 97.5th percentile are "too long" (Figure 1). These studies suggest that, for the adult population, normal QTc values for males are 350 to 450 ms and for females are 360 to 460 ms.[1,4,5,8]

Two limitations shared by these studies should be emphasized. (1) The QT and R-R intervals used to calculate QTc in these studies were mostly determined electronically using different computerized algorithms. This limitation is important because computer-determined results tend to overestimate the QT interval.[9] (2) The absence of genetic analysis precludes excluding the possibility that some of the QTc values (especially those in the lower and higher ends of the QTc spectrum) are from asymptomatic patients with SQTS or LQTS rather than from truly "normal" (i.e., healthy) individuals. Indeed, looking at the grossly abnormal T waves of the patients with the longest QT intervals in the study by Kobza et al[8] (their Figure 3), one must conclude that these are, in fact, patients with asymptomatic LQT2. Thus, the spectrum of truly normal QT probably is slightly narrower than that suggested by population studies.

Genetic studies

Carefully conducted studies performed at QT research institutes present the distribution of QTc values of patients with LQTS (with genetic confirmation) as well as the QTc values of family members who are noncarriers of the familial mutation. The last group (those with negative genotype)

Distribution of QTc intervals in large population-based studies.
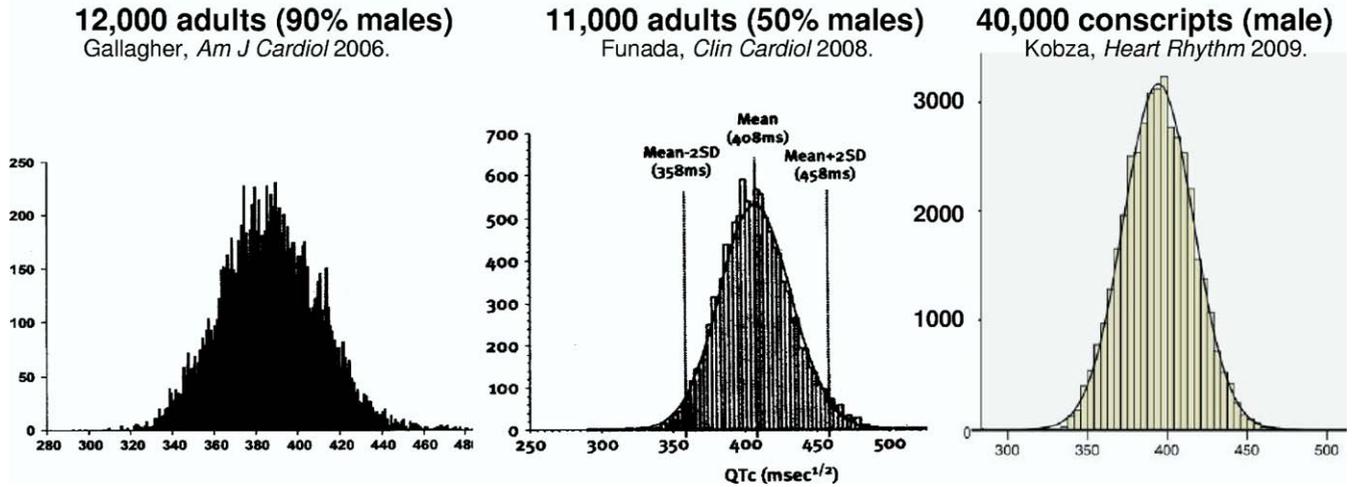
Figure 1 Distribution of QTc intervals in studies reporting more than 10,000 healthy individuals. **Left:** 12,500 young adults (90% male, age 30 ± 10 years) who underwent medical examination for employment purposes.[2] **Middle:** 11,000 adults (50% male, 50 ± 20 years) with negative cardiac evaluation at a Japanese hospital.[5] **Right:** 40,000 male conscripts of the Swiss Army reported by Kobza et al.[8] All studies show that QTc has a gaussian normal distribution.

then can be used to define with confidence the range of normal QT (Figure 2A). Naturally, the number of individuals included in genetic studies is smaller than in population-based studies. On the other hand, in these studies all the QT and R-R intervals were measured manually by QT experts, and the absence of QT-prolonging medications in the study group can be established with certainty. Therefore, it is rewarding that the boundaries of the normal QT determined by genetic studies[10] are not very different from those derived from population studies.

When is the QT "too long"?

The original descriptions of the congenital LQTS[11] were based on patients with obvious prolongation of the QT interval. As commonly occurs, increased awareness on the part of the medical community led to the recognition of patients with milder forms of the disease and lesser degrees of QT prolongation. Two decades after the initial description of LQTS, Schwartz[12] first suggested that some patients with LQTS have QT intervals that fall within normal limits. However, 12 more years elapsed before Vincent et al[10] finally established the existence of considerable overlap of QTc intervals between mutation-carriers and noncarriers (Figure 2A). The clinical implications of this significant overlap of QTc between LQTS patients and healthy controls can be better appreciated from Figure 2B, which depicts the QTc of LQTS patients and controls as percentiles. One can appreciate from Figure 2B that a QTc of 450 ms, which historically has been used to distinguish "long" from normal QT, fails to identify 10% of patients who actually are carriers of a LQTS mutation and incorrectly classifies 10% of healthy controls as "affected" (line A in Figure 2B). On the other hand, selecting a QTc of 430 ms has 100% sensitivity and will not miss any patient with LQTS, but at the expense of overdiagnosing 40% of healthy controls as "affected" (line B in Figure 2B).

Because no single QTc value separates all LQTS patients from healthy controls, one can adopt the diagnostic approach shown in Figure 3. At one end of the spectrum, males with QTc ≥470 ms and females with QTc ≥480 ms should be considered to have LQTS even if they are asymptomatic and have a negative family history. Acquired LQTS is the only differential diagnosis that can easily be excluded. The only caveat to this rule relates to the imperfection of the Bazett formula, which we generally use for calculating QTc (i.e., to correct QT for heart rate).[13] With a perfect formula, QTc should no longer depend on heart rate. That is not the case for the Bazett formula, which undercorrects at fast heart rates and overcorrects at slow heart rates.[14] Although QTc values >470 ms are practically never seen among healthy individuals when their heart rate is 60 to 70 bpm, 2% of healthy adults (and more children) have QTc ≥480 ms when their heart rate is greater than 90 bpm.[14] Thus, whenever a "long QTc" is found during sinus tachycardia, the first step should be to repeat the ECG once the heart rate slows down. Similarly, defining QTc is difficult in individuals with physiologic sinus arrhythmia because the QT shortening in response to heart rate changes is not immediate. Consequently, there is little change in the uncorrected QT interval as the R-R interval shortens and lengthens with respiration, often leading to "long" QTc during sinus rate acceleration and normal QTc during deceleration. One study (not confirmed with genetic data) suggests that QTc ≥460 ms during the shortest R-R interval, or marked variability (>40 ms) of the uncorrected QT during sinus arrhythmia, favors the diagnosis of LQTS.[15]

QTc values ≥450 ms for males and ≥460 ms for females are noteworthy because 90% of LQTS patients, but only 10% of healthy individuals, have longer QT intervals (remember the caveat of sinus tachycardia). Such patients are considered to have "high-probability for LQTS" if they
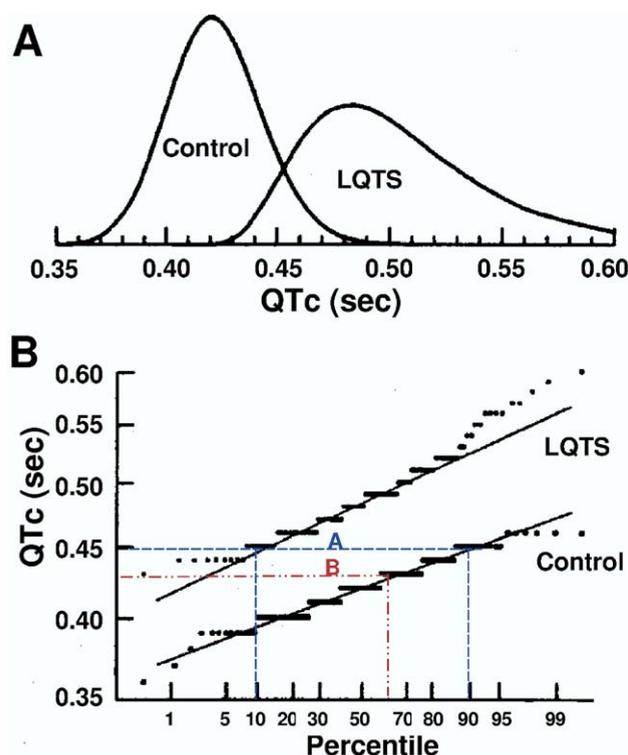
Figure 2 Distribution of QTc intervals in carriers (LQTS) and noncarriers (Control) of genetic mutations for long QT syndrome (LQTS). **A:** Distribution of QTc intervals of 117 LQTS mutation carriers and 113 healthy relatives (noncarriers) as reported by Vincent's groupp.[10,40] **B:** Same data as in panel A presented as percentiles. Line A shows the significance of selecting a cutoff value of QTc 450 ms to define LQTS. This line corresponds to the 10th percentile of LQTS patients and the 90th percentile of controls. Consequently, this cutoff value misses 10% of affected LQTS patients and overdiagnoses LQTS in 10% of the healthy population. Line B shows the effects of selecting QTc of 430 ms to define LQTS. This value has 100% sensitivity and will not miss any patient with LQTS, but at the expense of overdiagnosing 40% of healthy controls as "affected." (Reproduced and modified with permission from Allan WC, Timothy K, Vincent GM, et al. Long QT syndrome in children: the value of rate corrected QT interval and DNA analysis as screening tests in the general population. J Med Screen 2001;8:173–177.[40])

have a history of syncope and familial sudden death.[16] On the other end of the spectrum, LQTS is very unlikely among males with QTc ≤390 ms and females with QTc ≤400 ms.

The middle range of QT (QTc between 400 and 450 ms) is important because the majority of the general population falls within this range. Because the ratio of healthy to affected individuals in the general population is greater than 500:1, the vast majority of individuals within this QTc range will turn out to be healthy (unaffected) (Figure 2). However, LQTS still is possible within this range, and whenever the clinical history requires exclusion of LQTS, additional tests are indicated. The first step is to periodically repeat a resting ECG because of the considerable day-to-day variability in QTc of patients with LQTS. For example, 40% of patients with LQTS will have QTc >500 ms at least once during long-term follow-up, but only 25% will have that degree of QT prolongation during their initial evaluation.[17] The second step is to review the ECGs of all family members

because LQTS has dominant inheritance, and some family members may have obvious QT prolongation. Attention should be given to the T-wave morphology, which differs according to the LQTS genotype.[18] Holter recordings only rarely will show spontaneous arrhythmias but may reveal characteristic T-waves changes during sleep or following postextrasystolic pauses. When deemed necessary, a challenge test with either intravenous epinephrine or adenosine may provide additional information.

The epinephrine challenge test, independently studied by Ackerman et al[19] and Shimizu et al,[20] is particularly useful for identifying patients with LQT1.[21] This is important because LQT1 not only is the more common genotype but also is the most commonly missed. This is because, unlike other LQTS genotypes that commonly present with abnormal T waves,[18] patients with LQT1 only have broad T waves,[18] which can easily be mistaken for normal, and one third of the patients have QTc ≤450 ms.[22] Of note, as the normal response of healthy individuals to epinephrine infusion, the duration of the QT-interval remains stable and the U-wave amplitude increases as heart rate accelerates, leading to increased QTc and abnormal T-U morphology.[23] Consequently, only a 30-ms or greater increment of the uncorrected QT during low-dose epinephrine infusion[19,24] and the appearance of notched T waves (with T2>T1)[25] at any time can be considered diagnostic of LQT1 and LQT2, respectively.

Injection of adenosine during sinus rhythm invariably causes sudden short-lasting bradycardia, followed by sinus tachycardia. These rapid changes in heart rate are accompanied by marked QT changes. Therefore, we use adenosine injection as a diagnostic test and have found it useful for diagnosing LQT2.[26] However, most of the LQTS patients in our study had fairly obvious QT prolongation at baseline, and the value of the adenosine test for patients with borderline QT prolongation remains to be defined. Once a clinical diagnosis of LQTS is made, the diagnosis may be confirmed by genetic testing, keeping in mind that mutations are not found in all patients.

When is the QT "too short"?

The original publications on SQTS described patients with extremely short QT (QTc ≤300 ms), but subsequent cases of genetically confirmed SQTS had QTc intervals ≤320 ms[27] and ≤360 ms.[28] Therefore, we are going through the same stages as occurred during evolution of the definition of "long QT" (discussed earlier). It is unrealistic to expect that a single QTc value will distinguish all cases of SQTS from healthy individuals. Instead, overlapping between "short" and "normal" QT intervals emulates what clearly exists between "normal" and "long." Interestingly, we found that males with idiopathic ventricular fibrillation (VF), a group of patients generally considered to have normal QT, actually have QTc intervals in the low–normal range. Similarly, Fujiki et al[29] and Sugao et al[30] showed that patients with idiopathic VF have normal QT intervals that fail to prolong during sinus bradycardia. These findings are relevant be-

cause idiopathic VF and SQTS share important characteristics, including the morphology and mode of onset of their spontaneous arrhythmias and their response to therapy.[31] As a result, we suggested that some patients with idiopathic VF have "SQTS with not so short QT intervals."[32] Accordingly, one could view "short QT" as a continuum where the extreme cases are obvious, and additional tests are required for those with moderate QT shortening (Figure 3).

Population-based and genetic studies (Figures 1 and 2) show that QTc <330 ms is very rare.[2–5] For example, data from more than 10,000 adults suggest that, in the healthy population, the prevalence (with 95% confidence interval) of QTc <340 ms is less than 0.5%.[4] Thus, males with QTc ≤330 ms and females with QTc ≤340 ms have "very short" QT and should be considered to have SQTS even if they are asymptomatic (Figure 3). However, it should be emphasized that the prognosis of patients with asymptomatic SQTS remains undefined. Individuals with QTc ≤320 ms who reached adulthood without developing arrhythmic symptoms have been reported.[4,5]

Population studies also show that relatively few males and females have QTc intervals shorter than 360 and 370 ms,[1–5,7] respectively, and these values probably should be regarded as "short." A diagnosis of SQTS should be considered when such patients present with cardiac arrest, malignant syncope, or atrial fibrillation at a young age. As for patients with QT prolongation, the first step in clarifying the diagnosis among patients with "short QT" is performing repeat ECGs to further study the QT duration and T-wave morphology at different heart rates.

The importance of the heart rate recorded at the time of QTc calculation cannot be overemphasized. Because of the overcorrection of QTc at slow heart rates with use of the Bazett formula, relatively short QT intervals are not rare among young healthy males with sinus bradycardia. This can best be appreciated from Figure 2 of the article by Kobza et al[8]: only less than 5% of all young male conscripts had QTc ≤360 ms. However, when only the ECGs recorded during sinus bradycardia were counted, up to 20% of males had QTc between 340 and 360 ms.[8] On the other hand, patients with confirmed SQTS have a flat QTc/R-R relationship.[33,34] In other words, these patients have QTc intervals in the low–normal range at heart rates greater than 80 bpm that fail to prolong adequately at slower heart rates.[33,34] Thus, repeated resting ECGs showing different QT intervals at different heart rates may help distinguish the common patient with innocent QTc shortening during bradycardia from the rare SQTS patient with a flat QTc/R-R relationship.

T-wave morphology also is important. Healthy males have taller T waves and shorter ST segments than do healthy females,[35] and T-wave amplitude increases as heart rate decreases.[36] However, a recent study suggests that such characteristics are more striking in SQTS.[37] In that study, patients with symptomatic SQTS had tall peaked T waves with a very short J-point to T-wave-peak interval. As a result, patients with symptomatic SQTS had no flat ST segment.[37] However, in contrast to studies based on data from more than 300 patients demonstrating the value of T-wave morphology for diagnosing LQTS,[18] studies investigating the contour of T waves in SQTS are based on only a dozen patients.[37] Moreover, other studies show that 6% of healthy males have no visible transition between the ST segment and the ascent of the T wave.[35] Clearly, our knowledge about the value of T-wave morphology in SQTS is preliminary.

Finally, the role of electrophysiologic studies for diagnosing SQTS should be discussed. Patients with SQTS have very short atrial and ventricular effective refractory periods; however, these data come from patients with very short QT intervals.[33,34] The effective refractory periods of patients with lesser degrees of QT shortening are likely to overlap normal values. Similarly, patients with SQTS frequently have inducible VF during electrophysiologic study.[33,34] Because sudden death is commonly the presenting syndrome in SQTS, one may be tempted to perform electrophysiologic study in asymptomatic patients with short QT to "clarify the diagnosis." Therefore, it is important to emphasize that the clinical significance of inducible VF in asymptomatic patients is debatable.[38,39] Many asymptomatic and otherwise healthy young males who underwent defibrillator implantation because of "asymptomatic Brugada syndrome with inducible VF" never developed spontaneous arrhythmias but suffered from iatrogenic complications.[38] Performing electrophysiologic study for "asymptomatic J-waves"[37] or "asymptomatic short QT" could result in similar outcomes. Certainly, we ought to improve our means of diagnosing these diseases before we start treating them.

Figure 3 Proposed "QT scale" for defining the spectrum of QT intervals, ranging from very short to very long. See text for definitions and additional tests. This is a modification of the algorithm proposed by Vincent[41] for long QT syndrome (LQTS). SQTS = short QT syndrome.

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