Prolonged QT Interval: A Tricky Diagnosis?

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Prolonged heart-rate adjusted QT intervals on the electrocardiogram (ECG) are associated with an increased risk for coronary heart disease and sudden death. However, the diagnosis of the prolonged QT interval is hampered by lack of standards. We studied variations in the prevalence of prolonged QT, based on different common definitions, in a large nonhospitalized population, and compared our results with other studies applying the same definitions. The study population consisted of 2,200 men and 3,366 women participants of the Rotterdam Study, ≥55 years old. The QT interval was computed by our Modular ECG Analysis System (MEANS). Three different formulas to adjust QT for heart rate were used: Bazett's formula (QT_c), a linear regression equation (QT_{lr}), and the QT index (QTI). Prolonged QT occurred frequently in both men and women, and its prevalence increased with age. Women had longer heart-rate adjusted QT intervals than men (mean QT_c 433 ms vs 422 ms), and mean values for QT_{lr} were lower than for QT_c (mean QT_{lr} 422 ms in women and 412 ms in men). Prevalence was highest for prolonged QT_{lr} (31% in men and 26% in women) and lowest for prolonged QTI (6% in men and 9% in women). Comparison with other studies applying the same correction formulas showed large discrepancies in prevalence estimates of prolonged QT_c and QT_{lr}, and to a lesser degree of prolonged QTI, possibly due to differences in measurement techniques. Future research is needed to relate QT interval to prognosis, to obtain measurement technique specific reference values of heart-rate adjusted QT measurements, and to obtain age- and sex-specific threshold values for prolonged QT. Such data are needed to use the QT interval with confidence. ©1997 by Excerpta Medica, Inc.

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The QT interval is of potential use in cardiovascular risk profiling,[1–6] but the diagnosis of patients with prolonged QT intervals may be hampered by the lack of consensus regarding measurement techniques,[7] formulas to adjust QT for heart rate,[8–11] and criteria to define prolonged QT.[12] Little is known about the influence of these formulas and cut-off criteria on the prevalence of prolonged QT. Furthermore, comparison of the few studies that have been published has been limited by the application of different formulas to adjust QT for heart rate.[6,9,13] In the present study, we examined the distribution of QT interval length and the prevalence of prolonged QT, heart-rate adjusted, in a large nonhospitalized population of men and women, ≥55 years old. Three different formulas to adjust the QT interval for heart rate were used in order to establish differences between formulas and to compare our findings with published data from other population-based studies.

METHODS

Study population and data collection: This study is part of the Rotterdam Study,[14] a population-based cohort study aimed at assessing the occurrence and risk factors of chronic diseases in the elderly. Objectives and methods of the Rotterdam Study are described in detail elsewhere.[14] Briefly, in the Rotterdam Study, all men and women ≥55 years old and living in the Rotterdam district of Ommoord, were invited to participate. Of the 7,129 participants who took part in the study (response rate 69%), baseline data, collected from 1990 to 1993, included an electrocardiogram (ECG), history of cardiovascular disease, established cardiovascular risk factors, and use of medications. A digitally stored ECG was available for 6,160 participants (86%). Fourteen percent of the ECGs were missing due to temporary technical problems with the electrocardiographic recorder. Participants with arrhythmias (n = 290) and those with complete left or right bundle branch block (n = 304) were excluded, leaving 2,200 men and 3,366 women in the present study.

QT measurement and correction for heart rate: A 12-lead ECG at rest was recorded with an ESAOTE-ACTA cardiograph (Florence, Italy) with a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS)[15,16] to obtain electrocardiographic measurements and diagnostic interpretations. The QT interval was determined over all leads in 1 representative complex, which resulted from selective averaging of dominant beats.[15] To adjust QT for heart rate, 3 different methods were used. First, we calculated the corrected QT interval (QT_c) according to Bazett's formula: $QT_c = QT / \sqrt{RR}$, where RR is the RR

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TABLE I General Characteristics of the Study Population. Values Are Means (With SDs) or Proportions

	All (n = 5,566)	Men (n = 2,200)	Women (n = 3,366)
Age (yrs)	68.6 (8.8)	67.4 (8.0)	69.3 (9.2)
Body mass index (kg/m^2)	26.3 (3.7)	25.7 (3.0)	26.8 (4.1)
Systolic blood pressure (mm Hg)	139.0 (22.2)	138.5 (21.8)	139.3 (22.5)
Diastolic blood pressure (mm Hg)	73.6 (11.5)	74.6 (11.5)	73.0 (11.4)
Serum total cholesterol (mmol/L)	6.7 (1.2)	6.3 (1.1)	6.9 (1.2)
Serum total potassium (mmol/L)	4.1 (0.3)	4.1 (0.3)	4.1 (0.3)
Current cigarette smoking (%)	23.3	29.5	18.9
Systemic hypertension (%)*	18.4	17.1	19.3
Antihypertensive medication use (%)	30.4	27.4	32.3
Diabetes mellitus (%)†	11.6	11.5	11.6
History of MI (%)‡	12.5	17.8	9.1
Left ventricular hypertrophy by ECG (%)	4.7	5.6	4.1
Negative T-wave (%)§	7.7	8.4	7.3
Mean heart rate (beats/min)	70 (12)	68 (12)	71 (11)

*Hypertension: systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg.
†Diabetes mellitus: nonfasting blood glucose >11.1 mmol/L or antidiabetic medication.
‡History of MI: myocardial infarction by interview or by ECG.
§Negative T-wave: ≥1.0 mm negative deflection in any of leads I to III, aVL, aVF, V_2 to V_6.

TABLE II Mean Values of Heart-Rate Adjusted QT by Age in Men and Women

Age (yrs)	n	QT (ms)	RR (ms)	QT_c (ms)*	QT_{lr} (ms)†	QTI‡
Men						
55–59	434	396	921	415	407	100.0
60–64	520	397	905	420	410	101.1
65–69	495	399	896	424	414	102.1
70–74	350	399	893	424	414	102.3
75–79	231	402	894	428	417	103.1
>80	170	400	876	430	417	103.4
All	2,200	398	901	422	412	101.8
Women						
55–59	606	398	868	429	419	102.9
60–64	678	397	854	431	421	103.4
65–69	604	399	857	432	422	103.7
70–74	566	398	847	434	423	103.9
75–79	431	400	854	434	423	104.1
>80	481	400	843	437	426	104.7
All	3,366	398	854	433	422	103.7

*$QT_c = QT/\sqrt{RR}$.
†$QT_{lr} = QT + 0.140*(1-RR)$ (men)), $QT_{lr} = QT + 0.163*(1-RR)$ (women).
‡QTI = QT/(656/(1 + 0.01*heart rate)).

interval in seconds.[17] Second, we used a linear regression equation that was also applied in the Framingham Study[9]: $QT_{lr} = QT + \beta*(1-RR)$. Both QT_c and QT_{lr} can be interpreted as the QT interval at a heart rate of 60 beats/min. Third, we computed the QT index (QTI)[18] as used in the Cardiovascular Health Study[13]: $QTI = QT/QT_p$, where QT_p is the predicted interval and equals: $QT_{max}/(1 + 0.01*\text{heart rate})$, with $QT_{max} = 656$ ms. For example, a QTI of 110 denotes a QT interval that is 10% longer than the predicted QT interval. Based on the literature, 4 definitions of prolonged heart-rate adjusted QT interval were used: QT_c >440 ms[6] and 460 ms,[19] QT_{lr} >420 ms in men and >432 ms in women,[9] and QTI >110.[13]

Data analysis: The mean values of QT, RR, QT_c, QT_{lr}, and QTI, and the prevalence of prolonged heart-rate adjusted QT, defined in 4 different ways, were assessed in men and women separately and in different age groups. In addition, we studied whether QT_c, QT_{lr}, and QTI were still associated with the RR interval using a linear regression model. In this case, this would indicate that the correction for heart rate with the formula is not complete. Prevalences from published reports were compared with adjusted results from our study, using the same exclusion rules and, if necessary, adjusting for age using linear regression analysis. All analyses were performed for men and women separately, using BMDP statistical software (version 7, 1990, Los Angeles, California).

RESULTS

The general characteristics of the 2,200 men and 3,366 women are presented in Table I. Women were slightly older, had higher cholesterol levels, smoked less, and had a lower percentage of myocardial infarction than men.

QT interval and heart rate: The relation between QT and RR using linear regression formulas in our study was $QT_{lr} = QT + 0.140*(1-RR)$ in men and $QT_{lr} = QT + 0.163*(1-RR)$ in women. In the Framingham Study, application of the linear regression equation had very similar results: $QT_{lr} = QT + 0.147*(1-RR)$ in men and $QT_{lr} = QT + 0.167*(1-RR)$ in women.[9] Examination of the linear relation between QT_c, QT_{lr}, and QTI with RR showed a negative association of QT_c (regression coefficient $r = -0.08$, $p < 0.001$) and QTI ($r = -0.01$, $p < 0.001$) with RR. Consequently, QT_c and QTI do not completely correct QT for heart rate. As expected, there was no significant linear association of QT_{lr} with RR.

Distribution of heart-rate adjusted QT intervals: In Table II, the mean values of QT, RR, QT_c, QT_{lr}, and QTI are presented for different age groups. On average, the unadjusted QT interval was similar in both sexes. Women had shorter RR intervals and consequently longer heart-rate adjusted QT intervals than men. In men, mean QT_c increased from 415 ms in those age 55 to 59 years to 430 ms in those >80 years. In women, the corresponding values were 429 and 437

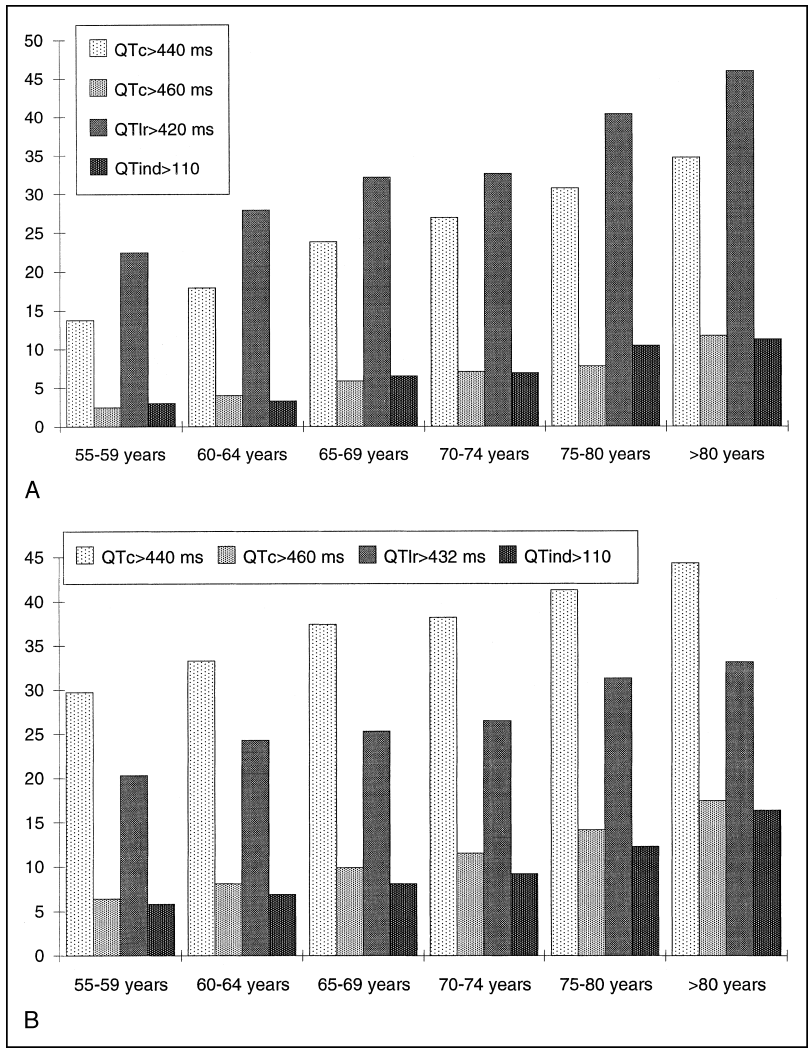

FIGURE 1. ***A,*** **prevalence of prolonged heart-rate adjusted QT interval in men, using 4 different definitions. $QT_c = QT/\sqrt{RR}$; $QT_{lr} = QT + 0.140*(1{,}000-RR)$; QTI = QT/(656/(1 + 0.01*heart rate)).** ***B,*** **prevalence of prolonged heart-rate adjusted QT interval in women, using 4 different definitions. $QT_c = QT/\sqrt{RR}$; $QT_{lr} = QT + 0.163*(1-RR)$; QTI = QT/(656/(1 + 0.01*heart rate)).**

ms, respectively. Overall, QT_c ranged from 345 to 628 ms in men and from 329 to 538 ms in women. In both men and women, mean QT_{lr} was about 10 ms shorter than mean QT_c in all age groups. Mean QTI increased from 100.0 to 103.4 in men and from 102.9 to 104.7 in women, from the youngest to the oldest age group.

Prevalence of prolonged heart-rate adjusted QT interval: The prevalence of prolonged heart-rate adjusted QT, using the 4 different definitions, is shown in Figure 1. The presence of prolonged QT_c, defined as $QT_c > 440$ ms ranged from 13.8% in men and 29.7% in women age 55 to 59, to 34.7% in men and 44.3% in women >80 years old, and was similar to the prevalence of prolonged QT_{lr}, but much more prevalent than prolonged QTI intervals. The prevalence of prolonged QT_c, defined as $QT_c > 460$ ms, was similar to the prevalence of QTI, ranging from 2.5% in men and 6.4% in women ages 55 to 59, to 11.8% in men and 17.5% in women in the oldest age group.

Comparison with other studies: Prevalences reported by 3 other studies and the adjusted prevalence in the Rotterdam Study, applying the same exclusion criteria and adjusting for age, are presented in Table III. Mean QT_c in men ages 65 to 84 was 411 ms (SD 27) in the Zutphen Study, about 10 ms shorter than the adjusted mean QT_c in the Rotterdam Study,[14] which was 425 ms (SD 22). Mean QT_{lr} was about 375 ms in men and 388 ms in women participating in the Framingham Study,[9] whereas the adjusted mean values of QT_{lr} were 401 ms (SD 19) in men and 416 ms (SD 18) in women in the Rotterdam Study.[14] Prevalences of prolonged QT_c and prolonged QT_{lr} were markedly higher in the Rotterdam Study than in other published studies[6,9,13] using the same formulas. Prevalence of prolonged QTI was lower in women in the Rotterdam Study compared with women in the Cardiovascular Health Study,[13] except for the highest age group, but estimates for men were similar.

DISCUSSION

The results of this study show that a prolonged heart-rate adjusted QT interval is more frequent in women than in men and that the prevalence in both sexes increases markedly with age. Mean values of heart-rate adjusted QT interval and prevalence of prolonged heart-rate adjusted QT vary substantially according to the correction formulas and threshold values used. Comparison of our findings with data presented from other studies showed that even if the same formulas to adjust QT for heart rate are used, large differences in estimates of prevalence of prolonged QT can be observed.

Because QT_{lr} was the only formula without a residual linear association with the RR interval, this formula may be preferable to QT_c and QTI when linear associations of QT with cardiovascular determinants are examined. The linear regression coefficients estimated from the Framingham Study[9] were very similar to our estimates. Thus, in studies with a relatively small number of participants, regression coefficients need not be derived, but coefficients from the Framingham Study or from the present study can be used.

Comparison with previous studies showed that marked differences in prevalence estimates of prolonged QT were present between studies using the same correction formulas. These discrepancies may at least partly be explained by differences in measure-

TABLE III Prevalence of Prolonged QT in the Rotterdam Study Compared With Three Population-Based Studies

	Definition Prolonged QT	n	Prevalence (95% CI)	Adj. Prevalence Rotterdam Study (95% CI)§
Zutphen Study[6]	QT_c >420 ms*			
Men, age 65–84		720	34.9 (31.4–38.5)	57.3 (54.4–60.2)
Framingham Study[9]				
Men, age 29–62	QT_{lr} >420 ms†	2,239	2.5 (1.9–3.2)	14.7 (13.1–16.4)
Women, age 28–62	QT_{lr} >432 ms†	2,779	2.5 (1.9–3.1)	17.1 (15.7–18.5)
Cardiovascular Health Study[13]	QTI >110‡			
Men,				
age 65–69		625	6.7 (4.9–9.0)	6.5 (4.5–9.0)
age 70–74		626	8.0 (6.0–10.4)	6.9 (4.4–10.0)
age 75–79		381	12.3 (9.2–16.1)	10.4 (6.8–15.1)
age 80–84		201	12.4 (8.2–17.8)	11.1 (5.9–18.6)
age >85		73	19.2 (10.9–30.1)	11.3 (4.7–21.9)
Women,				
age 65–69		1,097	13.4 (11.4–15.6)	8.1 (6.1–10.6)
age 70–74		836	16.4 (13.9–19.1)	9.2 (6.9–11.9)
age 75–79		541	16.3 (13.3–19.6)	12.3 (9.3–15.8)
age 80–84		229	20.1 (15.1–25.9)	13.7 (9.8–18.5)
age >85		76	22.4 (13.6–33.4)	19.7 (14.7–25.6)

*$QT_c = QT/\sqrt{RR}$.
†$QT_{lr} = QT + 0.140*(1-RR)$ in men and $QT_{lr} = QT + 0.163*(1-RR)$ in women.
‡$QTI = QT/(656/(1 + 0.01*\text{heart rate}))$.
§Adj. prevalence = adjusted prevalence after applying the same exclusion criteria as in the comparison study and adjusting for age using linear regression if necessary.
Numbers of participants in different age groups in the Rotterdam Study are presented in Table II.

ment techniques. In the Rotterdam Study,[14] the QT interval was measured by computer over all leads. The greatest differences were found between the Rotterdam Study and 2 studies[6,9] using manual measurements. In the Zutphen Study,[6] electrocardiographic intervals were measured manually with a digitizing tablet, taking the longest QT interval from leads I, II, III, V_2 or V_6, and in the Framingham Study[9] measurements were performed manually in all 12 leads. Our findings were more similar to those of the Cardiovascular Health Study[13] in which a computer program was used in combination with an interactive graphics procedure for correcting computer measurement errors. This computer program applies another method to detect the end of the T wave than our MEANS program. This is important, in view of the large variability reported between different human observers, different computer programs, and between human observers and computer programs, in measurements of the end of the T wave.[7] Another explanation for part of the discrepancies in prevalence estimates between populations may be differences in prevalences of cardiovascular risk indicators, such as body mass index, medication use, or coronary heart disease.

Which measurement technique should be preferred to diagnose prolonged QT is unclear. Even though QT intervals have been found to differ systematically, the association of prolonged QT intervals, established with different measurement techniques, with future cardiovascular disease, has been shown in many studies. However, it seems clear that computerized QT measurements using a single program, and excluding the problem of intra- and interobserver variability among different physicians measuring ECGs, are preferable to manual measurements.

The definition of prolonged heart-rate adjusted QT, depending on the threshold value used to distinguish between normal and prolonged QT, can be based on prognostic implications for clinical end points. Depending on the purpose of diagnosing prolonged QT, higher or lower thresholds and associated risk levels may be considered relevant, which also influences the number of subjects detected with prolonged QT. Instead of dichotomous thresholds, multilevel risk groups or continuous estimates associated with heart-rate adjusted QT may be studied. Because women have systematically longer (about 10 ms) heart-rate adjusted QT intervals,[5,9,20–22] it seems that the threshold value for prolonged QT_c and QT_{lr} should be higher in women than in men.

Using data from large population-based follow-up studies, such as the Rotterdam Study,[14] may offer an opportunity to circumvent the problem of the lack of standards by establishing specific reference values for each electrocardiographic computer program or manual measurement technique separately. For each method, age- and sex-specific normal values of QT interval can be assessed, together with threshold values for the prolonged heart-rate adjusted QT interval. Thresholds should depend on the additional risk associated with a certain length of the heart-rate adjusted QT interval, for example, a two- or threefold risk for cardiovascular morbidity or mortality. This would facilitate uniform diagnoses of those with prolonged heart-rate adjusted QT intervals, and link them to established levels of risk. Consequently, prevalence of prolonged heart-rate adjusted QT can be compared between different populations. More importantly, this would enable physicians to target preventive measures at patients with QT intervals, inferring increased cardiovascular risk. At present, in the absence of these measurement technique specific reference values, the prolonged QT interval remains a tricky diagnosis.

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