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QT Interval Prolongation Predicts Cardiovascular Mortality in an Apparently Healthy Population

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Background. **In myocardial infarction patients, heart rate–adjusted QT interval (QT_c), an electrocardiographic indicator of sympathetic balance, is prognostic for survival.**

Methods and Results. **In a 28-year follow-up, the association between QT_c and all-cause, cardiovascular, and ischemic heart disease mortality was studied in a population of 3,091 apparently healthy Dutch civil servants and their spouses, aged 40–65 years, who participated in a medical examination during 1953–1954. Moderate (QT_c, 420–440 msec) and extensive (QT_c, more than 440 msec) QT_c prolongations significantly predict all-cause mortality during the first 15 years among men (adjusted respective relative risks [RRs], 1.5 and 1.7) and among women (RRs, 1.7 and 1.6). In men, cardiovascular (RRs, 1.6 and 1.8) and ischemic heart disease mortality (RRs, 1.8 and 2.1) mainly account for this association. In women, the association cannot be attributed specifically to cardiovascular and ischemic heart disease mortality. RRs for a subpopulation without any sign of heart disease at baseline are similar. The same is observed for QT_c prolongation after light exercise, although in this situation most associations are not statistically significant, probably because of smaller numbers in the QT_c prolongation categories.**

Conclusions. **Our results suggest that QT_c contributes independently to cardiovascular risk. If autonomic imbalance is an important mechanism, it might be speculated that changes in life-style (e.g., with regard to physical exercise and smoking) may have a preventive impact. (*Circulation* 1991;84:1516–1523)**

Heart rate–adjusted QT interval prolongation (QT_c, more than 440 msec) is regarded as an indicator of imbalanced distribution of sympathetic nervous system activity on the heart. In experimental investigations, manipulation of the sympathetic nervous system affects QT interval duration.[1,2] In these experiments, QT prolongation is associated with a lowered ventricular fibrillation threshold and with the occurrence of ventricular arrhythmias after coronary occlusion.[3,4] This is generally viewed as a consequence of nonuniform recovery of excitability of the myocardium.[5] In patients with recent myocardial infarction[6,7] and patients who had 24-hour electrocardiography,[8] QT_c prolongation (QT_c, more than 440 msec) in the standard 12-lead electrocardiogram was reported to be a strong prognostic indicator of sudden cardiac death. Recently, in a preliminary report from the Cardiac Arrhythmia Suppression Trial,[9] certain type Ic antiarrhythmic drugs were associated with an increased risk of death from arrhythmia and cardiac arrest among myocardial infarction patients. This adverse effect may be related to a prolonged QT interval resulting from these drugs.[10]

The relation between QT_c and mortality has been exclusively studied in patients with specific autonomic or cardiovascular disease. Because electrocardiography is a simple, noninvasive, and inexpensive functional test of the heart, it may be used in periodic medical examination of nondiseased populations. Combined with other risk indicators, information on QT_c prolongation might have implications for prevention with respect to life-style, because physical

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exercise is reported to have a favorable[11,12] and cigarette smoking an unfavorable[13] influence on autonomic balance.

In the present study, the predictive value of QT_c at rest and after light exercise on all-cause, cardiovascular, and ischemic heart disease mortality was studied in a 28-year follow-up of 3,091 apparently healthy civil servants in The Netherlands.

Methods

Study Population

In 1953–1954, a cohort of 1,583 men and 1,508 women (civil servants and spouses of civil servants of Amsterdam aged 40–65 years) participated in a general health survey. Its purpose was to study the feasibility of a medical screening of apparently healthy persons to detect early manifestations of disease. Approximately 54% of the 11,700 eligible civil servants volunteered, with or without their spouses. The cohort consisted of an age- and sex-stratified sample with approximately equal numbers in 5-year age and sex categories. Information on survival or cause of death was missing for 19 men and 12 women, leaving 1,564 men and 1,496 women (896 and 521 deaths in the total follow-up period, respectively).

Coding of electrocardiograms is tedious and time consuming. Therefore, instead of studying the complete cohort, the case-cohort sampling design was applied.[14–16] According to this approach, all subjects who died were enrolled in the study as cases. They were studied in relation to a random sample from the cohort as referents instead of a sample of noncase referents as would be performed in a nested case-control study. Consequently, the deaths in this referent sample from the cohort are playing roles as both "case" and "referent." This way, electrocardiograms of only some of the noncases had to be coded. We took a sample of about twice the expected number of cardiovascular deaths (expectation, 40% of all deaths). This yielded sample sizes of 730 men and 502 women (sampling fraction, 46.1% and 33.2%, respectively).

The coding of electrocardiograms, however, had to start when determination of cause of death was still ongoing. Therefore, to include all cardiovascular deaths, coding had to be performed on all deaths; electrocardiograms were evaluated for a total of 1,219 men and 848 women. Exclusion of 14 men and nine women without data on QT_c left a study population of 1,205 men and 839 women, including deaths from all causes in the cohort (883 men and 512 women). In all analyses, the sample, representing the cohort, is identical, but the number of additional, nonsample deaths depends on the duration of follow-up and the cause-of-death category of any particular analysis.

To eliminate the possibility that an observed association might be a consequence of already manifest heart disease, associations were also studied in a subpopulation who had no signs of heart disease at baseline. Excluded were subjects who reported typical angina or had electrocardiographic infarction patterns, certain ST segment and T wave changes, ventricular hypertrophy, intraventricular conduction disturbances, or a Cardiac Infarction Injury Score (CIIS)[17] of more than 20 (205 men and 114 women).

Data Collection

The general health survey of 1953–1954 consisted of a detailed medical history obtained by a structured interview, a physical examination, an electrocardiogram, a chest radiograph, and some laboratory examinations. All results were published in a doctoral thesis by van der Heide,[18] who was one of two physicians who performed the examinations.

At baseline during 1953–1954, a 12-lead electrocardiogram was recorded on a one-channel, Elema ink-jet electrocardiographic recorder–type Mingograph. A second recording was made after the Master Two-Step Test.[19] Recently, the electrocardiograms were classified and coded according to the Minnesota Code[20] and the CIIS.[17] Coders were blinded for other baseline information and survival. Minute measurements of PQ, QT, and RR intervals; ST segment level; and T wave amplitude were also made.

The longest QT interval in lead I, II, or III was measured from the beginning of the first deflection of the QRS complex to the end of the T top, where it merges with the electric baseline. Adjustment for heart rate was made according to Bazett's[21] formula: $QT_c = QT/\sqrt{RR}$.

Blood pressure readings in multiples of 5 mm Hg were taken from the right arms of subjects in the supine position with the use of a standard mercury sphygmomanometer with a 12-cm cuff. Total serum cholesterol was measured according to the modification of the Liebermann-Burchard reaction by Saifer and Kammerer.[22] Body weight and length were measured to calculate body mass index, and subjects were asked about their smoking habits. Serum cholesterol information on 40 men and nine women and body mass index information on one woman were missing.

In 1981, survival of 99.9% of the population was established through the records of the Civil Servants Pension Fund (A.B.P.).[23] This was possible because by 1981, all participants were receiving their old-age pensions. The pension fund monitors survival of all civil servants and their spouses very closely for financial reasons. Survivors were documented as still receiving a pension in 1981. In 1989, the cause of death until 1981 was established for 98.0% of the deceased men and 98.1% of the deceased women by using the registers of the Dutch Central Bureau of Statistics. Loss to follow-up of cause of death was almost entirely due to emigration. The necessary death certificate number was obtained from the Dutch Central Bureau of Genealogy.

The classification of causes of death was based on the *International Classification of Diseases, 9th Revision (ICD-9)*.[24] For the analysis, total, cardiovascular (*ICD-9* 390–460), and ischemic heart disease mortality (*ICD-9* 410–414) were selected. Causes of death

before 1969, originally coded according to the sixth and seventh revisions, were recoded to the ninth revision by the Dutch Central Bureau of Statistics using the original death certificates. The eighth revision did not differ substantially from the ninth with regard to the chosen mortality categories.

Data Analysis

Participants were classified into one of three categories of QT_c at rest and after exercise: 420 msec or less, more than 420–440 msec, or more than 440 msec. In the sample, overall between-group differences of means of relevant characteristics were tested by analysis of variance and, if significant, by the Tukey-Kramer method[25] to adjust for multiple comparisons. Percentages were tested by *t* tests for the difference between two proportions.

To evaluate the effect of cardiovascular risk factors as potential confounders, a stratified analysis was performed. For this purpose, age strata were used with cutoff points of 50 and 60 years and strata based on approximate tertiles for the other confounders. For men, cutoff points of approximate confounder tertiles were 70 and 80 mm Hg for blood pressure, 5.9 and 7.0 mmol/l for serum cholesterol, 23.4 and 25.6 kg/m^2 for body mass index, and three and 70 cigarettes per week for smoking. For women, these cutoff points were 80 and 90 mm Hg, 6.2 and 7.5 mmol/l, and 24.7 and 27.6 kg/m^2, respectively. Smoking for women was divided in two categories: smoking and nonsmoking.

Relative risk (RR) of death was estimated using logistic regression analysis to adjust for two sets of potential confounders: age alone, and all potential confounders. For both sets of confounders, a separate analysis was performed for all-cause, cardiovascular, and ischemic heart disease mortality. Because application of logistic regression to case-cohort data as such does not produce a valid RR, we used a modification so that the deaths that had been drawn in the sample were used only once as cases. This procedure yields an unbiased estimate of the true multivariate RR (i.e., not the odds ratio).[26] Testing the significance of this RR estimate must be performed by an approximate method: The corresponding odds ratio estimated in case-control design was tested instead of the RR.[15]

If competing mortality by other causes is differential in the QT prolongation groups, the cause-specific RRs will not be adequately estimated by the RR (cumulative incidence ratio). The incidence–density ratio would then be the preferred measure of association because it accounts for differences in person–time at risk.[26] However, only crude and pooled incidence–density ratios can be estimated under case-cohort design; standard methods for testing significance are not available. To evaluate the validity of the RR estimates, age-adjusted case-cohort incidence–density ratios for cardiovascular and ischemic heart disease mortality were estimated for comparison.

Results

Table 1 gives the significant differences between QT_c categories of normal (420 msec or less), moderately prolonged (420–440 msec), or extensively prolonged (more than 440 msec) in mean age and diastolic blood pressure for men and women. Differences in mortality percentages between persons with and without QT_c prolongation were most pronounced and statistically significant for 15-year mortality of men. For 28-year mortality, significant differences were observed for all-cause mortality in both sexes and for cardiovascular mortality in women. Mean values of baseline characteristics and mortality percentages in the random sample were almost identical to those in the total cohort, and none of the observed differences was statistically significant.

Only age appeared to be a confounding variable of some importance; therefore, the results are not presented separately for each confounder. In Tables 2 and 3, the RRs in the QT_c categories for 15- and 28-year all-cause, cardiovascular, and ischemic heart disease mortality are presented; they are adjusted for age and other potential confounders. They were estimated for the study population as a whole as well as for a subpopulation, with participants with signs of heart disease at baseline excluded. For comparison, age-adjusted incidence density ratios are also included in the tables.

Adjusted for age and other potential confounders, the RRs of 15-year all-cause mortality differed significantly from 1.0 for moderate (RR: men, 1.5; women, 1.7) and extensive QT_c prolongations (RR: men, 1.7; women, 1.6) compared with normal QT_c. After 28 years, these associations were weaker. In the subpopulation, RRs were of similar magnitude but not all were statistically significant.

For cardiovascular mortality, a statistically significant multivariate RR was observed after 15 years of follow-up in men with moderate (RR, 1.6) or extensive QT_c prolongation (RR, 1.8). In the male subpopulation, only the 15-year cardiovascular mortality RR of moderate QT_c prolongation was significant (RR, 1.9).

Fifteen-year ischemic heart disease mortality in men was significantly associated with moderate (RR, 1.8) and extensive QT_c prolongation (RR, 2.1). In the subpopulation without known heart disease, this was observed, again only in men, for moderate QT_c prolongation after 15 years (RR, 2.4) and after 28 years (RR, 1.5). However, the number of cases of extensive prolongation was small.

Most of the age-adjusted incidence–density ratios in Tables 2 and 3 were somewhat larger than the corresponding RRs (no significance test possible).

The same analysis was performed for QT_c after exercise and adjusted according the Bazett[21] as well as by means of a linear regression model derived from the sample. The number of subjects with QT_c prolongation after exercise was considerably smaller than that at rest. In general, associations were of

TABLE 1. Baseline Characteristics and Mortality in Categories of QT_c at Rest in Random Sample From the Cohort

Group	QT_c (msec)		
	≤420	420–440	>440
Men (*n*)	605*	75*	36*
Age (years)	52.3±7.6	53.5±7.8	56.2±6.4‡
Total serum cholesterol (mmol/l)	6.7±1.3	6.7±1.2	6.4±1.1
Diastolic blood pressure (mm Hg)	79±10	81±10	84±12‡
Body mass index (kg/m^2)	24.6±2.6	25.0±3.1	24.6±2.6
Current smokers (%)	71.5	65.3	66.6
Cigarettes/week	74±51	76±59	80±62
15-Year mortality (%)			
All causes	18.5	37.3†	44.4†
CVD	8.9	18.7†	22.2†
IHD	5.6	12.0†	11.1
28-Year mortality (%)			
All causes	52.2	66.6	77.8†
CVD	23.5	30.7	36.1
IHD	12.4	16.0	16.7
Women (*n*)	316*	100*	79*
Age (years)	51.2±7.3	52.6±7.0	53.9±7.9‡
Total serum cholesterol (mmol/l)	7.2±1.5	7.2±1.8	7.0±1.3
Diastolic blood pressure (mm Hg)	86±12	90±15‡	92±16‡
Body mass index (kg/m^2)	26.3±3.6	26.8±3.4	26.5±3.4
Current smokers (%)	37.3	33.0	39.2
Cigarettes/week	21±28	11±17	15±15
15-Year mortality (%)			
All causes	8.5	12.0†	16.5†
CVD	3.8	3.0	8.9
IHD	2.5	2.0	2.5
28-Year mortality (%)			
All causes	30.7	33.0	48.1†
CVD	12.3	13.0	24.1†
IHD	6.0	7.0	6.3

CVD, cardiovascular disease; IHD, ischemic heart disease.
*Individual parameters have missing data.
†Significantly different from QT_c of 420 msec or less (*t* test for difference between two proportions, $p<0.05$).
‡Significant *F* test ($p<0.05$) over the three prolongation groups; indicated value significantly different from QT_c of 420 msec or less (Tukey-Kramer test, $p<0.05$).
Values are given as mean±SD.

similar magnitude, but only multivariate RR for 15-year all-cause mortality was significant.

Discussion

The results of the present study show that in a middle-aged population QT_c at rest is an independent predictor of total mortality in both sexes. In men, this predictive value is mainly determined by cardiovascular and ischemic heart disease mortality. The association appeared not to be a consequence of manifest heart disease at baseline.

In the only similar, recently published study, Goldberg et al[27] did not observe a significant association between QT_c and all-cause mortality, deaths due to sudden cardiac events, or coronary artery disease in 30 years of follow-up of the original Framingham cohort. There may be several reasons for this disparity. Differences in population and methods may play a role: The age range of the study populations was not the same; the Framingham population was somewhat younger. For QT measurements, we used the longest single interval in standard lead I, II, or III, whereas Goldberg et al took the average of two or three measurements from any electrocardiographic lead with the longest QT interval. Risk analysis was performed using different QT_c categories, including the reference category, which was less than 360 msec in their study and 420 msec or less in our study. Furthermore, mortality experienced by the reference category in the Framingham cohort was surprisingly high, particularly in the last part of the follow-up, which casts doubt on their adequacy as a reference group. Finally, the 15-year period in which we observed the strongest associations was not considered separately by Goldberg et al.

TABLE 2. Relative Risks for 15 and 28 Years of Follow-up for All-Cause, Cardiovascular Disease, and Ischemic Heart Disease Mortality in Categories of QT_c Prolongation at Rest Compared With QT_c of 420 Msec or Less Among Men

	Total population (QT_c)		Subpopulation (QT_c)*	
	420–440 Msec	>440 Msec	420–440 Msec	>440 Msec
15-Year follow-up				
All-cause (*n*)	898		736	
Age-adjusted RR	1.5‡	1.8‡	1.7‡	1.6
Multivariate RR†	1.5‡	1.7‡	1.7‡	1.5
CVD (*n*)	806		663	
Age-adjusted RR	1.6‡	2.0‡	2.0‡	1.4
Incidence–density ratio	1.8	2.3	2.2	1.5
Multivariate RR†	1.6‡	1.8‡	1.9‡	1.2
IHD (*n*)	768		641	
Age-adjusted RR	1.8‡	2.2‡	2.4‡	1.1
Incidence–density ratio	2.0	2.5	2.7	1.2
Multivariate RR†	1.8‡	2.1‡	2.4‡	1.0
28-Year follow-up				
All-cause (*n*)	1,205		1,000	
Age-adjusted RR	1.1	1.3‡	1.2‡	1.4
Multivariate RR†	1.1	1.3‡	1.2‡	1.4‡
CVD (*n*)	953		786	
Age-adjusted RR	1.3	1.5	1.3	1.4
Incidence–density ratio	1.5	1.9	1.7	1.8
Multivariate RR†	1.2	1.4	1.3	1.4
IHD (*n*)	854		711	
Age-adjusted RR	1.4	1.5	1.6‡	1.1
Incidence–density ratio	1.7	1.9	2.0	1.3
Multivariate RR†	1.4	1.5	1.5‡	1.2

RR, relative risk; CVD, cardiovascular disease; IHD, ischemic heart disease.
*Subjects with signs of heart disease at baseline were excluded.
†Adjusted for age, total serum cholesterol, diastolic blood pressure, current smoking, and body mass index.
‡$p<0.05$, two-sided significance test based on corresponding case-control odds ratio.
Incidence–density ratio, calculated to evaluate effect of competing mortality, was not tested for significance (see "Methods").

In previous clinical studies in myocardial infarction patients[6,7] and patients who had 24-hour electrocardiography,[8] a predictive value of QT_c in relation to sudden death has been demonstrated.

Manipulation of the autonomic nervous system in experiments demonstrated the influence of imbalanced sympathetic activity on heterogeneity of repolarization in the myocardium, resulting in QT interval prolongation and increased incidence of ventricular arrhythmias in the presence and absence of infarction.[2–5] This mechanism is also held responsible for the increased risk of sudden cardiac death due to ventricular fibrillation associated with prolonged QT interval (QT_c, more than 440 msec) in patients with recent myocardial infarction.[6,7] The observed association might be secondary to existing heart disease, causing both QT prolongation and death. In that case, however, exclusion of subjects with signs of heart disease at baseline would have weakened the associations.

Next, some potential methodological problems will be discussed. Our study population may not be a true representation of the total middle-aged population in The Netherlands because it is confined to relatively healthy, employed civil servants. However, for an etiological study, this is not regarded as a serious problem.

In the present study, the case-cohort design[14–16] was used to limit the number of electrocardiograms that had to be coded. If the cohort sample size is a small multiple of the size of the case series, loss of precision is expected to be limited. A comparison of baseline characteristics and mortality between the total cohort and the sample did not reveal substantial differences. Therefore, the sample was considered to be representative.

Bias resulting from competing mortality by other causes of death in the cause-specific analyses, as judged from the incidence–density ratios, was small and occurred mainly in the direction of the null value.

Error in the measurement and coding of QT interval as well as in the diagnosis and coding of causes of death may have resulted in some misclassification. Although QT_c does not vary much within individuals,[6] a single measurement may be insuffi-

TABLE 3. Relative Risks for 15 and 28 Years of Follow-up for All-Cause, Cardiovascular Disease, and Ischemic Heart Disease Mortality in Categories of QT_c at Rest Compared With QT_c of 420 Msec or Less Among Women

	Total population (QT_c)		Subpopulation (QT_c)*	
	420–440 Msec	>440 Msec	420–440 Msec	>440 Msec
15-Year follow-up				
All-cause (*n*)	591		508	
Age-adjusted RR	1.8‡	1.8‡	1.7‡	1.9
Multivariate RR†	1.7‡	1.6‡	1.6	1.6
CVD (*n*)	534		466	
Age-adjusted RR	1.7	1.8	1.4	1.9
Incidence–density ratio	1.6	1.7	1.4	1.9
Multivariate RR†	1.5	1.4	1.3	1.7
IHD (*n*)	503		442	
Age-adjusted RR	1.2	1.1	0.3	0.8
Incidence–density ratio	1.2	1.1	0.3	0.9
Multivariate RR†	1.0	1.0	0.3	0.9
28-Year follow-up				
All-cause (*n*)	839		725	
Age-adjusted RR	1.3	1.2‡	1.3	1.2
Multivariate RR†	1.3	1.1	1.3	1.1
CVD (*n*)	650		565	
Age-adjusted RR	1.3	1.4	1.4	1.3
Incidence–density ratio	1.2	1.4	1.3	1.4
Multivariate RR†	1.3	1.2	1.3	1.2
IHD (*n*)	558		489	
Age-adjusted RR	1.4	1.2	1.4	1.3
Incidence–density ratio	1.3	1.3	1.4	1.5
Multivariate RR†	1.4	1.1	1.4	1.3

RR, relative risk; CVD, cardiovascular disease; IHD, ischemic heart disease.
*Subjects with signs of heart disease at baseline were excluded.
†Adjusted for age, total serum cholesterol, diastolic blood pressure, current smoking, and body mass index.
‡$p<0.05$, significance test based on case-control odds ratio.
Incidence–density ratio, calculated to evaluate effect of competing mortality, was not tested for significance (see "Methods").

cient to characterize a person's long-term QT interval length, and heart rate adjustment according to Bazett[21] may be inadequate for both low and high heart rates.[28]

All mentioned that potential sources of error would have led to nondifferential misclassification, resulting in dilution of the existing association between QT_c prolongation and mortality.

A bias resulting from pharmacological effects interfering with QT_c length at baseline is not likely because at the time of the original investigation, such medication was rarely available and seldom used, particularly in a healthy population.

Although a stronger association was expected, the patterns for QT_c after exercise were similar, but most of the estimates were not significant, evidently because of smaller numbers. This may be due to inadequacy of Bazett's adjustment method in exercise or the low level of the exercise in the Master test. Adjustment by linear regression analysis based on the data at hand, however, did not make much difference. QT_c during instead of soon after exercise might have produced different results.

The association between QT_c prolongation and cardiovascular mortality may be explained in several ways. Patients with congenital long QT syndrome[29] have an extremely high incidence of ventricular fibrillation and sudden cardiac death, which are often triggered by physical or emotional stress. This syndrome, however, is very rare, and patients would have died before the age of 40 years. In healthy humans, extreme physical and psychological stresses sometimes also induce ventricular arrhythmias,[30–33] and sympathetic imbalance as manifest in QT_c prolongation may increase this risk in a similar way. Second, QT_c prolongation may increase the risk of sudden death in subjects who developed coronary heart disease although they had been healthy at baseline. This is probably the most likely explanation for the observed associations. Third, QT_c prolongation may be a risk factor for cardiovascular morbidity as well, resulting in an association with cardiovascular mortality. Last, the association with total mortality might demonstrate that autonomic imbalance is an indicator of poor health in general.

The difference between men and women in the cause-specific associations is not clear. It may have a

biologic background or indicate greater misclassification of cardiovascular and ischemic heart disease mortality in women compared with men during past decades.

Our conclusion is that in this middle-aged population, QT_c prolongation is predictive of mortality. QT prolongation probably indicates imbalanced distribution of sympathetic nervous activity to the heart, although other explanations (e.g., congenital, electrolyte disturbances, left ventricular hypertrophy) are possible. The association appears to be independent of cardiovascular risk factors and in men but not in women is largely explained by cardiovascular and ischemic heart disease mortality, but it is not a consequence of existing heart disease. It would be interesting to investigate the possibility that QT prolongation is a risk factor not only of cardiovascular mortality but also of morbidity.

QT interval length is derived from a simple, noninvasive diagnostic method. If the observations are confirmed in other studies, information on QT_c interval length combined with other risk factors may represent an improvement of cardiovascular risk profile. Because physical exercise appears to result in a favorable autonomic balance and smoking and stress appear to result in a less favorable autonomic balance,[11–13] it might be speculated that preventive life-style changes may improve autonomic balance in general and thus mortality risk in persons with prolonged QT interval.

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