

QT interval as a cardiac risk factor in a middle aged population

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Abstract

Objective—To evaluate the value of QT interval as a cardiac risk factor in middle aged people.

Methods—The association between QT interval and cardiac risk factors and mortality in a middle aged Finnish population of 5598 men and 5119 women was evaluated over a 23 year follow up. To adjust the QT interval confidently for heart rate, a nomogram was constructed from the baseline electrocardiograms separately for men and women.

Results—Nomogram-corrected QT interval (QT_{nc}) prolongation was associated with elevated blood pressure and signs of cardiovascular disease; QT_{nc} shortening was associated with smoking. Over 10% prolongation of QT_{nc} predicted death in men with heart disease; adjusted relative risk (RR) was 2.17 (95% confidence interval 0.67–7.45) for sudden death; 2.12 (1.25–3.59) for total cardiovascular mortality; and 1.92 (1.23–3.00) for all cause mortality. In healthy men the increase in RR was not significant: sudden death, 1.48 (0.67–3.25); total cardiovascular mortality, 1.25 (0.92–1.70); all cause mortality, 1.21 (0.96–1.53). However, healthy men with long QT_{nc} in the lowest heart rate quartile exhibited an RR of 2.75 (1.00–7.40) for sudden death. Over 10% shortened QT_{nc} predicted cardiovascular death in men with heart disease who smoked; RR 3.72 (1.45–9.54). Non-smoking men with short QT_{nc} had low mortality risks irrespective of possible signs of cardiovascular disease. The trends in mortality risks were similar but weaker for women.

Conclusions—In a middle aged population, prolonged QT interval predicts cardiac mortality in men with signs of cardiovascular disease. In women and healthy men this risk is weak and may reflect subclinical heart disease. A shortened QT interval predicts death in men with heart disease who smoke.

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Keywords: QT interval; cardiovascular mortality; cardiac risk factors; smoking

The QT interval in the electrocardiogram reflects the time registered for depolarisation and repolarisation of the ventricular myocardium—that is, the summation of action

potential durations in the ventricles.¹ Theoretically, long and disparate duration of ventricular action potentials predispose to re-entrant ventricular arrhythmias, which are harbingers of sudden death especially in cardiac patients.² Short action potentials, on the other hand, reflect rapid electrical recovery enabling short cycle length in ventricular arrhythmias³ and may predispose to ventricular fibrillation. Factors influencing action potentials change the QT interval; heart rate and autonomic tone are particularly important.⁴ For clinical and research purposes, QT intervals are corrected for heart rate. The most widely used method is based on Bazett's formula, despite the fact that this equation over corrects the QT interval at high heart rates and under corrects it at low heart rates.⁵

Clinical studies in subjects with congenital or acquired long QT syndrome and in patients with acute myocardial infarction have shown that long QT intervals predispose to malignant ventricular arrhythmias and sudden death.^{6,7} In epidemiological studies, however, the association between the length of the QT interval and the risk of cardiovascular mortality remains controversial.^{8–10} The explanation may be the weakness of the QT interval as a risk predictor, further obscured by the inadequate Bazett's method for adjusting the QT values for heart rate. Heart rate has been found to predict cardiac mortality.¹¹

We have recently created a nomogram to adjust the QT intervals for heart rate that is superior in accuracy to Bazett's and other methods.⁵ In this study, we used this nomogram principle to explore the value of QT interval as a cardiac risk factor in a middle aged Finnish population.

Methods

STUDY POPULATION

The study population consisted of the original cohort of 11 026 people participating in the Social Insurance Institution's Coronary Heart Disease Study.^{12,13} Subjects were aged between 30 and 59 years at study entry in 1966–72. The study population was taken from four areas (south-western, western, central, eastern) of Finland, and was a representative sample of the middle aged Finnish population. Of those invited to the initial examination the participation rate was 89% in men and 91% in women; 309 people were excluded from the study for missing data (232) or because of bundle branch block or second to third degree atrioventricular block (77), leaving 5598 men and 5119 women in the study group.

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Data analysis was made for the whole study group and for a subgroup free from known cardiovascular diseases. Exclusions from this subgroup were subjects with known heart disease, effort angina or signs of myocardial infarction in the electrocardiogram (Minnesota codes 1.1, or 1.2, and 5.1-5.2), and subjects who used digitalis, nitroglycerin or antiarrhythmic drugs. The subgroup comprised 5103 men and 4785 women. Data analysis was also made separately for the excluded subgroup of 495 men and 334 women with signs of cardiovascular disease.

EVALUATION OF CARDIAC RISK FACTORS

The procedure for the baseline examination has previously been described in detail.^{12,13} Briefly, it consisted of a questionnaire on the history of previous diseases, drug therapy, and smoking habits, an interview on cardiovascular symptoms, and a rest electrocardiogram based on the Minnesota code. Casual blood pressure, body mass index (weight kg/height m²), and serum cholesterol were measured.

QT INTERVAL ANALYSIS

Rest electrocardiograms (12 lead) were recorded at a paper speed of 50 mm/s at baseline. They were analysed by nine trained readers as reported earlier.¹⁴ Lead I, II, or III was chosen for the QT interval measurement on the basis of the visually longest QT interval. The measurement was made from the beginning of the QRS complex to the end of the T wave

where the terminal limb joins the TP baseline. Heart rate was the mean of two measurements from both ends of the lead I recording.

To adjust the measured QT interval for heart rate, a curve relating QT intervals and heart rates was constructed⁵ from the baseline electrocardiograms. Mean QT intervals at different heart rate ranges of five beats/min were plotted against the corresponding mean heart rates, and the best fitting curve relating QT intervals and heart rates was constructed visually. This was done separately for men and women. The QT interval at 60 beats/min was the reference QT interval—391 ms in men and 397 ms in women in the study population. The deviation of the QT interval-heart rate curve from the reference value at different heart rates generated the numbers for the adjustment nomogram. The nomogram corrected QT value was calculated as: $QT_{Nc} = QT + \text{correction number}$. For data analysis, the following five QT_{Nc} categories were created: QT_{Nc} compared with reference QT interval was within 5%, 5-10% shorter, > 10% shorter, 5-10% longer, and > 10% longer.

END POINTS

The study end points were death from all causes (total mortality), death from all cardiovascular diseases, death from coronary artery disease (lethal outcome for a patient hospitalised for myocardial infarction or death outside the hospital probably caused by coronary artery disease), and sudden cardiac death (deaths ensuing within one hour of symptom onset).

The mortality of the study population has been monitored continuously. Copies of death certificates of the deceased were obtained from the Central Statistical Office of Finland and additional information from the hospital and necropsy records were sought when needed.^{13,15} Deaths until the end of 1992 are included in the analyses for this report. However, sudden deaths are included only until the end of 1979, because a detailed analysis of time from onset of symptoms to the time of death was available only for these cases.¹⁵

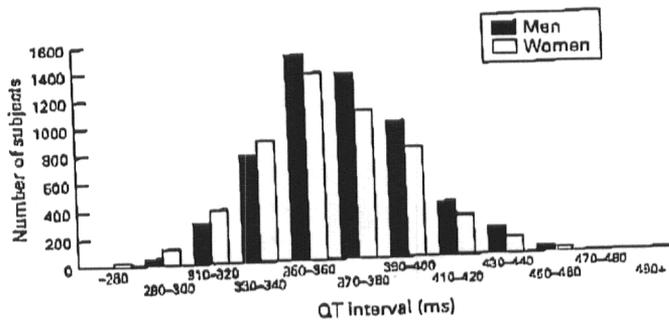


Figure 1 QT intervals in the whole study population.

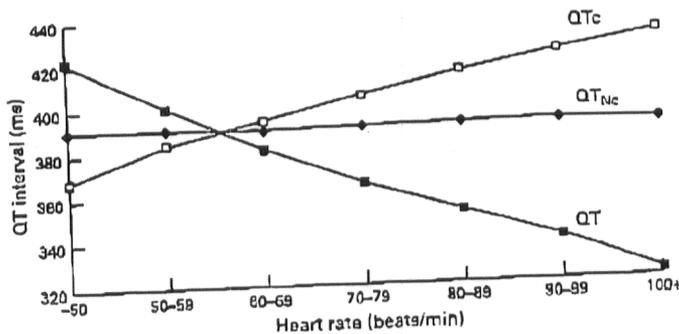


Figure 2 The QT-heart rate relationship curves in men of the study population. Heart rate adjustment with the nomogram method (QT_{Nc}) gives adjusted values close to the reference QT interval of 391 ms at all heart rates. For comparison, QT_c values obtained with Bazett's equation are shown. Data points are mean values at different heart rate subranges.

STATISTICAL ANALYSIS

Associations between the QT_{Nc} categories and risk factors were estimated based on the general linear model.¹⁶ The Cox proportional hazards model was used in the mortality analyses.¹⁷ Relative mortality risks were computed using the middle QT_{Nc} category (QT_{Nc} deviated less than 5% from the reference QT interval) as the reference category, and separately in both sexes. To adjust for risk factors subjects were divided by: age (into five-year groups); current smokers and non-smokers; four blood pressure groups (using the cut-points 140/90 mm Hg, 160/95 mm Hg, and 170/100 mm Hg, and/or antihypertensive treatment); serum cholesterol (cut off 7.2 mmol/l, exceeded by 20% of the population); body mass (30 was used to define subjects as obese or non-obese); and diabetes (all subjects with a known history). Statistical significances were tested using the likelihood ratio test based on Cox's models.

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Table 1 QT_{NC} categories, number (%) of subjects and cut points

	> 10% shortened	5-10% shortened	Within 5% (reference values)	5-10% prolonged	> 10% prolonged
Men, number (%)	131 (2.3)	760 (13.6)	3764 (67.2)	736 (13.1)	207 (3.7)
QT _{NC} (ms)	< 353	353-371	372-410	411-430	> 430
Women, number (%)	112 (2.2)	650 (12.7)	3554 (69.4)	629 (12.3)	174 (3.4)
QT _{NC} (ms)	< 358	358-377	378-417	418-437	> 437

Results

QT INTERVAL ANALYSIS

QT intervals in the whole study population are shown in figure 1. The nomogram method gave an excellent adjustment of the QT intervals for heart rate at all heart rates (fig 2). Mean QT_{NC} values at different heart rate ranges differed less than 1 ms from the reference QT interval in both men and women. The nomogram adjusted the QT intervals confidently in individuals with heart disease, mean QT_{NC} values at different heart rates differed no more than 2 ms from the reference QT interval in subjects with heart disease.

We classified the QT_{NC} values into the five categories as shown in table 1. The QT_{NC} was prolonged by more than 10% (> 430 ms in men and > 437 ms in women) in 3.7% of men and 3.4% of women.

QT_{NC} CATEGORIES, RISK FACTORS, AND SIGNS OF CARDIOVASCULAR DISEASE

Aging prolonged QT_{NC} by 0.1% per year in men and 0.05% per year in women. After adjustment for age, blood pressure (systolic and diastolic) and hypertension were associated with longer QT_{NC} intervals in both men

and women (table 2). In contrast, smoking was associated with shorter QT_{NC} intervals. Prevalence of diabetes was increased in men with moderately (5-10%) prolonged QT_{NC}. Serum cholesterol concentration or body mass index were not associated with QT_{NC}.

Because elevated blood pressure and smoking had opposite effects on QT interval, we analysed non-smoking and normotensive men separately. In non-smoking men the prevalence of elevated blood pressure (140/90 mm Hg or more) in the longest QT_{NC} category was 2.3 times that in the shortest QT_{NC} category. In normotensive men the prevalence of smoking in the shortest QT_{NC} category was 3.0 times that in the longest QT_{NC} category.

QT_{NC} value was associated with the signs of cardiovascular disease. Exclusions from the total study population when forming the "healthy" subpopulation were most common in the category with the longest QT interval (table 2).

MORTALITY

Until the end of 1992, 1848 men (33.0%) and 840 women (16.4%) had died. The respective numbers in the population free from cardio-

Table 2 Age, age adjusted cardiac risk factors, and exclusions in different QT_{NC} categories in the total study population

Risk factor	> 10% shortened	5-10% shortened	Within 5%	5-10% prolonged	> 10% prolonged	P
Men						
Age (years)	42	42	43	45	47	< 0.001
Serum cholesterol (mmol/l)	6.5	6.6	6.5	6.5	6.4	NS
Systolic blood pressure (mm Hg)	133	136	139	140	146	< 0.001
Diastolic blood pressure (mm Hg)	78	80	81	81	84	< 0.001
Hypertension (%)*	2	4	5	6	11	NS
Hypertension (%)*	25	26	26	25	25	< 0.05
Body mass index (kg/m ²)	61	56	53	51	44	< 0.01
Smokers (%)	1.6	1	2	3.3	1.9	< 0.001
Diabetes (%)	9.9	6.7	8.2	12.9	14	< 0.001
Exclusions (%)						< 0.001
Women						
Age (years)	43	43	44	45	47	< 0.001
Serum cholesterol (mmol/l)	6.5	6.6	6.5	6.5	6.5	NS
Systolic blood pressure (mm Hg)	136	135	138	140	144	< 0.001
Diastolic blood pressure (mm Hg)	85	82	83	84	84	< 0.05
Hypertension (%)*	12	5	9	12	18	NS
Hypertension (%)*	26	28	26	26	27	< 0.01
Body mass index (kg/m ²)	17	17	13	10	12	NS
Smokers (%)	1.8	1.8	1.5	1.6	2.3	< 0.05
Diabetes (%)	7.1	4.8	6.3	8.7	9.2	< 0.05
Exclusions (%)						< 0.05

*Blood pressure 170/100 mm Hg or more, or antihypertensive treatment.

Table 3 Relative risks (RR) for disease, and sudden mortality in different QT_{NC} categories of the total study population after adjustment for age and confounding risk factors

	> 10% shortened		5-10% shortened		Within 5%		5-10% prolonged		> 10% prolonged	
	n	RR (95% CI)	n	RR (95% CI)	n	RR	n	RR (95% CI)	n	RR (95% CI)
Men	(n = 131)		(n = 760)		(n = 3764)		(n = 736)		(n = 207)	
All cause	40	1.06 (0.78-1.46)	213	0.99 (0.86-1.15)	1225	1.00	268	0.99 (0.86-1.13)	102	1.33 (1.08-1.63)
Total cardiovascular	20	1.04 (0.67-1.63)	117	1.03 (0.83-1.26)	670	1.00	163	1.07 (0.90-1.27)	63	1.42 (1.09-1.84)
Coronary artery disease	13	0.93 (0.54-1.62)	89	1.07 (0.85-1.35)	484	1.00	114	1.04 (0.84-1.27)	45	1.44 (1.06-1.96)
Sudden death	2	0.73 (0.18-2.96)	14	0.86 (0.49-1.51)	96	1.00	37	1.21 (0.79-1.87)	10	1.50 (0.78-2.89)
Women	(n = 112)		(n = 650)		(n = 3554)		(n = 629)		(n = 174)	
All cause	20	1.19 (0.77-1.85)	96	0.99 (0.80-1.24)	566	1.00	119	1.04 (0.85-1.26)	38	0.98 (0.70-1.37)
Total cardiovascular	8	0.92 (0.45-1.86)	48	1.04 (0.76-1.41)	279	1.00	64	1.10 (0.83-1.44)	27	1.32 (0.89-1.97)
Coronary artery disease	4	0.86 (0.34-2.31)	22	0.87 (0.56-1.37)	150	1.00	38	1.21 (0.85-1.73)	15	1.98 (0.81-2.36)

Relative risks printed in bold differ significantly from the risk in the middle of the QT_{NC} category. CI = Confidence interval.

Table 4 Relative mortality risks (RR) in different QT_{nc} categories in the population free from cardiovascular disease after adjustment for age and risk factors

factors	> 10% shortened		5-10% shortened		Within 5%		5-10% prolonged		> 10% prolonged	
	n	RR (95% CI)	n	RR (95% CI)	n	RR	n	RR (95% CI)	n	RR (95% CI)
Men	(n = 118)		(n = 709)		(n = 3457)		(n = 641)		(n = 178)	
All cause	33	1.02 (0.79-1.44)	189	0.99 (0.85-1.16)	1052	1.00	207	0.93 (0.80-1.08)	78	1.21 (0.96-1.53)
Total cardiovascular	15	0.95 (0.56-1.56)	103	1.05 (0.85-1.30)	559	1.00	118	0.97 (0.80-1.19)	45	1.25 (0.92-1.70)
Coronary artery disease	10	0.89 (0.47-1.66)	78	1.11 (0.87-1.41)	396	1.00	80	0.93 (0.73-1.19)	32	1.29 (0.90-1.85)
Sudden death	1	0.49 (0.09-3.55)	10	0.80 (0.41-1.57)	69	1.00	16	1.00 (0.63-1.88)	7	1.48 (0.67-3.26)
Women	(n = 104)		(n = 619)		(n = 3330)		(n = 574)		(n = 158)	
All cause	16	1.09 (0.66-1.79)	84	1.01 (0.80-1.28)	482	1.00	84	1.07 (0.86-1.33)	28	0.91 (0.62-1.34)
Total cardiovascular	5	0.72 (0.30-1.74)	42	1.08 (0.78-1.51)	231	1.00	54	1.18 (0.87-1.58)	20	1.28 (0.80-2.02)
Coronary artery disease	3	0.78 (0.25-2.50)	20	0.94 (0.58-1.51)	124	1.00	30	1.21 (0.81-1.80)	11	1.32 (0.71-2.46)

CI = Confidence interval.

Table 5 Relative mortality risks (RR) in different QT_{nc} categories in subjects with signs of cardiovascular disease after adjustment for age and risk factors

factors	> 10% shortened		5-10% shortened		Within 5%		5-10% prolonged		> 10% prolonged	
	n	RR (95% CI)	n	RR (95% CI)	n	RR	n	RR (95% CI)	n	RR (95% CI)
Men	(n = 13)		(n = 51)		(n = 307)		(n = 95)		(n = 39)	
All cause	7	1.26 (0.59-2.71)	24	0.99 (0.65-1.53)	173	1.00	61	1.22 (0.91-1.65)	24	1.92 (1.23-3.00)
Total cardiovascular	5	1.30 (0.52-3.21)	14	0.90 (0.51-1.57)	111	1.00	45	1.41 (1.00-2.00)	16	2.12 (1.25-3.59)
Coronary artery disease	3	0.94 (0.30-3.00)	11	0.93 (0.48-1.78)	88	1.00	34	1.38 (0.92-2.08)	13	2.11 (1.14-3.88)
Sudden death	1	1.25 (0.17-9.35)	4	1.15 (0.39-3.39)	27	1.00	11	1.61 (0.79-3.82)	3	2.17 (0.63-7.45)
Women	(n = 8)		(n = 51)		(n = 224)		(n = 55)		(n = 16)	
All cause	5	1.95 (0.78-4.89)	12	0.87 (0.47-1.62)	84	1.00	19	0.91 (0.54-1.52)	10	1.22 (0.62-2.41)
Total cardiovascular	3	1.30 (0.55-5.88)	6	0.83 (0.35-1.95)	48	1.00	10	0.77 (0.38-1.54)	7	1.50 (0.66-3.41)
Coronary artery disease	1	1.20 (0.16-9.06)	2	0.50 (0.12-2.15)	26	1.00	8	1.18 (0.32-2.66)	4	1.62 (0.54-4.87)

Relative risks printed in bold differ significantly from the risk in the middle of the QT_{nc} category. CI = Confidence interval.

vascular disease were 1559 (30.5%) and 710 (14.8%). In the group with signs of cardiovascular disease, 289 (58.4%) of the men and 130 (38.9%) of the women had died. Until the end of 1979, 149 men and 18 women had died suddenly. Because of the small number of cases among women, the relative risks for sudden death could not be confidently calculated and are not presented.

Among the total study population, men with more than 10% prolongation of QT_{nc} intervals had significantly elevated age adjusted relative risk ratios for all cause mortality (1.40), total cardiovascular mortality (1.53), and coronary mortality (1.53). The relative risk was greatest for sudden death (1.63); however, because of the small number of cases the increase in the risk was not significant. Increased death risks were weakened after adjustment for other cardiovascular risk factors, but the order of the risk ratios was the same (table 3). In women, the age adjusted relative risk for total cardiovascular mortality was significantly elevated (1.50) in the longest QT_{nc} group but not for all cause mortality (1.07). After adjustment for other risk factors, no significant differences in relative mortality risks between QT_{nc} categories were found in women.

Normal population

After excluding subjects with signs of cardiovascular disease and adjusting for cardiac risk factors, there was still a tendency of greater mortality in the longest QT_{nc} category, especially in men, but the differences were not sig-

nificant (table 4). However, in a subanalysis of sudden death, the risk ratio was greatest in the lowest heart rate quartile (below 63 beats/min) with more than 10% QT_{nc} prolongation (RR 2.75; 95% confidence intervals (CI) 1.00-7.60).

PROGNOSTIC VALUE OF QT INTERVAL IN MEN WITH HEART DISEASE

We studied the predictive value of the QT_{nc} interval for death in the "excluded" subjects after adjusting for confounding risk factors. In men with signs of cardiovascular diseases the two longest QT_{nc} categories were associated with increased mortality risks (table 5). There was also an increased risk trend in the shortest QT_{nc} category, which was associated with smoking. When men with signs of cardiovascular diseases who smoked were analysed separately, their relative risk in the shortest QT_{nc} category for all cause mortality was 2.85 (95% CI, 1.23-6.63), for cardiovascular mortality it was 3.72 (1.45-9.54) (fig 3), and for sudden death 2.84 (0.36-22.54). However, these risk estimations are based on a small number of cases as only 13 men with heart disease had a more than 10% shortened QT_{nc} (table 5). All five men with cardiovascular death in this group smoked, while only one of the six surviving men smoked. Among the non-smoking men, a short QT interval seemed to protect from cardiovascular death in both "healthy" men and those with signs of cardiovascular disease. A U-shaped risk profile was also seen in smoking women, but the differences in relative mortality risks between the QT_{nc} categories were not significant.

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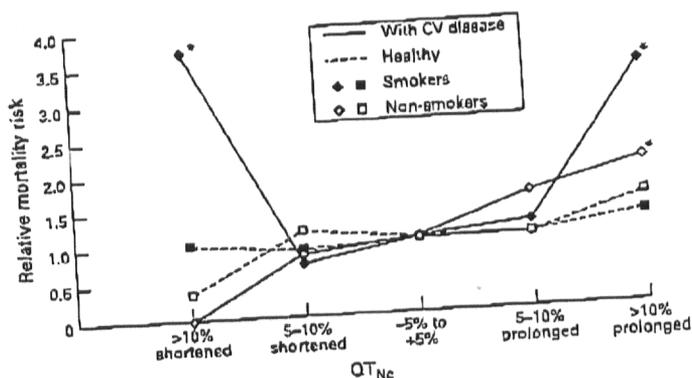


Figure 3 Relative risks for cardiovascular death in different QT_{Nc} categories of smoking and non-smoking men. CV, cardiovascular. *Mortality risk differs significantly from the risk in the middle QT_{Nc} category.

Discussion

These results show that QT interval length is a predictor of mortality in the middle aged Finnish population. The risk is clear in men with signs of cardiovascular disease, whereas in women and in apparently healthy men the risk is weak and associated with elevated blood pressure. The association between prolonged QT interval and mortality risk is strongest in cases with sudden deaths, and weakest in all cause mortality. A short QT interval predicted death in men with heart disease who smoked.

ASSOCIATION BETWEEN QT INTERVAL AND CARDIAC DEATH

The pathophysiological association between the length of the QT interval and death must be mediated mainly via increased susceptibility to malignant ventricular arrhythmias. It is therefore logical for the risk association to be greatest in cases of sudden death, intermediate in other causes of cardiac death, and weakest in all cause death, as was found in the present study. An arrhythmia death is more likely in cardiac patients than in healthy subjects.¹⁸ Thus higher mortality risk ratios are to be expected among subjects with signs of cardiovascular disease and long QT interval compared with healthy subjects with a long QT. However, it is noteworthy that the combination of low heart rate and long QT_{Nc} interval produced an increased risk of sudden death in men free from signs of cardiovascular disease. Some of these five men (0.1% of men without signs of cardiovascular disease) may have represented latent forms of long QT syndrome. Patients with this syndrome usually have low heart rate¹⁹ and no signs of structural heart disease.

ASSOCIATION BETWEEN QT INTERVAL AND CARDIAC RISK FACTORS

Subjects with longer QT_{Nc} had higher blood pressure, possibly because the QT interval is prolonged when left ventricular mass increases.²⁰ Moreover, we found QT interval prolongation to be associated with signs of cardiovascular disease. Subclinical disease has been identified as an independent risk factor for cardiovascular mortality.²¹ In fact, the tendency

to excess mortality even in the "healthy" sub-population with longest QT_{Nc} intervals may reflect the increased risk due to undiagnosed pathological left ventricular hypertrophy or other heart pathology.

Smokers exhibited shorter QT intervals than non-smokers. Smoking increases sympathetic tone,²² and heart rate variability changes in smokers point to decreased vagal control of the heart.²³ Both these effects shorten the QT interval^{24,25} and increase the arrhythmia risk.^{26,27}

The U-shaped risk profile observed among smokers with signs of cardiovascular disease (fig 3) is unexpected. Although this finding is based on a small number of smoking subjects with heart disease, it may explain why short QT interval tended to increase risk in the Framingham study.⁸ When subjects with heart disease suffer acute myocardial infarction the typical automatic rhythm disturbances may have faster rates as a consequence of short QT interval and enhanced sympathetic activity. Combined with reduced vagal activity the risk of ventricular fibrillation then rises.²⁷ On the other hand, a long QT interval, including increased dispersion of repolarisation in diseased heart, favours re-entrant mechanisms of ventricular arrhythmias.²⁸ When this is accompanied by smoking enhanced sympathetic activity, the susceptibility to non-sustained and sustained ventricular tachycardias increases, as recently shown by Huikuri *et al* in patients with arrhythmias.²⁹ Thus, the arrhythmic mechanisms may also contribute to the U-shaped risk profile among smokers. It should be noted that smoking cessation is accompanied by a marked reduction of arrhythmic death in high risk subjects.³⁰ On the other hand, smoking is a strong risk factor and can cause death by many mechanisms other than arrhythmia. In fact, the increased mortality risks and short QT in smokers may reflect heavy smoking.

One limitation of our study is that we were unable to analyse any impact of alcohol consumption or physical activity, both of which may influence the QT interval and mortality.^{30,31} Another limitation is the absence of sudden death data beyond 1979. However, in the case of sudden death the importance of a follow up longer than 10 years may be questioned. For QT interval measurements only leads I, II, and III were used as in other population studies.^{9,32} Thus the measured QT interval may have been too short in some cases.

EARLIER STUDIES AND METHODOLOGICAL ASPECTS

Most studies using Bazett's QT_c values have shown increased mortality in subjects with cardiovascular diseases and long QT interval, as reviewed by Algra *et al*.³³ Our study confirmed this, even when the confounding effect of heart rate was reliably excluded. Whether the QT interval predicts cardiac death even in apparently healthy subjects has been examined in three population studies, but with conflicting results. In the Framingham study no association between QT_c interval and mortality was found,⁹ whereas Schouten *et al*³ and Dekker *et al*¹⁰ found a clear association between cardio-

vascular mortality and prolonged QT_c in men. In healthy populations, the weakness of the QT interval as a risk factor and the use of an inadequate method of adjusting QT values for heart rate may explain the conflicting findings.

The method used to adjust the QT values for heart rate in this study resulted in excellent correction. In contrast, Bazett's QT adjustment reverses the QT-heart rate relation (fig 2), and thus the use of Bazett's QT_c values in risk analysis incorporates the risk of heart rate in addition to the QT duration. In our study, the observed risk order in the modalities of deaths was the same as expected, which we judge to be confirmation of the accuracy of our method. The results are thus linked logically to the underlying theoretical electrophysiological mechanisms.

CLINICAL IMPLICATIONS

The weak association between QT interval and cardiac death in healthy subjects limits its use as a risk factor. Nevertheless, a long QT interval in subjects without signs of cardiovascular disease may reflect subclinical hypertensive or other heart disease, plus an increased risk for sudden death if heart rate is low. However, a long QT interval predicts death in men with heart disease, as does a short QT interval if they smoke. To evaluate the risk of QT duration it is essential for it to be adjusted accurately for heart rate.

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