QT_c Duration is Associated With Levels of Insulin and Glucose Tolerance

The Zutphen Elderly Study

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Prolongation of heart rate–adjusted QT length (corrected QT interval [QT_c]) is associated with elevated risk of coronary heart disease and sudden death. This may have to do with autonomic cardiac control. Because insulin is known to stimulate sympathetic activity, we studied the association of insulin level and glucose tolerance with QT_c. In 1990, 383 elderly men 70–89 years of age without previous myocardial infarctions or known diabetes had a 12-lead electrocardiogram recorded and glucose tolerance determined in the frame of an ongoing follow-up study. QT_c was significantly associated with fasting glucose, insulin, and C-peptide and glucose levels 60 and 120 min after an oral glucose load. For fasting C-peptide and the area under the glucose curve (AUGC), this association could not be explained by the concomitant occurrence of other risk factors of coronary heart disease. Furthermore, fasting C-peptide and the AUGC were independent additive predictors of QT_c duration. The difference in QT_c between men in the extreme quintiles of both variables was 22 ms. QT_c prolongation seems to be part of the insulin resistance syndrome. The association may be explained by increased sympathetic activity induced by high insulin levels. An additional explanation could be an effect of high insulin, impaired glucose utilization, or both on membrane activity of myocardial cells. *Diabetes* 45: 376–380, 1996

A prolonged heart rate–adjusted QT (corrected QT interval [QT_c]) is a risk factor for sudden death in patients with the long-QT syndrome (1), myocardial infarction patients (2), subjects referred for Holter monitoring (3), and healthy men and women (4,5). Relative risks of 2 up to 5 have been reported. The length of the QT interval, which is easily obtained from a standard resting electrocardiogram, represents the time interval between the start of activation of the ventricle and completion of its repolarization. Two mechanisms have been formulated to explain the elevated risk in the presence of QT_c prolongation. In the first, dispersion of repolarization as a consequence of predominance of left sympathetic nerve activity is held responsible for a high risk of ventricular fibrillation (6). In the second, disturbed myocardial membrane function is believed to lead to electrical instability (7). Whatever the underlying mechanism, sympathetic stimulation unopposed by vagal activity may induce ventricular electrical instability, resulting in a high risk of arrhythmia and sudden death (8). Since insulin is known to increase sympathetic activity (9–11), hyperinsulinemia may be a determinant of QT_c prolongation.

Hyperinsulinemia and insulin resistance have been implicated as key factors in coronary heart disease etiology (12). They provide a basis for the clustering of several risk factors. Genetic predisposition, lack of physical activity, and positive energy balance, followed by increased body weight, result in high insulin levels. Hyperinsulinemia notably increases triglyceride level and lowers HDL cholesterol. QT_c prolongation and its sequelae may be an additional feature of this cluster. Therefore, we studied insulin, C-peptide, and glucose levels during an oral glucose tolerance test in relation to QT_c in a cohort of elderly Dutch men.

RESEARCH DESIGN AND METHODS

Subjects. The Zutphen Elderly Study is the continuation of the Zutphen Study, which is the Dutch contribution to the Seven Countries Study (13). In 1985, the survivors of the original cohort (555 men) and an additional sample of 711 men of the same age were invited to take part in the elderly study. Of these 1,266 men ages 65–84 years, 939 (74%) participated. The data of the present study were collected 5 years later, at the follow-up medical examination. In 1990, 560 of 718 surviving men (78%) took part in the study. Fasting levels of glucose and insulin were determined in 485 men, a 12-lead resting electrocardiogram was recorded in 549 men, and both were performed in 478 men. Because the QT interval prolongation may be a consequence of myocardial infarction (2) or diabetic neuropathy (14,15), men with previous myocardial infarction (64 men) or known diabetes (31 men) were excluded. Previous myocardial infarction was defined when subjects met two of the following three criteria: *1*) an episode of severe chest pain lasting for >20 min and not disappearing during rest; *2*) electrocardiographic changes corresponding to Minnesota code (16) 1.1 (major Q waves) or code 1.2 accompanied by 5.1 or 5.2 (lesser Q waves and major T wave findings); or *3*) specific enzyme level elevations. The remaining study population consisted of 383 elderly men. The procedures used in the Zutphen Study were approved by the Medical Ethical Committee of the Medical Faculty, University of Leiden.

Oral glucose tolerance test and electrocardiography. An oral glucose tolerance test was performed according to World Health Organization guidelines (17). In the morning, a fasting blood sample was obtained. A glucose load of 75 g was then given, and additional blood

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Received for publication 17 May 1995 and accepted in revised form 26 October 1995.

AUGC, area under the glucose curve; QT_c, corrected QT interval.

TABLE 1
Population characteristics according to diabetic category by World Health Organization guidelines

	Normal	Impaired glucose tolerance	Newly diagnosed diabetes
n	306	43	34
Age (years)	75.4 ± 4.4	77.7 ± 5.3*	74.4 ± 4.0†
BMI (kg/m^2)	25.4 ± 3.1	26.6 ± 4.2*	26.7 ± 3.2
Subscapular skinfold (mm)	16.8 ± 6.0	19.8 ± 6.8*	20.9 ± 6.6*
Systolic blood pressure (mmHg)	149 ± 22	155 ± 19	158 ± 21*
Diastolic blood pressure (mmHg)	82 ± 11	84 ± 12	87 ± 14*
HDL cholesterol (mmol/l)	1.18 ± 0.28	1.16 ± 0.34	1.05 ± 0.23*
Total cholesterol (mmol/l)	6.10 ± 1.06	5.83 ± 1.18	6.07 ± 1.28
Serum triglycerides (mmol/l)	1.35 ± 0.71	1.55 ± 0.85	1.75 ± 0.72*
Physical activity (min/week)	649 ± 551	456 ± 418	477 ± 388
Heart rate (beats/min)	74 ± 13	78 ± 15	79 ± 17*
Smoking (cigarettes/day)	2.66 ± 5.76	2.21 ± 5.29	2.56 ± 7.33

Values are means ± SD. *$P < 0.05$, significantly different from normal group; †$P < 0.05$, significantly different from impaired glucose tolerance group (Tukey test for both).

samples were taken after 1 and 2 h. One man did not complete the oral glucose tolerance test. Samples were collected in tubes with sodium fluoride. Plasma glucose was determined using the hexokinase method. Insulin was measured in serum using a radioimmunoassay from Pharmacia (Uppsala, Sweden). Within- and between-run coefficients of variation ranged from 6 to 7%. Levels of fasting C-peptide, a measure of insulin secretion, were determined in serum using a ^{125}I radioimmunoassay from Incstar (Stillwater, MN) after treatment with 25% polyethyleneglycol. The within-run coefficient of variation was 6.5%, and the between-run coefficient was 14%.

The areas under the postload glucose and insulin curves were calculated using the trapezoidal rule: (fasting level × 30 min) + (1-h level × 60 min) + (2-h level × 30 min).

Standard resting 12-lead electrocardiographic recordings and assessments of cardiovascular risk factors were performed according to the protocol of the Seven Countries Study (13). The electrocardiograms were classified and coded according to Minnesota codes (16). QT and RR intervals were measured on 12-lead resting electrocardiograms (paper speed 25 mm/s) using a digitizing tablet (Calcomp) and a personal computer. The resolution of the tablet is 100 lines/mm and the reproducibility is 0.25 mm (corresponding to 10 ms). QT intervals were read from three leads: V2, V6, and I, II, or III, in whichever the longest QT was observed. In each lead, QT intervals and the preceding RR intervals were measured in three consecutive normal complexes to reduce measurement error and because QT duration may slightly vary from beat to beat because of concomitant variability of heart frequency (18). The beginning of the QT interval was defined as the first deflection of the QRS complex. The end of the T wave was defined as the point of maximal change in the slope as the T wave merges with the baseline (19). All electrocardiograms were measured by one observer who was blinded from other information.

Other variables. Systolic and diastolic blood pressure were measured twice at the end of the physical examination on the right arm with the subject in supine position (13). The mean of duplicate measurements was used in the analyses. Nonfasting serum total and HDL cholesterol and fasting triglycerides were determined enzymatically at the standardized Lipid Laboratory at the Department of Human Nutrition, Agricultural University Wageningen, The Netherlands (20–22). BMI (weight/height^2) was calculated. Subscapular skinfold thickness was measured in duplicate with a Harpenden caliper at the right side of the body (13). Smoking habits were assessed using a standardized questionnaire. A 15-item questionnaire on physical activities, designed for retired men (23), was used to calculate minutes per week spent on activities like walking, gardening, odd jobs, sports, hobbies, and work. Participants were requested to bring all medication to the study center. Use of medication was assessed from the medication information and discussion between the physician and the participant at the medical examination.

Statistical analysis. QT intervals were adjusted for heart rate according to Bazett's formula (24). The means of three consecutive heart rate–adjusted QT intervals were calculated from each lead. The longest mean QT_c of these three leads (V2, V6, and lead I, II, or III) was used for the analysis. QT_c was described in categories of glucose tolerance. Men with a QT_c of 420 ms or more were considered to have a longer QT_c (4,5).

Regression analysis was carried out using QT_c as dependent variable. The analyses were performed separately for fasting glucose, insulin, and C-peptide and glucose and insulin responses to the glucose load, respectively. First, age and indicators of carbohydrate metabolism were evaluated one at a time. Because they were possible determinants of insulin level, BMI, subscapular skinfold thickness, smoking, and physical activity were further included in the models. Subsequently, diastolic blood pressure, total and HDL cholesterol, and triglycerides were added as well. Finally, the variables that significantly ($P < 0.05$, Wald test) contributed to the QT_c variation in the separate models of the indicators of carbohydrate metabolism were combined in one model. Because some variables were not normally distributed, analyses were repeated after log transformation. The results were almost identical. Therefore, only the coefficients of the nontransformed analyses are presented. All data analyses were performed on a VAX computer with SAS software (25).

RESULTS

In the present study, among 383 healthy elderly men aged 70–89 without previous myocardial infarctions or known diabetes, 43 had impaired glucose tolerance and 34 met diagnostic criteria for diabetes. Coronary heart disease risk factor levels were most favorable in men with normal glucose tolerance and least favorable in newly diagnosed diabetic patients (Table 1).

The mean QT_c was 413 ± 29 ms. QT_c was longer and the proportion of men with QT_c 420 ms or more was higher in men with impaired glucose tolerance or newly diagnosed diabetes compared with men with normal glucose tolerance (Table 2).

All indicators of carbohydrate metabolism except the area under the insulin curve were significantly correlated with QT_c. A significant correlation was also observed between QT_c on one hand and BMI, diastolic blood pressure, serum triglycerides, and subscapular skinfold thickness on the other (age-adjusted Pearson correlation coefficients [r] of 0.23, 0.17, 0.13, and 0.17, respectively). The associations of QT_c with physical activity and HDL cholesterol were somewhat weaker ($r = -0.11$ for both). Total serum cholesterol and smoking were not significantly associated with QT_c. Adjusted for coronary heart disease risk factors, fasting C-peptide and glucose levels after the glucose load were still significant contributors to QT_c length, although the estimates were somewhat lower (Table 3). In the most extensive models, fasting C-peptide, area under the glucose curve (AUGC), age, BMI, and diastolic blood pressure were the strongest predictors of QT_c. When these five variables were combined in one regression model, both AUGC and fasting C-peptide remained significant independent predictors of

TABLE 2
QT_c and indicators of carbohydrate metabolism according to diabetic category by World Health Organization guidelines

	Normal	Impaired glucose tolerance	Newly diagnosed diabetes
QT_c (ms)	410 ± 28	418 ± 25	429 ± 36*
$QT_c \geq 420$ ms (%)	33	49	59‡
Plasma glucose (mmol/l)			
Fasting	5.6 ± 0.5	6.0 ± 0.6*	8.1 ± 2.1*†
60-min	8.5 ± 2.2	11.1 ± 1.7*	15.4 ± 2.8*†
120-min	5.4 ± 1.3	9.0 ± 1.0*	13.9 ± 3.6*†
Area under curve (mmol · min · l^{-1})	839 ± 156	1,119 ± 122*	1,579 ± 305*†
Serum insulin (pmol/l)			
Fasting	62.8 ± 27.1	86.3 ± 36.5*	100.8 ± 67.3*
Area under curve (pmol · min · l^{-1})	36,756 ± 16,154	49,785 ± 20,495*	36,620 ± 23,932*
Fasting C-peptide (nmol/l)	0.68 ± 0.26	0.88 ± 0.43*	1.03 ± 0.65*

Values are means ± SD. *$P < 0.05$, significantly different from normal group; †$P < 0.05$, significantly different from impaired glucose tolerance group (Tukey test for both). ‡Significant by χ^2 test.

QT_c. This is illustrated in Fig. 1, where average QT_c is shown in combined categories of quintiles of fasting C-peptide and AUGC adjusted for age, BMI, and diastolic blood pressure.

When analysis was confined to subjects with normal glucose tolerance, the association between QT_c and glucose tolerance was smaller and no longer significant. The relationships with fasting insulin and C-peptide were stronger (regression coefficients in age-adjusted model: 0.19 ms · $pmol^{-1} \cdot l^{-1}$, $P = 0.002$, and 21.1 ms · $nmol^{-1} \cdot l^{-1}$, $P = 0.0004$, respectively), and the area under the insulin curve was significantly associated with QT_c as well (regression coefficient: 0.00025 ms · $pmol^{-1} \cdot min \cdot l^{-1}$, $P = 0.01$).

To exclude the possibility that the observed associations result from the use of medication or from prevalent heart disease, analysis was repeated after exclusion of subjects using antihypertensive medication, antiarrhythmics, β-blocking agents, calcium antagonists, or ACE inhibitors (60 men) or having electrocardiographic abnormalities (Minnesota codes 1.1, 1.2, 4.1, 4.2, 5.1, 5.2, 7.1, 7.2, 7.4) (95 men). A total of 133 men were excluded, 103 with normal glucose tolerance, 16 with impaired glucose tolerance, and 14 with newly diagnosed diabetes. The resulting coefficients for fasting C-peptide and for the glucose response after the glucose test from regression model 3, which adjusts for all other risk factors, were 10.5 ($P = 0.04$) and 0.013 ($P = 0.03$), respectively.

DISCUSSION

In the present study, both insulin secretion (fasting C-peptide) and glucose tolerance were independently associated with the length of the QT_c in the standard 12-lead electrocardiogram in men 70–89 years of age.

This study was conducted in elderly men because disturbances of glucose metabolism are rather prevalent in this age group. Our study population represents relatively healthy elderly men who were able to come to the study center by their own means.

It is recommended to measure the longest QT in the 12-lead electrocardiogram (26). Because that was not feasible in the present study, leads I, II, or III, lead V2, and lead V6 were selected. The axes of these leads are nearly orthogonal, optimizing the ability to detect electrical activity in any direction. Because one person who was unaware of other information measured all QT intervals, bias because of differential error in QT measurement and interobserver differences is impossible.

QT prolongation has been reported in diabetic patients with autonomic neuropathy (14,15). Subjects with newly diagnosed diabetes or impaired glucose tolerance possibly already had diabetic neuropathy. This possibility cannot be ruled out for the association between QT_c and glucose tolerance. However, the association of insulin levels with QT_c was significant in subjects with normal glucose tolerance, which indicates this relationship cannot be attributed to diabetic autonomic neuropathy.

The QT interval may also be affected by prevalent heart disease or use of medication. However, this does not seem to explain the observed associations, because they persisted after exclusion of men with these conditions.

In previous studies, a more than twofold risk of death from

TABLE 3
Regression coefficients of indicators of carbohydrate metabolism on QT_c

Independent variable	Age-adjusted	Model 2	Model 3
Glucose (mmol/l)			
Fasting	3.37*	2.43	2.16
60-min	1.88*	1.55*	1.43*
120-min	1.98*	1.63*	1.46*
Area under curve (mmol · min · l^{-1})	0.022*	0.018*	0.016*
Insulin			
Fasting (pmol/l)	0.15*	0.09	0.06
Area under curve (pmol · min · l^{-1})	0.00016	0.00004	−0.00001
Fasting C-peptide (nmol/l)	19.1*	13.4*	11.3*

Regression coefficients are change of QT_c in milliseconds per unit of the independent variable. Model 2 was adjusted for age, BMI, current smoking, minutes of physical activity, and subcapsular skinfold. Model 3 was adjusted for all previous variables and for diastolic blood pressure, serum triglycerides, serum total cholesterol, and HDL cholesterol. *$P < 0.05$, significantly different from 0.

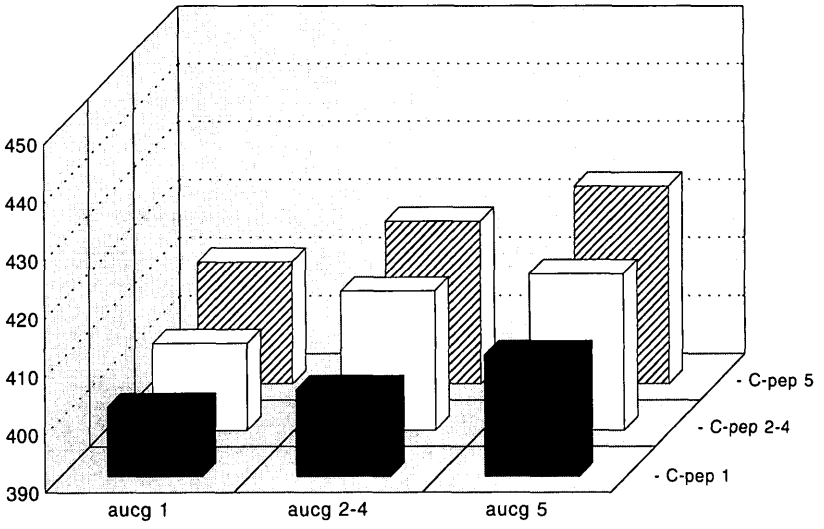

FIG. 1. QT_c in quintile categories of plasma C-peptide (C-pep) and AUGC adjusted for age, BMI, and diastolic blood pressure.

coronary heart disease was reported in apparently healthy individuals with a QT_c of 420 ms or more (4,5). In the present study, the proportion of men with a longer QT_c was twofold in the highest quintile of fasting C-peptide compared with the men in the lowest quintile and in men with newly diagnosed diabetes compared with men with normal glucose tolerance. The elevated risk in subjects with QT_c prolongation has been explained by ventricular electrical instability as a consequence of sympathetic stimulation unopposed by vagal activity (8). The observed association might be taken as evidence for the hypothesis that insulin-induced sympathetic activity may be one of the precipitating factors (8,9–11). Also, an association of QT_c with components of the "multiple metabolic cluster" or "insulin-resistance syndrome" (12) may provide an explanation for the previously reported elevated incidence of (nonfatal) myocardial infarction in men with QT_c prolongation (5). In the present study, cardiovascular risk factors including QT_c exhibited a tendency to cluster. Particularly BMI was observed to be an important predictor of QT_c. Scherrer et al. (27) reported body fat to be a major determinant of muscle sympathetic nerve discharge, and both were positively correlated with fasting insulin levels. Furthermore, weight loss is reported to lead to lower sympathetic activity and blood pressure (28), which have been attributed to a fall in insulin level. In the Normative Aging Study, the association between urinary norepinephrine excretion and hyperinsulinemia was partially explained by BMI (29). Interestingly, however, in our study, fasting C-peptide and the AUGC still contributed to QT_c prediction after adjustment for BMI, while insulin did not. Perhaps C-peptide, as a measure of insulin secretion, is a better indicator for the effect of insulin on the sympathetic nervous system than is fasting insulin level, which results from both insulin secretion and insulin uptake by all tissues.

Besides the association of QT_c with insulin, possibly mediated through sympathetic activity, these data suggest an effect of the disturbed glucose metabolism on the myocardium, as manifested in the association between glucose tolerance and QT_c. Furthermore, the insulin response to a glucose load is a good indicator of insulin resistance in normoglycemic subjects only (30). Therefore, the association between QT_c and the insulin response to the glucose load in men with normal glucose tolerance, but not in men with newly diagnosed diabetes or impaired glucose tolerance, suggests an effect of insulin resistance. Animal studies have shown that glucose-insulin infusion reduces ischemia-induced extracellular potassium accumulation and improves the associated conduction delay (31). Altered ion exchange activities may be induced by reduced myocardial glucose uptake resulting from impaired insulin binding (32). The observed additive effects of C-peptide, indicating hyperinsulinemia, and the AUGC, indicating disturbed glucose uptake, suggest that both mechanisms may contribute to a longer QT_c. However, it cannot be excluded that an unknown feature is responsible for QT_c prolongation, elevated insulin, and impaired glucose tolerance.

If QT_c is affected by carbohydrate metabolism, this may have implications for its use as an indicator of autonomic neuropathy in diabetic patients. In two recent studies among type I diabetic patients (33) and among type I diabetic identical twins (34), QT_c length did not correlate with the severity of autonomic neuropathy as indicated by other cardiovascular autonomic tests. However, diabetic twins did have longer QT_c than their nondiabetic co-twins, independent of autonomic neuropathy. This is in line with the present observation in subjects with impaired glucose tolerance and type II diabetes, and it may contribute to our understanding of the high mortality in diabetic patients. The excess ischemic heart disease mortality in diabetic patients in the National Health and Nutrition Examination Survey I epidemiological follow-up study (35) and the Zutphen Study (36) and the bad prognosis after myocardial infarction in diabetic patients in the Framingham Study (37) could not be attributed to differences in coronary heart disease risk factors. Ventricular instability, as manifest in QT_c prolongation, may add to the elevated risk.

In conclusion, the insulin resistance syndrome seems to involve myocardial repolarization. At least two mechanisms, e.g., insulin-induced sympathetic activity and reduced glucose uptake, may be responsible for this. Further research is needed to clarify this issue.

ACKNOWLEDGMENTS

This study was made possible by Grant 90.102 from The Netherlands Heart Foundation and grants from The Netherlands Prevention Foundation and the National Institute of Public Health and Environmental Protection.

We thank E.B. Bosschieter, MD, A.M. Thomassen-Gijsbers, and B.P.M. Bloemberg, PhD, for their efforts in the field work; G. Loeber, PhD, and L. Elvers for the analyses of insulin and C-peptide; the Laboratory of Clinical Chemistry and Haematology of the Nieuwe Spittaal Hospital in Zutphen; J.J.P.M. Jaspers, MSc, for the analyses of glucose; and R.E.J.M. van Rensen, MSc, for the electrocardiogram measurements. Without the continued interest of the Zutphen population, the study would have been impossible.

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