

RR interval variation, the QT interval index and risk of primary cardiac arrest among patients without clinically recognized heart disease

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Aims Autonomic tone influences RR interval variation (RRV) and the heart rate-corrected QT interval index (QTI). Together, QTI and RRV may improve characterization of sympathovagal control and estimation of risk of primary cardiac arrest. We therefore examined effects of QTI and short-term RRV from standard, 12-lead electrocardiograms on risk of primary cardiac arrest among persons without clinically recognized heart disease.

Methods and Results We analysed data from a case-control study of risk factors for primary cardiac arrest among enrollees in a large health plan. Cases (n=505) were enrollees aged 18 to 79 years without history of heart disease who had primary cardiac arrest between 1980 and 1994. Controls (n=529) were a demographically similar, stratified random sample of enrollees. We determined enrollee characteristics from ambulatory medical records, QTI and RRV from standard, 12-lead electrocardiograms, and medication use from automated pharmacy files. Low and high values of QTI and RRV were designated as the first and fifth quintiles of QTI (96% and 107%) and RRV (35 ms and 120 ms) among controls. In a model adjusting for clinical predictors of primary

cardiac arrest, RRV modified the association between QTI and risk of primary cardiac arrest ($P=0.05$). Compared to high RRV and low QTI, the risk of primary cardiac arrest (odds ratio [95% CI]) was 0.95 [0.73–1.23] at low RRV and QTI, 1.23 [0.97–1.57] at high RRV and QTI, and 1.55 [1.16–2.06] at low RRV and high QTI. Risk remained elevated after adjustment for other electrocardiographic predictors and medication use.

Conclusion Autonomic dysfunction, characterized by high QTI and low RRV on the standard, 12-lead electrocardiogram, is associated with an increased risk of primary cardiac arrest among persons without clinically recognized heart disease.

(*Eur Heart J* 2001; 22: 165–173, doi: 10.1053/euhj.2262.2175)

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Key Words: Autonomic function, cardiac arrest, electrocardiography, risk factors.

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Introduction

Several measures are available for predicting the extent of QT interval prolongation at a given heart rate. Although the predictive accuracy of the heart rate-corrected QT interval index (QTI)^[1] exceeds that of the

heart rate-corrected QT interval (QT_c)^[2], the measures share at least two important properties. QT_c and QTI are related directly to risk of cardiac arrest^[3,4] and each depends on autonomic tone. Both measures, for instance, decrease following intravenous administration of beta-antagonists and increase following intravenous administration of high dose muscarinic-antagonists like atropine^[5–11]. Furthermore, QT_c is strongly associated with diabetic autonomic failure^[12], but when confounding is taken into consideration, QTI detects pharmacologically simulated autonomic dysfunction with relative sensitivity and accuracy^[11].

Revision submitted 1 May 2000, and accepted 3 May 2000.

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The observation that measures of heart rate variability derived from 20 s and 24 h electrocardiographic recordings are strongly correlated suggests that autonomic tone also is reflected in short-term measures of heart rate variability that can be derived from the standard, 12-lead electrocardiogram^[13]. A precedent for using these short-term measures of heart rate variability exists in population-based studies of cardiac end-points. Lower, short-term measures of heart rate variability, for example, were associated with higher cardiac mortality in the Men Born in 1913, Zutphen and Rotterdam cohorts^[14–16].

The prognostic value of low heart rate variability following myocardial infarction putatively depends on its ability to reflect tonic activity of cardiac parasympathetic efferents, the post-infarction decline of which may be arrhythmogenic^[17,18]. Although inverse associations between heart rate variability, incident coronary heart disease and all-cause mortality in relatively healthy populations suggest that the prognostic value of low heart rate variability is not restricted to the peri-infarction period^[19,20], it is unknown whether heart rate variability is associated with risk of primary cardiac arrest in these populations. We therefore examined whether RR interval variation (RRV), a short-term measure of high-frequency variation in heart rate derived from the 12-lead electrocardiogram, contributes to the assessment of risk for primary cardiac arrest in a population without clinically recognized heart disease. Based on previous findings^[4] and the assumption that information about QTI and RRV could improve characterization of sympathovagal control of the heart, we examined their separate and combined effects on risk of primary cardiac arrest.

Methods

Setting and design

Data were originally collected for a population-based, case-control study of the relationship between risk of primary cardiac arrest and medications prescribed to enrollees in a large health plan within Washington state (Group Health Cooperative of Puget Sound, GHC).

Selection of cases

Potential cases (n=785) were GHC enrollees (for ≥ 1 year or ≥ 4 prior visits) aged 18 to 79 years with incident, out-of-hospital primary cardiac arrest between 1 January 1980 and 31 December 1994 and no prior history of clinically recognized heart disease (atherosclerotic heart disease, myocardial infarction, angina pectoris, congestive heart failure, valvular heart disease, arrhythmia, syncope, cardiomyopathy, coronary angioplasty, coronary artery bypass graft or a prescription for digoxin or nitrates in the year before the index date).

Primary cardiac arrest was identified from emergency medical service (EMS) and GHC death records^[21]. It was defined as a sudden, pulseless condition without a known non-cardiac cause (metastatic cancer, brain tumour, end-stage liver disease, end-stage kidney disease or respiratory failure). Clinical information was abstracted from the death certificate, EMS incident report, autopsy report and ambulatory care medical record, which were reviewed by at least one physician when case eligibility was in question. The index date for cases was defined as the date of primary cardiac arrest. Standard, 12-lead electrocardiograms recorded before the index date were available in the ambulatory care medical record for 64% of potential cases, of whom all were included in the study sample (n = 505). The index date–electrocardiogram date interval was 4.7 ± 4.9 years in this group.

Selection of controls

Potential controls (n=1,833) were a stratified, random sample of GHC enrollees frequency-matched to cases on age (decade), gender and index year. Like potential cases, they had no history of heart disease or major non-cardiac co-morbidity. An index date was assigned randomly to controls from the distribution of case index dates. Standard, 12-lead electrocardiograms recorded before the index date were available in the ambulatory care medical record for 66% of potential controls, of whom all diabetic (n=57) and a random selection of non-diabetic enrollees (n=472) were included in the study sample (n=529). The index date–electrocardiogram date interval was 5.4 ± 4.9 years in this group.

Electrocardiographic methodology

Recording conditions (other than the resting, supine state of patients) were non-standardized because we retrospectively obtained 12-lead electrocardiograms from ambulatory care medical records for the purposes of this study. We sent the electrocardiograms, which varied in duration from 10 s to 30 s, to the Epidemiological Cardiology Research Center (EPICARE), Wake Forest University School of Medicine for measurement and classification according to Novacode criteria^[22]. Measurement and classification were blinded to case-control status. The following continuous measures were obtained from each electrocardiogram using calipers: median RR interval (RR, ms), RR interval range, henceforth referred to as RRV (ms), and maximum QT interval (QT, ms). RR intervals were obtained from pairs of complete, normally conducted complexes originating in the sinus node. QT intervals were obtained under a large-field anastigmatic lens with fourfold magnification. Heart rate (HR, $\text{beats} \cdot \text{min}^{-1}$) = $60\,000 \div \text{RR}$ and the QT interval index (QTI, %) = $(\text{QT} \div 656) \times$

(HR+100) were derived from the above measures^[1]. Where noted, the JT interval index ($JTI = [JT \div 518] \times [HR + 100]$) was substituted for QTI in enrollees with a QRS interval >120 ms (bundle branch blocks)^[23]. For comparison, the QT interval was corrected for HR according to the formula of Bazett: $QT_c = QT \div RR^{1/2}$ ^[2].

Using Novacode algorithms, we also measured the severity of ventricular ectopy by counting ventricular ectopic beats, left ventricular hypertrophy by estimating left ventricular mass (g), and ischaemia, infarction and repolarization abnormality by scoring ST segment depression, Q waves and T wave negativity^[22]. We estimated left ventricular mass using the gender-specific formula: $LVM = c_1 \times (|R_{aVL}| + |V_3|) + c_2 \times (BW^{1/2} - c_3)$, where R=R wave amplitude (μV), S=S wave amplitude (μV), BW=body weight (kg), $c_1 = 0.025$, $c_2 = 21.54$ and $c_3 = 2.7$ (men) and $c_1 = 0.024$, $c_2 = 17.20$ and $c_3 = 2.1$ (women).

Reliability of electrocardiographic measures

We randomly selected 49 case and 49 control electrocardiograms for blinded re-reading. Absolute mean inter-reading differences in RRV and QTI were 4 ± 39 ms ($P = 0.48$) and $0 \pm 10\%$ ($P = 0.78$) among cases and 9 ± 31 ms ($P = 0.06$) and $0 \pm 8\%$ ($P = 0.68$) among controls, respectively. The intra-class correlation coefficients among cases were 0.83 for RRV and 0.59 for QTI. Corresponding values were 0.79 and 0.56 among controls.

Clinical characteristics

We abstracted information on age (years), race, gender and body mass index ($kg \cdot m^{-2}$); physician-diagnosed hypertension, diabetes mellitus, current smoking habit and hypercholesterolaemia; and most recent systolic blood pressure (mmHg), diastolic blood pressure (mmHg), plasma glucose ($mmol \cdot dl^{-1}$), total cholesterol ($mmol \cdot l$), serum creatinine ($\mu mol \cdot l^{-1}$) and potassium ($mmol \cdot l^{-1}$) from ambulatory care medical records. We randomly selected 71 ambulatory care medical records for blinded reabstraction. Absolute mean inter-abstraction differences in continuous clinical exposures were small. *P* values associated with the differences were large (0.11–0.97) as was inter-abstraction agreement (κ) for dichotomous clinical exposures (0.91–1.00).

Medication use

We used GHC computerized pharmacy records to determine drug treatment at the index date. Based on the results of earlier studies, we focused on drugs used to lower blood pressure (angiotensin converting enzyme inhibitors, beta adrenergic antagonists, calcium channel

antagonists, thiazide diuretics, thiazide / potassium sparing diuretic combinations, vasodilators and other anti-hypertensives) and loop diuretics^[24–26]. Assuming 80% compliance, we determined current drug treatment from the prescription–index date interval (d), dosing instructions and a formula for run-out time: $RT (d) = \text{number of pills prescribed} \div (\text{number of pills per day} \times 0.8)$, where number of pills per day = dosing frequency \times number of pills per dose. We also assumed that enrollees were taking a prescribed drug if the run-out date was no greater than one day before the index date. Only 1% of dosing instructions from the computerized pharmacy record disagreed with those abstracted from the ambulatory care medical record.

Statistical analysis

We evaluated the homogeneity of proportions with the chi-square test and difference in means with the t-test. All statistical tests were two sided with an $\alpha = 0.05$. Based on distributions of RRV and QTI in controls, we determined values of the first through fifth quintiles. We designated low and high values as the first and fifth quintile of each measure. We then estimated the relative risk of primary cardiac arrest (odds ratio [OR], 95% confidence interval [CI]) using conditional logistic regression (Statistical Analysis Software, SAS[®] Institute, Cary, NC). All models included age <50 years, gender, index year (5 year interval) and diabetes as stratum variables to account for our stratified random sampling of controls and reading of electrocardiograms. We estimated risk before and after adjustment for clinical predictors of primary cardiac arrest. Where appropriate, we added squared terms to models based on significance of the log likelihood statistic. On the same basis, we added the product term $QTI \times RRV$ to a model already containing QTI and RRV, thereby permitting risk estimation at several combinations of these continuous variables. We calculated Rothman's synergy index for models including product terms. In the absence of a statistically significant multiplicative interaction, a positive synergy index suggests that the log likelihood statistic failed to detect interaction on the additive scale^[27]. We individually included the remaining clinical, electrocardiographic and drug characteristics in the latter model to evaluate the potential for residual confounding. Because clinical characteristics of enrollees were related to electrocardiogram availability, we also weighted our models for the reciprocal of the probability of electrocardiogram availability (predicted separately for cases and controls by their clinical characteristics) to evaluate the potential impact of selection bias on reported measures of association.

Results

Cases were more likely than controls to have hypertension, a higher plasma glucose and a current smoking

Table 1 Population characteristics (% or mean \pm SD) in cases and controls

Characteristic		Cases n=505	Controls n=529	P	
Clinical	Age (years)	64.4 \pm 10.7	66.3 \pm 8.8	0.69	
	Female (%)	32	32	—	
	Hypertension (%)	45	29	<0.01	
	Diastolic blood pressure (mmHg)	82 \pm 12	81 \pm 10	0.05	
	Diabetes (%)	11	11	—	
	Glucose (mmol . l ⁻¹)*	6.7 \pm 3.2	6.3 \pm 3.0	0.01	
	Current smoker (%)	39	16	<0.01	
	Body mass index (kg . m ⁻²)	27 \pm 5	27 \pm 4	0.43	
	ECG	Heart rate (beats . min ⁻¹)	74 \pm 16	70 \pm 14	<0.01
		Ventricular ectopic beats (%)	7	5	0.11
Left ventricular mass (g)		163 \pm 30	160 \pm 28	0.10	
T wave negativity (%)		19	9	<0.01	
ST segment depression (%)		20	8	<0.01	
Q wave (%)		27	18	<0.01	
Drug	Beta antagonist (%)	14	7	<0.01	
	Calcium antagonist (%)	5	2	<0.01	

SD=standard deviation. One case was missing a value for diastolic blood pressure, 29 cases and 33 controls for glucose, 30 and 19 for current smoker, 29 and 23 for body mass index, and 9 and 5 for heart rate. *Values of glucose in mg . dl⁻¹, were 120 \pm 58 and 113 \pm 54 for cases and controls, respectively.

habit (Table 1). Other clinical characteristics, including gender and diabetes (matching variables), were similar across case-control status. Higher heart rates, T wave negativity, ST segment depression and Q waves were more common among cases. Cases were, in addition, twice as likely as controls to be taking beta or calcium channel antagonists. Case-control differences were smaller for the other antihypertensive medications and loop diuretics (not shown).

Mean QTI was higher and RRV lower among cases than controls (Fig. 1(a) and (b)). In addition, QTI more commonly exceeded traditional thresholds for prolongation (25% vs 13% >110%, P <0.01) among cases than controls. Cases also were more likely than controls to meet electrocardiographic criteria for the long QT syndrome (QT_c \geq 450 ms [32% vs 19%, P <0.01], \geq 460 ms [24% vs 12%, P <0.01] or \geq 480 ms [15% vs 5%, P <0.01])^[28].

Among controls, the first and fifth quintiles of QTI and RRV were 96% and 107% and 35 ms and 120 ms, respectively. Enrollee characteristics were associated with the QTI quintile (Table 2) and in many instances, the associations were opposite in direction to those between the same characteristics and the RRV quintile (Table 3). Female gender, hypertension and diabetes, for example, were more common at high than low QTI, but less common at high than low RRV. Whereas glucose and heart rate were directly associated with QTI, they were inversely associated with RRV. Electrocardiographic evidence of ischaemia and infarction was more common at high QTI, but in contrast, low RRV. Furthermore, use of beta and calcium channel antagonists was directly related to QTI, yet inversely related to RRV.

Addition of a product term to an adjusted model of primary cardiac arrest on RRV and QTI revealed a

significant RRV \times QTI interaction (P =0.05). Compared to high RRV and low QTI, risk (OR [95% CI]) was 0.95 [0.73–1.23] at low RRV and QTI, 1.23 [0.97–1.57] at high RRV and QTI, and 1.55 [1.16–2.06] at low RRV and high QTI. Risk remained elevated at low RRV and high QTI after further adjustment for electrocardiographic indicators of ischaemia, infarction and abnormal repolarization, although the magnitude of the increase in risk, 1.34 [1.00–1.81], and the significance of the RRV \times QTI interaction, P =0.11, were reduced (Table 4). However, the synergy index for this model exceeded unity (+5.67).

Exclusion of enrollees <40 years of age only slightly altered the magnitude of the estimates. The additional effects of adjustment for race, hypercholesterolaemia, total cholesterol (mmol . l⁻¹), serum creatinine (μ mol . l⁻¹) or potassium (mmol . l⁻¹) were negligible. Logarithmic transformation of RRV and QTI, substitution of JTI for QTI in enrollees with bundle branch block, or exclusion of enrollees with atrial fibrillation or flutter, second- or third-degree atrioventricular block or a wandering atrial pacemaker also had little effect. Estimates were similarly robust to adjustment for the remaining electrocardiographic measures (Table 1), the index date–electrocardiogram date interval (years) and use of beta or calcium channel antagonists, other antihypertensive medications or loop diuretics. Moreover, multivariate conditional logistic models weighted for the reciprocal of the probability of electrocardiogram availability produced comparable measures of association (not shown).

Discussion

Consensus statements recommend several measures for detecting autonomic abnormalities including heart rate,

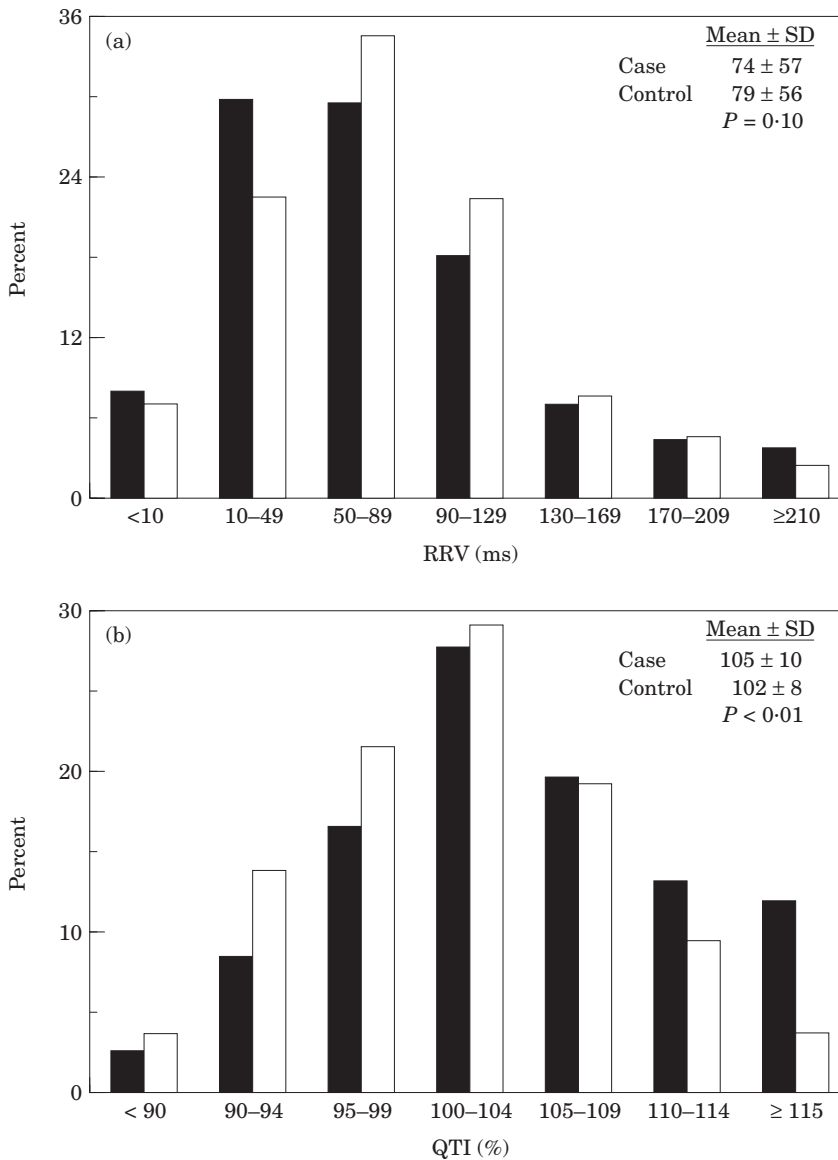


Figure 1 Distributions of (a) RRV (b) QTI in cases (■) and controls (□). QTI=QT interval index. RRV=RR interval variation. SD=standard deviation. Sixteen cases and 10 controls were missing values for RRV and 10 and 6 for QTI.

heart rate variability and QT_c ^[29,30]. Among persons with glucose intolerance or diabetes, for example, tachycardia, low heart rate variability and QT_c prolongation suggest the presence of autonomic dysfunction, i.e. increased sympathetic and decreased parasympathetic activity^[12,31-34]. Based on consensus recommendations, ease of measurement and availability, our study of primary cardiac arrest among persons without clinically recognized heart disease focused on two related measures derived from the standard, 12-lead electrocardiogram: QTI and RRV.

QTI predicts the extent of QT prolongation at a given heart rate more accurately than other published adjustment formulas^[1] and, after adjustment for confounding, more sensitively and accurately detects pharmacologi-

cally simulated autonomic dysfunction than QT_c ^[11]. QTI is also related directly to the risk of primary cardiac arrest among treated hypertensive patients^[4]. Our study extends the latter finding by demonstrating a previously unappreciated complexity of the QTI-primary cardiac arrest relationship in a population without clinically recognized heart disease, namely its dependence on RRV.

The physiological determinants of RRV have not been fully elucidated, but as a short-term measure of heart rate variability, RRV reflects high frequency variation in heart rate (respiratory sinus arrhythmia). Although the Heart Rate Variability Task Force recommends either 5 min or 24 h electrocardiographic recordings for measurement of heart rate variability

Table 2 Population characteristics (% or mean \pm SD) by QTI quintile

Characteristic	Q1 <96 n=176	Q2 96–100 n=177	Q3 100–103 n=206	Q4 103–107 n=186	Q5 \geq 107 n=273
Clinical					
Age (years)	65 \pm 10	65 \pm 11	66 \pm 9	66 \pm 9	66 \pm 10
Female (%)	22	27	34	33	39
Hypertension (%)	19	34	38	40	47
Diastolic blood pressure (mmHg)	80 \pm 10	81 \pm 11	81 \pm 11	82 \pm 10	81 \pm 12
Diabetes (%)	8	7	10	11	17
Glucose (mmol . l ⁻¹)*	6.2 \pm 2.4	6.1 \pm 2.2	6.4 \pm 2.8	6.8 \pm 4.4	6.9 \pm 3.3
Smoker (%)	27	27	27	26	30
Body mass index (kg . m ⁻²)	27 \pm 5	27 \pm 5	27 \pm 4	27 \pm 4	27 \pm 5
ECG					
Heart rate (beats . min ⁻¹)	66 \pm 11	66 \pm 12	71 \pm 14	73 \pm 13	80 \pm 17
Ventricular ectopic beats (%)	4	3	5	7	10
Left ventricular mass (g)	160 \pm 28	160 \pm 27	160 \pm 28	164 \pm 28	163 \pm 32
T wave negativity (%)	9	12	14	15	19
ST segment depression (%)	9	11	9	16	21
Q wave (%)	17	14	20	28	29
Drug					
Beta antagonist (%)	6	8	11	11	15
Calcium channel antagonist (%)	1	2	4	4	6

SD=standard deviation. Based on distributions in controls, Q1–Q5=first through fifth quintiles of QTI=QT interval index, %. *Values of glucose in mg . dl⁻¹ were 111 \pm 43, 109 \pm 40, 115 \pm 50, 122 \pm 79 and 124 \pm 60 for Q1–Q5, respectively.

Table 3 Population characteristics (% or mean \pm SD) by RRV quintile

Characteristic	Q1 <30 n=224	Q2 35–55 n=173	Q3 60–75 n=179	Q4 80–115 n=230	Q5 \geq 120 n=201
Clinical					
Age (years)	67 \pm 10	66 \pm 9	65 \pm 10	65 \pm 9	64 \pm 11
Female (%)	40	36	30	30	23
Hypertension (%)	43	40	35	34	32
Diastolic blood pressure (mmHg)	81 \pm 11	83 \pm 11	81 \pm 11	81 \pm 11	81 \pm 12
Diabetes (%)	15	12	11	11	5
Glucose (mmol . l ⁻¹)*	6.8 \pm 4.0	6.2 \pm 2.3	6.7 \pm 3.6	6.6 \pm 3.1	6.0 \pm 2.2
Smoker (%)	36	25	25	28	24
Body mass index (kg . m ⁻²)	27 \pm 5	27 \pm 5	27 \pm 4	27 \pm 4	27 \pm 6
ECG					
Heart rate (beats . min ⁻¹)	81 \pm 17	72 \pm 13	71 \pm 14	67 \pm 12	67 \pm 13
Ventricular ectopic beats (%)	5	3	6	6	9
Left ventricular mass (g)	160 \pm 29	162 \pm 30	162 \pm 30	161 \pm 28	163 \pm 28
T wave negativity (%)	20	18	15	10	7
ST segment depression (%)	19	14	12	13	10
Q wave (%)	32	21	20	17	22
Drug					
Beta antagonist (%)	12	9	12	11	8
Calcium channel antagonist (%)	4	4	6	2	2

SD=standard deviation. Based on distributions in controls, Q1–Q5=first through fifth quintiles of RRV=RR interval variation, ms. *Values of glucose in mg . dl⁻¹ were 123 \pm 72, 112 \pm 42, 120 \pm 64, 118 \pm 55 and 108 \pm 39 for Q1–Q5, respectively.

in clinical studies^[29], short- and long-term measures of heart rate variability are strongly correlated^[13] and the prognostic value of short-term measures of heart rate variability has been demonstrated by other investigators^[14–16]. Moreover, manual estimation of RRV only requires measurement of the smallest and largest RR intervals between normally conducted complexes in the standard, 12-lead electrocardiogram. Manually estimating other measures commonly used in computer analysis of heart rate variability (e.g. root mean square or standard deviation of successive differ-

ences) would have required measurement of all such RR intervals, a task considered too cumbersome given the large number of electrocardiograms needing evaluation.

In our study, differences in RRV between blinded re-readings of electrocardiograms were small. Established correlates of depressed vagal activity, including diabetes and increased plasma glucose levels^[33], were also more common in lower quintiles of RRV. Furthermore, the combination of low RRV and high QTI was associated with a risk of primary cardiac arrest. Adjustment for clinical characteristics of enrollees did not

Table 4 Effect of the combination of RRV and QTI on risk of primary cardiac arrest

RRV, ms	QTI, %	Adjusted					
		Unadjusted		Clinical		Clinical and ECG	
		OR	95% CI	OR	95% CI	OR	95% CI
120	96	1.00	—	1.00	—	1.00	—
35	96	0.97	0.76–1.23	0.95	0.73–1.23	0.94	0.72–1.23
120	107	1.30	1.05–1.61	1.23	0.97–1.57	1.12	0.87–1.44
35	107	1.65	1.28–2.12	1.55	1.16–2.06	1.34	1.00–1.81

QTI=QT interval index. RRV=RR interval variation. Tabulated values of RRV and QTI are the first and fifth quintiles among controls. OR, 95% CI=odds ratio, 95% confidence interval estimated from models containing RRV, QTI and the product term, $RRV \times QTI$. All models included age <50 years, gender, index year (5-year interval) and diabetes as stratum variables to account for sampling design. Models adjusting for clinical characteristics also included age (y), hypertension, diastolic blood pressure (DBP mmHg), DBP^2 , glucose ($\text{mmol} \cdot \text{l}^{-1}$), glucose^2 , current smoking status, body mass index ($\text{kg} \cdot \text{m}^{-2}$). Models adjusting for ECG characteristics also included ST segment depression, Q waves and T wave negativity. For the addition of $RRV \times QTI$ to the three models (unadjusted, adjusted for clinical characteristics and adjusted for clinical and ECG characteristics) $P=0.04$, $P=0.05$ and $P=0.11$, respectively.

explain the association. These findings suggest that RRV had high re-reading reliability, internal validity as a measure of parasympathetically mediated variation in heart rate and an important influence on the previously described QTI–primary cardiac arrest relationship. Although the reliability of QTI was lower than that of RRV, the observation that reliability did not differ by case-control status suggests that the estimates of association reported in this study could be biased towards the null and could increase with computerized reading of higher quality copies of longer duration electrocardiograms.

We also assessed the effect of further adjustment of electrocardiographic characteristics on the risk of primary cardiac arrest in our study. Although further adjustment reduced the magnitude of risk, the increase in risk of primary cardiac arrest at low RRV and high QTI persisted after adjusting for ST segment depression, Q waves and T wave negativity. Moreover, evidence for an additive interaction between RRV and QTI remained after further adjustment. These findings suggest that the combination of low RRV and high QTI provides additional information not reflected by electrocardiographic indicators of myocardial ischaemia, infarction and abnormal repolarization.

One explanation for our findings is that the combination of low RRV and high QTI better characterizes sympathovagal control of the heart. The efficacy of beta-blockade^[35] and left cardiac sympathetic denervation^[36] in reducing QT_c and preventing arrhythmic complications of the long QT syndrome suggests that QTI reflects sympathetic influences on ventricular repolarization. The combination of QTI and RRV may therefore improve the ability to identify autonomic dysfunction by jointly reflecting sympathetic and parasympathetic control of the heart. Alternatively, establishing the presence of two autonomic abnormalities

may enhance the ability to detect autonomic dysfunction by reducing misclassification of exposure^[30,37].

Our study relied on a case-control design to efficiently assemble cases of incident, out-of-hospital primary cardiac arrest, an uncommon event among persons without clinically recognized heart disease. Because of its retrospective design, we defined clinical, electrocardiographic and drug exposures using only that information recorded in the ambulatory medical record and automated pharmacy files before the index date. Our study was population-based, drawing its cases and a stratified random sample of controls from approximately 350 000 people enrolled in a large health plan over a 15-year period. However, the study population was a non-random subset of potential cases and controls with an available electrocardiogram. It was therefore possible for models not adjusting for characteristics associated with electrocardiogram availability to bias estimates of association away from the null. Because weighting models for the reciprocal of the probability of electrocardiogram availability did not change our results, we suggest that selection bias related to electrocardiogram availability was negligible.

Because the clinical characteristics in this study were associated with electrocardiogram availability and these characteristics are well-known risk factors for heart disease, it is possible that some electrocardiograms were ordered by practitioners to evaluate suspected, yet at the time, undocumented heart disease or arrhythmia. Although our results were susceptible to indication bias for this reason, all patients with hypertension and diabetes are currently recommended for an electrocardiogram to determine the presence of target organ damage as part of pre-treatment evaluation^[38,39]. Although an electrocardiogram is also indicated in the evaluation of syncope^[40], enrollees with syncope before the index date were excluded from our analyses as were enrollees with

heart disease, the most common indication for electrocardiographic testing. Moreover, electrocardiograms were recorded (on average, 5 years) before the index date and adjusting for the index date–electrocardiogram date interval produced comparable measures of association. Because models weighted and unweighted for the reciprocal of the probability of electrocardiogram availability produced similar results, we also suggest that indication bias was negligible.

We therefore conclude that the combination of a high QTI and low RRV is associated with an increased risk of primary cardiac arrest among persons without clinically recognized heart disease. In arriving at this conclusion, we acknowledge the need for additional population-based studies to confirm our findings. We also recommend that future research consider how diabetes mellitus and heart disease, two established risk factors for cardiac autonomic dysfunction, influence the relationships between RRV, QTI and primary cardiac arrest. In our view, such investigation reasonably focuses on a less costly, non-invasive alternative to standard measurement of heart rate variability in an attempt to identify populations at risk for sudden cardiac death.

The project was funded by National Heart, Lung and Blood Institute grant HL-42456-03. Preliminary findings were published as an abstract [*Circulation* 1999;99(8):1118]. Dr Whitsel was supported by the Veteran Affairs Puget Sound Health Care System Health Services Research and Development post-doctoral fellowship program. We are indebted to Bruce M. Psaty and Nathan R. Evers for their reviews of a prior version of this manuscript, to Leonard A. Cobb for his support of this research and to the Seattle Medic One Program, King County Emergency Medical System and Group Health Cooperative of Puget Sound for their assistance.

References

- [1] Rautaharju PM, Warren JW, Calhoun HP. Estimation of QT prolongation: A persistent, avoidable error in computer electrocardiography. *J Electrocardiol* 1991; 23S: 111–7.
- [2] Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920; 7: 353–70.
- [3] Algra A, Tijssen JGP, Roelandt JRTC, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation* 1991; 83: 1888–94.
- [4] Siscovick DS, Raghunathan TE, Rautaharju P, Psaty BM, Cobb LA, Wagner EH. Clinically silent electrocardiographic abnormalities and risk of primary cardiac arrest among hypertensive patients. *Circulation* 1996; 94: 1329–33.
- [5] Stern S, Eisenberg S. The effect of propranolol (Inderal) on the electrocardiogram of normal subjects. *Am Heart J* 1969; 77: 192–5.
- [6] Seides SF, Josephson ME, Batsford WP, Weisfogel GM, Lau SH, Damato AN. The electrophysiology of propranolol in man. *Am Heart J* 1974; 88: 733–41.
- [7] Milne JR, Camm AJ, Ward DE, Spurrell RAJ. Effect of intravenous propranolol on QT interval: A new method of assessment. *Br Heart J* 1980; 43: 1–6.
- [8] Evarsson N, Olsson SB. Effects of acute and chronic beta-receptor blockade on ventricular repolarisation in man. *Br Heart J* 1981; 45: 628–36.
- [9] Browne KF, Zipes DP, Heger JJ, Prystowsky EN. Influence of the autonomic nervous system on the Q-T interval in man. *Am J Cardiol* 1982; 50: 1099–1103.
- [10] Cappato R, Alboni P, Pedroni P, Gilli G, Antonioli G. Sympathetic and vagal influences on rate-dependent changes of QT interval in healthy subjects. *Am J Cardiol* 1991; 68: 1188–93.
- [11] Whitsel EA, Boyko EJ, Siscovick DS. Accuracy of QT_c and QTI for detection of autonomic dysfunction. *Ann Noninvasive Electrocardiol* 1999; 4: 257–66.
- [12] Whitsel EA, Boyko EJ, Siscovick DS. Reassessing the role of QT_c in the diagnosis of autonomic failure among patients with diabetes. A meta-analysis. *Diabetes Care* 2000; 23: 241–7.
- [13] Dekker JM, de Vries EL, Lengton RR, Schouten EG, Swenne CA, Maan A. Reproducibility and comparability of short- and long-term heart rate variability measures in healthy young men. *Ann Noninvasive Electrocardiol* 1996; 1: 287–92.
- [14] Tibblin G, Eriksson CG, Bjurö T, Georgescu D, Svärdsudd C. Heart rate and heart rate variability. A risk factor for the development of ischemic heart disease in the 'Men Born in 1913 Study' — A ten years follow-up. *IRCS Medical Science: Cardiovascular System; Social and Occupational Medicine* 1975; 3: 95.
- [15] Dekker JM, Schouten EG, Klootwijk P, Pool J, Sweeney CA, Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. *Am J Epidemiol* 1997; 145: 899–908.
- [16] de Bruyne MC, Kors JA, Hoes AW *et al.* Both decreased and increased heart rate variability on the standard 10-second electrocardiogram predict cardiac mortality in the elderly: The Rotterdam Study. *Am J Epidemiol* 1999; 150: 1282–8.
- [17] La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ, for the Autonomic Tone and Reflexes After Myocardial Infarction Investigators. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998; 351: 478–84.
- [18] Barron HV, Lesh MD. Autonomic nervous system and sudden cardiac death. *JACC* 1996; 27: 1053–60.
- [19] Liao D, Cai J, Rosamond WD *et al.* Cardiac autonomic function and incident coronary heart disease: A population-based case-cohort study. *Am J Epidemiol* 1997; 145: 696–706.
- [20] Tsujii H, Venditti Jr FJ, Manders ES *et al.* Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation* 1994; 90: 878–83.
- [21] Siscovick DS. Challenges in cardiac arrest research: Data collection to assess outcomes. *Ann Emerg Med* 1993; 22: 92–8.
- [22] Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang Z. The Novacode criteria for classification of ECG abnormalities and their clinically significant progression and regression. *J Electrocardiol* 1998; 31: 157–87.
- [23] Zhou SH, Wong S, Rautaharju PM, Karnik N, Calhoun HP. Should the JT rather than the QT interval be used to detect prolongation of ventricular repolarization? An assessment in normal conduction and ventricular conduction defects. *J Electrocardiol* 1992; 25S: 131–6.
- [24] Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X, Cobb L, Rautaharju PM, Copass MK, Wagner EH. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994; 330: 1852–7.
- [25] Psaty BM, Heckbert SR, Koepsell TD *et al.* The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; 274: 620–5.
- [26] Rautaharju PM, Manolio TA, Psaty BM, Borhani NO, Furberg CD. Correlates of QT prolongation in older adults (the Cardiovascular Health Study). *Am J Cardiol* 1994; 73: 999–1002.
- [27] Rothman KJ. The estimation of synergy or antagonism. *Am J Epidemiol* 1976; 103: 506–11.
- [28] Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: An update. *Circulation* 1993; 88: 782–4.
- [29] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; 93: 1043–65.

-
- [30] Kahn R. Proceedings of a consensus development conference on standardized measures in diabetic neuropathy. Autonomic nervous system testing. *Neurology* 1992; 42: 1831–7.
- [31] Dekker JM, Feskens EJM, Schouten EG, Klootwijk P, Pool J, Kromhout D. QT_c duration is associated with levels of insulin and glucose tolerance. The Zutphen Elderly Study. *Diabetes* 1996; 45: 376–80.
- [32] Genovely H, Pfeifer MA. RR-variation: The autonomic test of choice in diabetes. *Diabetes Metab Rev* 1998; 4: 255–71.
- [33] Liao DP, Cai JW, Barncati FL *et al.* Association of vagal tone with serum insulin, glucose, and diabetes mellitus — The ARIC study. *Diab Res Clin Prac* 1995; 30: 211–21.
- [34] Ewing DJ, Campbell IW, Clarke BF. Heart rate changes in diabetes mellitus. *Lancet* 1981; 1(8213): 183–6.
- [35] Moss AJ, Zareba W, Hall WJ *et al.* Effectiveness and limitations of β -Blocker therapy in congenital long-QT syndrome. *Circulation* 2000; 101: 616–23.
- [36] Schwartz PJ, Locati EH, Moss AJ, Crampton RS, Trazzi R, Ruberti U. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome. A worldwide report. *Circulation* 1991; 84: 503–11.
- [37] Report and recommendations of the San Antonio conference on diabetic neuropathy. *Diabetes Care* 1988; 11: 592–7.
- [38] The sixth report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure. *Arch Intern Med* 1997; 157: 2413–45.
- [39] Standards of medical care for patients with diabetes mellitus. American Diabetes Association. *Diabetes Care* 1998; 21(S1): S23–S31.
- [40] Linzer M, Yang EH, Estes NA III, Wang P, Vorperian VR, Kapoor WN. Diagnosing syncope. Part 1: Value of history, physical examination and electrocardiography. Clinical efficacy assessment project of the American College of Physicians. *Ann Intern Med* 1997; 126: 989–96.