Exercise-induced QT/R-R–interval hysteresis as a predictor of myocardial ischemia

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Abstract:

Objectives: Exercise-induced QT/RR hysteresis exists when, for a given R-R interval, the QT interval duration is shorter during recovery after exercise than during exercise. We sought to assess the association between QT/RR hysteresis and imaging evidence of myocardial ischemia.

Background: Because ischemia induces cellular disturbances known to decrease membrane action potential duration, we hypothesized a correlation between QT/RR and myocardial ischemia.

Methods: We digitally analyzed 4-second samples of QT duration and R-R–interval duration in 260 patients referred for treadmill exercise stress and rest single photon emission computed tomography myocardial perfusion imaging; a cool-down period was used after exercise. None of the patients were in atrial fibrillation or used digoxin, and none had marked baseline electrocardiographic abnormalities. Stress and rest myocardial perfusion images were analyzed visually and quantitatively to define the extent and severity of stress-induced ischemia. QT/RR hysteresis was calculated using a computerized algorithm.

Results: There were 82 patients (32%) who manifested myocardial ischemia by single photon emission computed tomography myocardial perfusion imaging. The likelihood of ischemia increased with increasing QT/RR hysteresis, with prevalence according to quartiles of 20%, 30%, 26%, and 49% (P = .003 for trend). In analyses adjusting for ST-segment changes, exercise

capacity, heart rate recovery, and other confounders, QT/RR hysteresis was independently predictive of presence of myocardial ischemia (adjusted odds ratio for 100-point increase of QT/RR hysteresis, 1.61; 95% confidence interval, 1.22-2.12; *P* = .0008). QT/RR hysteresis was also predictive of severe ischemia.

Conclusion: Exercise-induced QT/RR hysteresis is a strong and independent predictor of myocardial ischemia and provides additional information beyond that afforded by standard ST-segment measures.

Keywords: QT/RR hysteresis | Ischemia | myocardial ischemia | Exercise

Article:

Introduction

The relationship between heart rate and QT interval has been the subject of active investigation since the pioneering work of Bazett in 1920[1] who derived a mathematical formula relating QT-interval shortening to increases in heart rate. Under near steady-state conditions, his formula describes the QT-interval response to temporary deviations in instantaneous heart rate. Subsequent studies have shown that the actual processes are rarely steady state and usually involve transients that eventually result in a QT/RR hysteresis,[2 and 3] even in healthy cardiac muscle.[4]

Variations in QT and R-R intervals during and after exercise have been linked to autonomic and hormonal influences. For example, a recent report found that there exists a similar QT/RR hysteresis,[2] whereby QT intervals during recovery for any given R-R interval are less than during exercise in patients with long QT-syndrome and that β-blockers reduce this hysteresis.[5] Coronary artery disease and myocardial ischemia may also alter the behavior of the QT/RR relation during and after exercise, as ischemia itself has been shown to decrease action potential duration. [6, 7, 8 and 9] Likewise, because of changes in extracellular potassium activity, ischemia may also initiate a hysteresis-like evolution of ST-segment depression when ST-segment amplitudes during exercise are different from corresponding values at matched heart rates during recovery. [6, 10 and 11]

Recently, we hypothesized that moderating the rate of changes in load during exercise and recovery may facilitate a stronger link between exercise-induced electrophysiologic changes in cardiac muscle substrate and QT/RR hysteresis.[12] We performed a clinical study to determine whether there is an association between exercise-induced QT/RR hysteresis and myocardial ischemia as assessed by rest and stress single photon emission computed tomography (SPECT) myocardial perfusion imaging. Ischemia as identified by SPECT was chosen as the primary end point variable in part because of its proven prognostic importance.[13]

Methods

Patient population

The cohort was derived from adult patients referred for a symptom-limited exercise nuclear study at the Cleveland Clinic Foundation between April 20 and October 21 2003. Patients were eligible if they were willing to provide informed consent, had an interpretable electrocardiogram, and were able to walk on the treadmill. Exclusion criteria included age younger than 30 years, cardiac pacemaker placement, use of digoxin, atrial fibrillation at the time of testing, left ventricular hypertrophy with associated repolarization abnormality, complete left or right bundle-branch block, preexcitation, interventricular conduction defect, and ST-segment depression of at least 1 mm at rest before exercise testing. The Cleveland Clinic Institutional Review Board approved the research protocol and informed consent form.

Clinical data

A structured interview and chart review were conducted before the treadmill test for cardiac history, symptoms, medications, noncardiac diagnoses, and risk factors. Resting hypertension was defined as treatment with antihypertensive medication, or either systolic or diastolic blood pressure of 140/90 mm Hg or higher[14] Diabetes mellitus was determined on the basis of chart review and medication use. Hypercholesterolemia was defined as a recent total cholesterol value of 200 mg/dL or higher or use of lipid-lowering medication. Coronary artery disease was considered present if there was documented myocardial infarction, coronary angiography demonstrating at least one 50% stenotic lesion, and/or a history of prior coronary artery bypass surgery or percutaneous coronary intervention. All historical data and current height and weight were prospectively recorded online.

Exercise testing

Symptom-limited exercise testing procedures in our laboratory have been previously described.[15, 16,17 and 18] Each patient underwent a symptom-limited exercise test according to standard Cornell protocol which, unlike Bruce protocol, may be considered as a sufficiently gradual ramping up of exercise load. The initial grade (0%, 5%, or 10%) was determined by patient age and current exercise regimen. The recovery phase involved 2 minutes of walking at 1.5 mph and 2.5% grade followed by an additional 5 minutes sitting, or until any exercise abnormalities resolved. The same exercise physiologist performed each test. All physiologic and hemodynamic data were collected at baseline, during each stage of exercise, and at minutes 1, 2, 3, and 5 of recovery. Data including heart rate, blood pressure, arrhythmias, ST changes, and symptoms were entered into an online computer system. Estimated functional capacity in metabolic equivalents (METs; where 1 MET = 3.5 mL/kg per minute of oxygen consumption) corresponded with peak exercise time and maximal speed and grade of the treadmill. Functional capacity was further defined as poor, fair, average, good, or high, using a previously described scheme.[19] Functional capacity was considered fair among men if it was less than 11, 10, 8.5, 8, 7, 5.5, and 4.5 METs for those aged younger than 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79

years, and those 80 years or older, respectively. The corresponding values for women were 10, 9, 8, 7, 6, 4.5, and 4 METs. Functional capacity was considered poor among men in the same age ranges if it was less than 8, 7.5, 7, 6, 5.5, 4.5, and 3.5 METs. The corresponding values for women were 7.5, 7, 6, 5, 4.5, 3.5, and 2.5 METs. Exercise capacity in the average or above-average categories was not considered as a separate variable because previous studies have found little difference in outcomes between patients with average or above-average exercise capacities when stratified for age and sex.[19]

Chronotropic response was defined as the percentage of heart rate reserve used at peak exercise.[17] Chronotropic incompetence was defined as a failure to use 80% of the heart rate reserve.[17] ST segments were considered abnormal if there was at least 1 mm of horizontal or down-sloping depression 80 milliseconds after the J point for at least 3 consecutive beats in 2 contiguous leads. Heart rate recovery was defined as the difference in heart rate at peak exercise to that at 1-minute recovery. During the first 2 minutes of recovery, most patients walk at a cool-down rate of 1.5 mph and a 2.5% grade. An abnormal heart rate recovery was considered present if it was 12 beats per minute or less.[20 and 21]

QT/RR hysteresis measurements

The system for signal acquisition included a GE Medical (Waukesha, WI) exercise stress station CASE 8000, a digital portable NorthEast Monitoring Inc (Maynard, MA) Holter recorder DR180+ (NEMH), and a 12-lead analog test box that split the electrocardiogram (ECG) signals from each of the 12 leads and relayed them to both CASE 8000 and NEMH devices.

Digitized (720 samples per second) raw ECG data were first processed by NEMH software for simultaneous measurements of QT/R-R intervals in all available 12 standard leads. Calculated QT/R-R intervals sampled from 4-second-duration raw ECG data segments were analyzed to determine ischemia indices I_h based upon measurements of the area of QT/R-R–interval hystereses. The indices were determined in each better-quality lead where at least 5 QT/R-R interval measurements were available per each minute of exercise and recovery. In each subject, such I_h values were calculated for at least 3 leads with better quality of signal, and the final I_h value was defined as the maximum I_h across these leads.

Fig. 1 shows raw QT/R-R interval data sets (upper panels) and similar monotonically smoothed curves (lower panels), which are derived through the implementation of a polynomial fitting procedure.[12] Exercise and recovery stages corresponding to the increasing and decreasing exercise load periods are shown in each panel in the areas to the left and to the right of the QT/R-R interval minima. Left and right pairs of panels in Figs. 1 and 2 correspond to the same nonischemic and ischemic patients and show QT/R-R interval dependences and hysteresis loops in the aVF and V_3 leads. Maximal I_h values for these patients are equal to 157 and 478, respectively.

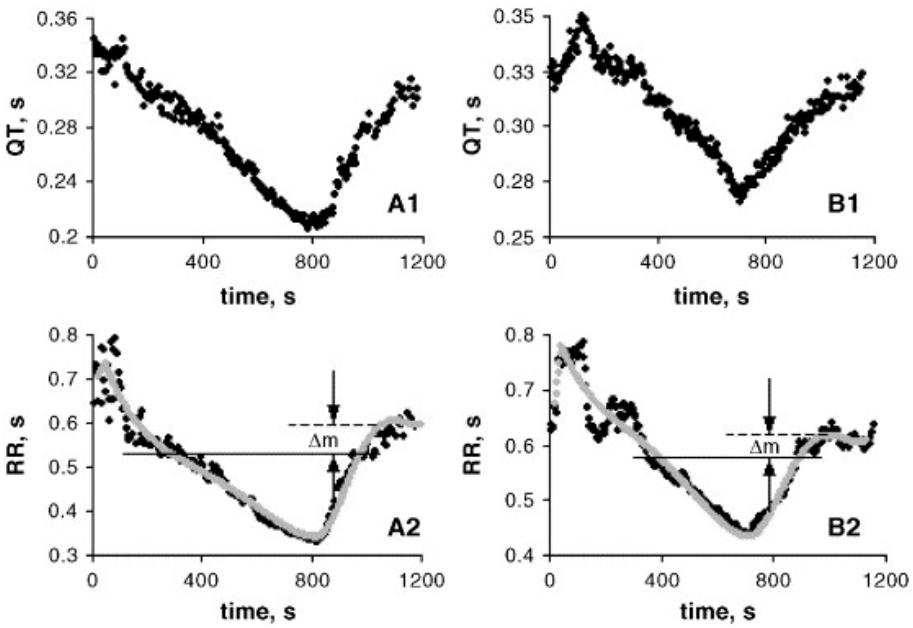

Fig. 1. Plots of QT duration (panels A1 and B1) and R-R interval (panels A2 and B2) dynamics during and after exercise in 2 representative patients. The left panels A1 and A2 come from a patient without myocardial ischemia, whereas the right panels B1 and B2 come from a patient with myocardial ischemia. The dashed lines in panels A2 and B2 refer to the establishment of a plateau of R-R interval during recovery, whereas the solid line refers to an R-R interval of 10% less. The distance between these 2 lines, Δm, is used to help construct QT/RR hysteresis loops shown in Fig. 2.

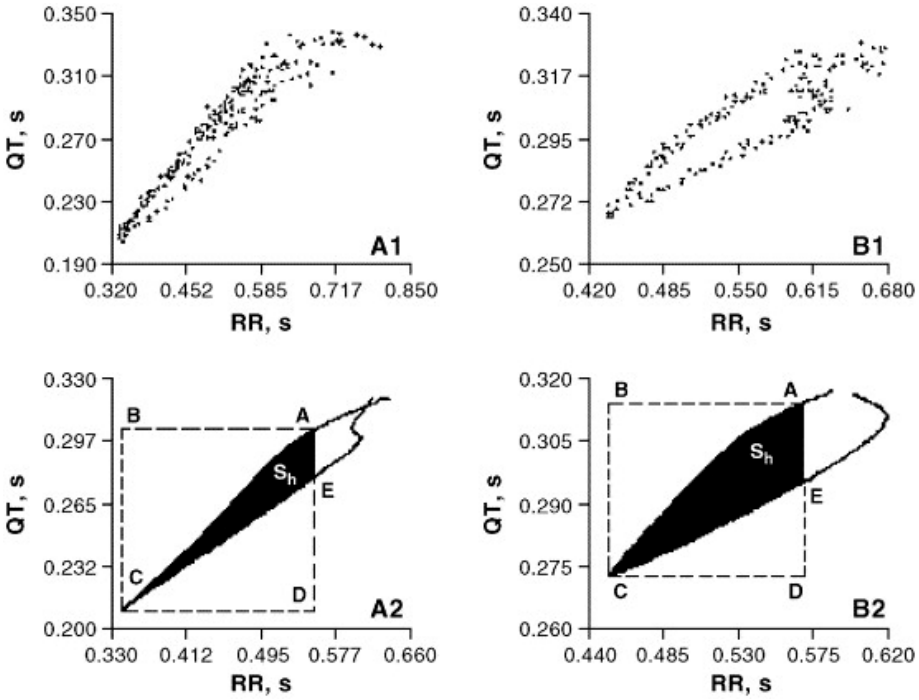

Fig. 2. Generation of QT/RR hysteresis loops based on data shown in Fig. 1. Again, panels A1 and A2 come from a nonischemic patient, whereas panels B1 and B2 come from an ischemic patient. The upper panels A1 and B1 show raw digital data, whereas the lower panels A2 and B2 show processed curves. The R-R interval at which the lines AE (shown in panels A2 and B2) are drawn correspond to the solid lines shown in panels A2 and B2 from Fig. 1. The domain S_h corresponds to QT/RR hysteresis extent. Details regarding the final calculation of QT/RR hysteresis values I_h are in the text.

Fig. 2 also shows exercise and recovery QT- and R-R–interval data (with the 4 panels corresponding to the data shown in Fig. 1), but present them in an alternative way through the arcs of the curves between the points A and C and points C and E shown in panels A2 and B2. The increasing exercise load period corresponds to either upper curves AC in panels A2 and B2 or upper groups of dots in panels A1 and B1. The decreasing exercise load period is depicted by either lower curves CE in panels A2 and B2 or lower groups of dots in panels A1 and B1. The vertical lines AE that close the hysteresis loops indicate the value of R-R interval that corresponds to the level immediately preceding the postexercise rest values. The derivation of these postexercise rest values is now explained in detail.

The 2 lower panels of Fig. 1 depict average postexercise R-R interval levels (dashed horizontal lines) that are located above separate solid horizontal lines. The dashed lines refer to the establishment of a plateau of R-R interval in the postrecovery period. The solid line shown as Δm was placed at an R-R interval level 10% lower than the dashed line. The R-R interval corresponding to the solid line determined the placement of line AE in panels A2 and B2 of Fig. 2; line AE thus closes the QT/RR hysteresis loops shown in these panels. Measures of the domains, S_h, bounded by the QT/RR hysteresis loops provided the basis for calculation of ischemia index I_h, which was defined as a product ρS_h. A weight factor ρ included 3 components: the ratio, $\sqrt{W_0/W}$, between the 4-stage standard Bruce protocol and our exercise protocol total workloads and reproduced a normalized patient exercise tolerance with respect to a conventional standard; the product $\{(RR_{A,D} - RR_{B,C})(QT_{A,B} - QT_{C,D})\}^{-1}$ (see dashed rectangular in Fig. 2), which reflected a total range of changes of QT and R-R intervals during active exercise stages; and a numeric constant, η, which was taken equal to 1100 to range I_h values between 100 and 1000.

Myocardial perfusion imaging

Imaging was performed using a dual-isotope imaging protocol. Rest SPECT myocardial images were acquired first, beginning 10 to 15 minutes after the intravenous administration of 3.0 to 3.5 mCi of thallium chloride 201. After acquisition of the rest images, the patient then underwent treadmill exercise (above), and 15 to 25 mCi of technetium Tc 99m sestamibi was administered at peak stress. Stress imaging was performed 30 to 45 minutes later. Tomographic images were acquired in a 64 × 64 matrix over 180°, using a step and shoot technique, with a dual headed camera (ECAM, Siemens Inc, Munich, Germany). For the sestamibi-gated images, 8 frames

were acquired per R-R interval, over 32 stops, using 15 to 20 seconds per stop. Images were reconstructed using standard filtered back-projection techniques.

Images were visually and quantitatively analyzed on computer workstations using 4D-MSPECT software developed at the University of Michigan. The physicians performing the analysis were blinded to the QT/RR hysteresis data. Relative tracer concentrations on the tomographic images were referenced to those of a sex-matched database, to assist in the definition of perfusion defects and the presence or absence of reversibility. Semiquantitative scores of tracer uptake on the stress and rest images were generated in each of 17 standard myocardial segments according to the following criteria: 0 = normal, 1 = equivocal, 2 = abnormal, 3 = severe, 4 = absent (equal to background), to generate summed stress scores and summed reversibility scores for each patient study. Any ischemia was defined as a reversibility score of 4 or greater, whereas severe ischemia was defined as a reversibility score of 7 or greater. A segment that had evidence of both scar and ischemia (eg, periinfarct ischemia) was considered as ischemic. Left ventricular ejection fraction, size, and regional function were also assessed on the gated SPECT sestamibi images.

Coronary angiography

In a supplementary analysis, we identified patients who, as part of their clinical care, underwent coronary angiography after stress testing. Angiographic results were reported in a semiquantitative manner by observers who were blinded to QT/RR hysteresis values and to the hypothesis of this study. The severity of coronary disease was coded according to the previously validated Duke prognostic weight score, which varies from 0 to 100 depending on the number, severity, and location of arterial stenoses.[22] Based on prior data relating this score to outcomes following different types of coronary disease therapies, we defined any coronary disease as a score of 19 or greater and severe coronary disease as a score of 42 or greater.[22]

Role of sponsor

MediWave Star Technology Inc participated in the study design and in the calculation of QT/R-R interval data. All other data were acquired, managed, and analyzed at the Cleveland Clinic Foundation. An agreement was made before study initiation that study results would be published at the discretion of the Cleveland Clinic Foundation investigators.

Statistical analyses

Sample size was prospectively determined by considering the estimate for the c or concordance statistic (concordance), analogous to the area under a receiver operating characteristic curve, along with its associated 95% confidence interval (CI). Assuming a rate of ischemia of 20% and a concordance of 0.80 with a corresponding half-width of 0.08, we estimated a need for 233 patients. We therefore decided to enroll 260 patients to buffer for unexpected findings.

Patients were divided according to quartiles of QT/RR hysteresis. Comparisons of continuous variables were made using the Kruskal-Wallis test, whereas comparisons of categorical variables were made using the χ^2 tests for trend. We defined an abnormal QT/RR hysteresis value as 375 or higher, corresponding to the highest quartile, whereas we defined an abnormal ST-segment deviation as 1 mm or more of horizontal or downsloping depression. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated according to standard definitions, with 95% CIs determined by exact binomial methods.

Multivariable stepwise logistic regression modeling was performed to determine the association of QT/RR hysteresis with any or severe ischemia after adjusting for all the variables listed in Table 1 and Table 2 and to calculate concordance statistics. Because of the very large number of variables considered, resulting in a risk of model overfitting, we also performed bootstrap resamplings in which 1000 new data sets were generated by random sampling with replacement. Logistic modeling was performed on each of those data sets; appearance of a variable in at least 50% of models was considered to constitute a robust association. At no time was any variable, including QT/RR hysteresis, forced into any models. We also formally tested for interactions of QT/RR hysteresis with ST-segment changes, standard cardiac risk factors, and medications including β-blockers and ACE inhibitors.

Table 1. Baseline characteristics according quartiles of QT/RR hysteresis

Variable	Hysteresis 152-252 (n = 64)	Hysteresis 253-312 (n = 66)	Hysteresis 313-374 (n = 65)	Hysteresis 376-703 (n = 65)	*P*
Demographics					
Age, mean (SD), y	53 (11)	61 (10)	59 (10)	65 (10)	<.0001
Men, n (%)	58 (91)	55 (83)	47 (72)	41 (63)	.001
Clinical history					
Diabetes with insulin, n (%)	1 (2)	3 (5)	3 (5)	10 (15)	.008
Diabetes without insulin, n (%)	3 (5)	11 (17)	8 (12)	17 (26)	.007
Hypertension, n (%)	33 (52)	42 (64)	39 (60)	47 (72)	.108
Tobacco use, n (%)	11 (17)	6 (9)	8 (12)	6 (9)	.449
Family history of	1 (2)	4 (6)	6 (9)	23 (35)	<.0001

coronary artery disease, n (%)					
Prior coronary artery disease, n (%)	37 (58)	45 (68)	44 (68)	46 (71)	.424
Prior coronary artery bypass graft, n (%)	8 (12)	10 (15)	23 (35)	20 (31)	.003
Prior percutaneous coronary intervention, n (%)	18 (28)	23 (35)	14 (22)	16 (25)	.356
Prior Q-wave MI, n (%)	1 (2)	4 (6)	3 (5)	3 (5)	.633
Prior MI, n (%)	17 (27)	23 (35)	18 (28)	20 (31)	.733
Medication use					
β-Blocker, n (%)	34 (53)	32 (48)	33 (51)	41 (63)	.354
Diltiazem/verapamil, n (%)	1 (2)	5 (8)	4 (6)	4 (6)	.456
Nifedipine, n (%)	2 (3)	5 (8)	5 (8)	9 (14)	.167
ACE inhibitor, n (%)	22 (34)	25 (38)	17 (26)	29 (45)	.171
Aspirin, n (%)	45 (70)	52 (79)	45 (69)	49 (75)	.571
Statin lipid-lowering therapy, n (%)	45 (70)	50 (76)	45 (69)	50 (77)	.69
Cardiovascular assessment					
Body mass index, mean (SD), kg/m^2	27 (4)	29 (5)	32 (18)	30 (5)	.022
Ejection fraction, mean (SD)	64 (6)	65 (8)	64 (8)	63 (9)	.975

ACE indicates angiotensin-converting enzyme; MI, myocardial infarction.

Table 2. Exercise and nuclear characteristics according quartiles of QT/RR hysteresis

Variable	Hysteresis	Hysteresis	Hysteresis	Hysteresis	*P*

	152-252 (n = 64)	253-312 (n = 66)	313-374 (n = 65)	376-703 (n = 65)	
Cardiovascular assessment and exercise capacity					
Resting heart rate, mean (SD), beats/min	64 (12)	66 (12)	67 (11)	72 (14)	.018
Resting blood pressure, mean (SD), mm Hg					
Systolic	131 (20)	133 (18)	133 (18)	138 (20)	.21
Diastolic	82 (11)	84 (10)	83 (10)	86 (10)	.112
Maximal blood pressure, mean (SD), mm Hg					
Systolic	192 (23)	192 (22)	184 (22)	181 (22)	.009
Diastolic	89 (12)	91 (12)	89 (12)	90 (13)	.528
Peak heart rate, mean (SD)	156 (16)	149 (21)	146 (20)	140 (17)	<.0001
Heart rate recovery, mean (SD), beats/min	23 (7)	18 (9)	17 (7)	12 (7)	<.0001
Abnormal heart rate recovery, n (%)	4 (6)	12 (18)	16 (25)	33 (51)	<.0001
Low chronotropic incompetence, no β-blocker, n (%)	2 (3)	6 (9)	6 (9)	9 (14)	.201
Ischemic ECG changes with stress					
ST depression 1-2 mm, n (%)	13 (20)	21 (32)	15 (23)	24 (37)	.128
ST depression ≥2 mm, n (%)	2 (3)	5 (8)	3 (5)	4 (6)	.702
Test terminating angina, n (%)	0 (0)	1 (2)	3 (5)	5 (8)	.079
Peak exercise capacity, mean (SD), METs					

Men	11.4 (1.4)	9.4 (1.2)	8.6 (1.2)	7.2 (1.2)	<.0001
Women	10.0 (1.7)	8.5 (1.2)	8.3 (1.2)	6.3 (0.9)	<.0001
Fair or poor physical fitness, n (%)	1 (2)	4 (6)	6 (9)	23 (35)	<.0001
Frequent ventricular ectopy in recovery, n (%)	1 (2)	2 (3)	5 (8)	4 (6)	.12
Nuclear scan					
Ischemia, n (%)	13 (20)	20 (30)	17 (26)	32 (49)	.003
Severe ischemia, n (%)	3 (5)	8 (12)	7 (11)	19 (29)	.0002
Scar, n (%)	13 (20)	14 (21)	11 (17)	13 (20)	.934
Severe Scar, n (%)	8 (12)	6 (9)	7 (11)	4 (6)	.653

In supplementary analyses, logistic regression models were constructed to assess the association between QT/RR hysteresis and angiographic severity of coronary disease.[22]

All other analyses were performed using the SAS version 8.2 statistical package (SAS, Inc, Cary, NC).

Results

Baseline characteristics

Adequate QT/RR hysteresis data were obtained in 260 of 272 patients. Among the 12 patients with inadequate data, there were 8 with excessively noisy files precluding signal processing, 2 with excessive premature ventricular beats (>250), 1 with incomplete recovery data, and 1 with an unreadable flashcard. The distribution of QT/RR hysteresis followed a bimodal pattern (Fig. 3) with peaks noted at 282 and 553. The median value was 312.5 (25th and 75th percentiles, 253 and 375; range, 152-703).

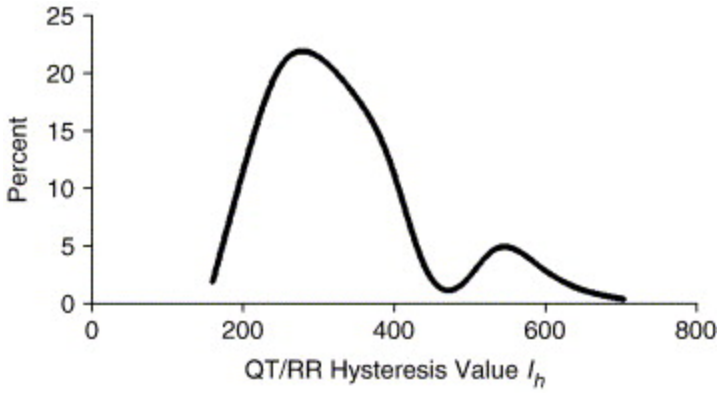

Fig. 3. Distribution of QT/RR hysteresis values (I_h).

Baseline characteristics according to quartiles of QT/RR hysteresis are shown in Table 1. Higher levels of QT/RR hysteresis were associated with older age, diabetes mellitus, a family history of early coronary disease, and prior coronary bypass surgery. There was no association of QT/RR hysteresis with ejection fraction.

Exercise characteristics

Exercise characteristics according to quartiles of QT/RR hysteresis are shown in Table 2. Higher levels of QT/RR hysteresis were strongly associated with impaired functional capacity, lower peak systolic blood pressure, and a greater likelihood of an abnormal heart rate recovery, but not with ST-segment depression.

Scintigraphic ischemia

Any evidence of myocardial ischemia was noted in 82 patients (32%), whereas severe ischemia, as assessed by polar mapping, was noted in 37 (14%). Fixed perfusion defects were present in 51 patients (20%), whereas 25 (10%) had fixed defects involving at least 4 of 17 segments.

As shown in Table 2, higher levels of QT/RR hysteresis were strongly associated with a greater likelihood of any or severe myocardial ischemia. Compared with patients in the lowest quartile, those in the highest QT/RR quartile were substantially more likely to have any ischemia (odds ratio, 3.80; 95% CI, 1.75-8.29; $P < .0001$) or severe ischemia (odds ratio, 8.40; 95% CI, 2.34-30.10; $P = .0011$). The sensitivity, specificity, positive predictive value, and negative predictive value of a QT/RR hysteresis value of 375 or higher (corresponding to the highest quartile) and abnormal ST-segment depression are shown in Table 3.

Table 3. Diagnostic accuracy values (95% CIs) for abnormal ST-segment depression and QT/RR hysteresis

Variable	Sensitivity	Specificity	c Statistic	PPV	NPV

Any ischemia					
ST depression (≥1 mm horizontal or downsloping)	27 (18-37)	83 (76-87)	0.63	42 (29-55)	71 (65-77)
QT/RR hysteresis ≥375 (fourth quartile for all)	39 (28-50)	81 (75-87)	0.65	49 (37-62)	74 (68-80)
ST depression and QT/RR hysteresis combined	–	–	0.70	–	–
Severe ischemia by polar mapping					
ST depression (≥1 mm horizontal or downsloping)	30 (17-46)	81 (76-86)	0.65	21 (12-33)	87 (82-91)
QT/RR hysteresis ≥375 (fourth quartile for all)	51 (30-67)	79 (74-84)	0.71	29 (20-41)	91 (86-94)
ST depression and QT/RR hysteresis combined	–	–	0.74	–	–

PPV indicates positive predictive value; NPV, negative predictive value.

Fig. 4 shows the association of QT/RR hysteresis and the presence of horizontal or downsloping ST-segment depression with any ischemia. These 2 variables were of additive value.

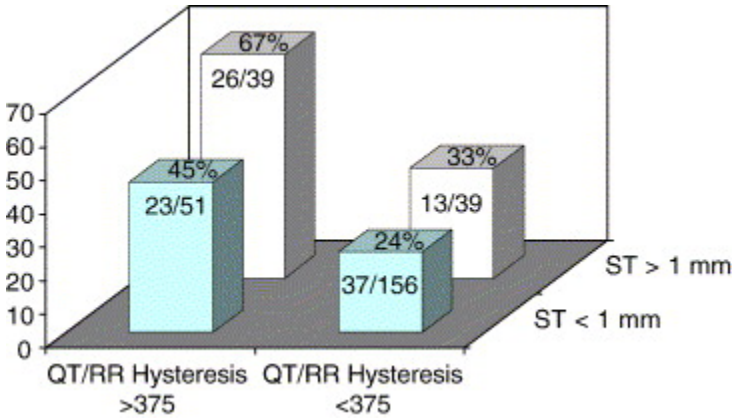

Fig. 4. Association of QT/RR hysteresis, horizontal or downsloping ST-segment depression with percentage of presence of any myocardial ischemia. The cutoff value of QT/RR hysteresis corresponds to the 75% percentile cutoff.

There was no association between QT/RR hysteresis and presence of fixed perfusion defects (Table 2).

Multivariable analyses

Results of multivariable analyses that incorporated all clinical and exercise variables listed in Table 1 and Table 2, but not ejection fraction, are shown in Table 4 and Table 5. For prediction of any ischemia, the only variables that were predictive in more than 50% of bootstrap resamplings were QT/RR hysteresis, amount of horizontal or downsloping ST-segment depression, and resting diastolic blood pressure. QT/RR hysteresis was the first variable to enter the stepwise model. Other clinical and exercise variables including resting and peak heart rate (R-R interval) values as well as heart rate recovery were not predictive of any or severe ischemia. Attempted transformations of QT/RR hysteresis and other continuous variables did not materially improve model fit. Amount of any ST-segment depression (as opposed to horizontal or downsloping ST-segment depression) was not predictive of ischemia. For prediction of severe ischemia, QT/RR hysteresis again emerged as the strongest correlate.

Table 4. Results of stepwise multivariable logistic regression analysis for prediction of any myocardial ischemia

Variable	Odds ratio (95% CI)	*P*	Bootstrap validation (%)
QT/RR hysteresis (per 100)	1.61 (1.22-2.12)	.0008	76
Amount of ST change (mm horizontal or downsloping)	2.33 (1.40-3.91)	.0012	78
Prior coronary artery bypass graft	2.25 (1.17-4.33)	.014	
Resting diastolic blood pressure (per 10 mm Hg)	1.03 (1.01-1.07)	.0088	71
Diabetes without insulin	2.57 (1.18-5.62)	.018	
Diltiazem/verapamil	3.57 (1.05-12.2)	.042	

Variables are shown in the order in which they entered the stepwise model. The c statistic for the model was 0.78.

Table 5. Results of stepwise multivariable logistic regression analysis of severe ischemia

Variable	Odds ratio (95% CI)	*P*	Bootstrap validation (%)
QT/RR hysteresis (per 100)	2.62 (1.79-3.84)	<.0001	84
Diltiazem/verapamil	6.73 (1.86-24.33)	.004	62

Male	6.80 (1.73-26.8)	.006	55
Prior myocardial infarction	2.81 (1.23-6.42)	.014	

Variables are shown in the order in which they entered the stepwise model. ST-segment changes did not enter the model. The c statistic for the model was 0.76.

There was no interaction between QT/RR hysteresis and amount of horizontal or downsloping ST-segment depression for prediction of ischemia (*P* for interaction, .76) or severe ischemia (*P* for interaction, .55). There was a possible interaction with use of *β*-blockade whereby QT/RR hysteresis tended to be a stronger predictor of ischemia in the absence of *β*-blockade (*P* for interaction, .06). Specifically, among the 120 patients not taking *β*-blockers, an increase of QT/RR hysteresis by 100 was associated with an odds ratio for ischemia of 2.45 (95% CI, 1.56-4.00, $P = .0001$). Among the 140 patients taking *β*-blockers, an increase in QT/RR hysteresis by 100 was associated with an odds ratio for ischemia of only 1.47 (95% CI, 1.07-2.02;$P = .017$).

In supplementary analyses, ejection fraction as assessed by SPECT was added to the multivariable models. Although lower ejection fraction was associated with a greater likelihood of ischemia ($P = .0011$) and severe ischemia ($P = .02$), there were no material effects on the association of QT/RR with any ischemia (adjusted odds ratio for increase of 100, 1.74; 95% CI, 1.31-2.31; $P < .0001$; 74% bootstrap validation) or with severe ischemia (adjusted odds ratio for increase of 100, 1.89; 95% CI, 1.37-2.58; $P < .0001$; 88% bootstrap validation).

Coronary angiography

There were 60 patients who underwent coronary angiography after stress testing; angiography took place a median of 20 days later (25th and 75th percentiles, 7 and 35 days). Any coronary disease was noted in 47 patients (78%), whereas 18 (30%) had severe disease. A trend was noted whereby patients with QT/RR hysteresis values of 313 or higher (the median for the whole cohort) were more likely to have any coronary disease (85% vs 69%, $P = .13$) and severe coronary disease (35% vs 23%, $P = .30$). In logistic models, an increase of QT/RR hysteresis by 100 tended to predict the presence of any coronary disease (odds ratio, 1.30; 95% CI, 0.77-2.19, $P = .33$) and severe coronary disease (odds ratio, 1.25; 95% CI, 0.82-1.90; $P = .29$).

Discussion

To the best of our knowledge, this is the first clinical study to examine the association between myocardial ischemia as assessed by myocardial perfusion scintigraphy and exercise-induced QT/RR hysteresis. Among a cohort of 260 patients referred for exercise nuclear imaging, we found that increasing QT/RR hysteresis was associated with a greater likelihood of myocardial ischemia and provided additive information to ST-segment changes. Combining ST-segment changes, QT/RR hysteresis, and clinical data yielded stronger prediction of any or severe

myocardial ischemia. In a supplementary analysis, we noted trends whereby higher values of QT/RR hysteresis were associated with more severe angiographic coronary disease.

The association of QT/R-R–interval hysteresis with exercise-induced demand myocardial ischemia may be related to changes in the electrophysiologic properties of the cardiac myocyte.[23] Specifically, hypoxia, acidosis, and hyperkalemia are thought to lead to decreased action potential duration and an increase in resting potential.[6, 7, 24 and 25] Hyperkalemia has a particularly marked effect on resting membrane action potential, which is reflected as ischemic ST-segment deviation.[23 and 24] In vitro experiments have demonstrated that action potential shortening is cumulative as anoxia duration increases.[7] The differential effects of hyperkalemia, acidosis, and anoxia on resting potential and action potential duration are consistent with our observation that QT/RR hysteresis provides additive information to ST-segment deviation.

We did not note an association between QT/RR hysteresis and fixed SPECT defects. The reasons for this lack of association are not clear. We did consider segments showing both scar and ischemia (eg, periinfarct ischemia) as showing ischemia. It is possible that in the absence of actively metabolizing muscle, dynamic alterations in repolarization times may be hard to demonstrate.

We believe that for QT/RR hysteresis to best reflect myocardial ischemia, it is important that workload be gradually increased and then gradually decreased after exercise; we refer to this as a "quasi-stationary" protocol.[12] With an abrupt and complete cessation of exercise during early recovery, observed QT/RR hysteresis loops may overwhelmingly reflect differences between adaptation rates of sympathetic and parasympathetic tone.[2 and 3] The exercise protocol used in this study was not optimally quasi-stationary, but it included a sufficient cool-down period to allow development of recovery curves and measurement of hysteresis.

Although we did find an association between QT/RR hysteresis and myocardial ischemia, more research is needed before this measure can be routinely incorporated into clinical decision making. We observed that both ST-segment depression and QT/RR hysteresis had relatively low sensitivity but high specificity, consistent with the fact that our study was designed to eliminate work-up bias,[26] that is, all patients underwent scintigraphy irrespective of QT/RR hysteresis values. Secondly, the sensitivity of QT/RR hysteresis may have been adversely affected by concurrent β-blockade therapy; protocols in which β-blockade is systematically held before testing may yield greater diagnostic accuracy.

An important utility of QT/RR hysteresis may be in its ability to identify CAD patients and predict risk of premature death or coronary events. However, larger and longer cohort studies[27] are needed to determine the prognostic value of QT/RR hysteresis over and above existing measures, including ST-segment deviation, functional capacity,[19] chronotropic response,[17] heart rate recovery,[20 and 21] and ventricular ectopy.[28]

Other limitations should be mentioned. We only had angiographic follow-up data in 60 patients; future studies will need to examine this association in larger angiographic cohorts. With this small number, it is difficult to readily explain the discordance between the associations of QT/RR hysteresis with ischemia on the one hand and angiographic disease on the other. It should be noted that ischemia, like QT/RR hysteresis, is a pathophysiologic process, whereas angiographic findings are primarily static and anatomical. Our study was not powered to assess the ability of QT/RR hysteresis to predict ischemia in potentially important subsets, such as women, the elderly, people with established coronary disease, and patients taking certain drugs likeβ-blockers or vasodilators. Finally, ST-segment measures were visual and not computer-based [10]; nonetheless, the ability of computerized ST-segment measures to improve diagnostic accuracy of exercise testing has not been demonstrated by all. [26]

Nonetheless, despite these limitations, we found that exercise-associated QT/RR hysteresis is an independent correlate of myocardial ischemia as assessed by standard perfusion scintigraphy. Future research is needed to determine how best to incorporate QT/RR hysteresis into exercise test interpretation and whether it can function as a prognostic tool for risk stratification of patients with known or suspected coronary disease.

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