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QT Interval–Heart Rate Relation During Exercise in Normal Men and Women: Definition by Linear Regression Analysis

PAUL KLIGFIELD, MD, FACC, KEVIN G. LAX, MD, PETER M. OKIN, MD, FACC

New York, New York

Objectives. This study sought to develop a regression-based method for characterization of QT interval behavior during exercise and to define the normal range of the resulting "dynamic" measures of repolarization during submaximal treadmill testing in men and women.

Background. The Bazett-corrected QT (QTc) interval during exercise has been used as a marker for ischemic disease, arrhythmogenic substrate and the long QT syndrome. However, recent studies indicate that the QTc interval is nonlinear with respect to heart rate during exercise, making the end-exercise QTc interval dependent on peak work load achieved. In contrast, the unadjusted QT interval measured from QRS onset to T wave offset (QTo) and from QRS onset to T wave peak (QTm) appears to vary linearly with heart rate during gently graded effort.

Methods. The QT interval relation to heart rate and cycle length was examined by linear regression in 50 normal men (mean age 48 years) and 30 normal women (mean age 51 years), all of whom had normal rest electrocardiograms. The QTo and QTm measurements were made from digitized lead V_5 complexes averaged by computer over 20-s periods, at upright control and after seven 2-min stages of the Cornell modification of the Bruce treadmill protocol (work load equivalent to Bruce stage 3).

Results. For each subject, regression of QTo (ms) versus heart rate (beats/min) resulted in a slope (reflecting the "dynamic" change in QTo during effort), an adjusted intercept (reflecting QTo extrapolated to a heart rate of 60 beats/min) and a significant correlation coefficient (r) value. Under these conditions, mean ± SD (5th to 95th percentile) values for men were −1.45 ± 0.34 ms/beat per min (−0.90, "less dynamic" to −1.96, "more dynamic") for the slope; 403 ± 21 ms (365 to 431) for the adjusted intercept; and −0.93 ± 0.06 (−0.81 to −0.99) for r. Values for women were more dynamic, with a mean slope of −1.74 ± 0.32 ms/beat per min (−1.23 to −2.18, $p < 0.0005$ vs. men) and higher adjusted intercept of 426 ± 23 ms (392 to 462, $p < 0.0001$ vs. men) at similar strength of correlation ($r = -0.95 \pm 0.06$). Corresponding normal data were also tabulated for QTm behavior and QT–RR interval behavior during exercise.

Conclusions. These data provide a "dynamic" definition of normal and abnormal repolarization and describe normal limits for the linear relations of the QTo and QTm intervals with respect to heart rate and cycle length during submaximal exercise in normal men and women.

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Shortening of the QT interval with increasing heart rate is a well recognized consequence of the interval–duration relation (1), but the QT interval is modulated by a number of additional rate-independent factors (2–5), and the adequacy of different methods of heart rate adjustment of repolarization at rest has been controversial since the early work of Bazett (6–11). Problems relating to adjustment of the QT interval adjustment at rest are further increased during exercise, when variable autonomic and neurohumoral responses to cardiovascular stress may also affect the manner of QT interval shortening (12–15). Abnormal QT responses to exercise have been associated with various forms of the long QT syndrome (16,17), with a predisposition to proarrhythmic effects of drugs (18), and with coronary artery disease (19,20). Clarification of effort-related repolarization behavior in normal subjects and in patients with heart disease is therefore of clinical importance, but the definition and description of repolarization must extend beyond the simple Bazett correction alone. Recent studies (21) indicate that the corrected QT (QTc) interval is nonlinear with respect to heart rate during exercise, making the end-exercise QTc interval dependent on peak work load achieved. In contrast, the group mean unadjusted QT interval measured from QRS onset to T wave offset (QTo) and from QRS onset to T wave peak (QTm) has been observed (22) to vary linearly with mean heart rate, and also with corresponding cycle length, under conditions of gently graded treadmill exercise. Accordingly, the present study examined the linear regression characteristics of the QT interval–heart rate relations in subjects to describe and define alternative "dynamic" features of repolarization during exercise in normal men and women.

From the Division of Cardiology, The New York Hospital–Cornell Medical Center, New York, New York. This study was supported in part by grants from the Elizabeth and Robert Rosenman Charitable Foundation and from George I. Lowy, New York, New York.

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Address for correspondence: Dr. Paul Kligfield, 525 East 68th Street, New York, New York 10021.

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Abbreviations and Acronyms

ECG = electrocardiographic, electrocardiogram
QTc = Corrected QT interval
QTm = QT interval measured from QRS onset to T wave peak
QTo = QT interval measured from QRS onset to T wave offset
QTo_{60} = QTo intercept at heart rate 60 beats/min

Methods

The underlying relations between the unadjusted QTo (Q to T wave offset) interval and heart rate and between QTm (Q to T wave peak) and heart rate were examined by linear regression during submaximal exercise in 50 normal men and 30 normal women. The men (mean [±SD] age was 48 ± 10 years) were consecutively drawn from a previously reported study (21) of temporal measures of repolarization and dispersion of repolarization during exercise. The women (mean age was 51 ± 10 years, $p = 0.19$ versus men) were selected from subjects studied during the same time period with protocols and exercise testing equipment that was identical to that used for the men. All subjects were asymptomatic, without clinical evidence of valvular or myopathic disease, and all had normal rest 12-lead electrocardiograms (ECGs), with no evidence of myocardial infarction, ventricular hypertrophy or intraventricular conduction defect (defined as QRS duration ≥110 ms, ST segment depression ≥0.05 mV at a point 60 to 80 ms after the J point or abnormal T wave configuration).

Exercise protocol and ECG methods. All rest and exercise measurements were made from digitized precordial lead V_5 complexes that were averaged by computer (Quinton Instruments, Inc., Q5000) over 20-s periods at upright control and at the end of each stage of exercise, using the gently graded Cornell treadmill protocol (23) that produces small heart rate increments between 2-min stages. All measurements were made manually, by a single experienced observer (K.G.L.), to the nearest 10 ms. QTo (ms) was measured from the onset of the earliest QRS deflection to the end of the T wave, or to the nadir of the T wave fusion with a U wave or with a P wave at faster heart rates. The QTm interval (ms) was measured from the onset of the earliest QRS deflection to the peak of the T wave. The duration of the terminal component of the T wave was defined by QTo–QTm. The relative proportion of QT subintervals was calculated from the ratio of QTm to QTo throughout exercise. Heart rates (beats/min) were determined by computer averaging of the final 20 s of each exercise stage, from which the corresponding RR intervals were calculated.

Regression analyses. Regression of QTo versus heart rate was selected for the primary analysis and presentation of the data because QTo is widely used and because heart rate, as opposed to cycle length, increases physiologically during exercise (22). However, parallel data derived from regression of QTo versus the RR interval, and from regression of QTm versus both heart rate and the RR interval were also examined and are reported in the results. Proportional changes in QT subintervals during exercise were explored by linear regression of the QTm/QTo ratio against heart rate.

The QTo–heart rate relation was examined at upright control and during submaximal exercise by means of linear regression, according to which

$$QTo = b - mHR,$$

where unadjusted QTo is measured in ms; HR is heart rate in beats/min, m is the slope of the linear relation; and b is the intercept in ms. Because the linear regression intercept b represents a theoretically awkward heart rate of 0 beats/min, the intercept at a more physiologic baseline heart rate of 60 beats/min was defined as the QTo_{60} and calculated as $(b - 60m)$. Similar equations were used to define the comparable relation involving QTm and heart rate, and the relation of both QTo and QTm to cycle length in ms.

A major goal of this study was to define the QT interval–heart rate relation in normal subjects at submaximal heart rates that could be achieved by general populations. Therefore, regression was calculated for eight data points acquired during exercise testing, including upright control and the first seven 2-min stages of the Cornell protocol, which is comparable to stage 3 of the standard Bruce protocol (23). At this level of exercise, mean heart rate in the group of 50 men was 135 ± 18 beats/min and 1[illegible]2 ± 21 beats/min in the group of 30 women ($p = 0.13$).

To explore the use of fewer data points at even lower exercise work loads, we also examined regression of six data points that included upright control through the first five stages of the Cornell protocol (comparable to standard Bruce stage 2), at which point the mean peak rate was 115 ± 17 beats/min in men and 130 ± 23 beats/min in women ($p < 0.005$). In some subjects there was a paradoxic increase in QTo from control during the very earliest stages of exercise, after which the linear decrease in QTo with heart rate was again apparent. To adjust for this occasional early nonlinearity, we also examined regression of six data points during exercise only, excluding the control measurements. Included in these regressions were data from the completion of 2 min of exercise through five additional stages of the Cornell protocol, at which point the mean peak rate was 125 ± 18 beats/min in men and 139 ± 22 beats/min in women ($p < 0.005$).

Complete data through the completion of seven stages of exercise (14-min duration) were not available for seven men: one was unable to exercise beyond the fifth stage (10 min); three were unable to exercise beyond the sixth stage (12 min) of exercise (in one of these subjects, a reliable offset of QTo could not be determined at 12 min only); two had undeterminable QTo at 12 and 14 min; and one had undeterminable QTo at 14 min only. Complete data were not available for nine women: two were unable to exercise beyond the fourth stage; two were unable to exercise beyond the fifth stage; and five were unable to exercise beyond the sixth stage (12 min); two of these subjects had undeterminable QTo (but measurable QTm) at one or more stages. In these cases, regression results were based only on the available data.

Table 1. QT-Heart Rate Relation in Men: Definition by Linear Regression Analysis

	Mean	SD	5th Percentile	95th Percentile
QTo-Heart Rate Relation				
From 8 data points, control plus exercise (mean peak rate 135 beats/min)				
Slope	−1.45	0.34	−1.96	−0.90
Intercept	490	38	415	539
r value	−0.93	0.06	−0.99	−0.81
SEE (ms)	10.7	3.9	5.7	18.6
From 6 data points, control plus exercise (mean peak rate 115 beats/min)				
Slope	−1.39	0.54	−2.30	0.70
Intercept	484	52	405	549
r value	−0.87	0.11	−0.98	−0.66
SEE (ms)	11.0	4.4	4.8	17.9
From 6 data points, exercise only (mean peak rate 125 beats/min)				
Slope	−1.53	0.39	−2.11	−0.99
Intercept	498	44	427	564
r value	−0.90	0.09	−0.98	−0.77
SEE (ms)	9.5	3.9	4.4	17.3
QTm-Heart Rate Relation				
From 8 data points, control plus exercise (mean peak rate 135 beats/min)				
Slope	−1.24	0.38	−1.89	−0.74
Intercept	386	43	327	455
r value	−0.94	0.06	−0.99	−0.85
SEE (ms)	8.2	3.2	5.1	13.2
From 6 data points, control plus exercise (mean peak rate 115 beats/min)				
Slope	−1.40	0.46	−2.20	−0.72
Intercept	401	49	321	475
r value	−0.93	0.06	−0.99	0.83
SEE (ms)	7.6	3.3	4.1	14.6
From 6 data points, exercise only (mean peak rate 125 beats/min)				
Slope	−1.35	0.47	−2.32	−0.64
Intercept	396	50	318	486
r value	−0.91	0.08	−0.99	−0.76
SEE (ms)	7.7	3.4	3.6	14.3

QTm = QT interval measured from onset of the QRS complex to the T wave peak; QTo = QT interval measured from onset of the QRS complex to the T wave offset.

Linear regression analysis was performed by the method of least squares, with each individual relation defined by the slope m, intercept b, correlation coefficient r and standard error of the estimate (SEE [in ms]) of the solution. Group data are presented with the standard deviation (SD) of the mean value as the index of dispersion, and with the 5% to 95% range of individual values by interpolation for each measurement. Comparison of independent mean values between men and women was performed by the Student *t* test, with $p < 0.05$ required for rejection of the null hypothesis.

Results

The regression data are shown in Tables 1 and 2 for men and in Tables 3 and 4 for women.

Table 2. QT–Cycle Length Relation in Men: Definition by Linear Regression Analysis

	Mean	SD	5th Percentile	95th Percentile
QTo–Cycle Length Relation				
From 8 data points, control plus exercise (mean peak rate 135 beats/min)				
Slope	237	71	109	351
Intercept	199	42	130	270
r value	0.90	0.09	0.72	0.98
SEE (ms)	12.4	4.0	6.7	18.9
From 6 data points, control plus exercise (mean peak rate 115 beats/min)				
Slope	197	86	74	326
Intercept	226	59	144	301
r value	0.85	0.12	0.61	0.98
SEE (ms)	11.2	4.4	5.6	19.7
From 6 data points, exercise only (mean peak rate 125 beats/min)				
Slope	276	84	157	430
Intercept	180	47	105	258
r value	0.90	0.09	0.72	0.98
SEE (ms)	9.9	4.0	4.9	17.4
QTm–Cycle Length Relation				
From 8 data points, control plus exercise (mean peak rate 135 beats/min)				
Slope	205	59	101	288
Intercept	137	34	91	191
r value	0.93	0.06	0.82	0.99
SEE (ms)	8.3	3.0	4.8	13.3
From 6 data points, control plus exercise (mean peak rate 115 beats/min)				
Slope	197	69	95	313
Intercept	143	42	69	203
r value	0.91	0.08	0.78	0.99
SEE (ms)	8.1	3.6	3.1	14.4
From 6 data points, exercise only (mean peak rate 125 beats/min)				
Slope	238	60	143	352
Intercept	118	35	55	175
r value	0.92	0.07	0.77	0.99
SEE (ms)	7.4	3.5	3.4	13.4

Abbreviations as in Table 1.

QT–heart rate relation. The regression data of QTo versus exercise heart rate in men are shown in Table 1. From eight data points, including upright control, the mean slope of the relation was −1.45 ± 0.34 ms/beat per min, with a 5% to 95% range of −1.96 to −0.90. The mean intercept was 490 ± 38 ms, corresponding to a mean calculated QTo_{60} of 403 ± 21 ms, with a 5% to 95% range for the adjusted intercept of 365 to 431 ms. The coefficients of linear regression were high, with a mean value of −0.93 ± 0.06 and a 5% to 95% range of −0.99 to −0.81. Mean heart rate after seven stages was 135 ± 18 beats/min in men and 142 ± 21 beats/min in women ($p = 0.13$). Values for the QTo–heart rate relation in women were more dynamic (Table 3), with a mean slope −1.74 ± 0.32 ms/beat per min (5% to 95% range −1.23 to −2.18, $p < 0.0005$ vs. men) and higher adjusted intercept of 426 ± 23 ms (5% to 95% range 392 to 462, $p < 0.0001$ vs. men) at similar correlation strength (mean r = −0.95 ± 0.06).

There was a strong inverse correlation between the slope

Table 3. QT–Heart Rate Relation in Women: Definition by Linear Regression Analysis

	Mean	SD	5th Percentile	95th Percentile
QTo–Heart Rate Relation				
From 8 data points, control plus exercise (mean peak rate 143 beats/min)				
Slope	−1.74	0.32	−2.18	−1.23
Intercept	531	41	468	598
r value	−0.95	0.05	−0.99	−0.84
SEE (ms)	12.3	5.4	4.4	18.5
From 6 data points, control plus exercise (mean peak rate 130 beats/min)				
Slope	−1.59	0.45	−2.25	−0.80
Intercept	516	50	425	577
r value	−0.89	0.12	−0.99	−0.59
SEE (ms)	12.1	5.2	4.0	20.7
From 6 data points, exercise only (mean peak rate 139 beats/min)				
Slope	−1.94	0.52	−2.85	−1.05
Intercept	556	66	447	672
r value	−0.93	0.09	−1.00	−0.74
SEE (ms)	9.3	4.9	3.0	17.9
QTm–Heart Rate Relation				
From 8 data points, control plus exercise (mean peak rate 143 beats/min)				
Slope	−1.33	0.31	−1.85	−0.99
Intercept	401	38	354	463
r value	−0.95	0.05	−0.99	−0.90
SEE (ms)	8.3	2.8	4.1	12.5
From 6 data points, control plus exercise (mean peak rate 130 beats/min)				
Slope	−1.46	0.36	−1.99	−0.93
Intercept	413	41	352	463
r value	−0.95	0.06	−1.00	−0.84
SEE (ms)	7.3	3.1	3.4	12.5
From 6 data points, exercise only (mean peak rate 139 beats/min)				
Slope	−1.31	0.39	−2.09	−0.85
Intercept	394	46	331	474
r value	−0.95	0.04	−0.99	−0.85
SEE (ms)	6.5	2.4	3.5	10.9

Abbreviations as in Table 1.

and the zero intercept of QTo regression versus heart rate both in men (r = −0.91) and women (r = −0.96), so that in general, subjects with longer QTo at lower heart rates tended to have more "dynamic" QTo shortening with exercise, whereas subjects with shorter QTo at lower heart rates tended to have less "dynamic" shortening.

An example of data from a subject with a typical linear decrease in QTo from upright control throughout exercise is shown in the top panel of Figure 1; the bottom panel of Figure 1 illustrates one of the weakest linear correlations in the sample (r = −0.80), resulting from a pattern characterized by an initial increase or absence of shortening of QTo during the early phases of exercise, which was seen in 14 (28%) normal men and 10 (33%) normal women.

When only six data points were used that included upright control, mean slope, intercept and correlation coefficient, values were slightly lower, with a larger range, in both women and men (Tables 1 and 3). When only six data points during

Table 4. QT–Cycle Length Relation in Women: Definition by Linear Regression Analysis

	Mean	SD	5th Percentile	95th Percentile
QTo–Cycle Length Relation				
From 8 data points, control plus exercise (mean peak rate 143 beats/min)				
Slope	333	127	167	574
Intercept	154	65	31	245
r value	0.91	0.06	0.79	0.98
SEE (ms)	17.0	8.2	7.9	26.0
From 6 data points, control plus exercise (mean peak rate 130 beats/min)				
Slope	274	131	171	518
Intercept	192	75	67	282
r value	0.87	0.13	0.56	0.99
SEE (ms)	14.2	6.3	5.0	23.7
From 6 data points, exercise only (mean peak rate 139 beats/min)				
Slope	452	197	171	742
Intercept	100	95	−37	241
r value	0.92	0.10	0.71	1.00
SEE (ms)	9.8	4.9	4.1	17.1
QTm–Cycle Length Relation				
From 8 data points, control plus exercise (mean peak rate 135 beats/min)				
Slope	256	65	159	331
Intercept	112	37	65	172
r value	0.96	0.05	0.88	0.99
SEE (ms)	8.0	2.7	4.6	13.1
From 6 data points, control plus exercise (mean peak rate 115 beats/min)				
Slope	249	79	138	395
Intercept	118	46	50	207
r value	0.95	0.07	0.79	0.99
SEE (ms)	7.5	3.1	3.8	11.9
From 6 data points, exercise only (mean peak rate 125 beats/min)				
Slope	286	65	204	394
Intercept	96	36	40	152
r value	0.95	0.04	0.87	0.99
SEE (ms)	6.2	2.3	3.3	10.6

Abbreviations as in Table 1.

exercise were used, the mean slope and intercept values were slightly higher in both women and men. The corresponding data for regression of QTm versus heart rate are also shown in Tables 1 and 3. The slopes of regression were lower for QTm than for QTo in both women and men. The proportional changes in QT subintervals during eight stages of exercise in men are examined below in further detail.

QT–cycle length relation. The regression data of QTo versus the RR interval (cycle length [s]) in men are shown in Table 2. From eight data points, including upright control, the mean slope of the relation was 237 ± 71 ms/s (5% to 95% range 109 to 351), mean intercept 199 ± 42 ms and mean coefficient of linear regression 0.90 ± 0.07. The relation was more dynamic in women (Table 4). When only six data points were used that included upright control, the mean slope was lower and the mean intercept higher in both women and men (Tables 2 and 4). When only six data points during exercise were used, the mean slope was higher and the intercept lower

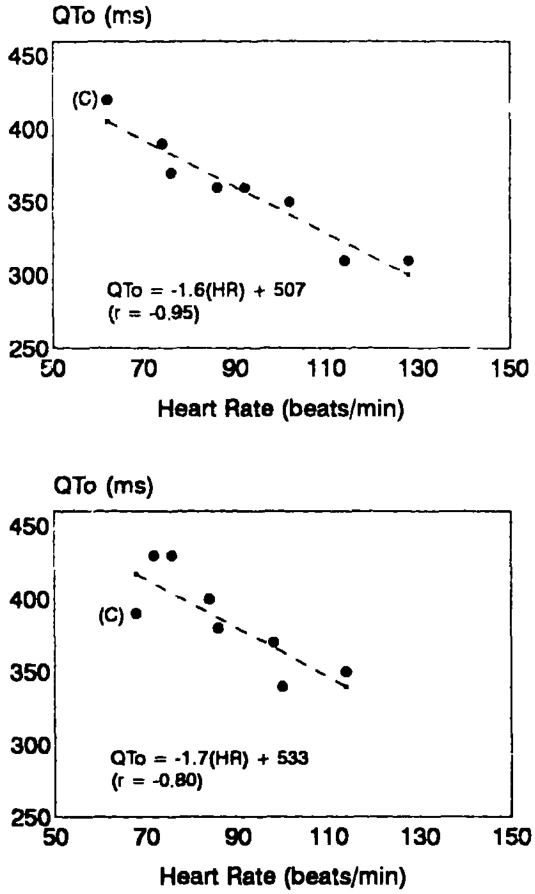

Figure 1. QT interval–heart rate (HR) relation during treadmill exercise in two normal men. **Top panel,** A typical inverse relation with strong linear correlation is shown from the upright control measurements (C) through seven subsequent end-stage measurements. **Bottom panel,** One of the weakest linear correlations in the present cohort is shown. This weaker relation results in part from a less common pattern in which there is an initial increase in QTo from upright control during the early phases of exercise followed by a linear decrease with further effort.

in both women and men. The corresponding data for regression of QTm versus the RR interval are also shown in Tables 2 and 4, from which it is seen that the slope of the regression was lower for QTm than for QTo over the range of the eight data points in both women and men.

Proportional shortening of QT subintervals during exercise. Because of differences in initial magnitudes, the lower slope of the regressions of QTm versus heart rate than for QTo versus heart rate does not necessarily indicate that the proportional change in QTm during exercise is less than that in the overall QTo. Indeed, regression of the QTm/QTo ratio versus heart rate, from control through 14 min of exercise, revealed a mean slope for the normal men of only −0.0004 ± 0.0010 (5% to 95% range −0.0022 to 0.0010), indicating a relatively proportional change in early and late QTo subintervals at this level of generally submaximal effort.

The mean decrease in QTo from upright control to 14 min of exercise was 82 ± 28 ms in men. This was associated with a mean decrease in QTm of 66 ± 19 ms and a mean decrease in end-repolarization defined by QTo–QTm of 16 ± 23 ms. To further explore the proportional shortening of the QT subintervals, the ratios of the 14-min measured intervals (or the intervals at the latest exercise stage at which all data could be measured in seven subjects) to the corresponding upright control measured intervals were calculated. Overall mean and standard deviation, with 5% to 95% values, for the ratio of shortening of the QTo subinterval during moderate treadmill exercise (the measured QTo subinterval at 14 min divided by the QTo subinterval at upright control) in normal men was 0.79 ± 0.07 (range 0.68 to 0.89). The ratio of shortening of the QTm subinterval in these subjects was strikingly similar: 0.78 ± 0.05 (range 0.69 to 0.87). Although the ratio of shortening of the QTo–QTm was similar at 0.84, the imprecision of determining this smaller measure by subtraction of larger numbers led to a large standard deviation of 0.27, with a wide 5% to 95% range of 0.47 to 1.27.

Discussion

A number of recent studies highlight the clinical significance of abnormal temporal measures of ECG repolarization (16–21). However, definition of normal and abnormal repolarization has been imprecise and controversial since the introduction of the Bazett correction (6). Most of the methods that have been proposed for rate correction of measured QT intervals have been based on pooled data from routine rest ECGs in populations (7–11,24). A number of recent studies have begun to explore the relation of QT intervals to changing cycle length within subjects by regression methods applied to data recorded during ambulatory electrocardiography (25–27). These methods can also be applied to exercise electrocardiography (28), as seen in the work of Vincent et al. (16) in patients with Romano Ward syndrome and Gill et al. (29) in patients with ischemic heart disease and exercise-induced ventricular tachycardia.

The present observations document the relatively wide range in which repolarization behavior of clinically normal subjects can be expected to vary during the neurohumoral activation provoked by slowly graded exercise. This extent of exercise-induced variability of repolarization is not inconsistent with available data regarding normal subjects at rest. Because our adjusted intercepts are extrapolated from upright exercise data, it must be appreciated that our QTo_{60} values are not equivalent to supine values found on the rest ECG. Even so, within the limits of observed slope and intercept values found in our individual regression analyses, the 365- to 431-ms values calculated for the 5% to 95% range of QTo_{60} in men are still close to the widely accepted rest range for the simple Bazett corrected QT interval, whereas the 392- to 462-ms range of QTo_{60} in women is slightly higher, consistent with recognized gender-based differences in rest QTc intervals (30). Because our observations indicate that the shortening of the QT interval in relation to heart rate during treadmill testing is more "dynamic" in women than in men, gender-related QT differences should decrease with exercise. Indeed, solution of the mean gender-specific linear regression equations derived in our study indicates that a theoretically equal average QTo in men and women should occur during exercise at a heart rate of ~140 beats/min.

QTo–heart rate relation during exercise. Our findings support previous observations that useful linear relations between the QTo interval and both heart rate (12,15,16,22,28) and cycle length (22,29) may be found during exercise testing. The presumption of linearity allows slope and intercept variables to be calculated from the underlying unadjusted QT interval–heart rate relation, which are simpler to interpret than coefficients of alternate nonlinear derivations (13). As a result, the regression data of Tables 1 and 3 can be used to determine whether the relation of QTo or QTm to changing heart rate during exercise in an individual study subject is consistent with the pattern found in normal men and women.

This presumption of linearity may not be entirely accurate in the isolated control and very earliest exercise phases of treadmill testing. Coughlin et al. (15) reported a paradoxic increase in the unadjusted QT interval during the first minute of exercise in patients with QT-dependent rate-responsive ventricular pacemakers, and we observed small increases in unadjusted QTo from upright control recordings through the first few stages of exercise in ~20% to 30% of our normal subjects. This phenomenon is reflected in the less dynamic slope values obtained when only five, versus seven, data points were used in addition to the upright control data for linear regression, and also in the more dynamic slope values that were obtained with fewer data points when the control data were eliminated from the regression calculation. It is possible that the slope and intercept derived from regression of exercise data alone will prove more useful than those that incorporate rest information; for the present, each approach is summarized in Tables 1 and 2 for men and separately in Tables 3 and 4 for women.

The regression of QT measures versus the RR interval instead of heart rate during exercise is similarly strong in these normal men and women, and the data of Tables 2 and 4 might be used as an alternative group of reference standards based on cycle length rather than rate. In the exercise setting, we believe that heart rate is preferable to cycle length as the independent variable. Because the QT response to increasing heart rate during exercise is also covariate with time, these physiologic relations are simpler to visualize and more practical to graph directly as a function of rate than inversely as a function of the corresponding RR intervals. For similar reasons, the magnitude of ST segment depression also has been linearly related to heart rate during exercise testing (31), and the noninvasively determined systolic time indexes have traditionally been related to rate rather than to cycle length by related linear regression methods (32).

Our results indicate that the decrease in QTm is proportional to, or at most only very slightly proportionally less than, the overall decrease in QTo during submaximal exercise in normal subjects. This finding is consistent with previous observations by O'Donnell et al. (33) that the terminal T wave subinterval QTo–QTm (defined as aT–eT in that report) is relatively unchanged or slightly increased as a fraction of QTo in normal subjects but may be significantly decreased in the presence of myocardial ischemia. The relative proportion and range of the terminal T wave calculated at rest from the observed QTm/QTo ratio in our normal men are nearly identical with the recent findings of Murray et al. (34) in a smaller group of semisupine subjects studied by routine electrocardiography.

Methodologic factors and limitations. An important limitation of these methods is the error inherent in manual measurement of T wave offset, and to a lesser degree in the measurement of T wave peak, in a single precordial lead. This measurement error is particularly problematic at the faster heart rates that occur with exercise because the end of the T wave tends to merge with the onset of the subsequent P wave. The magnitude of this problem was reduced but not eliminated in the present study by analyses that focused only on the earlier phases of exercise in which heart rates were generally <140 beats/min. All measurements were made by a single experienced observer (K.G.L.), but in several cases no reliable T wave offset could be obtained, and regression was limited to the available data points. During measurement, there was no blinding with regard to tracing sequence within subjects and no randomization of tracings between subjects.

The apparent linearity of unadjusted QT interval durations and changing heart rate during exercise may not occur during all conditions of exercise. Adaptation of the QT interval to changing heart rate in humans is not an instantaneous consequence of varying cycle length alone; rather, it depends on rate and the additional influence of duration of rate as further modified by complex neurohumoral factors during exercise (2–4,15). Accordingly, the strong linearity of our group mean data in normal men and women may not be found in other populations, particularly in the presence of disease or under other test conditions.

Thus, our findings are similar in magnitude to the QTo–heart rate slope of −1.87 and intercept of 522 ms (calculated QTo_{60} = 410 ms) found by Rickards and Norman (12) in patients with suspected ischemic heart disease who exercised according to the standard Bruce protocol. Our findings are also similar but not identical to the QTo–RR slope range of 250 to 300 and intercept range of 153 to 175 ms found by Gill et al. (29) in subsets of patients with ischemic heart disease, with and without exercise-related ventricular tachycardia who were studied during the Bruce protocol.

Although unfamiliarity with the Cornell protocol might limit application of these methods, findings with less gently graded exercise test protocols, such as the widely used Bruce protocol, may differ as a consequence of different restitution patterns of QT interval response to larger changes in work load and heart rate (1,4,15). Averaging of fewer complexes at a different level of exercise equilibration may also alter these relations, which may further be affected by the method of averaging and by the number of leads used for examination of repolarization intervals. The present data apply to adults only, and comparable data are required for application in children.

Clinical implications. These observations suggest that it might be appropriate to describe and define repolarization behavior by reference to the statistical distribution of slopes and intercepts from regression of unadjusted QT intervals and heart rate during exercise in normal subjects. These variables may provide insights that complement currently available data that can be obtained from the rest and the ambulatory ECG tracings. Although regression of QTo versus heart rate alone is unlikely to separate normal subjects from patients with ischemia (21), the behavior of QT subintervals during exercise requires further examination (33). The effect of exercise on repolarization in the Romano-Ward syndrome also requires clarification. These methods may also help to identify patients with otherwise subtle forms of the long QT syndrome, in whom a decrease in the slope of the QTo–heart rate relation during exercise has been observed (16); at the same time, an increase in the slope of this relation has been reported (35) in other patients in whom the QT interval is markedly prolonged at rest.

Because exercise repolarization can be influenced by both rate-dependent and rate-independent phenomena, careful attention to details of protocol are required to ensure reliable standardization of these methods in normal subjects and in patients with a variety of disorders. Under these conditions, characterization of repolarization during exercise might facilitate identification of otherwise subtle forms of the long QT syndrome, and it also might assist in the detection of subjects at increased risk of complex arrhythmias or for proarrhythmic effects of drugs.

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