Autonomic effects on QT-RR interval dynamics after exercise

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Sundaram S, Carnethon M, Polito K, Kadish AH, Goldberger JJ. Autonomic effects on QT-RR interval dynamics after exercise. Am J Physiol Heart Circ Physiol 294: H490–H497, 2008. First published November 9, 2007; doi:10.1152/ajpheart.00046.2007.—This study was designed to assess autonomic effects on the QT interval during recovery from exercise. Exercise is associated with an acute increased risk of sudden cardiac death. Evidence of impaired parasympathetic activity, such as low heart rate variability and heart rate recovery, and an increased QT interval are also associated with increased mortality. However, there is no clear pathophysiological link among these findings. Bicycle exercise testing was performed serially in 33 healthy volunteers (19 men; ages, 54 ± 7 yr) under four conditions: 1) baseline, 2) β-adrenergic blockade-intravenous propranolol (0.2 mg/kg) administered during exercise, 3) parasympathetic blockade-intravenous atropine (0.04 mg/kg) administered during exercise, and 4) double blockade with propranolol and atropine. ECGs were obtained every minute in recovery for 10 min and then at the 15th and 20th min, from which the QT and RR intervals were measured. Linear regression analyses were used to assess the individual QT-RR relationships for each subject for each condition. Relative to baseline, the QT-RR relationship with parasympathetic blockade was shifted to the left and had a steeper slope. In contrast, the QT-RR relationship with β-adrenergic blockade was shifted to the right and had a less steep slope. The baseline and double-blockade QT-RR relationships were in the middle and essentially superimposable. There was a negative relationship between QT-RR slope and heart rate or RR interval recoveries, but it was significant only for the 1- and 2-min RR interval recoveries with low R² values of 0.124 and 0.114. The main parasympathetic effect in the postexercise recovery period is to counteract the sympathetically mediated QT prolongation. These data support the concept that parasympathetic tone may provide a natural antiarrhythmic effect during this time.

parasympathetic; heart rate recovery; QT interval

THE PATHOPHYSIOLOGY of sudden cardiac death is not completely understood. A variety of epidemiologic findings has provided key insights into the potential roles of ventricular repolarization, autonomic tone, and exercise. Although exercise has overall salutary effects, it has been shown that the risk of sudden death is increased dramatically during and immediately after exercise (3, 36) compared with sedentary periods. Although there are several possible mechanisms for this marked increased risk of sudden cardiac death, including the induction of myocardial ischemia, it may be related to the acute changes in autonomic tone that accompany exercise. The prognostic significance of abnormalities of autonomic tone has been established in multiple studies that have evaluated autonomic control of the heart rate predominantly at rest or during daily activities. These studies have linked diminished parasympathetic control with increased mortality (8, 21, 24, 26, 39, 41). Finally, population studies have linked the QT interval on a 12-lead electrocardiogram (ECG) with an increased risk of ventricular arrhythmias and sudden death both in patients with coronary artery disease (1, 14, 50) and even in the general population (13, 40, 49).

Recent reports describing the independent prognostic significance of heart rate recovery 1 min after the cessation of exercise (11, 12, 19, 38, 51, 54) provided an important potential link between exercise and abnormal autonomic control of the heart rate. Interestingly, recent data link abnormal heart rate recovery with increased risk for sudden death (19). Once again, the prognostic significance of delayed heart rate recovery has been proposed to be related to its role as a marker for abnormal or delayed parasympathetic reactivation.

One potential hypothesis linking all these observations with a pathophysiological basis for sudden death is that abnormally depressed parasympathetic effects during and after exercise are associated with an increased QT interval. Conversely, normal parasympathetic control during exercise and recovery serves to shorten the QT, thereby providing an antiarrhythmic effect. We have previously shown that even with maximal exercise in normal, healthy subjects, parasympathetic effects on heart rate can still be demonstrated at peak exercise (20). Because the autonomic effects on QT interval dynamics following exercise are not well understood, this study was designed to evaluate the autonomic effects on the QT interval during recovery from moderate exercise in a normal population. We hypothesized that parasympathetic effects during recovery serve to shorten the QT interval.

METHODS

Study design. The aim of the present study was to evaluate the autonomic effects on the QT interval during recovery from moderate exercise. Moderate exercise was chosen for study since this is a common intensity of exercise and a reproducible level of exercise was required for all four conditions tested. Autonomic effects were studied using selective blockade with propranolol, atropine, and the combination of propranolol and atropine at separate exercise sessions. Evaluation of the autonomic effects on the QT interval is made complex by the need to simultaneously adjust for the well-known effects of heart rate on the QT interval. Various formulations, such as Bazett’s formula (6) or Friederica’s cube root equation (16), have been used in the past to adjust the QT interval for differences in heart rate. These different formulations, however, have been shown to have significant limitations precluding the use of adjustment formulas in this study (33). The QT-RR interval relationship, however, has been shown to be a reliable and reproducible description of cardiac repolarization over time (5, 15). Thus this study was designed to compare...
the QT-RR interval relationship during recovery with selective autonomic blockade administered during exercise.

Subjects. Healthy volunteers were recruited from the community. Potential subjects had to have normal physical examinations, ECGs, hemocrits, and serum electrolytes. Subjects with cardiac complaints (chest pain, shortness of breath, palpitations, and dyspnea on exertion), a cardiac history, or those taking cardioactive medications were excluded. Subjects with other major systemic illnesses (i.e., asthma and diabetes) were also excluded. In addition, only subjects who indicated that they participated in regular aerobic exercise a minimum of 60 min/wk were studied. Highly trained endurance athletes were excluded. All subjects provided written informed consent. The study was approved by the Northwestern University Institutional Review Board.

Exercise testing. All evaluations were performed on an outpatient basis in the General Clinical Research Center at Northwestern Memorial Hospital. Subjects underwent bicycle exercise testing on 4 separate days, each separated by at least 72 h. On each day of testing, a peripheral intravenous line was inserted into the forearm for blood draws and/or drug administration. A second intravenous line was inserted when needed for propranolol infusion. Subjects were attached to a cardiac monitor and a 12-lead ECG machine (Marquette Mac VU, Milwaukee, WI). Subjects were seated on an electrically braked bicycle ergometer (SciFit Pro II, Tulsa, OK). At the first session, a 12-lead ECG, blood pressure, chemistry panel, and complete blood count were obtained at rest, after the subject was seated for at least 5 min. Subjects were then instructed to exercise, keeping pedal speed at 80 revolutions/min. Workload was maintained at 50 W for 4 min and then increased every 2 min as tolerated in 25-W increments to a maximum of 125 W. The goal was to have all subjects exercise comfortably for a total duration of 24 min, achieving a heart rate of 120–130 beats/min. Heart rate was recorded before exercise, every minute during exercise, and every minute for the 20 min of recovery. After the completion of exercise, a 12-lead ECG was obtained (peak exercise, time 0 of recovery). Subjects remained in the seated position on the bicycle for 20 min. ECGs were obtained every minute in recovery for 10 min and then at the 15th and 20th minute. This initial test without the administration of either propranolol or atropine is labeled as the baseline condition.

At the second through fourth sessions, the identical exercise protocol was performed as it was for each subject on the first day with selective autonomic blockade administered during exercise. At sessions 2 and 3, the following drugs were administered in random order. First, intravenous atropine (0.04 mg/kg) was given in divided doses (0.01 mg/kg every 30 s) to achieve parasympathetic blockade (18). Atropine was administered between minutes 16 and 18 of exercise so that the last 6 min represented exercise during complete parasympathetic blockade. Second, intravenous propranolol (0.2 mg/kg) was given at 1 mg/min to achieve sympathetic blockade (18). Propranolol was administered at 1 mg/min so that the administration was completed by the 18th minute of exercise. At session 4, intravenous propranolol (0.2 mg/kg) was given at 1 mg/min followed by atropine (0.04 mg/kg) in divided doses (0.01 mg/kg every 30 s) to achieve double blockade. The propranolol was initiated so that administration was completed by the 16th min of exercise at which time the atropine was given over the next 2 min; the last 6 min represent exercise during double blockade. The order of all four studies could not be randomized. The first test needed to be done without pharmacological blockade to ensure subject safety for the proposed duration of exercise and to ensure that the subject could complete the exercise portion before exposing the subject to the risk of pharmacological blockade. For safety reasons, the double-blockade study was also done only after each drug individually was shown to be well tolerated.

QT interval. The QT interval was automatically measured from the 12-lead ECG using validated software (GE Healthcare, Milwaukee, WI) (55) applied to all 12 leads. Each ECG was visually overread to confirm the QT interval measurement and adjusted manually only when clear artifacts were present (<5%). The RR interval was also measured from the ECG.

Data analysis. Continuous data are expressed as means ± SD. In recovery, there were a total of 14 12-lead ECGs obtained over the first 20 min of recovery (every minute from 0–10, 15, and 20 min). Linear regression analysis was performed on the 14 QT-RR interval pairs obtained for each subject for each condition. Each subject had four linear regressions defining the QT-RR relationship in the baseline state (no autonomic blockade), during parasympathetic blockade, during β-adrenergic blockade, and during double blockade. With the use of the individual slope and intercept results from the regression analysis, a predicted QT interval (QTp) was calculated from the linear regression formula for cycle lengths 500, 550, 600, and 650 ms to provide rate-independent QT intervals for comparison across the conditions. The QTp was defined as follows: QTp_500 = intercept + slope × 500; QTp_550 = intercept + slope × 550; QTp_600 = intercept + slope × 600; and QTp_650 = intercept + slope × 650.

Repeated-measures analysis of variance (ANOVA) was used to assess for differences in the results of the regression analyses and predicted QT intervals. Post hoc comparisons were performed with Student’s t-test using Bonferroni adjustment for multiple comparisons. Linear regression was performed to evaluate the relationship of QT/RR slope to heart rate recovery. All statistical tests were two-tailed. Statistical significance was defined at P < 0.05. Heart rate recovery at 1 and 2 min was defined as the heart rate at end exercise minus the 1- or 2-min value. RR interval recovery was defined similarly, except in absolute value (so that the number is positive).

RESULTS

Subjects. Forty-three subjects were initially recruited to participate in the study. Ten subjects were unable to complete the protocol for the following reasons: five declined further participation, three had medical exclusions, and two were unable to complete the first exercise session. Thus 33 subjects completed all four exercise sessions and were included in this study. There were 19 men and 14 women with a mean age of 54 ± 7 yr.

Effect of exercise and selective autonomic blockade on the RR interval. Figure 1 shows the mean heart rate for all subjects recorded at rest, every minute during exercise, and every minute during recovery for each of the four test conditions. During exercise, no drug was infused for the first 4 min during any of the conditions tested. The recorded heart rates during this time period overlap. For the two conditions in which propranolol was given, the heart rates began to decrease, as expected, at the time of infusion relative to the baseline and parasympathetic-blockade conditions (in which no infusion was started at this point during exercise). The heart rates for the β-adrenergic blockade and the double-blockade conditions overlap until the 16th min of exercise when atropine was added to the double-blockade condition. The heart rates for the baseline condition and the parasympathetic-blockade condition overlap for the first 16 min of exercise. With the initiation of parasympathetic blockade, the heart rates values began to increase. Thus the heart rates during similar conditions were reproducible and changed in response to the administered pharmacological agents in the expected direction. During the recovery period, the heart rates with the baseline condition decreased dramatically within the first minute and then had a gradual decrease. The heart rates for the parasympathetic-blockade condition decreased gradually throughout recovery.

Mean RR intervals for the group at rest, peak exercise, and the 20th min of recovery are shown for all four exercise
sessions in Table 1. Baseline RR intervals were similar for all four sessions. During the baseline condition, the peak exercise RR interval was 454 ± 69 ms, whereas the final recovery RR interval was 711 ± 104 ms. With β-adrenergic blockade, the peak exercise RR interval was 591 ± 58 ms and increased to 890 ± 112 ms at the end of the recovery period. With parasympathetic blockade, the peak exercise RR interval was 403 ± 46 ms and increased to 539 ± 86 ms at the end of the recovery period. During double blockade, the peak exercise RR interval was 563 ± 47 ms and increased to 724 ± 107 ms at the end of recovery.

QT-RR relationship. Figure 2 shows the QT-RR relationships during the recovery period for each session for a single subject. Relative to baseline, the QT-RR relationship with parasympathetic blockade was shifted to the left and had a steeper slope. In contrast, the QT-RR relationship with β-adrenergic blockade was shifted to the right and had a less steep slope. The baseline and double-blockade QT-RR relationships were in the middle and essentially superimposable. This pattern was evident in the majority of subjects, as indicated by the summary slope and intercept data for the group shown in Table 2.

Table 2 shows the results of the linear regression analyses for all subjects for each condition. For all 132 analyses (4 per each of 33 subjects), there was a significant linear relationship between the QT and RR intervals; for 93% of the regression analyses, $P$ values were <0.0001. The mean $R^2$ during the baseline condition was 0.88 ± 0.08 (range, 0.63 to 0.98). With β-adrenergic blockade, the mean $R^2$ was 0.85 ± 0.12 (range, 0.56 to 0.98). The mean $R^2$ with parasympathetic blockade was 0.90 ± 0.06 (range, 0.86 to 0.99), and with double blockade, the mean $R^2$ was 0.87 ± 0.14 (range, 0.41 to 0.99). There were significant differences among the slope and intercept values for the four conditions ($P < 0.0001$ by ANOVA). The slope for the QT-RR relationships during parasympathetic blockade was 0.45 ± 0.12, which was significantly ($P < 0.0001$) greater than the slopes for the QT-RR relationships during baseline (0.30 ± 0.10), β-adrenergic blockade (0.21 ± 0.05), and double blockade (0.27 ± 0.07). The slope for the QT-RR relationships during β-adrenergic blockade was also significantly ($P < 0.0001$) less than the slopes for the other three conditions. There was no significant effect from sex difference or interaction on the slope for the QT-RR relationship by condition. The differences in the intercepts were also significant and reflective of the respective shifts in the QT-RR relationships for parasympathetic blockade and β-adrenergic blockade relative to the baseline and double-blockade data.

QTp intervals. Based on the individual regression parameters, Table 3 and Fig. 3 show the QTp 500, QTp 550, QTp 600, and QTp 650 values for each condition. There were significant differences among the QTp 500 ($P < 0.0001$ by ANOVA),
Nevertheless, the strength of the relation is poor with is significant only for the 1- and 2-min RR interval recoveries. There is a negative slope in all comparisons, but it demonstrates the relationship of the QT-RR slope to 1- and ventricular repolarization may only be loosely related to the of 0.124 and 0.114, indicating that the autonomic effects on sympathetic blockade, the QTp was consistently longer than for all other conditions (P < 0.002). With β-adrenergic blockade, the QT interval was significantly shortened only at a cycle length of 650 ms (P < 0.001).

Relationship of QT-RR slope to heart rate recovery. Figure 4 demonstrates the relationship of the QT-RR slope to 1- and 2-min heart rate and RR interval recovery for the baseline condition. There is a negative slope in all comparisons, but it is significant only for the 1- and 2-min RR interval recoveries. Nevertheless, the strength of the relation is poor with R² values of 0.124 and 0.114, indicating that the autonomic effects on ventricular repolarization may only be loosely related to the autonomic effects on heart rate recovery. With β-adrenergic blockade, parasympathetic blockade, and double blockade, there was no significant relationship between QT-RR slope and either heart rate or RR interval recovery.

DISCUSSION

This study provides new insights into the QT-RR interval dynamics in the recovery phase from submaximal exercise. First, the QT-RR interval dynamics in the baseline state (no pharmacological blockade) are most similar to the QT-RR interval dynamics in the setting of combined β-adrenergic and parasympathetic blockade; this suggests that in the baseline state, there is a balanced sympathovagal effect on cardiac repolarization. In the absence of parasympathetic effects, the QT-RR relationship is shifted to the left and with a steeper slope, resulting in longer QT intervals for any given RR interval. In the absence of β-adrenergic effects, the QT-RR relationship is shifted to the right and with a less steep slope. Although both parasympathetic and β-adrenergic effects on the QT-RR relationship can be detected, the most prominent parasympathetic effect is to counteract the sympathetically mediated QT prolongation noted during recovery. These data support the concept that parasympathetic tone may provide a natural antiarrhythmic effect during this time.

Given the cycle length dependence of the QT interval, quantifying the effects on cardiac repolarization is challenging when the heart rate is changing. As many as 30 different methods have been used to correct for heart rate effects on the QT interval (32). Many of these methods, such as Bazett’s formula, have been shown to be imprecise when determining the QT interval at differing heart rates (9, 42). The QT-RR relationship, however, has been shown to be a dependable description of cardiac repolarization, in the same individual, over time. For instance, Batchvarov et al. (5) showed that in the same subjects, when the QT-RR relationship was repeated over a period of 1 mo, the QT-RR relationship was preserved. More recently, the QT-RR relationship has been shown to be stable over a period of 2 yr (4). Once a subject’s QT-RR relationship has been characterized, the effects of interventions on the QT-RR relationship can therefore be analyzed to assess the effects of the intervention on cardiac repolarization. This is a particularly useful tool when the intervention also affects heart rate. Therefore, evaluations of the QT-RR relationships were chosen for analysis in this study. For all 132 analyses, there was a significant linear relationship with mean R² values of 0.85–0.90. Thus this analysis provided a robust methodology to evaluate the effects of selective blockade on the QT interval following exercise.

The physiology of autonomic effects on cardiac electrophysiology during the postexercise recovery period is not well characterized. This is due, in part, to the changing autonomic profile and the complex interaction of sympathetic and parasympathetic activity on cardiac electrophysiology during exer-
Exercise is characterized by activation of the sympathetic nervous system, increase in serum catecholamines, and parasympathetic withdrawal (45). Recovery has the opposite autonomic changes. However, previous studies evaluating autonomic effects on recovery have provided conflicting evidence. Savin et al. (48) proposed that sympathetic withdrawal contributes more to heart rate recovery soon after peak exercise, with parasympathetic reactivation playing a greater role later in recovery. In contrast, Imai et al. (17) concluded that the initial heart rate recovery after exercise is mainly due to a prompt restoration of vagal tone.

Studies evaluating the effect of exercise on the QT interval have uniformly demonstrated that it shortens (43, 44, 46). However, the imprecision of rate correction formulas, particularly in the more rapid heart rate range, has precluded a fundamental understanding of the autonomic effects of exercise (and recovery) on cardiac repolarization. To overcome the limitation of the inadequacy of rate correction formulas, several investigators (2, 9, 10, 35, 52) have studied autonomic effects on the QT interval using atrial pacing that allows direct comparison of QT intervals without the need for rate correction. Most studies (2, 9, 10, 52) have shown that propranolol does not affect the QT interval at paced rates of 90 to 150 beats/min, although one study (35) has found that propranolol lengthened the QT interval at paced rates of 100–130 beats/min. Atropine has been shown to shorten the QT interval at paced rates of 100–150 beats/min (9, 52). Double blockade has similarly been shown to shorten the QT interval at paced rates of 100–150 beats/min (9, 10).

In contrast to these findings, we found that in the postexercise recovery phase, propranolol was associated with rate-dependent shortening of the QT interval. Atropine was associated with a significant lengthening of the QT interval. Finally, double blockade had no significant effect on the QT interval in the 90–120 beats/min range. We believe that these differences are related to the different autonomic milieus present during exercise versus atrial pacing. For example, Sarma et al. (46) plotted the QT-RR relationship for a subject during complete exercise tests—once with a 40-mg oral dose of propranolol administered 2 to 3 h before the test and once without drug. The QT-RR relationship appeared to be exponential. However, it was piecewise linear; that is, at cycle lengths of 700 ms and below, the QT-RR relationship was linear. Furthermore, in this range of cycle lengths, the QT-RR relationship was shifted to the right for propranolol, as we noted in the present study. Additionally, the slope of the QT-RR relationship at cycle lengths of 700 ms and below was much steeper than the slope of the QT-RR relationship at cycle lengths >700 ms. Clearly, the longer cycle lengths were recorded at rest and at the very early stages of exercise, and therefore the autonomic milieu at this time is different than the autonomic milieu later in exercise when shorter cycle lengths were recorded. Given the exponential nature of the QT-RR relationship over the whole range of cycle lengths associated with exercise, it is important to define the operating point for analysis of the autonomic effects on QT-RR interval dynamics. The autonomic effects may be different at the shorter cycle lengths.
lengths associated with a steeper slope of the QT-RR interval relationship than at the longer cycle lengths.

When using atrial pacing to assess the autonomic effects on the QT interval, the baseline autonomic milieu against which the changes are being compared is the one that corresponds to the longer cycle lengths; although the heart rate can be artificially raised by pacing, the subjects are resting and would therefore be expected to display the QT-RR dynamics associated with the resting state. In contrast, when we use the postexercise recovery period to assess the autonomic effects on the QT interval, the baseline autonomic milieu against which the changes are being compared is the one that corresponds to the shorter cycle lengths and the steeper QT-RR interval relationship. Thus using atrial pacing as a surrogate to understand autonomic effects on the QT interval at rates that may be observed during exercise and the postexercise recovery period may be misleading. The present study provides a new and more physiological paradigm by which to evaluate the autonomic effects on the QT interval during the postexercise recovery period.

The sympathetic-parasympathetic interactions on the QT interval during recovery observed in this study are consistent with previous observations regarding “accentuated antagonism” in relation to contractility, excitability, vulnerability, and refractoriness (22, 23, 29–31, 34, 37). Specifically, the parasympathetic effects on the QT interval are greatly enhanced in the presence of sympathetic tone versus when the effect of β-adrenergic activity is blocked. In the presence of sympathetic tone (the baseline and parasympathetic-blockade conditions), there are substantial effects on the QT interval attributable to the parasympathetic effect. In contrast, when the effect of β-adrenergic activity is blocked (the β-blockade and double-blockade conditions), the presence or absence of parasympathetic effect has much less a profound effect on the QT interval. Multiple mechanisms may account for this effect (27, 28).

Although the present study defines the autonomic effects on the QT-RR relationship in recovery, it is important to consider that the QT interval represents a global parameter of repolarization. Since there are regional differences in sympathetic and parasympathetic innervation to the ventricles, localized effects on both repolarization and refractoriness may differ. For example, Yanowitz et al. (56) demonstrated QT interval prolongation with either right stellate ganglionectomy (but not left stellate ganglionectomy) or left stellate stimulation (but not right stellate stimulation); refractory period prolongation was noted with both right and left stellate ganglionectomy, albeit over the anterior left ventricle for the former and the posterior left ventricle for the latter. Interestingly, Kannankeril and Goldberger (20) demonstrated that the right ventricular effective refractory period shortens during exercise and recovery in normal subjects. Since the T wave is generated by repolarization gradients, QT prolongation could be explained by a regional shortening of repolarization time resulting in an unmasking of previously cancelled activity (due to lack of a gradient) (56). Further studies will be needed to assess the local autonomic effects on repolarization and refractoriness during recovery from exercise.

The present study demonstrates the important role of the autonomic nervous system on the QT-RR relationship in the postexercise recovery period. In the last several years, heart rate recovery from exercise, another parameter evaluating dynamic changes in autonomic effects on the sinus node in the postexercise recovery period, has been shown to have important prognostic implications (11, 12, 19, 38, 51). It is interesting that although there appears to be some correlation between the QT-RR slope and heart rate recovery, it is not strong. Given that abnormalities in the autonomic effects on cardiac repolarization may be more directly linked to the pathophysiology of ventricular tachyarrhythmias than abnormalities in the autonomic effects on the sinus node, it is possible that the QT-RR relationship could provide more specific prognostic information relative to sudden cardiac death. Further studies evaluating the prognostic importance of the QT-RR relationship are necessary.

Limitations. The present study relied on repeated measurements of QT and RR intervals on 4 separate days. Because the autonomic profiles during recovery in the conditions tested were continuously changing, it is not possible to quantitatively relate β-adrenergic or parasympathetic effects to the QT interval. As noted previously, the QT-RR relationship is exponential or curvilinear and defining the operating set of RR intervals may impact the linear regression values. Although the range of RR intervals studied could not, by nature of the interventions, be identical, there was overlap in ranges. Importantly, the different lines noted for β-adrenergic blockade and parasympathetic blockade cannot be fully explained by different RR interval ranges since these lines were clearly discontinuous and the QT-RR relationship is a continuous function. Thus the qualitative analyses over the course of recovery are reflective of the actual in vivo effects. As with any study employing acute β-blockade as a pharmacological probe to evaluate β-adrenergic effects, these results could differ in the setting of chronic β-blocker therapy related to alterations in β-receptor density and function.

Another limitation is that the order of testing was not randomized due to the need to establish that subjects could safely complete the protocol before administering atropine and propranolol during exercise. Additionally, sympathetic and parasympathetic activities were not directly measured in this study. Nevertheless, pharmacological blockade with atropine (7) has been considered the gold standard by which to evaluate parasympathetic effects. Another limitation is that the period immediately after exercise was investigated, rather than exercise. We chose to study the recovery period to enhance compliance with the completion of the same exercise protocol at each session by administering the drugs during exercise (administration of drugs was not complete until the 18th min of exercise). Thus complete exercise QT-RR data were not available with selective autonomic blockade. Furthermore, ECG quality during the recovery period is better than during exercise. Finally, hysteresis in the QT-RR relationship between exercise and recovery has been reported and could therefore affect the findings (47). We have recently shown that the hysteresis phenomenon is mediated by the different autonomic balance noted in exercise and recovery (25). Thus this should not have affected our results.

Implications. There have been multiple studies showing that decreased markers of parasympathetic activity are associated with increased mortality in patients with cardiac disease (8, 21, 26, 39, 41). Similarly, multiple studies have linked an increase in the QT interval with mortality. Importantly, it has been...
shown that there is an ~20-fold relative risk of sudden death during exercise and the postexercise recovery period compared with sedentary periods. Whereas these epidemiologic findings have been consistently shown, the pathophysiological link between these findings has not been elucidated. Based on the data presented in this study, we propose the following unifying mechanism that serves as the pathophysiological link among these epidemiologic findings. In the normal, healthy subject who exercises, the QT-RR interval dynamics in recovery demonstrate “sympathovagal balance”; that is, the QT-RR relationship in this setting reflects the parasympathetically mediated opposition to the lengthening of the QT interval induced by enhanced sympathetic activity. The parasympathetic effects are so pronounced that the QT-RR relationship coincides with the QT-RR relationship noted with double blockade in which neither parasympathetic nor β-adrenergic sympathetic effects are present. The prominent role of parasympathetic activation in the physiology of repolarization recovery is matched by the prominent parasympathetic innervation of the ventricles (53). In individuals with cardiac disease who may have diminished parasympathetic tone or effect, there may be less effective protection against the sympathetically mediated QT prolongation noted during exercise. If so, the prolongation of the QT interval may be involved in the susceptibility to ventricular arrhythmias at this time. This is supported by Zhou et al. (57) who have shown that QT interval prolongation is causally related to the occurrence of life-threatening ventricular arrhythmias in a canine model of sudden death following myocardial infarction. Further work will be necessary to define the “natural antiarrhythmic” effect of parasympathetic tone during exercise and the postexercise recovery period in patients with cardiac disease.

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REFERENCES


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