Autonomic Effects on QT-RR Interval Dynamics After Exercise

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Brief Title: Autonomic Effects on QT-RR Dynamics

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ABSTRACT

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 pathophysiologic link among these findings. Bicycle exercise testing was performed serially in 33 healthy volunteers (19 male, age 54± 7 years) under four conditions: 1) Baseline; 2) Beta-adrenergic blockade—intravenous propranolol 0.2 mg/kg administered during exercise; 3) Parasympathetic blockade—intravenous atropine 0.04 mg/kg administered during exercise; 4) Double blockade with propranolol and atropine. ECGs were obtained every minute in recovery for 10 minutes and then at the 15th and 20th minute, 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 beta-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 one and two minute RR interval recoveries with low R2 values of 0.124 and 0.114. The main parasympathetic effect in the post-exercise 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.
KEYWORDS:

Exercise, parasympathetic, heart rate recovery, QT interval
INTRODUCTION

The pathophysiology of sudden cardiac death is not completely understood. A variety of epidemiologic findings have provided key insights into the potential roles of ventricular repolarization, autonomic tone, and exercise. While 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 to sedentary periods. While 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 one minute 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 pathophysiologic 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 as 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 Friedricia’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, hematocrits, and serum electrolytes. Subjects
with cardiac complaints (chest pain, shortness of breath, palpitations, dyspnea on
exertion), a cardiac history, or those taking cardioactive medications were excluded.
Subjects with other major systemic illnesses (i.e. asthma, diabetes) were also excluded.
In addition, only subjects who indicated that they participated in regular aerobic exercise
a minimum of 60 minutes per week 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 four separate days, each separated by at least 72 hours. 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 minutes. Subjects were then instructed to exercise, keeping pedal speed at 80 revolutions per minute. Workload was maintained at 50 Watts for 4 minutes, and then increased every 2 minutes as tolerated in 25 Watt increments to a maximum of 125W. The goal was to have all subjects exercise comfortably for a total duration of 24 minutes achieving a heart rate of 120-130 beats per minute. Heart rate was recorded prior to exercise, every minute during exercise, and every minute for the 20 minutes of recovery. After completion of exercise, a 12-lead electrocardiogram was obtained (peak exercise, time zero of recovery). Subjects remained in the seated position on the bicycle for 20 minutes. ECGs were obtained every minute in recovery for 10 minutes and then at the 15th and 20th minute. This initial test without 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 two and three, the following drugs were administered in random order:

a) intravenous atropine (0.04 mg/kg) in divided doses (0.01 mg/kg every 30 seconds) to achieve parasympathetic blockade(18). Atropine was administered
between minutes 16 and 18 of exercise so that the last six minutes represented exercise during complete parasympathetic blockade.

b) intravenous propranolol (0.2 mg/kg) given at 1 mg/min to achieve sympathetic blockade(18). Propranolol was administered at 1 mg/min so that administration was completed by the 18th minute of exercise.

At session four, 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 seconds) to achieve double blockade. The propranolol was initiated so that administration was completed by the 16th minute of exercise at which time the atropine was given over the next two minutes; the last six minutes represent exercise during double blockade. The order of all four studies could not be randomized. The first test needed to be done without pharmacologic blockade to ensure subject safety for the proposed duration of exercise and to ensure the subject could complete the exercise portion prior to exposing the subject to the risk of pharmacologic 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 ± standard deviations. In recovery, there were a total of fourteen 12-lead ECGs obtained over the first 20 minutes of recovery (every minute from 0-10 minutes, 15 minutes, 20 minutes). 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 beta-adrenergic blockade, and during double blockade. Using 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:

\[
\begin{align*}
\text{QTp}_{500} &= \text{intercept} + \text{slope} \times 500 \\
\text{QTp}_{550} &= \text{intercept} + \text{slope} \times 550 \\
\text{QTp}_{600} &= \text{intercept} + \text{slope} \times 600 \\
\text{QTp}_{650} &= \text{intercept} + \text{slope} \times 650
\end{align*}
\]

Repeated measures analysis of variance 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 2-tailed. Statistical significance was defined at \( p < 0.05 \). Heart rate recovery at one and two minutes was defined as the HR at end exercise.
minus the one or two minute 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 males and 14 females with a mean age of 54±7 years.

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 four minutes 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 beta-adrenergic blockade and the double blockade conditions overlap until the 16th minute 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 minutes 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 pharmacologic 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 20th minute 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 while the final recovery RR interval was 711±104 ms. With beta-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 beta-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 and Figure 3.

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 $0.88\pm0.08$ (range 0.63 to 0.98). With beta-adrenergic blockade, the mean $R^2$ was $0.85\pm0.12$ (range 0.56 to 0.98). The mean $R^2$ with parasympathetic blockade was $0.90\pm0.06$ (range 0.86 to 0.99) and with double blockade, the mean $R^2$ was $0.87\pm0.14$ (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 $0.45\pm0.12$, which was significantly (p<0.0001) greater than the slopes for the QT-RR relationships during baseline ($0.30\pm0.10$), beta-adrenergic blockade ($0.21\pm0.05$), and double blockade ($0.27\pm0.07$). The slope for the QT-RR relationships during beta-adrenergic blockade was also significantly (p<0.0001) less than the slopes for the other three conditions. There was no significant gender effect 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 beta-adrenergic blockade relative to the baseline and double blockade data.
Predicted QT Intervals

Based on the individual regression parameters, Table 3 and Figure 3 show the QTp500, QTp550, QTp600, and QTp650 values for each condition. There were significant differences among the QTp500 (p<0.0001 by ANOVA), QTp550 (p<0.0001 by ANOVA), QTp600 (p<0.0001 by ANOVA) and QTp650 (p<0.0001 by ANOVA). With parasympathetic blockade, the QTp was consistently longer than for all other conditions (p<0.002). With beta-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 one and two minute 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 one and two minute RR interval recoveries. Nevertheless, the strength of the relation is poor with R^2 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 beta-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 pharmacologic blockade) are most similar to the QT-RR interval
dynamics in the setting of combined beta-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 beta-adrenergic effects, the QT-RR relationship is shifted to the right and with a less steep slope. While both parasympathetic and beta-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 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 has, however, 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 one month, the QT-RR relationship was preserved. More recently, the QT-RR relationship has been shown to be stable over a period of two years(4). Once a subject’s QT-RR relationship has been characterized, 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,
evaluation of the QT-RR relationships were chosen for analysis in this study. For all 132 analyses, there was a significant linear relationship with mean $R^2$ 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 post-exercise 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 exercise and recovery. 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 initial heart rate recovery after exercise is mainly due to 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 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) studied autonomic effects on the QT interval using atrial pacing which 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, though one study \(^{(35)}\) 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 post-exercise 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 beat/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 2-3 hours 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 msec 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 msec and below was much steeper than the slope of the QT-RR relationship at cycle lengths greater than 700 msec. Clearly, the longer cycle lengths were recorded at rest and 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 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 using the post-exercise
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 post-exercise recovery
period may be misleading. The present study provides a new and more physiologic
paradigm by which to evaluate the autonomic effects on the QT interval during the post-
exercise 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 beta-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 beta-adrenergic activity is blocked (the Beta-blockade and Double blockade conditions), the presence or absence of parasympathetic effect has much less profound effect on the QT interval. Multiple mechanisms may account for this effect(27, 28).

While 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. As 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, we(20) have demonstrated that the right ventricular effective refractory period shortens during exercise and recovery in normal subjects. As 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 post-exercise 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 post-exercise recovery period, has been shown to have important prognostic implications\cite{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 four separate days. Because the autonomic profiles during recovery in the conditions tested were continuously changing, it is not possible to quantitatively relate beta-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. While 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 beta-adrenergic blockade and parasympathetic blockade cannot be fully explained by different RR interval ranges as 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 beta-blockade as a pharmacologic probe to evaluate
beta-adrenergic effects, these results could differ in the setting of chronic beta-blocker therapy related to alterations in beta-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 prior to administering atropine and propranolol during exercise. Additionally, sympathetic and parasympathetic activity were not directly measured in this study. Nevertheless, pharmacologic 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 completion of the same exercise protocol at each session by administering the drugs during exercise (administration of drugs was not complete until the 18th minute 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 approximately 20-fold relative risk of sudden death during exercise and the post-exercise recovery period compared to sedentary periods. While these epidemiologic findings have been consistently shown, the pathophysiologic 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 pathophysiologic 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 beta-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 post-exercise recovery period in patients with cardiac disease.
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FIGURE LEGENDS

Figure 1. Plot of the average heart rate for all 33 subjects for each of the four conditions at rest, every minute during exercise, and every minute during recovery. The first arrow indicates the time of initiation of propranolol infusion. The second arrow indicates the time of initiation of atropine infusion.

Figure 2. Individual QT-RR data for one subject from the recovery period for each of the four sessions. The results of each of the QT-RR linear regression analyses are plotted.

Figure 3. Predicted QT intervals at RR intervals of 500, 550, 600 and 650msec (QTp 500, QTp 550, QTp 600 and QTp 650 respectively) based on the individual linear regression analyses of QT interval to RR interval obtained for each subject for each condition.

Figure 4. Plot of QT-RR slope (both QT and RR interval are measured in msec, so slope is unitless) versus one and two minute heart rate and RR interval recovery in the baseline condition (no pharmacologic blockade).
Figure 1

![Graph showing heart rate (bpm) over time for Baseline, Beta-adrenergic blockade, Parasympathetic blockade, and Double blockade. The graph includes time markers for rest, exercise, and recovery periods.]

- **Baseline**
- **Beta-adrenergic blockade**
- **Parasympathetic blockade**
- **Double blockade**
Figure 2

![Graph showing the relationship between QT interval (msec) and RR interval (msec) with various slopes and conditions labeled: Baseline, Beta-adrenergic blockade, Parasympathetic blockade, Double blockade.](image)
Figure 3

![Graph showing predicted QT interval (msec) for different conditions: Baseline, Beta-adrenergic blockade, Parasympathetic blockade, and Double blockade.](image)

- **QT500**: Baseline and Beta-adrenergic blockade show significant differences, with the latter being higher. Parasympathetic blockade and Double blockade show no significant differences.
- **QT550**: Similar to QT500, Baseline and Beta-adrenergic blockade show significant differences, and Parasympathetic blockade and Double blockade show no significant differences.
- **QT600**: Baseline and Beta-adrenergic blockade show significant differences, with the latter being higher. Parasympathetic blockade and Double blockade show no significant differences.
- **QT650**: Baseline and Beta-adrenergic blockade show significant differences, with the latter being higher. Parasympathetic blockade and Double blockade show no significant differences.
Figure 4
Table 1. RR intervals at rest, at peak exercise, and after 20 minutes of recovery on each of the four test days. Note that the resting RR intervals were obtained prior to the administration of any pharmacologic agents. The peak exercise and 20 minute recovery values reflect the effects of the indicated pharmacologic blocking agents.

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<th>Baseline</th>
<th>Beta-adrenergic Blockade</th>
<th>Parasympathetic Blockade</th>
<th>Double Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting RR interval (msec)</td>
<td>879±118</td>
<td>856±105</td>
<td>813±102</td>
<td>839±120</td>
</tr>
<tr>
<td>Peak Exercise RR interval</td>
<td>454±69</td>
<td>591±58</td>
<td>403±46</td>
<td>563±47</td>
</tr>
<tr>
<td>(msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR interval at 20 min of</td>
<td>711±104</td>
<td>890±112</td>
<td>539±86</td>
<td>724±107</td>
</tr>
<tr>
<td>recovery (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Results of the individual linear regression analyses of QT interval to RR interval. The mean ± standard deviation of the values obtained for each subject for each condition are shown.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Beta-adrenergic Blockade</th>
<th>Parasympathetic Blockade</th>
<th>Double Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Slope</strong></td>
<td>0.30±0.10</td>
<td>0.21±0.05 *</td>
<td>0.45±0.12 **</td>
<td>0.27±0.07</td>
</tr>
<tr>
<td><strong>Intercept</strong></td>
<td>149±50</td>
<td>198±40 *</td>
<td>90±52 **</td>
<td>166±47</td>
</tr>
<tr>
<td><strong>R²</strong></td>
<td>0.88±0.08</td>
<td>0.85±0.12</td>
<td>0.90±0.06</td>
<td>0.87±0.14</td>
</tr>
</tbody>
</table>

* p < 0.0001 versus baseline  
** p < 0.001 versus all others
Table 3. Predicted QT intervals at RR intervals of 500, 550, 600 and 650 msec (QTp 500, QTp 550, QTp 600, and QTp 650, respectively) based on the individual linear regression analyses of QT interval to RR interval obtained for each subject for each condition.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Beta-adrenergic Blockade</th>
<th>Parasympathetic Blockade</th>
<th>Double Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTp 500 (msec)</td>
<td>301±12</td>
<td>305±18</td>
<td>314±14 *</td>
<td>302±18</td>
</tr>
<tr>
<td>QTp 550 (msec)</td>
<td>317±14</td>
<td>316±16</td>
<td>337±19 *</td>
<td>315±16</td>
</tr>
<tr>
<td>QTp 600 (msec)</td>
<td>332±17</td>
<td>326±15</td>
<td>360±25 *</td>
<td>329±16</td>
</tr>
<tr>
<td>QTp 650 (msec)</td>
<td>347±21</td>
<td>337±14 **</td>
<td>382±31 *</td>
<td>342±16</td>
</tr>
</tbody>
</table>

* p < 0.0001 versus all others (except QTp500 versus Beta-adrenergic blockade where p<0.002)
** p < 0.001 versus Baseline and p < 0.007 versus Double Blockade