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ORIGINAL INVESTIGATION

Parasympathetic Effects on Heart Rate Recovery after Exercise

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ABSTRACT

Background: Exercise and its recovery period are associated with increased risk of death relative to sedentary periods. They are also accompanied by dynamic changes in autonomic tone. Little information is available regarding parasympathetic effects during high-intensity exercise and recovery.

Methods: Ten normal subjects (five women; age 33 ± 2 years) underwent exercise testing on a bicycle ergometer. On day 1, subjects exercised to maximum tolerated workload using a graded protocol with 5 minutes at maximal workload (peak heart rate achieved 174.7 ± 5.4 bpm). On day 2, subjects performed the identical exercise protocol as on day 1; 1 minute into the maximum exercise stage, atropine (0.04 mg/kg) was administered. Heart rate was recorded every minute during exercise, and an electrocardiogram was recorded every minute in recovery for 10 minutes. The parasympathetic effect on heart rate was defined by the difference in heart rate with and without atropine.

Results: The parasympathetic effect during maximal exercise was 3.4 to 6 bpm ($p < .05$). During recovery, a large parasympathetic effect on heart rate was noted by 1 minute (22.8 bpm; $p < .0002$), increased until 4 minutes, and then remained stable until 10 minutes. Despite faster heart rates with parasympathetic blockade, the P–R interval was shorter ($p < .002$), consistent with a significant parasympathetic effect on the atrioventricular node in recovery. Evaluation of the Q–T–R–R relationship on the 2 days demonstrated significant changes in both the slope ($p < .0001$) and the intercept ($p < .0001$), consistent with a modification of ventricular repolarization by parasympathetic tone in recovery.

Conclusion: These data indicate that in normal subjects, parasympathetic effects persist during high-intensity exercise and are prominent in the early phases of recovery. These parasympathetic effects may play an important role in prevention of sudden cardiac death during these periods of increased risk.

Key Words: parasympathetic tone, P–R interval, Q–T interval

Several studies have now established the important prognostic significance of attenuated heart rate recovery after exercise in patients referred for exercise testing.[1–5] These studies have highlighted the potential role of abnormal parasympathetic reactivation after exercise. It is also well known that the risk of sudden cardiac death is markedly increased during and following exercise compared with the risk during sedentary periods.[6–8] Furthermore, exercise may serve as a trigger for life-threatening ventricular arrhythmias; in patients with implantable defibrillators, appropriate shocks may be precipitated by exercise in 26 to 53% of cases.[9,10] The role of exercise as a trigger of life-threatening ventricular arrhythmias may be linked, at least in part, to the autonomic changes that accompany exercise and the postexercise recovery period. Exercise and the postexercise recovery period are associated with enhanced sympathetic tone and diminished parasympathetic tone,[11–13] conditions that have been associated with increased mortality in various population studies. It is therefore plausible that the dynamic changes in autonomic tone associated with exercise may be linked to the triggering of sudden cardiac death and ventricular arrhythmias during and following exercise.

Although it is well appreciated that there are dynamic changes in autonomic tone with exercise, the extent of parasympathetic withdrawal during exercise has not been well defined. Using heart rate variability analysis, it has been shown that beyond 50 to 60% maximal oxygen consumption, there is continued sympathoexcitation and no further reduction in parasympathetic tone.[14–19] It is unclear whether during maximal exercise, there is a background parasympathetic effect or complete parasympathetic withdrawal.

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Supported in part by grant RR-00048 from the National Center for Research Resources, National Institutes of Health, to the General Clinical Research Center of Northwestern Memorial Hospital, and by grant 1 RO1 HL 70179-01A2 from the National Heart, Lung, and Blood Institute.

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Prior studies evaluating the recovery of parasympathetic tone after exercise in normal subjects have reported conflicting results.[20,21] Savin and colleagues reported that sympathetic withdrawal contributes more to heart rate recovery early after exercise with parasympathetic reactivation, playing a more prominent role later in recovery.[21] In contrast, Imai and colleagues reported "prompt vagal reactivation after exercise."[20] Understanding the role of parasympathetic reactivation during recovery is necessary to evaluate whether it is implicated in the adverse prognosis related to attenuated heart rate recovery after exercise. Furthermore, we recently demonstrated that in subjects without structural heart disease with implanted pacemakers, there are measurable parasympathetic effects on cardiac electrophysiology during moderate exercise and during the postexercise recovery period.[22] Thus, the objective of this study was to evaluate parasympathetic effects during high-intensity exercise and recovery in normal subjects by measuring heart rate in the presence and absence of parasympathetic blockade with atropine. In addition, parasympathetic effects on the P–R and Q–T interval were assessed. We hypothesized that even during high-intensity exercise and the recovery period, parasympathetic effects will be demonstrated.

METHODS

Study Design

During exercise and recovery, sympathetic tone is enhanced compared with the tone during resting conditions. The aim of this study was to evaluate the parasympathetic effects that exist during these conditions of sympathetic activation. To do so, subjects were studied on two separate occasions. At the first session, subjects exercised without administration of drugs. In this setting, we hypothesized that there would be increased sympathetic tone and a decreased, but intact, parasympathetic effect on the heart. At the second session, subjects underwent parasympathetic blockade with atropine during exercise. In this setting, minimal to no parasympathetic effects should be noted. Thus, the difference in heart rate between the two sessions defines the parasympathetic effect on heart rate in the setting of increased sympathetic tone. It is important to note that the parasympathetic effects defined in this manner incorporate the potential sympathetic-parasympathetic interactions, resulting in accentuated antagonism,[23–27] and therefore reflect the total effect that the parasympathetic nervous system has in this setting. Pharmacologic blockade with atropine has been considered the gold standard for evaluating cardiac parasympathetic effects.[28] Finally, because the aim of the current study was to assess the parasympathetic effect during a state of sympathoexcitation, plasma catecholamines were obtained at various times to determine the degree of sympathoexcitation.

Subjects

The study group consisted of 10 normal volunteers (5 men, 5 women; mean age 33 ± 2 years) who were free from significant medical or cardiovascular disease. No subject was taking any cardioactive medication. These subjects participated in regular aerobic exercise an average of 152 ± 36 minutes per week. Written, informed consent was obtained prior to the study. The study was approved by the Northwestern University Institutional Review Board.

Exercise Tests

Subjects were studied in two separate sessions, separated by at least 24 hours. Subjects were attached to a cardiac monitor and an electrocardiogram machine (Marquette Mac VU, Milwaukee, WI). All measurements were made with subjects seated on an electrically braked bicycle ergometer (SciFit Pro II, Tulsa, OK). At the first session, a 12-lead electrocardiogram and blood pressure were recorded at rest after assuming a seated position for at least 5 minutes. Subjects were then instructed to exercise, keeping the pedal speed at 80 revolutions per minute. Workload was maintained at 50 W for 4 minutes and then increased by 25 W every 2 minutes, until the subject felt that a higher stage could not be maintained. Heart rate was recorded every minute during exercise. Once reaching the maximum stage, exercise was maintained for 5 minutes. The peak heart rate and blood pressure were recorded, and exercise was stopped. A 12-lead electrocardiogram was obtained immediately postexercise and every minute thereafter for 10 minutes. Blood pressure was recorded 5 minutes into recovery.

At the second session, a peripheral intravenous catheter was inserted into the forearm for phlebotomy and administration of atropine. Subjects were then seated in the bicycle for at least 5 minutes, and a 12-lead electrocardiogram and blood pressure were recorded. Blood was drawn through the intravenous catheter for measurement of plasma catecholamine levels at rest. The exercise protocol performed on the first day was then repeated exactly. After 1 minute at the submaximal stage, blood was again drawn for plasma catecholamines. After 1 minute at the maximum exercise stage, intravenous atropine (0.04 mg/kg) was administered in divided doses (0.01 mg/kg every 30 seconds). One minute after atropine administration was completed, a third blood sample was obtained for plasma catecholamines. Heart rate was again recorded every minute during exercise. Peak heart rate and blood pressure were recorded, exercise was stopped, and 12-lead electrocardiograms were obtained immediately postexercise and every minute thereafter for the next 10 minutes. Given that atropine has a half-life of approximately 4 hours,[29] a steady effect should be noted for the 12-minute period studied after atropine administration. This dose of atropine has been shown to result in effective blockade for at least 1 hour.[30]

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Electrocardiogram Analysis

P–R and Q–T intervals were measured from the electrocardiogram. The P–R interval was measured from the onset of the P wave to the onset of the QRS complex. The Q–T interval was measured from the onset of the QRS complex to the end of the T wave. The longest Q–T interval across all 12 leads was used.

Parasympathetic Effect

The basic principle used in this study to evaluate parasympathetic effects is that the parameters of interest were evaluated twice: once in the absence of parasympathetic blockade and once in the presence of parasympathetic blockade. In theory, the difference between the parameter measured in the absence of parasympathetic blockade and the presence of parasympathetic blockade should provide a measure of parasympathetic effects. This paradigm is effective in analyzing the parasympathetic effects on heart rate. The parasympathetic effect on heart rate was therefore defined as the heart rate in the presence of parasympathetic blockade minus the heart rate in the absence of parasympathetic blockade. However, analysis of the parasympathetic effect on the P–R and Q–T intervals is confounded by their rate dependence. The analysis of the parasympathetic effect on the P–R and Q–T intervals therefore focuses on the combined effects of changes in heart rate (noted with time during recovery and with parasympathetic blockade) and changes in the P–R and Q–T intervals induced by parasympathetic blockade.

Plasma Catecholamine Levels

Blood was collected in 7 cc tubes containing egtazic acid and reduced glutathione. Tubes were centrifuged at 3,000 rpm for 10 minutes, and plasma was removed within 1 hour of collection. Samples were frozen at −70°C. Measurement of plasma catecholamines was performed with high-performance liquid chromatography with electrochemical detection (HPLC-EC) (Specialty Laboratories, Santa Monica, CA).

Data Analysis

Reproducibility of the heart rates on both days' exercise tests prior to atropine was evaluated by linear regression analysis. Time-dependent changes were assessed with repeated measures analysis of variance. Post hoc comparisons of heart rate on day 1 (without atropine) and day 2 (after atropine) were done with one-tailed Student's *t*-tests because parasympathetic blockade was postulated to increase the heart rate. Each individual's heart rate data in recovery were fit to a monoexponential decay of the form:

$$HR = a + b * \exp(-t/\tau)$$

where HR is heart rate, t is time in recovery, τ is the time constant for heart rate recovery, and a and b are constants (a + b represents the heart rate at time 0, and a is the steady-state heart rate).

The relationship between the Q–T and the R–R interval was evaluated with multiple linear regression analysis for all subjects on both days, coding for the presence or absence of parasympathetic blockade and for repeated measures in the individual subjects. A p value of $< .05$ was considered significant. All data are presented as mean ± standard error.

RESULTS

Ten subjects exercised an average of 14.2 ± 0.7 minutes (median 15, range 11–19 minutes), including 5 minutes at a peak workload of 140 ± 9 W (median 150, range 100–200 W) on the first day. On the second test day, 8 of 10 subjects completed the 5-minute maximal exercise stage, and 2 of 10 subjects could complete only 4 minutes. For the purposes of analysis, the 4-minute heart rate in these two subjects was used as their 5-minute values as well. Heart rates for both sessions, prior to atropine, correlated extremely well for each subject (R^2 range = .963–.997; Figure 1). The mean heart rates for the group at baseline, exercise, and recovery are shown for both days in Table 1 and Figure 2. The peak heart rate on day 1 was 174.7 ± 5.4 bpm and on day 2 (after atropine) was 178.1 ± 4.4 bpm ($p = .05$). Systolic and diastolic blood pressures on day 1 were as follows: 119 ± 6 and 68 ± 2 mm Hg at rest, 184 ± 7 and 78 ± 6 mm Hg

FIGURE 1 Heart rate at rest and during each minute of exercise on day 1 versus on day 2 prior to atropine administration. Linear regression analysis revealed excellent correlation of heart rate at the two sessions prior to parasympathetic blockade with atropine ($n = 112$; $R^2 = .97$; slope = 0.98; $p < .00001$). Each symbol represents an individual subject.

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TABLE 1. Heart Rate and Parasympathetic Effect on Heart Rate during Peak Exercise and Recovery in Normal Subjects

Stage (min)	*Day 1 Heart Rate (bpm)*	*Day 2 Heart Rate (bpm)*	*Parasympathetic Effect on Heart Rate (bpm)**
Peak exercise			
1 (pre-atropine)	165.3 ± 5.1	165.7 ± 5.0	
2	169.5 ± 5.1	175.5 ± 4.5	6.0 ± 1.3
3	172.6 ± 5.0	177.1 ± 4.4	4.5 ± 1.4
4	173.7 ± 5.2	177.8 ± 4.5	4.1 ± 1.6
5	174.7 ± 5.4	178.1 ± 4.4	3.4 ± 1.8
Recovery			
0	174.5 ± 5.4	178.2 ± 4.4	3.7 ± 1.7
1	133.0 ± 5.7	155.8 ± 5.0	22.8 ± 4.0
2	117.9 ± 6.1	143.7 ± 5.0	25.8 ± 3.7
3	110.0 ± 6.6	138.2 ± 5.2	28.2 ± 3.2
4	103.7 ± 6.7	135.6 ± 5.2	31.9 ± 3.4
5	103.5 ± 6.7	134.3 ± 5.6	30.8 ± 3.6
6	101.3 ± 7.1	133.6 ± 5.7	32.3 ± 3.9
7	101.9 ± 7.6	133.1 ± 5.9	31.2 ± 3.5
8	100.6 ± 7.5	132.2 ± 5.6	31.6 ± 3.2
9	101.3 ± 7.5	131.4 ± 6.0	30.1 ± 2.9
10	98.2 ± 6.8	129.8 ± 5.7	31.6 ± 2.8

Data shown as mean ± standard error.
*$p < .05$ for parasympathetic effect throughout peak exercise and recovery. See text for detailed statistical analysis.

FIGURE 2 Mean (± standard error) heart rates for the 10 subjects are plotted at rest and at each minute during the first (Stage 1), submaximal (Submax), and maximal (Max) stages of exercise. Atropine was given after the first minute of maximal exercise on day 2 (marked by an asterisk). Recovery heart rates are plotted every minute for 10 minutes starting immediately postexercise.

at peak exercise, and 115 ± 5 and 63 ± 2 mm Hg at 5 minutes of recovery. Systolic and diastolic blood pressures on day 2 were as follows: 111 ± 5 and 64 ± 3 mm Hg at rest, 181 ± 6 and 70 ± 4 mm Hg at peak exercise, and 105 ± 4 and 55 ± 3 mm Hg at 5 minutes of recovery. There were no differences between systolic or diastolic blood pressure on the 2 days. Heart rate recovery, defined as the heart rate at peak exercise minus the heart rate 1 minute into recovery, for the group was 41.7 ± 3.0 bpm (median 42, range 30–55 bpm) on day 1 and 22.3 ± 2.4 bpm (median 21, range 14–37 bpm) on day 2.

The parasympathetic effects on heart rate during maximal exercise and recovery are shown in Table 1. Atropine was given after the first minute of exercise, so the parasympathetic effect is measurable only after this point. There was a significant parasympathetic effect on heart rate during the second minute of maximal exercise (parasympathetic effect = 6.0 ± 1.3 bpm; $p = .0005$). At this point, 0.02 mg/kg (half the total dose) of atropine had been administered. By 3 minutes, all of the atropine had been administered, and the parasympathetic effect was 4.5 ± 1.4 bpm ($p = .006$). At 4 and 5 minutes of maximal exercise and immediately postexercise (0 minutes in recovery), the parasympathetic effect was 4.1 ± 1.6 bpm ($p = .02$), 3.4 ± 1.8 bpm ($p = .05$), and 3.7 ± 1.7 bpm ($p = .03$), respectively. By 1 minute of recovery, there was a large increase in the parasympathetic effect (22.8 ± 4.0 bpm; $p = .0002$), which then trended upward for 4 minutes, at which point, the parasympathetic effect remained stable through 10 minutes ($p < .0001$ for the parasympathetic effect for minutes 2 to 10). The change in parasympathetic effect during exercise and recovery was significant ($p < .001$ by analysis of variance). The parasympathetic effects noted during exercise and immediately in recovery were significantly less than the parasympathetic effects noted from 1 to 10 minutes of recovery ($p \leq .0001$).

All subjects demonstrated a monoexponential decay in heart rate during recovery on both days. R^2 values for individual subjects ranged from .94 to 1.0 (mean .98 ± .02) on day 1 and .95 to .99 (mean .99 ± .01) on day 2. The time constant for heart rate recovery was 1.4 ± 0.1 minutes on day 1 and 1.6 ± 0.2 minutes on day 2 (p = not significant). There were significant negative relationships between the time constants and heart rate recovery at 1 minute on day 1 ($r = -.7$; $p < .02$) and on day 2 ($r = -.7$; $p < .03$).

Mean P–R intervals at baseline and during recovery are shown in Table 2. At the end of exercise (beginning of recovery), the P–R interval was 107.4 ± 3.1 ms, which was substantially shorter than at baseline (149.8 ± 3.9 ms) or at any point later in recovery ($p < .0001$). At 1, 2, and 3 minutes of recovery, the P–R interval lengthened to 134.2 ± 2.5, 140.0 ± 2.4, and 143.4 ± 3.2 ms, respectively ($p < .0001$ compared with the immediate postexercise P–R interval). There were

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TABLE 2 P–R Interval (in ms) at Rest and during Recovery in Normal Subjects

Stage	*Day 1*	*Day 2*
Rest	149.8 ± 3.9	146.0 ± 3.4
Recovery (min)		
0	107.4 ± 3.1	101.3 ± 3.0
1	134.2 ± 2.5	120.4 ± 3.2
2	140.0 ± 2.4	126.2 ± 2.2
3	143.4 ± 3.2	130.4 ± 2.5
4	143.4 ± 3.5	130.5 ± 1.8
5	142.0 ± 4.1	132.0 ± 2.2
6	139.2 ± 3.8	132.0 ± 2.2
7	138.9 ± 4.4	134.0 ± 2.0
8	140.7 ± 3.4	133.6 ± 2.0
9	140.5 ± 3.7	133.6 ± 2.9
10	141.8 ± 3.4	133.6 ± 2.2

Data shown as mean ± standard error.
See text for detailed statistical analysis.

TABLE 3 Q–T Interval (in ms) at Rest and during Recovery in Normal Subjects

Stage	*Day 1*	*Day 2*
Rest	399.0 ± 17.8	394.2 ± 12.8
Recovery (min)		
0	242.4 ± 6.5	243.5 ± 5.1
1	282.2 ± 9.5	257.9 ± 3.8
2	301.8 ± 11.1	272.2 ± 6.4
3	315.4 ± 12.4	283.0 ± 9.7
4	325.8 ± 13.9	293.2 ± 8.3
5	334.9 ± 13.9	297.0 ± 9.7
6	334.4 ± 14.9	296.0 ± 9.9
7	335.4 ± 15.1	298.2 ± 10.0
8	340.6 ± 15.2	304.6 ± 10.8
9	341.2 ± 15.0	305.4 ± 10.6
10	345.4 ± 14.3	306.0 ± 10.9

Data shown as mean ± standard error.
See text for detailed statistical analysis.

no significant changes in the P–R interval after 3 minutes of recovery. On day 2, the same pattern of change in the P–R interval was noted. Parasympathetic blockade was associated with a shorter P–R interval in recovery ($p < .002$). Of note, the heart rate was faster on day 2 with parasympathetic blockade (see Figure 2), yet the P–R interval was shorter. Given that the increased heart rate is expected to produce an increase (or no change) in the P–R interval owing to decremental atrioventricular nodal conduction,[31] the observed change in the P–R interval is an underestimate of the true parasympathetic effect on the atrioventricular node. This confirms a significant parasympathetic effect on the atrioventricular node during recovery.

Mean Q–T intervals at baseline and during recovery are shown in Table 3. At the end of exercise, the Q–T interval was 242.4 ± 6.5 ms, which was shorter ($p < .0001$) than at baseline (399.0 ± 17.8 ms) or later in recovery (282.2–345.4 ms). A similar pattern of change in the Q–T interval was noted after parasympathetic blockade on day 2. However, analysis of the parasympathetic effect on the Q–T interval is confounded by the fact that the increased heart rate noted with parasympathetic blockade causes the same directional change in the Q–T interval as the postulated effect of parasympathetic blockade on the Q–T interval. Figure 3 shows the Q–T–R–R relationship for all subjects on each day. A multiple linear regression model coding for repeated measures in the subjects and the presence or absence of atropine had an R^2 of .95 ($p < .0001$). Atropine significantly decreased the intercept by 60 ms ($p < .0001$) and increased the slope by 0.16 ($p < .0001$). In this model, therefore, the net effect of atropine on the Q–T interval at heart rates of 120, 133, 150, and 162 bpm was to increase the Q–T interval by 22, 14, 5, and 0 ms. This suggests that parasympathetic blockade modifies the Q–T–R–R relationship.

Plasma catecholamine levels were measured at rest (heart rate 66 ± 4 bpm), during the submaximal exercise stage (115 ± 9 W, 8.2 ± 0.7 minutes of exercise, heart rate 153 ± 6 bpm), and during the maximal exercise stage (140 ± 9 W, 12.8 ± 0.9 minutes of exercise, heart rate 178 ± 4 bpm). Epinephrine and norepinephrine levels were 26.9 ± 5.8 and 350.1 ± 55.9 pg/mL at rest, 140.5 ± 37.8 and 718.6 ± 98.1 pg/mL during the submaximal exercise stage, and 469.7 ± 191.9 and 2,188.0 ± 466.4 pg/mL during the maximal exercise stage, respectively. The increase in plasma

FIGURE 3 The Q–T versus R–R intervals are plotted for all subjects from 0 to 10 minutes of recovery on days 1 and 2 (after atropine).

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catecholamines observed with exercise was significant ($p < .02$ for epinephrine, $p < .0001$ for norepinephrine by analysis of variance). All pairwise differences between rest, submaximal exercise, and maximal exercise were significant ($p < .02$ for epinephrine, $p < .004$ for norepinephrine).

DISCUSSION

This study demonstrates that during high-intensity exercise in normal subjects, there are demonstrable parasympathetic effects on heart rate, suggesting that parasympathetic withdrawal is not complete, even during high-intensity exercise. During the early recovery period, reactivation of parasympathetic effects on heart rate occurs rapidly in the first minute. From 4 to 10 minutes of recovery, parasympathetic effects on heart rate remain relatively constant. Furthermore, sympathetic withdrawal also contributes significantly to early heart rate recovery, as demonstrated by the brisk heart rate recovery (with a similar time constant) noted after atropine administration. Additionally, parasympathetic reactivation was shown to affect both the P–R and the Q–T interval in recovery. These data reveal that parasympathetic effects can be measured during high-intensity exercise and recovery and contribute to heart rate recovery after exercise. Normal subjects had a > 20 bpm drop in heart rate from peak exercise to 1 minute of recovery, even after parasympathetic blockade. Thus, abnormal heart rate recovery (previously defined as < 12 bpm drop)[1] may be due to a defect in sympathetic withdrawal, parasympathetic reactivation, or both.

Autonomic physiology during exercise has been assessed by selective autonomic blockade.[11–13] Low-intensity exercise is associated with rapid parasympathetic withdrawal, whereas moderate-intensity exercise results in an increased heart rate from both continued parasympathetic inhibition and sympathetic activation.[11–13] Several studies have attempted to assess autonomic modulation of the sinus node during maximal exercise using heart rate variability analysis.[14–19] High-frequency power, felt to be a marker of parasympathetic modulation, decreases during moderate exercise, until reaching 50 to 60% maximal oxygen consumption. Beyond this point, at higher levels of exertion, there is continued sympathoexcitation, but high-frequency power remains stable. It is not known whether this reflects complete withdrawal of parasympathetic tone. The current study demonstrates that in normal subjects, parasympathetic effects persist, although at a reduced level, even at maximal exercise.

The physiology of autonomic effects on heart rate during recovery is not well understood. Savin and colleagues studied the heart rate recovery of six men with selective autonomic blockade on different days administered prior to the initiation of exercise.[21] Although they performed exponential fits, they found time constants nearly an order of magnitude larger than those noted in the current study (in their study, b = −0.15 and −0.1 for control and parasympathetic blockade, respectively, representing time constants of 1/0.15 = 6.7 minutes and 1/0.1 = 10 minutes). This is likely due to the absence of a constant term in their regression equation. They interpreted their findings as suggesting that "sympathetic withdrawal contributes more to heart rate recovery soon after peak exercise cessation, with parasympathetic activation playing a greater role later in recovery at lower rates." In contrast, Imai and colleagues reported that "the initial heart rate recovery within 30 seconds is mediated primarily by vagal reactivation."[20] In this study, the investigators evaluated groups of young (age 20 years) subjects, trained athletes, older (age 55 years) subjects with congestive heart failure, and age-matched sedentary controls. Atropine was administered prior to exercise, and subjects exercised submaximally to anaerobic threshold. Heart rate recovery was evaluated only up to 2 minutes. In the present study, atropine was administered only near the end of exercise, and the level of exertion on both days was carefully matched. By doing so, we were able to demonstrate significant parasympathetic effects on heart rate during high-intensity exercise.

The studies of heart rate variability during recovery are conflicting, revealing either an increase or a decrease in high-frequency power when compared with during exercise.[14,16] Heart rate variability, however, is an indirect marker of parasympathetic effect that relies on a steady state that is not present in recovery and may be confounded by the increased respiratory rates that accompany exercise. These factors make the interpretation of heart rate variability as a measure of parasympathetic effect during exercise and recovery difficult.

Exercise is a complex autonomic condition because the autonomic changes do not appear to be continuous with exercise intensity. Mild to moderate exercise is associated with parasympathetic withdrawal and only small degrees of sympathoexcitation. Parasympathetic blockade with atropine during mild to moderate exercise increases the heart rate by approximately 30 bpm, whereas β-adrenergic blockade decreases the heart rate by 5 to 15 bpm.[11,13] In addition, mild to moderate exercise is associated with only small increases in plasma catecholamines.[32,33] Even in the present study, during the submaximal exercise stage, when the heart rate was approximately 150 bpm (78% of the increase in heart rate from rest to maximal exercise had been achieved), the increase in plasma catecholamines was only 20 to 25% of the increase noted from rest to maximal exercise. These data suggest that the primary modality for increasing heart rate in mild to moderate exercise is parasympathetic withdrawal. The question arises as to whether the shift to sympathoexcitation occurs when the potential for parasympathetic withdrawal has been completely exhausted or whether some basal level of parasympathetic effect persists. In the current study, during maximal exercise, plasma catecholamines were markedly elevated when compared with the submaximal levels. This finding is consistent with previous data showing a four- to

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eightfold increase in catecholamines going from 70 to 120% maximal oxygen consumption.[32] Even in this setting of exceptional sympathoexcitation, parasympathetic effects on heart rate were observed. The data suggest that during high-intensity exercise, parasympathetic effects on the heart rate are present.

The modulation of the P–R interval and Q–T interval with exercise is well known. However, to our knowledge, there are no previous data evaluating parasympathetic effects on the P–R interval during exercise and recovery. In this study, parasympathetic effects on the atrioventricular node were clearly evident. In our previous study of subjects with pacemakers in whom the Q–T interval was measured during fixed-rate atrial pacing of 120 bpm, a 19 ms parasympathetic effect on the Q–T interval was noted during recovery.[22] This is similar to the 22 ms effect predicted by the multiple linear regression model for the same heart rate in the present study.

Limitations

The present study relied on repeated measurements of heart rate and P–R and Q–T intervals on 2 days. Day to day variability and variability owing to the changing autonomic conditions associated with exercise and recovery may affect the measurements. In addition, the order of testing was not randomized owing to the need to establish that subjects could safely complete the protocol prior to administering atropine during exercise. To ensure comparability, the exercise protocols on the 2 days were identical, and excellent correlation of the heart rate on the 2 days prior to atropine administration was noted. Parasympathetic activity was not directly measured in this study. Although pharmacologic blockade with atropine has been considered the gold standard by which to evaluate parasympathetic effects,[28] blockade of presynaptic muscarinic receptors may be associated with augmented neurotransmitter release,[29] which may lead to enhancement of the sympathetic effect. Interestingly, with increasing doses of atropine, there was no dose-dependent increase in heart rate or in the defined parasympathetic effect. It is therefore likely that the predominant effect remains blockade of parasympathetic effect.

Implications

This study demonstrates that normal subjects have persistent parasympathetic effects during high-intensity exercise, with rapid recovery of the parasympathetic effect after exercise. Furthermore, at these times, there may be important parasympathetic effects on the Q–T interval that could be "beneficial" because longer Q–T intervals are associated with increased mortality risk.[34–36] It is possible that patients with heart disease or any individual with evidence of low baseline parasympathetic tone (ie, low heart rate variability) may have further suppression of the "beneficial" parasympathetic effects during exercise and recovery. This could explain the 17-fold increase in the risk of sudden cardiac death during and immediately after exercise.[6,7] Furthermore, this abnormality could be reversible. Vanoli and colleagues demonstrated that stimulation of the vagus nerve decreases the incidence of ventricular fibrillation during ischemia in exercising dogs with myocardial infarctions.[37] Thus, further studies assessing the parasympathetic effects on the heart during exercise and recovery in subjects with heart disease are warranted.

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J Investig Med 2004 52: 394-401
doi: 10.1136/jim-52-06-34

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