Parasympathetic effects on cardiac electrophysiology during exercise and recovery

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Methods

Kannankeril, Prince J., and Jeffrey J. Goldberger. Parasympathetic effects on cardiac electrophysiology during exercise and recovery. Am J Physiol Heart Circ Physiol 282: H2091–H2098, 2002. First published January 31, 2002; 10.1152/ajpheart.00825.2001.—Depressed parasympathetic tone is associated with an increased risk of sudden cardiac death. Exercise and the postexercise recovery period, which are associated with parasympathetic withdrawal, are high risk periods for sudden death. However, parasympathetic effects on cardiac electrophysiology during exercise and recovery have not been described. Electrophysiology studies were performed using noninvasive programmed stimulation (NIPS) in nine subjects (age 59 ± 18 yr) with implanted dual-chamber devices and normal left ventricular function during multiple bicycle exercise sessions. NIPS was performed at rest, during exercise, and in the early recovery period both before and after parasympathetic blockade with atropine. Parasympathetic effect was defined as the value of the parameter of interest in the absence of atropine minus the value of the parameter in the presence of atropine. During exercise, sinus cycle length, atrioventricular (AV) block cycle length, AV interval, and ventricular effective refractory period shortened; in recovery, the values were intermediate between the rest and exercise values ($P < 0.0001$ by ANOVA). Parasympathetic effects on sinus cycle length, AV block cycle length, AV interval, and ventricular effective refractory period were 247 ± 140, 58 ± 20, 76 ± 20, and 8.6 ± 7.5 ms at rest, 106 ± 20, 37 ± 14, 24 ± 13, and 2.6 ± 7.8 ms during exercise, and 209 ± 114, 50 ± 23, 35 ± 21, and 9.5 ± 11.8 ms during recovery, respectively. There was poor correlation among the parasympathetic effects noted at the sinus node, AV node, and ventricle. Further work evaluating parasympathetic effects on cardiac electrophysiology during exercise and recovery in patients with heart disease is required to elucidate its role in modulating the risk of sudden cardiac death noted at these times.

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The risk of sudden death is increased nearly 17-fold during and immediately after exercise (2, 23). While there are several potential mechanisms for this marked increased risk of sudden cardiac death, it is possibly related in part to the acute changes in autonomic tone that accompany exercise. Exercise is associated with increased sympathetic tone and parasympathetic withdrawal in normal subjects (11, 12, 36).

Numerous clinical and experimental studies have provided evidence linking diminished parasympathetic nervous system activity at rest with increased mortality and sudden cardiac death (6, 16, 18, 28, 31). Experimental data suggest that dogs with myocardial infarctions prone to ventricular fibrillation during exercise and induced ischemia have greater reductions in parasympathetic tone, as measured by heart rate variability, during exercise compared with nonsusceptible animals (7). Recent human data have shown that a small heart rate decrease in the early recovery phase after exercise is associated with an increased mortality (9, 10, 27). These data suggest that depressed parasympathetic tone during exercise or depressed recovery of parasympathetic tone after exercise may be important factors resulting in an increased risk of sudden cardiac death. Conversely, enhanced parasympathetic tone may be protective against sudden death (39).

One potential mechanism for the protective effect of parasympathetic tone is related to its direct effects on cardiac electrophysiology (35). Parasympathetic effects on cardiac electrophysiology have been described in animal (30) and human (32) subjects at rest. However, parasympathetic effects on cardiac electrophysiology during exercise and recovery have not been described. This study was designed to evaluate parasympathetic effects on cardiac electrophysiology during rest, exercise, and recovery. We hypothesized that there are demonstrable parasympathetic effects on cardiac electrophysiology during exercise and recovery.

Methods

Study design. In this study, cardiac electrophysiologic parameters were measured using noninvasive programmed stimulation (NIPS) in subjects with implanted dual-chamber devices (pacemakers or defibrillators). With the use of the device, electrophysiological studies could be performed at rest, during exercise, and during recovery. Directed electrophysiological studies were performed to assess parasympathetic effects at the sinus node, atrioventricular (AV) node, and ventricle. Because most people do not exercise to peak exertion levels and a several-minute period of “stable” exercise was required to obtain all the electrophysiological measurements, a moderate level of exertion was used. To evaluate parasympathetic effects, subjects were studied on
PARASYMPATHETIC EFFECTS ON ELECTROPHYSIOLOGY DURING EXERCISE

multiple occasions, so that each state (rest, exercise, and recovery) was evaluated at least twice: once in the setting of intact autonomic tone and once after pharmacologic parasympathetic blockade with atropine. Parasympathetic effect at any state for a given electrophysiological parameter was defined as the value of the parameter in the absence of atropine (no parasympathetic blockade) minus the value of the parameter in the presence of atropine (with parasympathetic blockade). For example, if sinus cycle length during exercise was 600 ms and during exercise with atropine was 500 ms, the parasympathetic effect on sinus cycle length during exercise was 100 ms. In a recent committee report, it was stated that the gold standard for estimating cardiac vagal tone in humans is derived from pharmacological blockade (5).

Subjects. The study group consisted of nine subjects (3 men and 6 women; mean age 59 ± 18 yr) with normal left ventricular function and a dual-chamber pacemaker (n = 1) capable of NIPS (Medtronic; 7860 DR, 7960; KDR 701, GEM DR 7271; Pacesetter: 2360, 5330). A tenth subject was excluded due to excessive ventricular ectopy during exercise. Because most patients with devices have some inherent conduction system disease, attempts were made to recruit subjects with chronotropic competence and intact AV conduction. All nine subjects had some degree of chronotropic competence, defined by an increase in the sinus rate of >15 beats/min during moderate exercise at the first study. Eight of nine subjects had intact AV node conduction, defined by no more than first-degree heart block as an underlying rhythm during rest, exercise, and recovery; the ninth subject had 2:1 AV block during exercise and was not included in the analysis of AV node function. Table 1 describes the subjects’ clinical characteristics and medications. Subjects were on a stable medical regimen throughout the study period. No subjects had evidence of unstable angina, congestive heart failure, or myocardial infarction within the preceding 3 mo. Subjects participated in regular aerobic exercise an average of 150 ± 95 min/wk. Written informed consent was obtained before the study. The study was approved by the Northwestern University Institutional Review Board.

Exercise tests. Subjects were studied in four separate sessions, separated by at least 24 h each for the first three sessions. The third and fourth sessions were separated by at least 48 h. Subjects were attached to a pacemaker program-mer and electrocardiogram (ECG) machine (Marquette MAC VU; Milwaukee, WI). All measurements were taken with subjects seated on a mechanically braked bicycle ergometer (Monark 818E; Vansbro, Sweden). At the first session, a baseline heart rate and blood pressure were recorded. NIPS (see below) was performed through the device before exercise. Subjects then performed exercise, keeping pedal speed between 50 and 60 rpm, with a starting workload of 25–50 W, and adjusting resistance every 2 min until the heart rate reached 100–110 beats/min. If the target heart rate was not achieved, a target workload was chosen that would allow the subject to maintain exercise comfortably at that level for ~10 min. One minute after reaching the target heart rate or stage, NIPS was repeated during exercise. Peak heart rate and blood pressure were recorded at the end of exercise. One minute after exercise ended, NIPS was performed during recovery, and heart rate and blood pressure were recorded. At the first session, the appropriate bicycle resistance (target workload) was determined, and the feasibility of NIPS was evaluated.

The second session was identical to the first except that resistance was set to the target workload (which produced a heart rate of 100–110 beats/min) at the beginning of exercise and was maintained throughout the duration of exercise. NIPS was performed at rest, during exercise, and during recovery. The third session was similar to the second. However, during exercise, just before NIPS, subjects underwent complete parasympathetic blockade with intravenous atropine (0.04 mg/kg) in divided doses (0.01 mg/kg every 30 s) (15). NIPS was then performed during exercise with parasympathetic blockade. Because this dose is effective for at least 1 h (21), recovery measurements made during NIPS on session 3 were also performed during parasympathetic blockade. On a fourth session, subjects were seated on the bicycle ergometer, but exercise was not performed. NIPS was performed at baseline and then repeated after administration of intravenous atropine (0.04 mg/kg).

One subject experienced chest pain after atropine administration during exercise on the third session, causing cessation of testing. For that subject, only data from the first two sessions are included in the analysis. One subject declined to continue after the first and third test session. Thus nine subjects completed at least one session of the protocol. Two sessions were completed by eight subjects, three sessions by seven subjects, and all four sessions by six subjects.

Noninvasive programmed stimulation. Before NIPS on session 1, atrial and ventricular pacing thresholds were measured. All subsequent stimulation was performed at a fixed output of approximately twice the late diastolic threshold. Rate-responsive features were turned off for the duration of the test. Lower rate limits and (when possible) paced AV intervals were adjusted to allow for sinus rhythm with native AV conduction. Each study consisted of the following:

A 12-lead rhythm strip was recorded for measurement of sinus cycle length (measured as the mean R-R interval over a 10-s period). Atrial and ventricular electrograms were recorded when possible through the device. Atrial pacing was performed with a 12-beat drive train at 500, 400, and 330 ms. The AV interval at these fixed paced cycle lengths was measured from the onset of the atrial pacing stimulus to the onset of the QRS complex or ventricular electrogram. The Q-T interval (after the last paced beat) was also measured at these fixed paced cycle lengths unless AV block occurred. The Q-T interval could be measured only during rest and recovery, due to excessive motion artifact during exercise. The measurement of AV interval and Q-T interval at fixed cycle lengths allowed for evaluation of the rate-independent effects

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Table 1. Clinical characteristics and medications

<table>
<thead>
<tr>
<th>Number of Subjects</th>
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<tbody>
<tr>
<td>Hypertension</td>
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<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Diabetes mellitus (type II)</td>
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<tr>
<td>Device indication</td>
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<tr>
<td>Sinus bradycardia</td>
</tr>
<tr>
<td>Carotid sinus hypersensitivity</td>
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<tr>
<td>AV block</td>
</tr>
<tr>
<td>Syncope</td>
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<tr>
<td>Underlying rhythm</td>
</tr>
<tr>
<td>Sinus with 1:1 AV conduction</td>
</tr>
<tr>
<td>Sinus with AV block</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>ACE inhibitors</td>
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<tr>
<td>Diuretics</td>
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n = 9 Subjects total. AV, atrioventricular; ACE, angiotensin-converting enzyme.
on these parameters. The atrial pacing cycle length was then decremented by \(-10\)-ms intervals to determine AV block cycle length, defined as the longest cycle length that did not result in 1:1 AV conduction. Ventricular effective refractory period was assessed after a 1-min conditioning period in which drive trains of eight stimuli (S1) at the drive cycle length without an extrastimulus (S2) were applied with \(4\)-s intertrain pauses (generally related to the delay inherent in using the pacemaker programmer for NIPS). The ventricular effective refractory period was then measured using the extrastimulus technique, with a drive train of eight stimuli and shortening the extrastimulus by \(8\) to \(10\)-ms intervals until ventricular capture did not occur or a minimum coupling interval of 200 ms was reached. The effective refractory period was defined as the longest S1-S2 interval that did not result in ventricular capture. The minimum S1-S2 interval of 200 ms precluded assessment of changes in ventricular effective refractory period in only one subject. Attempts were made to measure ventricular effective refractory period at drive cycle lengths of 500, 450, and 400 ms so that effective refractory periods were available in each subject at a particular cycle length for all conditions. The ventricular effective refractory periods available at the longest cycle length for all conditions were used for analysis of parasympathetic effect.

At the end of the session, devices were programmed back to pretest settings.

**Parasympathetic effect.** Parasympathetic effect on the above parameters at each condition was defined as the difference in the parameter with and without atropine. Atropine was given on session 3 during exercise, so measurements made during exercise and recovery on session 3 were in the setting of parasympathetic blockade. The difference between values obtained during exercise and recovery on session 3 and those obtained during exercise and recovery on sessions 1 and 2 defined parasympathetic effect during exercise and recovery. Atropine was given on session 4 at rest; therefore, the difference between values obtained after atropine at session 4 and those obtained at rest preatropine at session 4 and at sessions 1–3 defined parasympathetic effect at rest.

**Data analysis.** There were up to four baseline and two exercise and recovery measurements per subject. The reproducibility of these multiple measurements was assessed by linear regression or, in the case of more than two measurements, by calculating the intra-class correlation coefficient. For the baseline states, the intra-class correlation coefficients were as follows: 0.82 for sinus cycle length, 0.71 for AV block cycle length, 0.74 for AV interval, 0.81 for Q-T interval, 0.83 for ventricular effective refractory period at 500 ms, and 0.75 for ventricular effective refractory period at 450 ms. For the exercise states, regression analysis revealed the following \(R^2\) values: 0.82 for sinus cycle length, 0.73 for AV block cycle length, 0.62–0.73 for AV interval (at various paced cycle lengths), and 0.94–0.99 for ventricular effective refractory period (at various drive cycle lengths). For the recovery states, the \(R^2\) values were 0.73 for sinus cycle length, 0.87 for AV block cycle length, 0.68–0.96 for AV interval (at various paced cycle lengths), and 0.75–0.89 for ventricular effective refractory period (at various drive cycle lengths). Thus electrophysiological data had good-to-excellent reproducibility, and the results from the multiple sessions were averaged for analysis. Changes in electrophysiological parameters and parasympathetic effect among the rest, exercise, and recovery states were assessed with repeated-measures ANOVA. Pairwise comparisons were performed with Student’s \(t\)-test. Parasympathetic effects on different parameters were correlated using linear regression analysis. All tests were two-tailed. A \(P\) value \(<0.05\) was considered significant.

**RESULTS**

**Exercise.** Resting heart rate was 67 ± 11 beats/min; resting systolic and diastolic blood pressures were 128 ± 17 and 69 ± 11 mmHg. Subjects exercised for 12 ± 2 (range 7–15) min at a workload of 70 ± 27 (range 25–100) W. NIPS was performed at 5.5 ± 1.3 min into exercise when the heart rate was 100 ± 9 beats/min. Upon completion of NIPS, heart rate was 107 ± 8 beats/min. At the end of exercise, systolic and diastolic blood pressures were 165 ± 18 and 77 ± 13 mmHg. During recovery, NIPS started 1 min after exercise (heart rate was 83 ± 10 beats/min) and was completed by 6.6 ± 1.0 min when the heart rate was 79 ± 12 beats/min. Systolic and diastolic blood pressures were 125 ± 20 and 69 ± 9 mmHg after NIPS was completed in recovery.

**Electrophysiological changes with exercise and recovery.** The changes in electrophysiological parameters among baseline, exercise, and recovery states are shown for each parameter in Figs. 1-5. As expected, sinus cycle length shortened, from 925 ± 157 ms at rest to 604 ± 56 ms during exercise, and increased to 731 ± 106 ms 1 min in recovery (\(P < 0.0001\) by ANOVA; all pairwise comparisons, \(P < 0.005\)). AV interval at a paced cycle length of 500 ms was 259 ± 28 ms at rest, shortened to 217 ± 31 ms during exercise, and increased to 232 ± 29 ms during recovery (\(P < 0.0001\) by ANOVA; pairwise comparisons significant for baseline vs. exercise, \(P < 0.0001\), and baseline vs. recovery, \(P = 0.0003\)). AV block cycle length was 392 ± 53 ms at rest, 304 ± 37 ms during exercise, and 338 ± 48 ms during recovery (\(P < 0.0001\) by ANOVA; all pairwise comparisons, \(P < 0.005\)). Q-T interval, measured at a fixed atrial pacing rate of 500 ms, was 356 ± 23 ms at rest and shortened to 331 ± 18 ms in recovery (\(P < 0.002\)). Ventricular effective refractory period at a drive cycle length of 500 ms was 257 ± 19 ms at rest, shortened to
229 ± 16 ms during exercise, and lengthened to 246 ± 16 ms in recovery (P < 0.0001 by ANOVA; all pairwise comparisons, P < 0.005).

Parasympathetic effects. Parasympathetic effects on all parameters during rest, exercise, and recovery are shown in Table 2 and Fig. 6. At rest, parasympathetic effects were noted on the sinus cycle length (247 ± 140 ms, P < 0.008), AV block cycle length (58 ± 20 ms, P < 0.003), AV interval (76 ± 20 ms, P < 0.02), ventricular effective refractory period (8.6 ± 7.5 ms, P < 0.06), and Q-T interval (17.9 ± 15.9 ms, P < 0.1). During exercise, there was also significant parasympathetic effect on the sinus cycle length (106 ± 20 ms, P < 0.0001), AV block cycle length (37 ± 14 ms, P < 0.001), and AV interval (24 ± 13 ms, P < 0.007); no significant parasympathetic effect on ventricular effective refractory period was noted. During recovery, parasympathetic effects were noted on the sinus cycle length (209 ± 114 ms, P < 0.003), AV block cycle length (50 ± 23 ms, P < 0.003), AV interval (35 ± 21 ms, P < 0.02), ventricular effective refractory period (9.5 ± 11.8 ms, P < 0.005), and Q-T interval (19.2 ± 14.6 ms, P < 0.02).

Overall, there was poor correlation between parasympathetic effects on the sinus and AV nodes, the sinus node and the ventricular effective refractory period, and the AV node and the ventricular effective refractory period. There was no correlation between the parasympathetic effect on sinus cycle length and parasympathetic effect on AV block cycle length (n = 17, R² = 0.002, P = 0.84). There was a weakly positive correlation between parasympathetic effect on sinus cycle length and parasympathetic effect on ventricular effective refractory period (n = 17, R² = 0.30, P = 0.02). Finally, there was no correlation between parasympathetic effect on the AV node and parasympathetic effect on ventricular effective refractory period (n = 14, R² = 0.06, P = 0.38).

**DISCUSSION**

This study provides the first comprehensive assessment of cardiac electrophysiology during exercise and
recovery. Moderate exercise is associated with a shortening of sinus cycle length, AV block cycle length, AV interval, and ventricular effective refractory period. This study also provides the first assessment of parasympathetic effects on cardiac electrophysiology during exercise and recovery. Although exercise is known to be associated with parasympathetic withdrawal, there are still measurable parasympathetic effects at the sinus node, AV node, and ventricle during moderate exercise and recovery. Parasympathetic effects during exercise are less than those noted at rest. Parasympathetic effects in the early postexercise recovery period trend toward the resting values. These data have important implications on the interaction between exercise, autonomic tone, and the risk for sudden death.

Exercise is characterized by sympathoexcitation and parasympathetic withdrawal. Whereas the shortening of sinus cycle length with exercise is well known, the direct effects of exercise on AV nodal and ventricular electrophysiology have not been directly measured. The lack of investigations on electrophysiological changes during exercise likely stems from the practical difficulties of performing electrophysiological studies in exercising subjects. The effects of sympathoexcitation on AV nodal and ventricular electrophysiology have been studied with catecholamine infusions. In this setting, AV nodal conduction is enhanced, and there is a decrease in ventricular refractoriness (4, 8, 24, 25, 40). However, catecholamine infusion may not be a perfect model for the autonomic changes that occur with exercise. The relative changes in sympathovagal balance may differ and may change from exercise to recovery, although both states are characterized by sympathoexcitation. Robinson et al. (36) showed that upright tilt and exercise titrated to produce similar heart rates that were associated with different autonomic effects. They state “It is thus apparent that achievement of the same heart rate involved a different balance of autonomic activity, depending on whether the stimulus was provided by exercise in supine position or by tilting.” The present study provides, to our knowledge, the first direct electrophysiological data on the AV node and ventricle during exercise and recovery. During exercise, we observed marked effects on AV node conduction and ventricular effective refractory period, which trended toward resting values within minutes of cessation of exercise.

Parasympathetic effects on cardiac electrophysiology have been studied by nerve stimulation or pharmacological blockade in resting conditions (13, 22, 30, 32). Parasympathetic activation prolongs sinus cycle length, AV conduction time, and ventricular refractory period. Our findings that parasympathetic blockade at rest shortened sinus cycle length, AV block cycle length, AV interval, Q-T interval, and ventricular effective refrac-

### Table 2. Parasympathetic effects on cardiac electrophysiology at rest, during moderate exercise, and during recovery

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>Recovery</th>
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<tbody>
<tr>
<td></td>
<td>Parasympathetic effect, ms</td>
<td>P value</td>
<td>Parasympathetic effect, ms</td>
</tr>
<tr>
<td>Sinus cycle length</td>
<td>247±140</td>
<td>0.008</td>
<td>106±20</td>
</tr>
<tr>
<td>AV block CL</td>
<td>58±20</td>
<td>0.003</td>
<td>37±14</td>
</tr>
<tr>
<td>AV interval (at 400-ms paced CL)</td>
<td>76±20</td>
<td>0.02</td>
<td>24±13</td>
</tr>
<tr>
<td>Ventricular effective refractory period</td>
<td>8.6±7.5</td>
<td>0.06</td>
<td>2.6±7.8</td>
</tr>
<tr>
<td>Q-T interval</td>
<td>17.9±15.9</td>
<td>0.1</td>
<td>19.2±14.6</td>
</tr>
</tbody>
</table>

Data are means ± SD. CL, cycle length.
tory period are consistent with these prior data. Previous studies attempting to evaluate parasympathetic tone during exercise have utilized heart rate variability. Most (but not all) of these studies demonstrated a decrease in high-frequency power, felt to be a marker of parasympathetic modulation, during exercise (3, 26, 29, 37, 38). Generally, no further changes in “parasympathetic” components of heart rate variability are noted after reaching 50–60% maximal oxygen consumption (26, 37, 38). Whether this reflects complete parasympathetic withdrawal or withdrawal to some continual level of parasympathetic effect cannot be ascertained from these data. The present study documents that there are significant parasympathetic effects on cardiac electrophysiology during moderate exercise.

The recovery period after exercise is also associated with autonomic changes. Heart rate is known to decrease and likely reflects both sympathetic withdrawal and parasympathetic reactivation (14). Yet, studies of heart rate variability during recovery provide conflicting results. Compared with exercise, high-frequency power in recovery has been noted to increase (3) or decrease (29), although heart rate variability in recovery has consistently been shown to be diminished compared with baseline evaluations (1, 3, 29). In this study, parasympathetic effects were clearly demonstrated in recovery and were intermediate between those noted at rest and those noted during exercise.

Parasympathetic innervation of the heart demonstrates regional differences (34). Vagal preganglionic pathways to the sinus node are situated in the pulmonary vein fat pad, whereas those supplying the AV node lie in the fat pad overlying entry of the coronary sinus into the inferior interatrial septum. Compared with the sinus and AV nodes, there are relatively few ganglia found in ventricular tissues. Parasympathetic nerves are distributed to highly restricted regions of the heart over discrete anatomical pathways, which can be selectively altered (33). On the basis of these differences in innervation, it is reasonable to presume that parasympathetic effects at these different sites may differ. In fact, no consistent or strong correlations among the parasympathetic effects at the sinus node, AV node, or ventricle were noted.

**Limitations.** In the present study, the parasympathetic effect was measured as the difference in the parameter of interest noted in the absence and presence of parasympathetic blockade. Pharmacological parasympathetic blockade with atropine has effects on multiple muscarinic receptors. However, as used in the present study, atropine administration is considered the gold standard for estimating cardiac vagal tone in humans (5). It is well known that there may be significant sympathetic-parasympathetic interactions. These interactions may result in enhanced parasympathetic effects (17, 22) during exercise and/or recovery, a phenomenon termed “accentuated antagonism” (17, 19, 20, 25). Nevertheless, the physiology of interest is the parasympathetic effect that is noted during exercise and recovery, when there is enhanced sympathetic tone.

The present study also relied on repeated measurements of cardiac electrophysiological parameters. Day-to-day variability and variability due to the changing autonomic conditions associated with exercise and recovery may affect the measurements. Nevertheless, good to excellent correlation of the multiple measurements was noted.

Because the study protocol required pacemakers or defibrillators, the subjects do not represent a “normal” population. Most subjects had at least some degree of conduction system disease. However, attempts were made to select patients who were not pacemaker dependent; all subjects had an increase in heart rate with exercise. Although all subjects had normal left ventricular function, they were not free of cardiovascular disease and some were taking cardioactive medications. As previously noted, cardiac parasympathetic effects may be reduced in individuals with cardiovascular disease. Thus the parasympathetic effects defined during this study may be an underestimate of the parasympathetic effect present in a truly normal population. While medications may alter the autonomic regulation of the heart, all subjects were on stable doses of medications throughout the study period. Thus the identified changes in electrophysiological properties due to parasympathetic blockade do reflect the parasympathetic effects present in these subjects. It is therefore important to note that this study provides qualitative (rather than quantitative) evidence regarding the persistence of parasympathetic effects during exercise and recovery. It is also likely that the parasympathetic effects are not exaggerated in the presence of mild conduction system and/or cardiovascular disease (they are more likely to be understated).

**Implications.** There are several important findings related to parasympathetic tone, exercise, and mortality that highlight the implications of the current study. There is a large body of work demonstrating that decreased markers of parasympathetic activity are associated with increased mortality in patients with cardiovascular disease (6, 16, 18, 28, 31). This epidemiological finding has been shown consistently, but the pathophysiological link between diminished parasympathetic tone and increased mortality remains uncertain. It has also been shown that the risk of sudden cardiac death is increased nearly 17-fold during and immediately after exercise compared with sedentary periods (2, 23). Recently, abnormal “heart rate recovery” has been identified as a predictor of mortality (9, 10, 27). A drop in heart rate of <12 beats/min from peak exercise to 1 min in recovery was associated with an increased risk of mortality, even after adjusting for age, sex, risk factors, and medications. These findings suggest that the autonomic milieu during exercise and recovery may predispose susceptible patients to sudden death.

One proposed mechanism for the adverse prognosis related to diminished parasympathetic tone is that the
presence of parasympathetic tone provides cardiac protection. For example, prolongation of ventricular refractoriness may provide an “antiarrhythmic” effect. We demonstrated that during moderate exercise in subjects with normal left ventricular function, there are persistent parasympathetic effects on cardiac electrophysiology. In subjects with left ventricular dysfunction, there is diminished parasympathetic tone at rest. Exercise (and recovery) may be associated with further decreases in parasympathetic tone, thereby increasing the risk of sudden cardiac death at these times. Further studies investigating the “antiarrhythmic” effect of parasympathetic tone during exercise and recovery in both normal and diseased populations will provide a better understanding of the pathophysiological relationship among diminished parasympathetic tone, exercise, and increased mortality.

REFERENCES


