Assessment of parasympathetic reactivation after exercise

Jeffrey J. Goldberger, Francis Kiet Le, Marc Lahiri, Prince J. Kannankeril, Jason Ng, and Alan H. Kadish

Division of Cardiology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Submitted 24 October 2005; accepted in final form 19 December 2005

Goldberger, Jeffrey J., Francis Kiet Le, Marc Lahiri, Prince J. Kannankeril, Jason Ng, and Alan H. Kadish. Assessment of parasympathetic reactivation after exercise. Am J Physiol Heart Circ Physiol 290: H2446–H2452, 2006.—The objective of this study was to evaluate whether heart rate variability (HRV) can be used as an index of parasympathetic reactivation after exercise. Heart rate recovery after exercise has recently been shown to have prognostic significance and has been postulated to be related to abnormal recovery of parasympathetic tone. Ten normal subjects [5 men and 5 women; age 33 ± 5 yr (mean ± SE)] exercised to their maximum capacity, and 12 subjects (10 men and 2 women; age 61 ± 10 yr) with coronary artery disease exercised for 16 min on two separate occasions, once in the absence of atropine and once with atropine (0.04 mg/kg) administered during exercise. The root mean square residual (RMS), which measures the deviation of the R-R intervals from a straight line, as well as the standard deviation (SD) and the root mean square successive difference of the R-R intervals (MSSD), were measured on successive 15-, 30-, and 60-s segments of a 5-min ECG obtained immediately after exercise. In recovery, the R-R interval was shorter with atropine (P < 0.0001). Without atropine, HRV, as measured by the MSSD and RMS, increased early in recovery from 4.1 ± 0.4 and 3.7 ± 0.4 ms in the first 15 s to 7.2 ± 1.0 and 7.4 ± 0.9 ms after 1 min, respectively (P < 0.0001). RMS (range 1.7–2.1 ms) and MSSD were less with atropine (P < 0.0001). RMS remained flat throughout recovery, whereas MSSD showed some decline over time from 3.0 to 2.2 ms (P < 0.002). RMS and MSSD were both directly related (r² = 0.47 and 0.56, respectively; P < 0.0001) to parasympathetic effect, defined as the difference in R-R interval without and with atropine. In conclusion, RMS and MSSD are parameters of HRV that can be used in the postexercise recovery period as indexes of parasympathetic reactivation after exercise. These tools may improve our understanding of parasympathetic reactivation after exercise and the prognostic significance of heart rate recovery.

heart rate variability; heart rate recovery; autonomic effects

OVER THE LAST SEVERAL DECADES, there has been increasing interest in the study of heart rate variability as an index of autonomic control of the heart and as a prognostic index. Low heart rate variability, a marker, in part, of diminished parasympathetic modulation of heart rate, has been consistently shown to be a predictor of mortality (6, 15, 16, 26). Recently, low heart rate recovery after exercise has also been identified as a strong predictor of mortality in patients undergoing stress testing, independent of information obtained regarding ischemia (9, 10, 20, 24). Most recently, it has also been shown to be a predictor of sudden death (13). It has been postulated that depressed recovery of parasympathetic tone may be linked to the adverse prognosis. While standard heart rate variability analyses have been used in an attempt to understand autonomic physiology during exercise and in recovery (3, 4, 8, 19, 21, 22, 25, 28), the reported studies have yielded highly variable or conflicting results. At least part of the problem in applying these techniques to the recovery period is the changing heart rate that is noted during this time period. Furthermore, there have been no studies validating the use of indexes of heart rate variability to characterize parasympathetic effects in the recovery period. Thus the objective of this study was to test whether indexes of heart rate variability characterize parasympathetic reactivation during the postexercise recovery period. In addition, because of the changing heart rate that occurs during recovery, a new index of heart rate variability in recovery that specifically accounts for the changing heart rate was evaluated.

METHODS

Subjects. All subjects were studied at the Clinical Research Center at Northwestern Memorial Hospital (Chicago, IL). Written, informed consent was obtained before the study from each subject. The study protocols were approved by the Northwestern University Institutional Review Board. Two groups of subjects were studied. Group I included 10 healthy volunteers [5 men and 5 women; age 33 ± 5 yr; median age 31.5 yr, range 23–40 yr] in whom parasympathetic effects on heart rate (R-R interval) were evaluated during peak exercise and the early recovery period. These results have been previously reported, as well as the detailed study protocol (14). All subjects were free from significant medical or cardiovascular disease and had a normal physical examination, blood pressure, and resting electrocardiogram. No subject was taking cardioactive medications. Group II included 14 volunteers with coronary artery disease documented by either prior myocardial infarction or by >50% stenosis of at least one coronary artery on coronary angiography. Two subjects were excluded from analysis because of frequent premature ventricular complexes during the recovery period. Thus 12 subjects (10 men and 2 women; age 61 ± 10 yr; median 61 yr, range 44–77 yr) were studied. All subjects had left ventricular ejection fractions >50%. Subjects were excluded if they had had a recent acute coronary event or angioplasty within the prior 3 mo, had stress-induced myocardial ischemia, atrial fibrillation, frequent premature ventricular complexes, or had a history of diabetes or other conditions that could affect autonomic function. Subjects were on a stable medication regimen for at least 3 mo preceding their participation in the study.

Study protocol. Subjects performed exercise while seated on an electrically braked bicycle ergometer (SciFit Pro II, Tulsa, OK) on two separate days with electrocardiographic monitoring. Electrocardiographic data were recorded on a commercially available system (Predictor I, Arrhythmia Research Technology using the standard X, Y, and Z lead configurations, or Quest Exercise Stress System, Burdick, Deerfield, WI, using a 12-lead ECG).

In group I, on day 1, subjects exercised at an initial workload of 50 W, keeping pedal speed at 80 revolutions per minute. Workload was
Immediately after exercise, a baseline recovery 5-min continuous electrocardiographic recording was obtained. Peak heart rate on day 1 was 127 ± 6 beats/min. Heart rates measured at each exercise stage for both sessions, before atropine, correlated extremely well for each subject ($r^2$ range = 0.653 to 0.991). Bland-Altman plots revealed no systematic bias in the heart rates on the two days.

Heart rate variability in recovery: defining the new index. The 5-min ECG recordings made on cessation of exercise were analyzed. R-R interval tachograms were generated using custom software. QRS detection was performed using a template-matching algorithm developed in Matlab (Mathworks, Natick, MA). First, median templates of the QRS complexes were generated from a 10-s segment for each of the ECG leads using a slope-based detection algorithm with the point of maximum negative slope chosen as the fiducial point. The cross correlations of the templates with their respective 5-min signals were then summed, and the QRS complexes were detected by finding the peaks of the resulting signal that exceeded a third of the maximum value. After premature atrial and ventricular beats were manually identified, the R-R interval preceding the premature beat and the two R-R intervals following the premature beat were excluded from further analysis. The ECG was visually overread to ensure correct beat-to-beat interval markings. A typical R-R interval tachogram is shown in Fig. 1. While there is a progressive increase in the R-R interval over the 5 min, on shorter scales, i.e., 15–60 s, the curve is piecewise linear with superimposed oscillations. Thus linear regression analysis (R-R interval versus time) was performed (in Matlab) on short-scale segments (15, 30, and 60 s). From the linear regression analysis, the root mean square residual (RMS) provides a statistical measure that quantifies the deviation of the R-R interval from a straight line. If the R-R interval change over time were purely linear (no oscillations), RMS would be zero. Conversely, if there are significant oscillations of the R-R interval over time, the RMS will be high.

Because the R-R interval changes in a curvilinear fashion (Figs. 1 and 2), shorter segments will better approximate a linear change over time than longer-duration segments. However, shorter-duration segments have fewer data points that could affect the reliability of the results. To assess the optimal duration for analysis, each 5-min recording was divided for analysis into 1) 20 successive 15-s segments; 2) 10 successive 30-s segments; and 3) five successive 60-s segments.
segments. Correlation of RMS to parasympathetic effect (as defined in Data analysis) was evaluated for each duration of analysis.

In addition to the RMS, standard time domain parameters of heart rate variability were calculated for each of the 15-, 30-, and 60-s segments. The standard deviation (SD) of the R-R intervals in the segment of interest and the root mean square successive difference of the R-R intervals (MSSD) in the segment of interest were evaluated. The percentage of R-R intervals that differed by >50 MS was nearly uniformly zero and was therefore not studied. To smooth out transient outliers in the heart rate variability plots (heart rate variability versus time in recovery), a median filter operation was performed in which each value was replaced with the median of the value and the preceding and following values. The first and last values were not median filtered.

Data analysis. Parasympathetic effect was defined as the difference of the R-R interval without (day 1) and with (day 2) atropine. The mean R-R interval in each of the segments was calculated and used for this analysis. Time-dependent changes in R-R interval and heart rate variability (baseline recovery and after parasympathetic blockade) as well as the effects of parasympathetic blockade and the presence of coronary artery disease were assessed using multifactor repeated-measures analysis of variance. Post hoc comparisons were performed with paired t-tests. Linear regression analysis was used to calculate the correlation of parasympathetic effects to RMS, SD, and MSSD, using the effective sample size adjusted for intraclass correlation. The effect of outliers on the regression was examined, and individual outlier data points that overly influenced the regression results were excluded in a second analysis. All data are presented as means ± SE. A P value <0.05 was considered statistically significant.

RESULTS

Figure 1 demonstrates typical R-R interval tachograms from the baseline postexercise recovery period in the absence of drugs (day 1) and after parasympathetic blockade (day 2). During the baseline recovery period, as the R-R interval increases, R-R interval oscillations are seen to increase. On day 2, with parasympathetic blockade, R-R interval oscillations do not appear, despite the steady increase in the R-R interval during the recovery period. The bottom three panels of Fig. 1 show the corresponding RMS, SD, and MSSD values for this subject on both day 1 and day 2. During the baseline recovery period, the R-R interval increased quickly over the first minute without significant variability in the R-R intervals. At this time, the RMS and MSSD are small. After ~60 s, the amplitude of R-R interval oscillations, or heart rate variability, increases dramatically, as do the RMS and MSSD. Note the fluctuations in the RMS and MSSD when measured every 15 s compared with the relatively monotonic change when measured every 30 or 60 s. The SD did not demonstrate this same consistent pattern of change over time in recovery. After parasympathetic blockade, when the R-R interval increases without significant R-R interval oscillations, the RMS and MSSD remain uniformly low.

Figure 2 shows the average R-R intervals in recovery for the normal subjects and those with coronary artery disease in the 15-s segments. After parasympathetic blockade, the R-R intervals were shorter and recovered less briskly (P < 0.0001). For each time interval, the R-R interval with parasympathetic blockade is shorter than during the baseline recovery period (P < 0.0001 for all pairwise comparisons).

Figures 3, 4, and 5 show the heart rate variability results for all subjects for the 15-, 30-, and 60-s time segments. The SD data are shown only for the 15-s segments to highlight the relatively flat response over the 5-min period. After parasympathetic blockade, the SD decreases over time, as the R-R interval recovers rapidly. Qualitative results for the RMS and MSSD were similar for the analyses of the 15-, 30-, and 60-s time segments (Tables 1 and 2). On day 1, during the baseline recovery period, RMS increased rapidly in the first minute after...
exercise, from 3.7 ± 0.4 ms in the first 15-s segment to 7.4 ± 0.9 ms in the 60- to 75-s segment, and reached a maximum of 9.9 ± 1.6 ms. MSSD also increased in the first minute after exercise, from 4.0 ± 0.4 ms in the first 15-s segment to 7.2 ± 1.0 ms in the 60- to 75-s segment, and reached a maximum of 7.9 ± 1.1 ms. Significant time-dependent increases in RMS and MSSD were noted (P < 0.0001). After parasympathetic blockade, RMS remained flat throughout the 5 min (with a minimum value of 1.7 ms and a maximum value of 2.1 ms; P = not significant), consistent with minimal heart rate variability after parasympathetic blockade. In contrast, the MSSD did demonstrate some decline over time from a maximum of 3.0 ms to a minimum of 2.2 ms (P < 0.002).

RMS and MSSD on day 1 were significantly greater than the values after parasympathetic blockade (P < 0.0001). Table 1 also demonstrates that for any given time period, a longer duration of analysis was associated with an increased RMS value. For example, for 0–15 and 15–30 s, the RMS values were 2.7 ± 0.3 and 3.8 ± 0.9 ms, respectively, whereas for 0–30 s, the RMS was 4.6 ± 0.7 ms. For the 30- to 60-s period, RMS was 5.7 ± 0.7 ms, whereas for 0–60 s, the RMS was 7.3 ± 1.0 ms. This is consistent with the notion that shorter segments better approximate a linear change over time than longer duration segments.

The presence or absence of coronary artery disease was not a significant factor affecting the RMS whether measured on the 15-, 30-, or 60-s segments. In contrast, the MSSD tended to be greater in patients with coronary artery disease than those without (P < 0.06 for the 15-s segments and P < 0.05 for the 30- and 60-s segments).

Figure 6 shows the relationship of RMS and MSSD to parasympathetic effect for the 30-s segments. RMS and MSSD were both directly related to parasympathetic effect (r² = 0.47 and 0.56 and slope = 0.05 and 0.04, respectively; P < 0.0001). With three outliers removed in each case, the relationship remained (r² = 0.52 and 0.58 and slope = 0.05 and 0.04, respectively; P < 0.0001).

Similar relationships were noted for the 15- and 60-s analyses (r² = 0.39 and 0.49, slope = 0.04 and 0.04, and P < 0.0001 for the 15-s analyses; and r² = 0.52 and 0.58, slope = 0.06 and 0.04, and P < 0.0001 for the 60-s segments). With influential outliers removed, r² for the 15-s analyses increased to 0.43 and 0.61, respectively, with no change in slope for the 60-s analysis; with outliers removed, r² increased to 0.57 and 0.58 with slope = 0.06 and 0.05, respectively. Overall, the SD did not demonstrate a direct relationship to parasympathetic effect.
outliers were removed from the MSSD analysis, and \( P = 0.04 \), respectively; 

**DISCUSSION**

In this study, we demonstrated that heart rate variability can be measured in the immediate postexercise recovery period and correlates with the parasympathetic effects present at this time in both normal subjects and those with coronary artery disease. Both the MSSD and the newly defined parameter, RMS, describe heart rate variability during the postexercise recovery period and are related to the parasympathetic effect, defined by the difference in R-R interval in the presence and absence of parasympathetic tone. The SD does not perform as well; after atropine, time-dependent changes in SD were seen, whereas

<table>
<thead>
<tr>
<th>Time Interval, s</th>
<th>15-s Segment Day 1 RMS, ms</th>
<th>15-s Segment Day 2 RMS, ms</th>
<th>30-s Segment Day 1 RMS, ms</th>
<th>30-s Segment Day 2 RMS, ms</th>
<th>60-s Segment Day 1 RMS, ms</th>
<th>60-s Segment Day 2 RMS, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>3.7 ± 0.4</td>
<td>2.0 ± 0.2</td>
<td>0–30</td>
<td>7.9 ± 1.2</td>
<td>2.6 ± 0.2</td>
<td>0–60</td>
</tr>
<tr>
<td>15–30</td>
<td>5.5 ± 0.8</td>
<td>2.1 ± 0.2</td>
<td>30–60</td>
<td>8.5 ± 1.2</td>
<td>2.4 ± 0.2</td>
<td>60–90</td>
</tr>
<tr>
<td>30–45</td>
<td>7.1 ± 1.4</td>
<td>2.1 ± 0.2</td>
<td>60–90</td>
<td>9.6 ± 1.3</td>
<td>2.4 ± 0.3</td>
<td>0–120</td>
</tr>
<tr>
<td>45–60</td>
<td>7.4 ± 1.3</td>
<td>2.1 ± 0.3</td>
<td>90–120</td>
<td>10.5 ± 1.4</td>
<td>2.3 ± 0.2</td>
<td>60–120</td>
</tr>
<tr>
<td>60–75</td>
<td>7.8 ± 1.0</td>
<td>2.0 ± 0.2</td>
<td>120–150</td>
<td>10.3 ± 1.3</td>
<td>2.4 ± 0.3</td>
<td>120–180</td>
</tr>
<tr>
<td>75–90</td>
<td>8.2 ± 1.4</td>
<td>2.0 ± 0.2</td>
<td>180–210</td>
<td>11.3 ± 1.5</td>
<td>2.1 ± 0.2</td>
<td>180–240</td>
</tr>
<tr>
<td>90–105</td>
<td>9.0 ± 1.5</td>
<td>1.9 ± 0.2</td>
<td>210–240</td>
<td>11.3 ± 1.5</td>
<td>2.0 ± 0.2</td>
<td>270–300</td>
</tr>
<tr>
<td>105–120</td>
<td>8.7 ± 1.3</td>
<td>1.9 ± 0.1</td>
<td>240–270</td>
<td>11.5 ± 1.5</td>
<td>2.3 ± 0.2</td>
<td>240–300</td>
</tr>
<tr>
<td>120–135</td>
<td>8.4 ± 1.0</td>
<td>2.0 ± 0.2</td>
<td>270–285</td>
<td>9.4 ± 1.2</td>
<td>1.8 ± 0.2</td>
<td>270–300</td>
</tr>
<tr>
<td>135–150</td>
<td>8.5 ± 1.1</td>
<td>2.0 ± 0.2</td>
<td>285–300</td>
<td>9.9 ± 1.6</td>
<td>2.0 ± 0.3</td>
<td>285–300</td>
</tr>
</tbody>
</table>

Values are means ± SE. RMS, root mean square residual.

**Table 2. MSSD results from sequential linear regression analyses of 15-, 30-, and 60-s segments of first 5 min after exercise**

<table>
<thead>
<tr>
<th>Time Interval, s</th>
<th>15-s Segment Day 1 MSSD, ms</th>
<th>15-s Segment Day 2 MSSD, ms</th>
<th>30-s Segment Day 1 MSSD, ms</th>
<th>30-s Segment Day 2 MSSD, ms</th>
<th>60-s Segment Day 1 MSSD, ms</th>
<th>60-s Segment Day 2 MSSD, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>4.1 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>0–30</td>
<td>4.9 ± 0.5</td>
<td>3.0 ± 0.3</td>
<td>0–60</td>
</tr>
<tr>
<td>15–30</td>
<td>5.2 ± 0.7</td>
<td>2.9 ± 0.3</td>
<td>30–60</td>
<td>6.3 ± 0.9</td>
<td>3.1 ± 0.4</td>
<td>0–60</td>
</tr>
<tr>
<td>30–45</td>
<td>6.7 ± 1.6</td>
<td>2.9 ± 0.3</td>
<td>60–90</td>
<td>7.3 ± 1.0</td>
<td>2.9 ± 0.4</td>
<td>60–120</td>
</tr>
<tr>
<td>45–60</td>
<td>7.1 ± 1.6</td>
<td>3.0 ± 0.4</td>
<td>90–120</td>
<td>7.7 ± 1.1</td>
<td>2.7 ± 0.3</td>
<td>60–120</td>
</tr>
<tr>
<td>60–75</td>
<td>7.2 ± 1.0</td>
<td>2.9 ± 0.4</td>
<td>120–150</td>
<td>7.8 ± 1.1</td>
<td>2.5 ± 0.2</td>
<td>120–180</td>
</tr>
<tr>
<td>75–90</td>
<td>7.5 ± 1.1</td>
<td>2.8 ± 0.4</td>
<td>150–180</td>
<td>7.5 ± 1.0</td>
<td>2.4 ± 0.2</td>
<td>120–180</td>
</tr>
<tr>
<td>90–105</td>
<td>7.8 ± 1.1</td>
<td>2.7 ± 0.4</td>
<td>180–210</td>
<td>7.6 ± 1.1</td>
<td>2.4 ± 0.2</td>
<td>180–240</td>
</tr>
<tr>
<td>105–120</td>
<td>7.7 ± 1.3</td>
<td>2.4 ± 0.2</td>
<td>210–240</td>
<td>7.8 ± 1.0</td>
<td>2.3 ± 0.2</td>
<td>210–240</td>
</tr>
<tr>
<td>120–135</td>
<td>7.7 ± 1.1</td>
<td>2.4 ± 0.2</td>
<td>240–270</td>
<td>7.7 ± 1.0</td>
<td>2.3 ± 0.2</td>
<td>240–270</td>
</tr>
<tr>
<td>135–150</td>
<td>7.4 ± 1.0</td>
<td>2.4 ± 0.2</td>
<td>270–285</td>
<td>7.9 ± 1.1</td>
<td>2.2 ± 0.2</td>
<td>270–285</td>
</tr>
<tr>
<td>150–165</td>
<td>7.2 ± 1.0</td>
<td>2.4 ± 0.2</td>
<td>285–300</td>
<td>7.9 ± 1.1</td>
<td>2.4 ± 0.3</td>
<td>285–300</td>
</tr>
</tbody>
</table>

Values are means ± SE. MSSD, mean square successive difference of R-R intervals.
they were small for MSSD and not present for RMS. On the basis of the results of this study, the 30-s segments provide an adequate window for analysis. On the basis of these data, MSSD and RMS provide a strong index measuring reactivation of parasympathetic tone after exercise.

Autonomic physiology during exercise and recovery has been evaluated by selective autonomic blockade, measurement of plasma catecholamines, and assessing indexes of heart rate variability (3, 4, 8, 12, 21, 22, 25, 28). It is generally agreed that with exercise, there is parasympathetic withdrawal and sympathetic excitation, resulting in acceleration of the heart rate; these effects are reversed in recovery. However, the timing of these changes in recovery has been debated (12, 23). We (14) previously reported that parasympathetic reactivation occurs early in the recovery period on the basis of the heart rate recovery patterns with and without atropine, the use of which provides the most direct measure of parasympathetic effect. However, quantifying parasympathetic effect by pharmacologic blockade is impractical in clinical practice. There are no other validated parameters of parasympathetic effect in recovery. Thus this study demonstrates for the first time that the easily measured, noninvasive MSSD and RMS provide an index of parasympathetic reactivation in recovery.

Heart rate recovery after exercise has recently been shown to be an important prognostic index (9, 10, 13, 20, 24). Parasympathetic activity has been shown to confer protection against arrhythmias in the setting of exercise-induced ischemia (7, 27), while sympathetic activity has also been shown to provoke ventricular arrhythmias (18). Thus equally plausible hypotheses for the prognostic significance of delayed heart rate recovery are that it represents heightened sympathetic effects or attenuated recovery of parasympathetic effects, or both. As noted, heart rate recovery cannot be used as a pure index of parasympathetic reactivation because it is likely mediated by both sympathetic withdrawal and parasympathetic reactivation (14). To further explore whether delayed parasympathetic reactivation is responsible for the adverse prognosis associated with low heart rate recovery, it would be ideal to have a simple, noninvasive tool that could be used to measure parasympathetic reactivation.

Heart rate variability has been considered to be a marker of parasympathetic modulation of the heart rate (11). Traditional methods to measure heart rate variability include time and frequency domain analyses. However, these methods have been validated in the setting of a steady-state heart rate, which does not occur during the exercise and postexercise recovery periods. In fact, applying these techniques to assess heart rate variability after exercise has given rise to conflicting or inconsistent results (3, 4, 21, 24). In general, the studies show that during exercise, both low- and high-frequency power decrease (3, 8, 25), but the results for the normalized low- and high-frequency power, as well as the ratio of low to high frequency, have been inconsistent (4, 19, 21, 22, 25, 28). More importantly, exercise studies using selective β-adrenergic and parasympathetic blockade (28) do not support the validity of these measures as indexes of parasympathetic or sympathetic effect. During recovery, these indexes are again unreliable indicators, because the reported results of absolute and normalized low- and high-frequency power and the ratios of low to high frequency have also been discordant (1, 3, 4, 8, 19, 21, 22, 25, 28). Furthermore, while heart rate variability parameters such as low- and high-frequency power and/or their ratio have been measured in recovery, no studies have validated the physiological relationships of these parameters to autonomic effects in the postexercise recovery period.

In the present study, RMS was defined to take into account the changing heart rate. Over the short term, the R-R interval can be analyzed in a piecewise linear fashion. The calculation of RMS is based on the results of linear regression analysis over a period of time that is short enough for the heart rate
change to be approximately linear over that duration; thus fluctuations of the R-R interval from this linear change are measured by the RMS. It is easy to measure, because it only requires the measurement of the R-R intervals and a linear regression analysis. We showed that it correlates well with parasympathetic effect, as measured by parasympathetic blockade. Thus RMS is a useful noninvasive index of parasympathetic reactivation in the recovery period after exercise. MSSD is also a useful measure, although it does have a clear component that is due to the changing heart rate noted early in recovery.

Limitations. The order of the two exercise tests was not randomized because the first exercise test was used to calibrate the exercise intensity and/or time and to ensure safe completion of the test before administration of atropine during exercise. Thus a small training effect is possible, as well as a minor effect secondary to the unblinded administration of atropine. The two groups were also not matched for either age or exercise intensity. The consistency of the findings (Fig. 6) demonstrates the robustness of these measures of parasympathetic reactivation.

Implications. There is a heightened risk of sudden cardiac death related to exercise and during the postexercise period (2, 17). The negative prognosis related to diminished heart rate recovery has highlighted the potential role of autonomic factors in the pathophysiology of sudden cardiac death at this time. MSSD and RMS are now validated indexes of parasympathetic reactivation in the recovery period after exercise. If delayed parasympathetic reactivation is the component of heart recovery that is important prognostically, then MSSD and RMS may provide an even more powerful prognostic index than heart rate recovery.

ACKNOWLEDGMENTS

We thank Haris Subacius for tremendous assistance in the statistical analyses.

GRANTS

This research is supported in part by Grant M01 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.

REFERENCES