Heart rate recovery after exercise: a predictor of ventricular fibrillation susceptibility after myocardial infarction

Lauren L. Smith, Monica Kukielka, and George E. Billman

Department of Physiology and Cell Biology, The Ohio State University, Columbus, Ohio

Submitted 3 August 2004; accepted in final form 18 November 2004

Heart rate recovery after exercise: a predictor of ventricular fibrillation susceptibility after myocardial infarction. 

Heart rate recovery after exercise has been shown to be an independent predictor of mortality across substantial and diverse population groups (10, 11, 13, 31, 33, 41, 47) with minimal exception (20). For example, Cole et al. (11) demonstrated in a multicenter study of 5,234 individuals that abnormal heart rate recovery after submaximal exercise predicts death, even after adjustment for various cofounders; Nishime et al. (33) published similar results from a total of 9,454 patients. Subsequent investigations have established that low heart rate recovery is linked to attenuated parasympathetic reactivation following the termination of exercise (1, 10, 11, 13, 25, 35, 37). Despite the large number of studies that have examined heart rate recovery, the application of heart rate recovery data for patients recovering from myocardial infarction (MI), a population known to be at risk for sudden death, is sparse.

Numerous studies have suggested that, in MI survivors, heightened parasympathetic activity protects against ventricular fibrillation (8, 12, 28) or that attenuated parasympathetic tone indicates a high risk for sudden cardiac death (29, 33, 40, 45). For instance, the Autonomic Tone and Reflexes After Myocardial Infarction trial (29), a multicenter study that examined 1,284 patients with recent MI, established that autonomic tone is a strong independent indicator of mortality risk and that information from autonomic markers significantly increases prognostic ability. For several years, assorted measures of heart rate variability (HRV), an established index of cardiac parasympathetic activity, have been used to evaluate parasympathetic tone in patients with cardiovascular disease. It has been well established that low HRV, typically measured over a 24-h period, is a marker of high arrhythmia risk in post-MI subjects (2, 19, 23, 27, 29, 41, 45). Yet, there is room for criticism of this method, because it requires hand-editing of ectopic beats that can be quite common in MI patients; there is no consensus on the best HRV measure to use, and standardization of commercial systems is lacking (24).

Because of these findings, it seems reasonable that heart rate recovery may offer additional insight into the parasympathetic function of MI patients and, therefore, the risk for malignant arrhythmias. Heart rate recovery is a more straightforward and easily obtained measurement compared with HRV and other indexes of cardiac vagal tone, because it requires less time for data collection and fewer data processing algorithms. In addition, heart rate recovery may show the vagal reactivity necessary for combating ventricular fibrillation during ischemic or other stress conditions when irregular heart rhythm could potentially occur. In a pioneering study, Nissinen et al. (34) examined heart rate recovery among survivors of acute MI and found it to be a more powerful predictor of all-cause mortality than traditional autonomic markers. However, the specific relationship of heart rate recovery following exercise and a confirmed susceptibility to lethal cardiac arrhythmias remains to be determined.

It was, therefore, the purpose of this study to investigate the relationship among heart rate recovery, cardiac parasympathetic activity, and susceptibility to malignant arrhythmias. In particular, the hypothesis that attenuated cardiac parasympathetic reactivation with the corresponding decline in heart rate recovery following exercise would be associated with an increased risk for ventricular fibrillation was tested. Time-series analysis of HRV, with and without atropine pretreatment, was used to evaluate cardiac parasympathetic reactivation in dogs with healed MI that were subsequently found to be either susceptible or resistant to ventricular fibrillation.

METHODS

Archived data from 105 (56 female and 47 male, weight 18.2 ± 0.4 kg) heartworm-free, purpose-bred mongrel dogs (Kaiser Lake Ken-
nels, Kaiser Lake, OH and Covance Research Products, Cumberland, VA), judged to be less than 1 yr old by inspection of the teeth and the presence of the thymus gland at the time of surgery, were used in this study. A consecutive sequence of animals in which a high-quality ECG signal was recorded throughout the submaximal exercise test was selected. In a subset of these animals (n = 23), the submaximal exercise test was also performed after treatment with atropine sulfate. In some animals (n = 18), the heart rate recovery was evaluated during a second control exercise test recorded within 1 wk of the first. The principles governing the care and treatment of animals as expressed by the American Physiological Society were followed at all times during this study. In addition, the Ohio State University Institutional Animal Care and Use Committee approved the procedures used in this study.

Surgical preparation of canine model. The surgical preparation of the dogs has been described in previous publications (4–6, 40). Briefly, the dogs were anesthetized and, with the use of strict aseptic techniques, a left thoracotomy was made in the fourth intercostal space. The heart was exposed and supported by a pericardial cradle. A hydraulic occluder and a 20-MHz Doppler flow transducer were placed around the left circumflex coronary artery. Insulated silver-coated copper wires were sutured to the epicardial surface of the left and right ventricle for later use in recording a ventricular electrogram. The left anterior coronary artery was ligated, producing an anterior wall MI. All leads to the instrumentation were tunneled under the skin to exit at the back of the neck. Dogs were medicated to control postoperative pain and infection, as described previously (4, 5).

Exercise protocol. Three to four weeks after surgery, the animals were trained to walk on a motor-driven treadmill for several days to familiarize them with the laboratory. Preexercise values of all the variables were obtained while the animals were standing on the treadmill before the onset of running. The response to exercise was then assessed using a submaximal exercise protocol previously described by Tipton et al. (44) and as modified by Stone (42). Briefly, the treadmill exercise lasted a total of 18 min and was divided into 3-min blocks. The protocol began with a 3-min warm-up period during which the animal ran at 4.8 km/h, 0% grade. The speed was increased to 6.4 km/h, and the grade of the treadmill was increased every 3 min as follows: 0, 4, 8, 12, and 16%. In agreement with previous studies (4, 6, 42, 44), heart rate increased to ~70% (~210 beats/min) of the maximum canine heart rate (46) during the last 3 min of exercise in the dogs included in the present study. After the completion of 18 min of exercise, the treadmill was stopped, and the animal remained standing while a postexercise ECG was obtained.

The effects of atropine were examined in a subsequent submaximal exercise test to evaluate the role of the parasympathetic nervous system. In the atropine subgroup of dogs, on a later day, a catheter was percutaneously placed in a cephalic vein so that atropine sulfate (50 μg/kg; American Pharmaceutical Partners, Schaumberg, IL) could be administered while the animal was running, ~2–3 min before the treadmill was stopped (i.e., when a new steady-state heart rate had been achieved).

Susceptibility classification: exercise-plus-ischemia test. On a subsequent day (after completion of the submaximal exercise studies), exercise-plus-ischemia testing was used to classify the animals as either susceptible or resistant to ventricular fibrillation. This convention of categorizing the animals has been used since the original study employing this canine exercise model was published in 1982 (6). Briefly, the exercise level was increased every 3 min in the same manner as the submaximal exercise protocol. During the last minute of exercise, the left circumflex coronary artery was occluded. The treadmill was then stopped, and the occlusion was maintained for an additional minute for a total occlusion time of 2 min. Metal plates (11-cm diameter) were placed across the animal’s chest so that electrical defibrillation could be achieved with minimal delay, but only after the animal was unconscious. The ECG was recorded throughout the test, and left circumflex coronary blood flow was measured to confirm that the coronary occlusion was complete.

Data analysis. All data were recorded on a Gould model 2800S eight-channel chart recorder (Cleveland, OH). A ventricular electrogram was recorded using the leads sutured to the epicardium, and heart rate was determined with a Gould biotachometer. Coronary blood flow was measured with a University of Iowa model 545C pulsed Doppler flowmeter (Iowa City, IA).

Heart rate data are reported as the average of a 30-s time interval. Heart rate was recorded for the last 30 s of exercise, from cessation to 30 s postexercise, from 30 s to 60 s postexercise, and from 90 s to 120 s postexercise. These average values are reported as 0, 30, 60, and 120 s, respectively, and are given in units of beats per minute. The heart rate recovery is defined as the absolute difference between the average heart rate during the last 30 s of exercise and the average heart rate for the given time period.

An estimate of cardiac vagal tone index (VT) was obtained using a Delta-Biometrics vagal tone monitor triggering off the electrocardiogram R-R interval (Urbana-Champaign, IL). This device employs the time-series signal processing techniques as developed by Borges (38) to estimate the amplitude of respiratory sinus arrhythmia. Details of this analysis have been described previously (4). Similarly, the variance of the R-R intervals was recorded and transformed to its natural logarithm to normalize the distribution; it is expressed as standard deviation of the R-R interval (SDRR). Finally, the range, which is the difference between the longest and shortest R-R intervals within each 30-s time period, also was obtained.

The data were analyzed by using a two-factor (group × time) ANOVA for repeated measures. Because repeated-measures ANOVA depends on the homogeneity of covariance (equal correlations between treatments), this sphericity assumption was tested using Mauchley’s test. If the sphericity assumption was violated, then the F ratio was corrected using Huynh-Feldt correction. When the F ratio exceeded a critical value of < 0.05, the means were compared using the Tukey-Kramer multiple comparison test. Values are reported as means ± SE. Microsoft Excel (Redmond, WA) and NCSS statistical software (Jerry Hintze, Kaysville, UT) were used for data processing.

RESULTS

Susceptibility classification. The exercise-plus-ischemia tests induced ventricular fibrillation in 66 of the 105 animals, which were categorized as susceptible (S), whereas 39 animals did not develop arrhythmias and were categorized as resistant (R) to sudden death. There were no gender or weight differences between the two groups. The resistant dogs (18.4 ± 0.5 kg, range 14.1–26.2 kg) included 21 females and 18 males, whereas the susceptible group (18.1 ± 0.4 kg, range 13.2–27.7 kg) was composed of 36 females and 30 males.

Preexercise variables. Before the onset of exercise, there were no significant differences in any of the variables measured (heart rate: S = 123.7 ± 2.7 beats/min, R = 125.9 ± 2.7 beats/min; VT: S = 6.9 ± 0.2 ln ms², R = 7.0 ± 0.3 ln ms²; R-R interval range: S = 320 ± 24 ms, R = 303 ± 24 ms; SDRR: S = 74 ± 7 ms, R = 68 ± 6 ms).

Control heart rate recovery measures. The average heart rate and absolute change in heart rate for both groups are shown in Fig. 1. A scatterplot for the change in heart rate following the cessation of exercise averaged over the first 30 s for each animal is displayed in Fig. 2. The maximum heart rate achieved during exercise did not differ between the susceptible and resistant groups (212.4 ± 3.3 and 212.1 ± 4.5 beats/min, respectively). However, resistant animals clearly exhibited a more rapid heart rate recovery, with significant differences between the two groups in absolute heart rate changes noted at
the 30-, 60-, and 120-s time periods. There also was a significant \((P < 0.001)\) susceptibility group effect for the heart rate change.

**Cardiac parasympathetic indexes.** The corresponding vagal activity is shown in Fig. 3. The VT was reduced to nearly the same level during exercise for both groups \((R = 1.8 \pm 0.2–2\) ln ms\(^2\), \(S = 1.4 \pm 0.2\) ln ms\(^2\)). Through recovery, however, resistant animals had a significantly higher vagal tone when measured at 30 and 60 s. The mean vagal tone began to equalize at the 120-s mark. Similarly, the R-R interval range was the same for both groups during maximum exercise, but resistant animals showed significantly higher values at 30 and 60 s before achieving the same level as susceptible animals at 120 s. Finally, the SDRR followed a similar trend, although the difference between groups was significant only when measured at 30 s. Overall, the susceptibility group effect was significant for all three measurements \((VT, P = 0.009; range, P = 0.016; SDRR, P = 0.019)\), and the susceptibility-time interaction was significant for the R-R interval range and SDRR \((P = 0.031\) and \(P = 0.017\), respectively) but not for the VT \((P = 0.154)\).

**Heart rate recovery after atropine treatment.** Of the 23 dogs in the atropine subgroup, 14 were susceptible and 9 were resistant. The mean heart rate recovery results for the atropine subgroup of animals are shown in Fig. 4. Heart rate was elevated overall for both groups \((S = 231.4 \pm 5.7\) and \(R = 232.4 \pm 6.8\) beats/min during exercise) but still displayed qualitatively the same trend of exponential decline seen without parasympathetic blockade. Heart rate recovery was less than in the control condition overall, but more notably, the difference between susceptible and resistant animals was eliminated (susceptibility group effect, \(P = 0.868)\).

**Cardiac parasympathetic indexes after atropine treatment.** Figure 5 displays the vagal activity in the atropine subgroup. All three measurements were lower overall (maximum VT: \(R = 0.2 \pm 0.1\) ln ms\(^2\), \(S = 0.4 \pm 0.1\)). More importantly, after atropine treatment, there were no longer any differences noted between the susceptible and resistant animals in any of the three vagal indexes at any given time. Overall, there were no significant susceptibility group or susceptibility group-time interactions for any of the three parameters.

**Comparisons between repeated submaximal exercise tests.** In a subset of animals, the heart rate recovery and vagal indexes were compared on two different days. The two groups were combined (18 dogs total: 11 susceptible and 7 resistant). The response to the exercise was similar on each presentation. For example, the absolute change in heart rate during the first 30 s was 27.9 \(\pm 3.5\) beats/min for the first exercise test and 29.2 \(\pm 3.6\) beats/min during the second exercise test. Similar responses were noted at both the 60-s (first trial, 63.5 \(\pm 3.8\) beats/min; second trial, 62.9 \(\pm 3.0\) beats/min) and 120-s time points (first trial, 66.8 \(\pm 3.8\) beats/min; second trial, 66.1 \(\pm 2.9\) beats/min). When ANOVA was performed, there was no significant difference between days in any of the parameters measured. Furthermore, the average change in heart rate during the first 30 s following exercise varied by only 5.0 \(\pm 10.3\%\) (coefficient of variation \(= 12.3\%\)) between the first and second submaximal exercise tests.

**DISCUSSION**
The major findings of this study were that 1) heart rate recovery after exercise was slower in animals susceptible to ventricular fibrillation than in animals resistant to malignant
arrhythmias; 2) susceptible animals had an attenuated parasympathetic reactivation corresponding with the reduced heart rate recovery; and 3) the differences in heart rate recovery and cardiac vagal indexes of the two groups were eliminated with administration of atropine. These data suggest that the post-infarction animals with attenuated heart rate recovery, which probably reflects a reduced reactivation of cardiac parasympathetic control following exercise, also are at a high risk for lethal arrhythmias in either the general population or in patients with preexisting cardiovascular disease.

Heart rate recovery and cardiac autonomic regulation.

Heart rate recovery has been shown to be a function of parasympathetic activity immediately after exercise (1, 10, 11, 25, 35, 37). For example, Imai et al. (25), using logarithmic transformation of heart rate recovery in humans after four different levels of exercise, found two linear components: initial rapid decrease and subsequent slow decrease. In agreement with the present study, the initial rapid decrease disappeared after the administration of atropine, suggesting that this component depends on vagal reactivation. Other studies (26, 30) have further demonstrated that heart rate recovery correlates with HRV immediately after exercise. The present study confirms these findings, because it is clear that when susceptible animals were compared with resistant animals, impaired heart rate recovery corresponded with a reduced cardiac vagal recovery, and the difference between the groups was eliminated when parasympathetic activity was blocked by atropine.

According to Eckberg (18), reduced vagal activity following exercise is indicative of poor parasympathetic responsiveness.

Numerous investigations have suggested that heart rate recovery can predict all-cause mortality in general populations (10, 11, 13, 31, 33, 47). A limited number of these studies have shown the usefulness of heart rate recovery for subjects with MI. For example, Cole et al. (10) also studied a subgroup of patients with coronary artery disease and found heart rate recovery to be predictive of death among these 225 individuals. Nissinen et al. (34) also found heart rate recovery to be a predictor of all-cause death in a group of 229 post-MI patients, even claiming that heart rate recovery was a more powerful predictor of death than traditional autonomic markers. In addition, heart rate recovery data recently were shown to enhance the prognostic power of SPECT (single photon emission computed tomography) imaging and other clinical variables in patients with MI (3, 17), although Desai et al. (16) did not find this correlation. However, it must be emphasized once again that none of the aforementioned studies evaluated the relationship between heart rate recovery and an increased risk for ventricular fibrillation induced by acute ischemia. To the best of our knowledge, this is the first study to demonstrate a specific relationship between heart rate recovery and a confirmed increased risk for lethal arrhythmias.
animals noted at the 120-s time period, a time when the various indexes of cardiac parasympathetic activity have already equalized between the groups. However, any sympathetic contribution to the heart rate recovery differences is probably not large, because atropine eliminated the differences between the groups. One would predict that the inhibition of cardiac vagal activity would have allowed for the full expression of sympathetic effects and would thereby exacerbate any heart rate differences due to sympathetic activation. In the present study, both groups of animals exhibited a similar heart rate recovery after the atropine treatment. It therefore seems less likely that sympathetic activation contributed to the different heart rate recovery noted in the susceptible and resistant dogs. Because sympathetic activation was not evaluated in the present study, a complete assessment of the potential role of altered sympathetic response to the attenuated heart rate recovery noted in the susceptible remains to be determined.

**Limitations of the study.** In addition to the issue concerning the contribution of the sympathetic nervous system to the heart rate recovery, there are other limitations of the present study that should be considered. First, the best method for measuring heart rate recovery remains to be determined. Among previous studies, there is inconsistency in the type of exercise and recovery period. In addition, heart rate recovery has been analyzed as the time elapsed before a certain change (beats/min) was achieved (13), as a continuous variable of absolute change or percent change from the stop of exercise (10, 11, 26, 30, 32), as a categorical variable with varying cut-off points for abnormality (10, 11, 16, 17, 33, 41, 47), as an exponential decay model (25, 37, 39), or with the use of more complex curve-fitting techniques (9, 25). In addition, there is no consensus as to the optimal time for monitoring heart rate postexercise (48).

The current study utilized submaximal testing because of evidence that this is a more reliable alternative than the use of maximal tests (25, 37). In the present study, heart rate recovery was analyzed as a continuous variable, because it is likely that the absolute value of the cut-off point in the dog would be different from that in humans, because of the higher maximum heart rate in the former species. However, a cut-off point based on the same percentage of maximum heart rate is likely to be similar in both species. In addition, heart rate recovery was evaluated as the absolute change for reasons of simplicity and to be consistent with related studies (26, 30). An exponential decay model was not considered because it has been shown to be ineffective in time periods shorter than 3 min (37). Heart rate recovery measurements were limited to 120 s because it has been suggested that during this 2-min window, heart rate recovery is primarily due to parasympathetic recovery, with minimal change in sympathetic activity (13, 25, 47). In regards to optimal time for measurement, the most dramatic difference between all variables in the current study occurred at 30 s after exercise (48). Heart rate recovery remains to be determined. Among previous studies, there is inconsistency in the type of exercise and recovery period. In addition, heart rate recovery has been analyzed as the time elapsed before a certain change (beats/min) was achieved (13), as a continuous variable of absolute change or percent change from the stop of exercise (10, 11, 26, 30, 32), as a categorical variable with varying cut-off points for abnormality (10, 11, 16, 17, 33, 41, 47), as an exponential decay model (25, 37, 39), or with the use of more complex curve-fitting techniques (9, 25). In addition, there is no consensus as to the optimal time for monitoring heart rate postexercise (48).

The current study utilized submaximal testing because of evidence that this is a more reliable alternative than the use of maximal tests (25, 37). In the present study, heart rate recovery was analyzed as a continuous variable, because it is likely that the absolute value of the cut-off point in the dog would be different from that in humans, because of the higher maximum heart rate in the former species. However, a cut-off point based on the same percentage of maximum heart rate is likely to be similar in both species. In addition, heart rate recovery was evaluated as the absolute change for reasons of simplicity and to be consistent with related studies (26, 30). An exponential decay model was not considered because it has been shown to be ineffective in time periods shorter than 3 min (37). Heart rate recovery measurements were limited to 120 s because it has been suggested that during this 2-min window, heart rate recovery is primarily due to parasympathetic recovery, with minimal change in sympathetic activity (13, 25, 47). In regards to optimal time for measurement, the most dramatic difference between all variables in the current study occurred at 30 s after exercise, which is consistent with the results of Imai et al. (25).

Second, a few authors have questioned the reproducibility of heart rate recovery in a given individual (9, 48). In the present study, the heart rate recovery response was very similar on separate days in the same animals. For example, the average change in heart rate during the first 30 s after the cessation of exercise varied by only $5.0 \pm 10.2\%$ (coefficient of variation = 12.3%) between the first and second exercise test. Other studies
(7, 25) also have reported a similar level of reproducibility of results when a limited number of individuals were compared.

Third, it should be acknowledged that in the present study, cardiac vagal tone was only indirectly evaluated by using various measures of HRV. In this study, we did not measure the parasympathetic nerve activity directly. However, previous investigations have verified that HRV provides an accurate representation of parasympathetic function (18). In addition, in the current study, atropine effectively eliminated the changes in both heart rate and the parasympathetic indexes obtained using time-series analysis. Therefore, it is reasonable to conclude that the method used in the present study provided reliable indirect measurements of cardiac parasympathetic nerve activity.

Finally, it is well established that both respiratory rate and tidal volume can alter HRV (amplitude of the respiratory sinus arrhythmia) (22). As such, differences in the respiratory response after exercise could indirectly contribute to the differences in the cardiac vagal indexes in the susceptible and resistant animals. Respiratory parameters were not measured in this study because of the profound panting response induced by exercise that continued throughout the postexercise recovery period in both groups of animals. However, previous studies (4) demonstrated that exercise elicits similar increases in respiratory rate in both susceptible and resistant animals. Furthermore, the vagal tone indexes decreased to greater extent after β-adrenergic receptor blockade, yet respiratory frequency increased to a similar extent after this intervention (4, 5). These studies (4, 5) also established that panting did not alter HRV. Because both groups panted to a similar degree, it is unlikely that panting contributed significantly to differences in heart rate recovery response noted in the susceptible and resistant animals.

There are some obstacles in the application of heart rate recovery to post-MI patients in a clinical setting because of the medications often prescribed. Patients recovering from MI typically receive β-adrenergic receptor-blocking drugs, which blunt the chronotropic response to exercise and could indirectly affect heart rate recovery (17). Other common drugs such as digitalis and angiotensin-converting enzyme inhibitors also have vagotonic actions (20, 21, 36) and could potentially heighten heart rate recovery so that it incorrectly denotes low risk. Further study of the effect of these drugs on heart rate recovery in MI patients is one of the many necessary steps toward clinical implementation of this new tool for evaluating ventricular fibrillation susceptibility.

In summary, results of the present study suggest that impaired heart rate recovery, measured as the absolute change in heart rate shortly after exercise cessation, is associated with high arrhythmia risk in dogs with healed MI. The attenuated heart rate recovery seen in the animals subsequently shown to be susceptible to ventricular fibrillation almost certainly reflects reduced parasympathetic recovery after exercise. Therefore, heart rate recovery after exercise can offer insight into the parasympathetic regulation of the heart under dynamic conditions similar to those that provoke arrhythmia formation. Findings of the present study further suggest that heart rate recovery after exercise may provide an additional marker of arrhythmia risk in patients surviving MI.

ACKNOWLEDGMENTS

L. Smith completed this study as part of an undergraduate summer research program.

Present address of L. Smith: Dept. of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44106.

GRANTS

This study was supported by National Heart, Lung, and Blood Institute Grant HL-68609.

REFERENCES


