Cardiac vagal modulation of heart rate during prolonged submaximal exercise in animals with healed myocardial infarctions: effects of training

Monica Kukielska,1 Douglas R. Seals,2 and George E. Billman1

1Department of Physiology and Cell Biology, The Ohio State University, Columbus, Ohio; and 2Department of Integrative Physiology, University of Colorado at Boulder, Boulder, Colorado

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Kukielska, Monica, Douglas R. Seals, and George E. Billman. Cardiac vagal modulation of heart rate during prolonged submaximal exercise in animals with healed myocardial infarctions: effects of training. Am J Physiol Heart Circ Physiol 290: H1680–H1685, 2006. — The present study investigated the effects of long-duration exercise on heart rate variability as a marker of cardiac vagal tone (VT). Heart rate variability (time series analysis) was measured in mongrel dogs (n = 24) with healed myocardial infarctions during 1 h of submaximal exercise (treadmill running at 6.4 km/h at 10% grade). Long-duration exercise provoked a significant (ANOVA, all P < 0.01, means ± SD) increase in heart rate (1st min, 165.3 ± 15.6 vs. last min, 197.5 ± 21.5 beats/min) and significant reductions in high frequency (0.24 to 1.04 Hz) power (VT: 1st min, 3.7 ± 1.5 vs. last min, 1.0 ± 0.9 ln m/s²), R-R interval range (1st min, 107.9 ± 38.3 vs. last min, 28.8 ± 13.2 ms), and R-R interval SD (1st min, 24.3 ± 7.7 vs. last min 6.3 ± 1.7 ms). Because endurance exercise training can increase cardiac vagal regulation, the studies were repeated after either a 10-wk exercise training (n = 9) or a 10-wk sedentary period (n = 7). After training was completed, long-duration exercise elicited smaller increases in heart rate (pretraining: 1st min, 156.0 ± 13.8 vs. last min, 189.6 ± 21.9 beats/min; and posttraining: 1st min, 149.8 ± 14.6 vs. last min, 172.7 ± 8.8 beats/min) and smaller reductions in heart rate variability (e.g., VT, pretraining: 1st min, 4.2 ± 1.7 vs. last min, 0.9 ± 1.1 ln m/s²; and posttraining: 1st min, 4.8 ± 1.1 vs. last min, 2.0 ± 0.6 ln m/s²). The response to long-duration exercise did not change in the sedentary animals. Thus the heart rate increase that accompanies long-duration exercise results, at least in part, from reductions in cardiac vagal regulation. Furthermore, exercise training attenuated these exercise-induced reductions in heart rate variability, suggesting maintenance of a higher cardiac vagal activity during exercise in the trained state.

parasympathetic nervous system; exercise training; autonomic nervous system

MYOCARDIAL INFARCTION elicits profound alterations in cardiac autonomic regulation (10). In particular, cardiac vagal regulation is depressed in both animals and patients after myocardial infarction (3, 7, 20, 39). In fact, animals or patients with the greatest reductions in heart rate variability, an accepted non-invasive marker of cardiac vagal regulation (13, 40), exhibit the greatest risk for sudden death due to malignant changes in cardiac rhythm, i.e., ventricular fibrillation (7, 17, 22, 24, 36). It is therefore likely that interventions that enhance cardiac vagal function could also reduce mortality in these high-risk patients.

It is well established that regular exercise can improve cardiac autonomic balance (increasing parasympathetic while decreasing sympathetic regulation of the heart) (35, 41). In both humans and animals, heart rate at submaximal workloads is reduced in trained individuals compared with sedentary controls (35, 41), whereas the presence of a resting bradycardia is frequently used to confirm that training has been effective (9, 16, 27, 37, 44). Exercise training programs have also been reported to increase heart rate variability in patients recovering from myocardial infarction (25, 28, 31) and may reduce the incidence of sudden death and arrhythmias in both human and animal models (5, 8, 29, 33). As such, aerobic exercise conditioning has become an essential component of most cardiac rehabilitation programs (14, 26). To achieve the maximum benefit, i.e., reductions in secondary cardiovascular events, an individual should exercise continuously for at least 20–60 min several days a week (14, 26).

Acute exercise, however, could pose a risk in some patients (1). Exercise provokes increases in heart rate by both increasing cardiac sympathetic and reducing cardiac parasympathetic activity. These autonomic changes have been linked to an enhanced risk for sudden death in postmyocardial infarction patients (10). Furthermore, during long-duration exercise, heart rate continues to rise throughout the exercise period, a phenomenon known as cardiovascular (or heart rate) drift (11). The mechanisms responsible for this heart rate increase are presently unknown. A gradual withdrawal or inhibition of cardiac parasympathetic activity could contribute to this heart rate increase, which potentially could increase the risk for adverse events in the patients with cardiovascular disease.

It was therefore the purpose of this study to investigate the effects of long-duration exercise on heart rate variability in mongrel dogs with healed myocardial infarctions. In particular, the hypothesis that exercise-induced increases in heart rate were accompanied by progressively increasing reductions in heart rate variability was tested. The effects of exercise training on the heart rate and heart rate variability response to long-duration exercise were also examined. As such, the hypothesis that exercise training would attenuate the progressive reductions in heart rate variability induced by long-duration exercise was also tested.

METHODS

The principles governing the care and use of animals as expressed by the Declaration of Helsinki and as adopted by the American Physiological Society were followed at all times during this study. In

Address for reprint requests and other correspondence: G. E. Billman, Dept. of Physiology and Cell Biology, The Ohio State Univ., 304 Hamilton Hall, 1645 Neil Ave., Columbus, OH 43210-1218 (e-mail: billman.1@osu.edu).

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addition, the Ohio State University Institutional Animal Care and Use Committee approved all the procedures used in this study.

Surgical preparation. Thirty-six heartworm-free mongrel dogs (age, 1–3 yr; weight, 16.4–24.5 kg (19.2 ± 1.8 kg, mean ± SD)) were used in this study. The animals were anesthetized and instrumented as previously described (7, 8, 17, 36). Briefly, with the use of strict aseptic procedures, a left thoracotomy was made in the fourth intercostal space. The heart was exposed and supported by a pericardial cradle. The left circumflex coronary artery was dissected free of the surrounding tissue. Both a 20-MHz pulsed Doppler flow transducer and a hydraulic occluder were then placed around this vessel. Two pairs of silver-coated copper wires were also sutured on the epicardial surface of the left and right ventricles and were used to obtain a ventricular electrogram. A two-stage occlusion of the left anterior descending artery was then performed approximately one-third the distance from its origin to produce an anterior wall myocardial infarction. This vessel was partially occluded for 20 min and then tied off. Twelve dogs died within the first 72 h of the myocardial infarction. Thus studies were completed on 24 dogs.

Long-duration exercise protocol. The studies began 3–4 wk after the production of the myocardial infarction. During this recovery period, the dogs were trained to run on a motor-driven treadmill. The cardiac response to long-duration exercise was then determined. Preexercise values for heart rate and heart rate variability were first obtained (5 min before exercise onset). The exercise protocol began with a 5-min warm-up period (running at a low intensity, 0% grade and speed, 4.8 km/h). The speed was increased to 6.4 km/h, the grade increased to 10%, and this intensity level was maintained for the next 60 min. This exercise level increased heart rate to ~65% of the maximum canine heart rate. The treadmill was stopped at the end of this 60-min period. Heart rate and the indexes of heart rate variability (see Data analysis below) were monitored continuously throughout the exercise. These studies were repeated after the completion of the 10-wk exercise training or 10-wk sedentary time periods.

Exercise training protocol. The first four dogs were used to provide “proof-of-concept” data, and, as such, the 1-h exercise test was not repeated in these animals. In addition, four dogs died (all in the sedentary group) during the 10-wk period after the initial 1-h exercise test. The remaining dogs (n = 16) were randomly assigned to either a 10-wk exercise-training period (n = 9) or an equivalent sedentary period (n = 7). The dogs in the exercise-training group ran on a motor-driven treadmill for 10 wk, 5 days per wk at approximately 70–80% of maximum heart rate. The exercise intensity and duration progressively increased as follows: week 1, 20 min at 4.8 km/h at 0% grade; week 2, 40 min at 5.6 km/h at 10% grade; week 3, 40 min at 6.4 km/h at 10% grade; week 4, 60 min at 6.4 km/h at 10% grade; week 5, 60 min at 6.4 km/h at 12% grade; week 6, 75 min at 6.4 km/h at 12% grade; week 7, 90 min at 6.4 km/h at 12% grade; and weeks 8–10, 90 min at 6.4 km/h at 14% grade. Each exercise session included 5-min warm-up and 5-min cool-down periods (running at a low intensity, 0% grade and speed, 4.8 km/h). The dogs in the sedentary group were placed in a transport cage for equivalent time periods but without exercise.

Citrate synthase assay. The effects of exercise on skeletal muscle oxidative capacity were evaluated by measuring citrate synthase activity in the diaphragm. The enzyme capacity was assayed by using the modified technique described by Srere (38).

Echocardiography studies. Left ventricular free wall thickness was determined by echocardiography 3–4 wk after surgery (i.e., myocardial infarction) and at the end of the 10-wk exercise training or the 10-wk sedentary period. Briefly, the dogs were lightly sedated with acepromazine (0.5 mg/kg im; Ft. Dodge Animal Health, Ft. Dodge, IA) before the studies. A conventional M-mode echocardiogram was obtained by using a Sonos 1000 system (Hewlett-Packard, Palo Alto, CA) with a 5.5-MHz transducer.

Data analysis. All data are reported as means ± SD. The data were digitized (1 kHz) and recorded by using a Biopac MP-100 data acquisition system (Biopac Systems, Goleta, CA). Heart rate variability (0.24 to 1.04 Hz, as an index of cardiac vagal tone index) was obtained by 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 Porges (32) to estimate the amplitude of respiratory sinus arrhythmia. Details of this analysis have been described previously (6). Briefly, the ECG signal was digitized at 1 kHz, and sequential R-R intervals were timed to the nearest millisecond. The nonperiodic baseline fluctuations were removed by using a moving third-order 21-point polynomial function. These procedures prevented leakage of trends and harmonics of nonsinusoidal periodic activity, i.e., transient changes, into the respiratory frequency component. Once the filtering procedures had been performed, the output of the moving polynomial was processed with a digital band-pass filter to extract the variance in the 0.24- to 1.04-Hz frequency band. The variance measure was then transformed to its natural logarithm to normalize the distribution of the variance estimates to limit the impact of large differences, i.e., outliers.

Data were averaged over 30-s intervals during exercise. Data are reported for the first minute after the onset exercise, then every 5 min during the 60-min exercise period. The following data were recorded: heart rate, vagal tone (VT) index (the variability in 0.24 to 1.04 frequency window), SD of the R-R interval, and R-R interval range (longest to shortest R-R interval for that 30-s period).

A one-way ANOVA with repeated measures (NCSS statistical software, Kaysville, UT) was used to evaluate the effects of long-duration exercise on heart rate or heart rate variability (VT, SD of R-R interval and R-R interval range). The effects of the 10-wk exercise training or the 10-wk sedentary period on the response to long-duration exercise before and after the 10-wk period (pre-post) were analyzed by using a two-way ANOVA [pre-post (2 levels) × time (13 levels)] with repeated measures. A similar two factor (group × pre-post) ANOVA with repeated measures on one factor (pre-post) was used to evaluate the effects of the interventions on left ventricular systolic wall thickness. Because repeated-measures ANOVA depends on the homogeneity of covariance (equal correlares between the treatments), this sphericity assumption was tested by using Mauchley’s test. If the sphericity assumption was violated, then the F ratio was corrected by using Huynh-Feldt correction. If the F ratio was found to exceed a critical value (P < 0.05), then the difference between the means was determined by using Scheffé’s test. Finally, citrate synthase activity data (exercise trained vs. sedentary) were evaluated by using Student’s t-test.

RESULTS

Confirmation of exercise training. There were no significant differences in body weight between the sedentary and trained animals (pretraining, 19.6 ± 2.7 kg; posttraining, 20.2 ± 3.3 kg; presedentary, 19.1 ± 2.4 kg; and postsedentary 20.0 ± 2.9 kg). However, left ventricular systolic wall thickness was significantly larger (P < 0.03) in the exercise-trained animals (pretraining, 9.1 ± 1.5 mm; and posttraining, 10.0 ± 1.2 mm) compared with the sedentary dogs (presedentary, 8.9 ± 1.3 mm; and postsedentary, 9.2 ± 1.1 mm), indicating that the training had produced ventricular hypertrophy. In a similar manner, citrate synthase activity was significantly (P < 0.02) higher in skeletal muscle obtained from exercise-trained (n = 7, 9.8 ± 4.2 μM·mL−1·min−1) compared with sedentary (n = 5, 7.3 ± 3.8 μM·mL−1·min−1) dogs. Finally, exercise training provoked significant (P < 0.01) reductions in the peak heart rate response to exercise (pretraining, 189.6 ± 22.9 vs. posttraining, 172.7 ± 8.8 beats/min) that were accompanied by significant (P < 0.01) increases in R-R interval variability (VT index: pretraining, 0.9 ± 1.1 vs. posttraining, 2.0 ± 0.6 In

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ms²), whereas these variables did not change in the sedentary animals (heart rate: presedentary, 193.3 ± 20.6 vs. postsedentary, 197.1 ± 17.7 beats/min; VT index: presedentary, 1.1 ± 0.9 vs. postsedentary, 1.4 ± 1.0 ln ms²). These data confirm the effectiveness of the exercise-training program.

Effect of long-duration exercise on heart rate variability.
The heart rate and the heart rate variability responses to the long-duration exercise are displayed in Fig. 1. Exercise rapidly elicited significant ($P < 0.01$) increases in heart rate within the first minute of exercise, which continued to increase gradually during the remaining 60 min. The peak response was achieved by 45 min. Most of the heart rate increase occurred during the first 10 min of exercise with smaller, but significant ($P < 0.05$), increases between the 10th and 60th min (10th min, 193.4 ± 20.5 vs. 60th min, 200.3 ± 22.5 beats/min). All three indexes of heart rate variability rapidly decreased (all $P < 0.01$) within the first minute of exercise and continued to decline throughout the 60-min exercise period. The peak reductions were also achieved between 45 and 50 min. The largest reductions occurred during the first 10 min with smaller, but significant ($P < 0.01$), changes recorded between the 10th and 60th min (VT index: 10th min, 1.8 ± 1.2 vs. 60th min, 1.0 ± 0.9 ln ms²; R-R interval range: 10th min, 52.7 ± 22.2 vs. 60th min, 28.8 ± 13.2 ms; and R-R interval SD: 10th min, 11.5 ± 5.0 vs. 60th min, 6.3 ± 2.6 ms). These data are consistent with a continuous withdrawal or inhibition of cardiac vagal modulation as exercise progressed.

Effect of exercise training on the heart rate variability response to long-duration exercise.
The heart rate and the heart rate variability responses to long-duration exercise for the exercise-trained animals are displayed in Fig. 2, whereas the response for the sedentary dogs is displayed in Fig. 3. Exercise training significantly ($P < 0.01$) attenuated the increase in heart rate elicited by the long-duration exercise. After exercise training was completed, the peak heart rate was reached earlier (pretraining, 40 min, and posttraining, 5 min) and was ~20 beats/min lower than the heart rate achieved in the same dogs before the training. Furthermore, the gradual increase in heart rate associated with prolonged submaximal exercise (heart rate drift) was absent in the trained animals (pretraining: 10th min,
Heart rate variability is reduced during exercise. The observation that heart rate variability is present even during higher intensity exercise in dogs and that atropine injection during exercise in humans and animals provokes further heart rate increases (6, 7, 30, 34) demonstrates that at least some cardiac vagal modulation is retained even during heavy submaximal exercise intensities. As such, further reductions in cardiac vagal activity could contribute to the heart rate increase that occurs during prolonged (i.e., ≥30 min) dynamic exercise performed at fixed submaximal exercise intensity. In the present study, heart rate increased and heart rate variability progressively decreased during long-duration submaximal exercise. These data suggest that at least part of the progressive tachycardia that occurs during sustained exercise is mediated by further reductions in cardiac vagal modulation of heart rate.

This observation may have important clinical implications. Regular dynamic exercise is an essential component of successful cardiac rehabilitation after myocardial infarction. Most programs recommend that a patient exercise continuously for at least 20–60 min/day, 3 to 5 days/wk (14, 26). Because it is well established that interventions that reduce cardiac vagal modulation also increase the propensity for sudden cardiac death (10), acute episodes of strenuous exercise could pose a risk in patients recovering from myocardial infarction (1). There are numerous anecdotal accounts of individuals, including trained athletes, who died suddenly during a bout of exercise. However, systematic studies of this phenomenon are limited. Bartels et al. (4) demonstrated that the incidence of sudden death increased during a bout of exercise for both sedentary and regular exercisers with the greatest incidence in the sedentary group. However, it is important to emphasize that the overall incidence of sudden death was much lower in fit than in sedentary individuals. Thus the authors concluded that the protective effect of regular physical activity far exceeded the very modestly increased risk for sudden death during exercise. In a similar manner, a large prospective study of male physicians found that although the incidence of sudden death increased during and shortly after exercise, the “absolute risk for sudden death during any particular episode of vigorous exertion was extremely low (1 sudden death per 1.51 million episodes of exertion)” (1). These investigators further reported that a history of regular exercise reduced the relative risk for sudden death. In other words, the probability for sudden death, even during exercise, was significantly reduced in those physicians that exercised regularly compared with their more sedentary colleagues. Several authors (4, 5, 15, 23, 42), after reviewing the existing literature, concluded that the potential benefits of regular exercise, even in high-risk populations of patients, far exceeded the small risk associated with exercise.

Effect of endurance exercise training on heart rate variability. Exercise training can alter cardiac autonomic regulation. In both humans and animals, the heart rate at submaximal workloads is reduced in trained individuals compared with sedentary controls (35, 41). Furthermore, exercise training increased cardiac acetylcholine content and cholineacetyl transferase activity (12, 18), as well as increasing resting heart rate variability in patients recovering from myocardial infarction (25, 28, 31). However, there is surprisingly little information on the effects of exercise training on the modulation of heart rate variability during an acute episode of exercise. In the
present study, heart rate variability was higher in trained dogs compared with the sedentary time-control animals. Importantly, the enhanced heart rate variability was maintained even when the heart was challenged by long-duration exercise. These data suggest that exercise training improves cardiac parasympathetic regulation of heart rate even when the heart is stressed, as during prolonged exercise at a constant intensity. As was previously noted, low cardiac vagal activity is associated with a much greater risk for sudden cardiac death. The results of the present study suggest that exercise training can restore a more normal cardiac parasympathetic balance, potentially reducing the risk for adverse changes in cardiac rhythm. Regular exercise is, in fact, associated with a lower risk for arrhythmias and sudden death in both humans and animals (5, 8, 29, 33). For example, meta-analysis of 22 randomized trials of rehabilitation with exercise after myocardial infarction found that exercise training elicited both significant reductions in the reinfarction rate and in the incidence of sudden death (29). There was an overall reduction in cardiac mortality of 20% (due largely to the reduction in sudden death), a reduction that is comparable to the mortality reductions noted for β-adrenoceptor antagonists (21). In a similar manner, exercise training prevented ventricular fibrillation induced by myocardial ischemia (8) and increased the amount of electrical current necessary to produce this malignant arrhythmia (23). The mechanisms responsible for the exercise-induced cardioprotection remain to be determined. However, it seems likely that exercise training-induced preservation of cardiac vagal regulation plays an important role in decreased incidence of sudden death in trained individuals. This intriguing hypothesis merits further investigation.

Limitations of study. It should be acknowledged that in the present study, cardiac VT was only indirectly evaluated by using various measures of heart rate variability. This study did not measure the parasympathetic nerve activity directly. However, a number of previous investigations (6, 13, 32, 39, 40) have verified that heart rate variability provides an accurate representation of parasympathetic function. For example, interventions that deceased cardiac parasympathetic regulation, e.g., muscarinic antagonists, increased heart rate and reduced heart rate variability (6). Conversely, interventions that increased parasympathetic responses reduced heart rate and increased heart rate variability (6). In the present study, exercise training, which is well established to increase cardiac vagal control (9, 16, 37, 44), increased (or maintained) heart rate variability, even during prolonged exercise. Therefore, it is reasonable to conclude that the techniques used in the present study provided a reliable indirect measurement of cardiac parasympathetic nerve activity.

It is also well established that both respiratory rate and tidal volume can alter heart rate variability (19). As such, differences in the respiratory response after exercise training could indirectly contribute to the differences in the cardiac vagal indexes in the trained animals. Respiratory parameters were not measured in this study due to the profound panting response induced by exercise both before and after exercise training. It is possible that, despite the panting, respiratory rate or tidal volume was altered in the exercise-trained animals.

Finally, reductions in cardiac sympathetic activity could also contribute to the lower heart rate response to prolonged endurance exercise noted in the trained animals. It is well established that plasma norepinephrine and epinephrine levels are reduced at the same absolute submaximal exercise condition in trained compared with sedentary subjects (35, 41). However, plasma catecholamine concentration only provides an indirect assessment of total body sympathetic nerve and adrenal responses to exercise. As such, changes in circulating catecholamine levels provide little insight in the specific contribution of alterations in cardiac sympathetic activity to the reduced heart rate response to exercise in trained individuals. Furthermore, Winder et al. (43) actually demonstrated a dissociation between plasma catecholamine levels and heart rate at a given submaximal exercise level. To the best of our knowledge, there currently are no studies in which the effects of exercise training on cardiac sympathetic nerve activity have been evaluated.

In summary and in conclusion, heart rate variability progressively decreased during prolonged submaximal exercise performed at constant intensity in dogs with healed myocardial infarctions. These data suggest that the heart rate increase associated with long-duration exercise results, at least in part, from a progressive withdrawal of vagal control of cardiac pacemaker cells. This reduction in heart rate variability was attenuated in exercise-trained animals. As such, endurance exercise training may preserve cardiac vagal regulation, even during a prolonged exercise session. This enhanced cardiac vagal regulation would be expected to reduce the incidence of adverse changes in cardiac rhythm, decreasing cardiac mortality in postmyocardial infarction patients.

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