Effects of endurance exercise training on heart rate variability and susceptibility to sudden cardiac death: protection is not due to enhanced cardiac vagal regulation

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Billman, George E., and Monica Kukielka. Effects of endurance exercise training on heart rate variability and susceptibility to sudden cardiac death: protection is not due to enhanced cardiac vagal regulation. J Appl Physiol 100: 896–906, 2006. First published December 1, 2005; doi:10.1152/japplphysiol.01328.2005.—Low heart rate variability (HRV) is associated with an increased susceptibility to ventricular fibrillation (VF). Exercise training can increase HRV (an index of cardiac vagal regulation) and could, thereby, decrease the risk for VF. To test this hypothesis, a 2-min coronary occlusion was made during the last min of a 18-min submaximal exercise test in dogs with healed myocardial infarctions; 20 had VF (susceptible), and 13 did not (resistant). The dogs then received either a 10-wk exercise program (susceptible, n = 9; resistant, n = 8) or an equivalent sedentary period (susceptible, n = 11; resistant, n = 5). HRV was evaluated at rest, during exercise, and during a 2-min occlusion at rest and before and after the 10-wk period. Pretraining, the occlusion provoked significantly (P < 0.01) greater increases in HR (susceptible, 54.9 ± 8.3 vs. resistant, 25.0 ± 6.1 beats/min) and greater reductions in HRV (susceptible, −6.3 ± 0.3 vs. resistant, −2.8 ± 0.8 ln ms²) in the susceptible dogs compared with the resistant animals. Similar response differences between susceptible and resistant dogs were noted during submaximal exercise. Training significantly reduced the HR and HRV responses to the occlusion (HR, 17.9 ± 11.5 beats/min; HRV, −1.2 ± 0.8 ln ms²) in the susceptible dogs; similar response reductions were noted during exercise. In contrast, these variables were not altered in the sedentary susceptible dogs. Posttraining, VF could no longer be induced in the susceptible dogs, whereas four sedentary susceptible dogs died during the 10-wk control period, and the remaining seven animals still had VF when tested. Atropine decreased HRV but only induced VF in one of eight trained susceptible dogs. Thus exercise training increased cardiac vagal activity, which was not solely responsible for the training-induced VF protection.

parasympathetic nervous system; ventricular fibrillation; myocardial ischemia; myocardial infarction

REDUCTIONS in cardiac parasympathetic control have been associated with an increase risk for sudden death (44). Kleiger and coworkers (3, 28) found that the patients recovering from myocardial infarctions with the smallest heart rate variability [HRV; a noninvasive index of cardiac parasympathetic regulation (6, 40, 47)] had the greatest risk of dying suddenly. The relative risk of mortality was 5.3 times greater in patients with an R-R interval variability <50 ms compared with patients with variability >100 ms. This initial observation has been confirmed in numerous clinical studies (1, 21). For example, the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) group found that postmyocardial infarction patients with either low HRV or reduced baroreflex sensitivity had a much greater risk of sudden death than those with well-preserved cardiac vagal function (31).

Similar results have been obtained in animal studies. Our laboratory previously reported that HRV was much lower in animals susceptible to ventricular fibrillation compared with animals resistant to these malignant arrhythmias (7, 12, 18, 22). In particular, the susceptible animals exhibited a much greater reduction (withdrawal) of vagal activity in response to either submaximal exercise (7, 18, 22) or acute myocardial ischemia (12, 18, 22) than did the resistant dogs. In a similar manner, bilateral vagotomy (13) or the cholinergic antagonist atropine increased arrhythmia formation (14), whereas cholinergic agonists or electrical stimulation of the vagus nerves increased ventricular fibrillation threshold, antagonized the effects of sympathetic stimulation, and decreased the incidence of ventricular fibrillation (4, 27, 29, 48). These data demonstrate that subnormal cardiac parasympathetic regulation increases the risk for malignant arrhythmias, whereas interventions that enhance cardiac vagal function can protect against ventricular fibrillation. However, to be an effective antiarrhythmic therapy, an intervention not only must increase baseline vagal activity but also must maintain this enhanced activity when the heart is stressed, as during myocardial ischemia. Indeed, low doses of cholinergic antagonists paradoxically increased the baseline cardiac vagal activity (30) but failed to maintain this increase in HRV when the heart was stressed by either submaximal exercise or a coronary artery occlusion (18). As a consequence, this intervention proved to be ineffective in the prevention of lethal arrhythmias induced by acute myocardial ischemia (18, 25).

It is well established that regular exercise can improve cardiac autonomic balance (increasing parasympathetic while decreasing sympathetic regulation of the heart) (5, 42). In both humans and animals, heart rate at submaximal workloads is lower in trained individuals compared with sedentary controls (5, 42), while the presence of a resting bradycardia is frequently used to confirm that training has been effective (17, 34, 45). Exercise training programs can increase HRV in patients recovering from myocardial infarction (32, 33, 35, 39) and may reduce the incidence of sudden death and arrhythmias in both human and animal models (8, 23, 32, 37, 38, 41). In a similar manner, meta-analysis of 22 randomized trials of rehabilitation with exercise after myocardial infarction found that exercise...
training elicited significant reductions in both reinfarction and the incidence of sudden death (38). In animals, regular exercise either increased the electrical current necessary to induce ventricular fibrillation (37, 41) or reduced the susceptibility to ventricular fibrillation induced by myocardial ischemia (8, 24). However, the contributions of changes in cardiac autonomic balance to the protection afforded by exercise training were not extensively examined in these studies and remain largely to be determined. Although exercise training has been shown to increase baseline HRV in animals prone to lethal arrhythmias (24), the effects of this intervention on HRV when the heart is stressed (i.e., during exercise or coronary occlusion) remain to be determined.

Therefore, it was the purpose of this study to investigate the effects of exercise training on HRV and susceptibility to ventricular fibrillation using a conscious canine model of sudden death. Specifically, the hypothesis that exercise training would increase HRV even during physiological stress (exercise or acute ischemia) and, thereby, could prevent ventricular fibrillation induced by myocardial ischemia was tested.

The present study demonstrates that exercise training improves cardiac autonomic function such that cardiac vagal regulation is maintained even when the heart is stressed by either exercise or acute myocardial ischemia in animals with healed infarctions. Furthermore, exercise training completely suppressed ventricular fibrillation induced by myocardial ischemia. However, because atropine pretreatment did not reintroduce lethal arrhythmias in these dogs, the exercise-induced protection from ventricular fibrillation did not result solely from enhanced cardiac vagal regulation.

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

**Surgical preparation.** Sixty heartworm-free mongrel dogs weighing 15.4–24.5 kg (19.1 ± 0.4 kg) were used in this study. The animals were anesthetized and instrumented as previously described (7, 12, 18, 22). Briefly, using 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 heart and used to obtain a ventricular electrogram (from which heart rate and various indexes of HRV were measured, see below). One pair of electrodes was placed in the potentially ischemic area (lateral left ventricular wall, an area perfused by the left circumflex artery) and the other pair in a nonischemic region (right ventricular outflow tract). 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.

**HRV protocols.** The studies began 3–4 wk after the production of the myocardial infarction (see flow chart, Fig. 1). First, over the period of 3–5 days, the dogs learned to run on a motor-driven treadmill. The cardiac response to submaximal exercise was then evaluated as follows: exercise lasted a total of 18 min with workload increasing every 3 min. The protocol began with a 3-min warm-up period, during which the dogs ran at 4.8 kilometers per hour (kph) at 0% grade. The speed was then increased to 6.4 kph, and the grade increased every 3 min (0, 4, 8, 12, and 16%). The submaximal exercise test was repeated three times (1/day). Before the third submaximal exercise test, a catheter was placed percutaneously in a cephalic vein to administer the muscarinic antagonist, atropine sulfate (50 μg/kg), 3 min before the end of the exercise period. On a subsequent day, with the dogs lying quietly unrestrained on a table, a 2-min left circumflex coronary occlusion was made. At least 48 h after the completion of these studies, the animals were tested for susceptibility to ventricular fibrillation using an exercise plus ischemia test that is described in the following section. Heart rate, left circumflex blood flow, and HRV were monitored continuously throughout the exercise or occlusion studies. These studies were repeated after the completion of the 10-wk exercise training or the 10-wk sedentary time period.

**Exercise plus ischemia test: classification of the dogs.** The susceptibility to ventricular fibrillation was tested as previously described (7, 12, 18, 22) (Fig. 1). Briefly, the animals ran on a motor-driven treadmill while workload progressively increased until a heart rate of 70% of maximum (~210 beats/min) had been achieved. During the last minute of exercise, the left circumflex coronary artery was occluded, the treadmill stopped, and the occlusion maintained for an additional minute (total occlusion time = 2 min). The exercise plus ischemia test reliably induced ventricular flutter that rapidly deteriorated into ventricular fibrillation. Therefore, large metal plates (11-cm diameter) were placed across the animal’s chest so that electrical defibrillation (Zoll M series defibrillator, Zoll Medical, Burlington, MA) could be achieved with a minimal delay but only after the animal was unconscious (10–20 s after the onset of ventricular fibrillation). Of the 60 animals that underwent surgery, 21 animals could not be tested due to either death within 72 h of the myocardial infarction (n = 14, 23.3%) or occluder failure (n = 7). Thus the exercise plus ischemia test was performed on 39 of the original 60 animals. The occlusion was immediately released if ventricular fibrillation occurred. Twenty-six dogs developed ventricular fibrillation (susceptible), whereas the remaining 13 did not (resistant). Three susceptible animals were not successfully defibrillated and, as such, were not available for additional studies. This exercise plus ischemia test, using
the same exercise intensity, was repeated after the completion of a 10-wk exercise training or a 10-wk sedentary time period (see below).

**Exercise training protocol.** The susceptible (n = 23) and resistant dogs (n = 13) were randomly assigned to either a 10-wk exercise training period (susceptible, n = 9; resistant, n = 8) or an equivalent sedentary period (susceptible, n = 14; resistant, n = 5) (Fig. 1). The dogs in the exercise training group ran on a motor-driven treadmill for 10 wk, 5 days/wk, at ~70–80% of maximum heart rate. The exercise intensity and duration progressively increased as follows: 1st wk, 20 min at 4.8 kph/0% grade; 2nd wk, 40 min at 5.6 kph/10% grade; 3rd wk, 40 min at 6.4 kph/10% grade; 4th wk, 60 min at 6.4 kph/10% grade; 5th wk, 60 min at 6.4 kph/12% grade; 6th wk, 75 min at 6.4 kph/12% grade; 7th week, 90 min at 6.4 kph/12% grade; 8th to 10th wk, 90 min at 6.4 kph/14% grade. Each exercise session included 5-min warm-up and 5-min cooldown periods (running at a low intensity: 0% grade and speed of 4.8 kph). The dogs in the sedentary group were placed in transport cages for equivalent time periods but without exercise. All 17 animals (both the susceptible and resistant dogs) in the exercise group successfully completed the training program. Four dogs in the susceptible sedentary group died spontaneously between the 6th and the 10th wk of the sedentary period and were eliminated from the study. The exercise plus ischemia test could not be repeated in three of the susceptible animals due to failure of the coronary artery occluder, and these animals were also eliminated from the study (Fig. 1). Finally, the exercise plus ischemia test was repeated after the administration of the muscarinic antagonist atropine sulfate (50 μg/kg iv bolus 3 min before the occlusion) in the exercise-trained susceptible dogs (n = 8).

**Citrate synthase assay.** The effects of exercise on skeletal muscle oxidative capacity were evaluated by measuring citrate synthase activity in the diaphragm. After the completion of the 10-wk exercise training or 10-wk sedentary studies, the animals were anesthetized (pentobarbital sodium, 50 mg/kg iv; Abbott Laboratories, North Chicago, IL). The heart was rapidly removed, and tissue samples were frozen in liquid nitrogen and stored in a −80°C freezer. At the same time, a small piece of the diaphragm was also placed in liquid nitrogen. The citrate synthase activity of this skeletal muscle was assayed using the modified technique described by Srere (46). The skeletal muscle was harvested at least 48 h after the last exercise session.

**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. These studies were performed before the animals were classified by the exercise plus ischemia test. 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 using a Sonos 1000 system (Hewlett-Packard, Palo Alto, CA) with a 5.5-MHz transducer.

**Data analysis.** All data are reported as means ± SE. The data were digitized (1 kHz) and recorded using a Biopac MP-100 data-acquisition system (Biopac Systems, Goleta, CA). HRV was obtained using a Delta-Biometrics vago 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 (40) to estimate the amplitude of respiratory sinus arrhythmia. Details of this analysis have been described previously (6). Data were averaged over 30-s intervals during either exercise or the coronary occlusion. The following three indexes of HRV were determined: vagal tone index, the high-frequency (0.24–1.04 Hz) component of R-R interval variability; R-R interval range, the difference between the longest and shortest R-R interval for the same 30-s time period; and standard deviation of the R-R intervals for the same 30-s time period. The heart rate response to the exercise plus ischemia test was averaged over the last 5 s before the occlusion and at the 60-s time point (or ventricular fibrillation onset) after occlusion onset.

The data were compared using ANOVA for repeated measures (NCSS statistical software, Kaysville, UT). For example, the effect of exercise training on the HRV data (heart rate; vagal tone index, i.e., 0.24–1.04-Hz component of the R-R interval variability; SD of R-R interval; and R-R interval range) were analyzed using three-way ANOVA (group (2 levels) × pretraining − postraining (2 levels) × exercise level (7 levels), or occlusion time (6 levels)) with repeated measures on two factors (pretraining − postraining and exercise level, or occlusion time). Comparisons between the susceptible and resistant dogs were made using a two factor (group × exercise level, or occlusion time) ANOVA with repeated measures on one factor (exercise level or occlusion time). A similar two-factor (group × pretraining − postraining) ANOVA with repeated measures on one factor (pretraining-postraining) 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, this sphericity assumption (i.e., the assumption that the variance of the difference scores in a within-subject design are equal across the groups) was tested using Mauchley’s test (23). If the sphericity assumption was violated, then the F-ratio was corrected using Huynh-Feldt correction (23). If the F-ratio was found to exceed a critical value (P < 0.05), then the difference between the means was determined using Scheffe’s test. The effect of exercise training on the incidence of ventricular fibrillation was evaluated using Fisher’s exact test. Finally, citrate synthase activity data (exercise trained vs. sedentary) were evaluated using Student’s t-test.

**RESULTS**

**Confirmation of exercise training.** There was no significant difference in body weight between the sedentary and trained animals for either the resistant (trained, 20.4 ± 1.1; sedentary, 19.6 ± 1.8 kg) or the susceptible (trained, 20.0 ± 0.6; sedentary, 19.8 ± 0.8 kg) dogs. However, left ventricular systolic wall thickness was significantly larger (P < 0.025) in both susceptible (pretraining, 10.0 ± 0.6 vs. postraining, 11.1 ± 0.4 mm; wall thickness increased by 10.1 ± 4%) and resistant (pretraining, 8.8 ± 0.5 vs. postraining, 9.4 ± 0.5 mm; wall thickness increased by 8.0 ± 2.6%) animals after training but was unchanged in the sedentary dogs (susceptible pretraining sedentary 9.8 ± 0.4; postraining sedentary 9.6 ± 0.3 vs. resistant pretraining sedentary 10.1 ± 0.7; postraining sedentary 10.7 ± 0.4 mm), indicating that the training had produced a small ventricular hypertrophy. In the susceptible dogs, exercise training provoked significant (P < 0.0025) reductions in the peak heart rate response to exercise (pretraining 209.0 ± 7.4 vs. postraining 184.4 ± 5.3 beats/min) that were accompanied by significant increases in R-R interval variability (e.g., vagal tone index, P < 0.04; pretraining 1.0 ± 0.3 vs. postraining 2.4 ± 0.3 ln ms²), whereas these variables did not change in the sedentary animals (peak exercise response: HR, pretraining sedentary 209.4 ± 6.0 vs. postraining sedentary 211 ± 5.3 beats/min; vagal tone index pretraining sedentary 1.2 ± 0.1 vs. postraining sedentary 1.5 ± 0.3). Similar but smaller changes were noted for the exercise trained resistant dogs (peak exercise response: HR, pretraining 200.2 ± 3.4 vs. postraining 178.4 ± 7.4 beats/min; vagal tone index, pretraining 2.4 ± 0.3 vs. postraining 2.8 ± 0.4 ln ms²). Finally, citrate synthase activity was significantly (P < 0.02) higher in skeletal muscle obtained from exercise-trained (n = 10, 11.6 ± 1.0 μmol·ml⁻¹·min⁻¹) compared with sedentary (n = 10, 7.5 ± 1.4 μmol·ml⁻¹·min⁻¹) dogs. Because there were no differences between resistant and susceptible dogs, these data were pooled for the analysis. These data confirm the exercise train-
ing program was effective; that is, there was a significant skeletal muscle and cardiac adaptation induced by the training program.

Pretraining HRV responses. The heart rate and HRV responses to submaximal exercise before training are displayed in Fig. 2. Submaximal exercise elicited significant (both $P < 0.001$) increases in heart rate for both the susceptible and the resistant dogs. Furthermore, the heart rate increase was significantly (group $\times$ exercise level, $P < 0.01$) greater in the susceptible dogs (peak heart rate change from preexercise values, susceptible $91.8 \pm 2.0$ vs. resistant $84.8 \pm 3.1$ beats/min) compared with the resistant dogs. The exercise-induced increases in heart rate were accompanied by significant (all, $P < 0.001$) reductions in all three markers of HRV (vagal tone index, i.e., $0.24$- to $1.04$-Hz component of the R-R interval variability; SD of R-R interval; and R-R interval range). Greater reductions (group $\times$ exercise level, $P < 0.001$) were again noted in the susceptible animals compared with the resistant dogs (Fig. 2).

The contribution of cardiac parasympathetic regulation to the HRV response to submaximal exercise was also evaluated by the intravenous injection of atropine during the last exercise level. Atropine provoked larger increases ($P < 0.01$) in heart rate (resistant, $28.2 \pm 3.6$ vs. susceptible, $17.9 \pm 2.8$ beats/min), and reductions in the HRV indexes (e.g., vagal tone index: resistant, $-2.1 \pm 0.2$ vs. susceptible $-1.1 \pm 0.3$ ms$^2$) in the resistant animals compared with the susceptible dogs. In fact, heart rate and HRV were no longer different between groups after the atropine treatment.

The heart rate and HRV responses to the coronary occlusion at rest before training are displayed in Fig. 3. The coronary artery occlusion elicited significantly (group $\times$ occlusion time, $P < 0.001$) larger increases in heart rate in the susceptible compared with the resistant dogs. The coronary occlusion induced increases in heart rate were accompanied by larger reductions (group $\times$ occlusion time, $P < 0.001$) in all three HRV indexes (vagal tone index, i.e., $0.24$- to $1.04$-Hz component of the R-R interval variability; SD of R-R interval; and R-R interval range) in the susceptible animals compared with the resistant dogs.

Posttraining HRV responses. The heart rate and HRV responses to submaximal exercise for the susceptible dogs after the 10-wk training or 10-wk sedentary period are displayed in Fig. 4. Submaximal exercise elicited significant increases in heart rate ($P < 0.001$) for both the sedentary and trained susceptible dogs. However, the heart rate increase was significantly (group $\times$ exercise, $P < 0.001$) greater in the sedentary dogs compared with the exercise-trained animals. The exercise-induced increases in heart rate were also accompanied by significant (all $P < 0.001$) reductions in all three markers of HRV (vagal tone index, i.e., $0.24$- to $1.04$-Hz component of the R-R interval variability; SD of R-R interval; and R-R interval range). Once again, greater reductions (group $\times$ exercise, $P < 0.01$) were noted in the sedentary animals compared with the exercise-trained dogs (Fig. 4). Similar, but smaller, differences were noted between the sedentary and trained resistant dogs (data not shown). After exercise training, the susceptible and resistant dogs exhibited similar heart rate and HRV responses to exercise; that is, no statistically significant differences were noted when comparing these animals (Fig. 5).

The contribution of cardiac parasympathetic regulation to the HRV responses to submaximal exercise was also evaluated after either the 10-wk exercise training or 10-wk sedentary time period by the intravenous injection of atropine during the last exercise level. Atropine injection elicited larger increases ($P < 0.01$) in heart rate and greater reductions ($P < 0.01$) in
HRV in the susceptible trained (heart rate, 36.8 ± 3.2 beats/min; vagal tone index, −2.3 ± 0.3 ln ms²) compared with the susceptible sedentary dogs (heart rate, 23.7 ± 5.4 beats/min; vagal tone index, −1.1 ± 0.5 ln ms²).

The heart rate and HRV responses to the coronary occlusion at rest after either the 10-wk exercise training or 10-wk sedentary period are displayed in Fig. 6. The coronary artery occlusion elicited significantly (group × occlusion time, $P < 0.01$) larger increases in heart rate that were accompanied by greater reductions in the various indexes of cardiac vagal regulation in the susceptible animals compared with the resistant dogs. Pre, last 30 s before the coronary occlusion; Post, 1 min after coronary occlusion release (i.e., average over 30–60 s post release). Values are means ± SE.
0.001) larger increases in heart rate in the sedentary animals compared with the exercise-trained dogs. The coronary occlusion-induced increases in heart rate were accompanied by larger reductions (group × occlusion time, \( P < 0.001 \)) in the HRV (vagal tone index, i.e., 0.24- to 1.04-Hz component of the R-R interval variability; and R-R interval range) indexes in the sedentary susceptible compared with the susceptible trained dogs (Fig. 6). After training, the response to the coronary occlusion in the resistant and susceptible dogs was indistinguishable (Fig. 7). Thus, after the completion of exercise training, the susceptible animals exhibited a “resistant” HRV response pattern consistent with an increase in cardiac para-

Fig. 5. Effect of exercise training on the heart rate and heart rate variability responses to submaximal exercise in animals susceptible or resistant to ventricular fibrillation. Note that there no longer were any differences between the susceptible and resistant animals. Exercise levels: 1 = 0 kph/0% grade, 2 = 4.8 kph/0% grade, 3 = 6.4 kph/0% grade, 4 = 6.4 kph/4% grade, 5 = 6.4 kph/8% grade, 6 = 6.4 kph 12% grade, 7 = 6.4 kph/16% grade. Values are means ± SE.

Fig. 6. Effect of the 10-wk exercise training or 10-wk sedentary period on the heart rate and the heart rate variability responses to a 2-min coronary occlusion in animals susceptible to ventricular fibrillation. The coronary occlusion elicited significantly smaller increase in heart rate and smaller reductions in the various indexes of cardiac vagal regulation in the exercise-trained dogs compared with animals that received a similar sedentary period. The posttraining response in the susceptible exercise trained animals was no longer different from that noted for the resistant (either exercise trained or sedentary) dogs. Pre, last 30 s before the coronary occlusion; Post, 1 min after coronary occlusion release (i.e., average over 30–60 s after release). Values are means ± SE. \(* P < 0.01 \) exercise trained vs. sedentary.
sympathetic regulation. In contrast, the HRV response in the susceptible sedentary dogs did not change over time.

Effect of training on susceptibility to ventricular fibrillation. The exercise plus ischemia test was repeated after the completion of the either the 10-wk exercise training period (susceptible \( n = 9 \), resistant \( n = 8 \)) or 10-wk sedentary period (susceptible \( n = 7 \), resistant \( n = 5 \)). The heart rate responses to the coronary occlusion are displayed in Fig. 8. The coronary occlusion elicited significant \(( P < 0.0002)\) increases in heart rate in both the sedentary and the exercise-trained susceptible animals but did not alter heart rate in the resistant dogs. Both the preocclusion and occlusion heart rate were lower \(( P < 0.04)\) in the susceptible exercise-trained animals compared with the sedentary dogs. However, the change in heart rate elicited by the coronary occlusion was similar in both groups either before (sedentary \( 31.0 \pm 8.5\) trained \( 32.4 \pm 11.1 \) beats/min) or after the 10-wk period (sedentary \( 32.5 \pm 7.4\), trained \( 29.3 \pm 11.9 \) beats/min). In addition, the exercise plus ischemia test provoked a similar ST segment depression in the sedentary and exercise-trained susceptible dogs both before (sedentary \( 4.8 \pm 1.2 \) vs. exercise trained \( -4.7 \pm 0.4 \) mm) and at the end of the 10-wk period (sedentary \( -4.8 \pm 1.7 \) vs. exercise trained \( -4.8 \pm 0.4 \) mm). When considered together, these data suggest that the coronary occlusion elicited a similar ischemic response before and at the end of the 10-wk sedentary or 10-wk exercise training period.

Exercise training significantly (Fisher’s exact test \( P = 0.0014)\) reduced the incidence of ventricular fibrillation in the trained susceptible animals, protecting all nine animals tested. In marked contrast, ventricular fibrillation was induced in all seven sedentary susceptible dogs. In addition, four susceptible animals died spontaneously during the 10-wk sedentary period. The exercise plus ischemia test failed to induce ventricular fibrillation in any of the resistant dogs in either the sedentary or the exercise-trained groups.

The exercise plus ischemia test was repeated after pretreatment with atropine in the susceptible exercise-trained dogs. Atropine significantly \(( P < 0.01)\) increased heart rate \((36.8 \pm 3.2 \) beats/min) and reduced HRV \((-2.3 \pm 0.3 \) ln ms\(^2\)) both before and during the coronary occlusion (Fig. 9). Despite these changes, this intervention only reintroduced ventricular fibrillation, or any other arrhythmia, in one of eight dogs tested.
The present study demonstrates the following: 1) Exercise or acute myocardial ischemia provoked greater increases in heart rate that were accompanied by greater reductions in three HRV markers (indexes of cardiac vagal regulation) in animals subsequently shown to be susceptible to ventricular fibrillation compared with animals resistant to malignant arrhythmias. 2) Endurance exercise training reduced heart rate and increased HRV even when the heart was stressed by either exercise or acute ischemia in the susceptible animals, such that the cardiac autonomic regulation was similar to that noted in resistant dogs. 3) Exercise training completely suppressed ventricular fibrillation induced by acute myocardial ischemia, protecting all nine susceptible dogs that completed the 10-wk exercise program. In marked contrast, an equivalent sedentary period not only failed to protect any of the susceptible dogs that completed the 10-wk period but also four dogs died spontaneously during this period. 4) Treatment with the cholinergic antagonist, atropine, provoked large increases in heart rate and reductions in HRV yet failed to reintroduce arrhythmias in the majority of the trained susceptible animals, triggering ventricular fibrillation in only one of eight dogs tested. These data suggest that exercise training can restore a more normal cardiac autonomic balance by increasing cardiac parasympathetic regulation and also reduce the incidence of malignant arrhythmias. However, this protection did not solely result from the training-induced enhanced cardiac vagal control. To the best of our knowledge, these findings represent the first demonstration that exercise training can improve cardiac parasympathetic control in diseased hearts even when the heart is stressed by acute myocardial ischemia or by an episode of submaximal exercise.

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**DISCUSSION**

Exercise training and susceptibility to ventricular fibrillation. Exercise training can alter autonomic neural balance by both increasing cardiac parasympathetic and decreasing sympathetic activity (5, 42). In both humans and animals, the heart rate at submaximal workloads is reduced in trained individuals compared with sedentary controls (5, 42). Furthermore, acetylcholine content and cholineacetyl transferase activity is increased in the hearts of trained rats (15). In humans, exercise training can increase HRV in patients recovering from myocardial infarction (32, 33, 35, 38, 39). In the present study, HRV was higher in trained dogs compared with the sedentary time-control animals. Importantly, the enhanced HRV was maintained even when the heart was challenged by either exercise or acute ischemia. Furthermore, atropine elicited much greater increases in heart rate in the exercise-trained animals than was noted for the sedentary dogs, data that are consistent with training-induced increases in the cardiac vagal regulation. Thus endurance exercise training can elicit changes in cardiac autonomic control that could, in turn, protect against ventricular fibrillation.

Regular exercise is also associated with a lower risk for arrhythmias and sudden death in both humans and animals (5). For example, Bartels et al. (2) found that the incidence of sudden cardiac death was inversely related to the level of regular physical activity; that is, sedentary individuals had the highest rate of sudden death (4.7 deaths per 10^5 person-years), whereas those in the most active group had the lowest (0.9 deaths per 10^5 person-years). Furthermore, meta-analysis of 22 randomized trials of rehabilitation with exercise after myocardial infarction found that exercise training elicited significant reductions in both the reinfarction rate and the incidence of sudden death (38). 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 (19, 26).

Experimental studies also report that exercise training decreases the risk for arrhythmias (5, 8, 24) or increases the electrical current necessary to induce ventricular fibrillation (37, 41). In agreement with the present study, Billman et al. (8) and Hull et al. (24) reported that daily exercise prevented ventricular fibrillation induced by acute ischemia in dogs with healed anterior wall myocardial infarctions, a protection that was accompanied by an improved baroreflex sensitivity (8) and an increase in baseline HRV (24). However, neither group examined the effects of training on autonomic regulation in response to physiological stressors such as exercise or acute ischemia. Improvement in the autonomic balance at rest might laboratory previously reported HRV was reduced by myocardial infarction and that the dogs with the greatest reduction were also more susceptible to ventricular fibrillation (7, 12, 18, 22) than those dogs in which cardiac vagal regulation was not impaired by the ischemic injury. In particular, the susceptible animals exhibited a much greater reduction (withdrawal) of vagal activity in response to either submaximal exercise (7, 18, 22) or acute myocardial ischemia (12, 18, 22). When considered together, these clinical and experimental studies clearly suggest that reductions in cardiac parasympathetic regulation play an important role in the development of sudden cardiac death. Thus one would predict that interventions that alter cardiac parasympathetic control should also alter susceptibility to ventricular fibrillation.

**EXERCISE TRAINING IMPROVES CARDIAC VAGAL REGULATION**

![Fig. 9. Effect of atropine on the heart rate responses to the exercise plus ischemia in exercise-trained susceptible dogs. Atropine (50 μg/kg iv given as a bolus 3 min before the coronary occlusion) elicited a large increase in heart rate. Values are means ± SE. *P < 0.01 preocclusion vs. occlusion. #P < 0.01 No drug vs. atropine.](image-url)
not provide sufficient protection against arrhythmias when the heart is stressed during dynamic situations. Indeed, the observation that low doses of cholinergic antagonists paradoxically increased the level of cardiac vagal activity (31) led to the proposal that this treatment could provide an acceptable means of enhancing cardiac parasympathetic activity in patients (10, 49). However, Halliwill et al. (18) and Hull et al. (25) both demonstrated that, although low doses of cholinergic antagonists increased baseline cardiac vagal activity (R-R interval variability), this treatment failed to prevent ventricular fibrillation induced by myocardial ischemia. Halliwill et al. (18) further demonstrated that the enhanced baseline vagal activity was not maintained when the heart was stressed by either exercise or myocardial ischemia. As such, it was not surprising that this therapy failed to prevent ventricular fibrillation. It would appear that to be an effective antiarrhythmic therapy, an intervention must not only increase baseline vagal activity but, more importantly, must also maintain this enhanced activity when the heart is stressed.

The present study confirms and extends these previous studies. Training enhanced cardiac vagal control (as noted by increases in HRV), whereas an equivalent sedentary time period did not change cardiac parasympathetic regulation. The restoration of a more normal cardiac parasympathetic regulation, however, was not solely responsible for the protections associated with exercise training. The cholinergic antagonist atropine did not reintroduce malignant arrhythmias in the majority of animals, inducing ventricular fibrillation in only of one of eight dogs tested. Other factors must play a more central role in the protection that results from training. Exercise training also alters sympathetic regulation. Our laboratory previously reported that the susceptible dogs, in addition to reduced parasympathetic control, exhibit an enhanced β2-adrenocceptor responsiveness (9). Therefore, training could also improve β-adrenocceptor balance by decreasing the enhanced β2-adrenocceptor and could, thereby, remove the trigger for malignant arrhythmias during myocardial ischemia. The effects of exercise training on β2-adrenocceptor responsiveness merit further investigation.

Limitations of the study. There are a few limitations with the present study that could affect the interpretations of the results. First, dogs have extensive coronary collateral vessels (36) that exercise training may (43) or may not (11) increase. Therefore, exercise training-induced increases in coronary collateral circulation could contribute to the protection noted in the susceptible dogs. However, acute myocardial ischemia provoked similar increases in heart rate in the susceptible sedentary (pretraining 31.0 ± 8.5 beats/min) and in the susceptible trained (pretraining 32.4 ± 1.1 beats/min) dogs before or after the 10-wk period (posttraining sedentary 32.5 ± 7.4, postraining sedentary 29.3 ± 1.9 beats/min). In addition, the exercise plus ischemia test provoked a similar ST segment depression in the sedentary and exercise-trained susceptible dogs both before (sedentary −4.8 ± 1.2 vs. exercise trained −4.7 ± 0.4 mm) and at the end of the 10-wk period (sedentary −4.8 ± 1.7 vs. exercise trained −4.8 ± 0.4 mm). When considered together, these data suggest that the coronary occlusion elicited a similar ischemic response before and at the end of the 10-wk sedentary or exercise training period.

Second, myocardial infarction size could also contribute to the differences noted between susceptible and resistant dogs; animals with larger infarctions would be expected to have poorer ventricular function and a higher risk for ventricular fibrillation. Myocardial infarction size was not measured in the present study (the hearts were removed for in vitro studies). Therefore, we performed a retrospective analysis of animals in which infarction size had been determined and found that the susceptible dogs had larger infarctions (susceptible, n = 93, 17.7 ± 0.9%; resistant, n = 50, 12.6 ± 1.4%). Because the exercise program did not begin until after the myocardial infarction was healed (at least 4 wk after the induction of the infarction), it seems unlikely that training would reduce the infarction size in these animals.

Third, exercise training reduced the peak heart rate achieved during either exercise or acute myocardial ischemia. By decreasing metabolic demand, a lower heart rate per se could reduce the risk for arrhythmias. However, atropine pretreatment elicited large increases in heart rate, increases that exceeded the maximum heart rate values induced by the coronary occlusion before training, yet only modestly increased the arrhythmia frequency. Thus heart rate reductions, alone, cannot be responsible for the training-induced protection from ventricular fibrillation.

Fourth, it must be acknowledged that in the present study, cardiac vagal regulation was only indirectly evaluated using various measures of HRV. This study did not measure the parasympathetic nerve activity directly. However, previous investigations have verified that HRV provides an accurate representation of parasympathetic function (16). Additionally, in the present study, atropine effectively eliminated the heart rate and HRV differences noted between the susceptible and resistant dogs; that is, heart rate increased and HRV fell to zero in both groups after atropine treatment. These data are consistent with an atropine-induced inhibition (removal) of cardiac vagal regulation. Therefore, it is reasonable to conclude that the method used in the present study provided reliable indirect measurements of cardiac parasympathetic regulation.

Finally, it is well established that both respiratory rate and tidal volume can alter HRV (20). As such, differences in the respiratory response after exercise training 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 in both groups of animals (before and after exercise training). It is possible that, despite the panting, respiratory rate or tidal volume was altered in the trained animals. However, the coronary occlusion at rest did not elicit any obvious change in respiration (or induce panting) either before or after training, yet HRV was profoundly increased in the exercise-trained susceptible animals. Furthermore, our laboratory previously demonstrated that exercise elicited similar respiratory rate changes in resistant and susceptible dogs and that panting did not alter HRV (7, 18, 22). It seems unlikely that training-induced changes in respiration can explain HRV increase or the protection from ventricular fibrillation.

In conclusion, the present study demonstrates that exercise training improves cardiac autonomic function such that cardiac vagal regulation is maintained even when the heart is stressed by either exercise or acute myocardial ischemia in animals with healed infarctions. Furthermore, exercise training completely suppressed ventricular fibrillation induced by myocardial is-
chemia. However, because atropine pretreatment did not reintroduce lethal arrhythmias in these dogs, the exercise-induced protection from ventricular fibrillation did not result solely from enhanced cardiac vagal regulation. The mechanisms by which exercise training improved cardiac vagal regulation and prevented ventricular fibrillation remain to be determined.

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GRANTS

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REFERENCES


