Exercise Training Confers Anticipatory Protection From Sudden Death During Acute Myocardial Ischemia

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Abstract

Seven conscious dogs documented to be at high risk by the occurrence of ventricular fibrillation (VF) during acute myocardial ischemia were randomly assigned to 6 weeks of either daily exercise training or cage rest followed by exercise training. After 6 weeks of daily treadmill training, heart rate variability, a marker of vagal tone, increased by 74% (P<.001); baroreflex sensitivity, a marker of the capability to reflexly augment vagal activity, increased by 69% (P<.01); the repetitive extrasystole threshold, a marker of ventricular electrical stability, increased by 44% (P<.05). After exercise training, the incidence of ventricular fibrillation during acute myocardial ischemia decreased by 100%, as all animals survived. Neither passage of time nor heart rate level during ischemia contributed to the outcome. The most likely mechanism to explain the striking change in risk status is the shift in autonomic balance characterized by increased cardiac vagal activity, which was previously shown to have an antifibrillatory effect. These results suggest that exercise training in healthy individuals may decrease their likelihood of developing lethal arrhythmias during acute myocardial ischemia. (Circulation. 1994;89:548-552.)

Key Words • exercise • death, sudden • fibrillation

Exercise training was associated with health benefits and specifically with decreased cardiovascular mortality in two large observational studies.1-2 The lack of a randomized controlled clinical trial of physical activity with sufficient power3 has made meta-analysis necessary for the assessment of its effect on cardiovascular mortality. Even though a reduction in cardiovascular mortality and sudden death has been suggested,4 the simultaneous presence of other beneficial lifestyle changes makes data interpretation difficult. At this time, whether exercise training actually reduces the risk of sudden death remains undemonstrated. Similarly, the mechanisms that might be involved in this putative protective effect are speculative.

Sudden cardiac death is often the first (and last) manifestation of ischemic heart disease and remains a leading cause of mortality in healthy, middle-aged men.5 These unexpected deaths represent a major limitation for a widespread and effective preventive strategy. As a consequence, most interventions on groups already identified as being at high risk, eg, post-myocardial infarction (MI) patients. We have demonstrated previously that daily exercise in conscious dogs with a healed MI exerts a powerful antifibrillatory effect.6

Although exercise training increases heart rate variability in healthy subjects,7 no information exists demonstrating that this intervention is protective from arrhythmogenic death resulting from an episode of acute myocardial ischemia. We addressed this issue using an established and clinically relevant experimental model for sudden death in which a physiologically induced elevation in cardiac sympathetic autonomic activity was combined with brief myocardial ischemia.8

Methods

Surgical Instrumentation

Healthy mongrel dogs were selected for the study, and all procedures were conducted following federal, state, and institutional guidelines pertaining to the appropriate use of laboratory animals. Briefly, during general anesthesia, the animals were instrumented with a vascular occluder and proximal blood flow probe, both implanted on the left circumflex coronary artery. The occluder allowed later temporary reversible occlusion of the left circumflex artery as verified by the flow signal.8 All instrumentation was exteriorized at the neck.

Autonomic Assessments

Heart rate variability (HRV)9 and baroreflex sensitivity (BRS)10 were measured according to previously described methodology. All autonomic assessments were performed after an appropriate time of acclimation to the recording environment, with the animal lying quietly on a warmed, padded table. Briefly, HRV was derived from 25 minutes of continuous digitized ECG recordings. Time domain analysis of HRV was expressed as the standard deviation of the mean RR interval and the coefficient of variance (normalizing the standard deviation to heart rate).9 Frequency domain analysis of HRV was performed using fast Fourier transformation with Hanning windowing technique11 to express total power from 0...
to 0.5 Hz. Percentage of the total power in the low frequency band (0.03 to 0.15 Hz) and high frequency band (0.15 to 0.5 Hz) then was calculated.

BRS was quantified by calculating the slope of the regression line relating the increase in systolic arterial pressure, caused by a bolus intravenous injection of phenylephrine (2 to 5 μg/kg), to the prolongation of the adjacent ECG RR interval.10

Repetitive Extrasystole Threshold
Repetitive extrasystole thresholds were performed after cardiac catheterization as previously described.12 Briefly, using fluoroscopic guidance, a 6F quadripolar catheter was placed via the jugular vein into the right ventricular apex. Appropriate ventricular electrograms were confirmed together with efficacy of ventricular pacing (150 beats per minute) using a pacing current 150% of diastolic threshold. Using a 2-millisecond pulse width, repetitive extrasystole threshold was assessed starting at 1 mA. Diastole was scanned in 2-millisecond decrements to determine the effective refractory period. Current was incrementally increased by 1 to 2 mA until a repetitive electrical response was observed in two of three consecutive trials.

Risk Assessment
After 3 weeks of recovery and daily acclimation to the laboratory and treadmill, each dog was initially evaluated for the presence or absence of lethal ventricular arrhythmias during a submaximal exercise and myocardial ischemia test.8 Dogs ran on a motorized treadmill for 12 to 15 minutes at increasing speed and elevation from 3 mph at a 0% incline up to 4 mph at a 12% to 16% incline until the heart rate reached approximately 200 to 220 beats per minute. These heart rates represent 70% to 75% of the highest heart rate expected in a dog during maximal exercise.13,14 Two minutes of acute myocardial ischemia followed; after 1 minute of coronary occlusion, the treadmill was stopped. Of the 39 animals undergoing this exercise and ischemia test, 8 (21%) developed ventricular fibrillation (VF) and were immediately defibrillated. These 8 high-risk animals constituted the study population. The absence of spontaneous VF during the exercise and ischemia test is the gold standard for survival in this experimental preparation. Hemodynamic deterioration did not precede VF because mean arterial pressure before the onset of VF was not different between the groups.

Exercise Training Intervention
Daily (Monday through Friday) exercise training consisted of 60 to 90 minutes of treadmill exercise with warm-up, sprints, endurance runs, and cool-down with weekly increases in the workload. Of the eight high-risk dogs, five were assigned to 6 weeks of daily exercise training, and the remaining three dogs were assigned to 6 weeks of cage rest (Fig 1). Two of the three dogs initially assigned to cage rest subsequently underwent 6 weeks of exercise training. The third dog had behavioral difficulty with the training program and was reassigned to another 6 weeks of cage rest intervention, serving as an in-study control. Training effects were evaluated by examining the heart rate response to graded submaximal exercise testing performed every 15 days throughout the exercise training protocol. Exercise training was confirmed by a 10% reduction in the heart rate response to submaximal exercise. Autonomic and arrhythmia susceptibility assessments were performed after each treatment period. Six of the seven trained animals were exposed to a second exercise and ischemia test where the occlusion was performed at a workload higher by one step.

Statistical Analysis
Data were statistically analyzed using the Student’s t test for paired data. The Fisher’s exact test was used to calculate the probability of binomial events (presence or absence of VF). An α level of P<.05 was considered statistically significant. Data are presented as mean±SEM.

Results
Exercise training modified all the parameters under study (Fig 2). A time domain measure of HRV, the standard deviation of mean RR intervals, increased by 74%, from 185±36 to 322±41 milliseconds (P<.001), and the mean RR interval lengthened by 28%, from 730±38 to 931±44 milliseconds (P<.01). To eliminate the influ-
Fig 2. Bar graph illustrating the percent change observed after exercise training in baroreflex sensitivity (BRS), heart rate variability (HRV, standard deviation of the mean RR intervals), repetitive extrasystole threshold (RET), and incidence of ventricular fibrillation (VF) during the exercise and ischemia test in the seven dogs. Exercise training produced a concomitant increase in BRS, HRV, and RET and protected all animals from recurrence of VF.

ence of the heart rate, the coefficient of variance (×1000) was also calculated and increased by 40%, from 244±39 to 342±38 (P<.01). Exercise training modified frequency domain measurements of HRV by increasing percentage power in the high frequency band by 40%, from 40±6% to 56±7% (P<.005). The low frequency band decreased by 29%, from 53±6% to 37±6% (P<.003). Sympathovagal balance, as calculated by the low frequency to high frequency power ratio, decreased by 52%, from 1.7±0.4 to 0.8±0.2 (P<.005). BRS increased by 69%, from 16±3 to 27±5 ms/mm Hg (P<.05). Regression coefficients averaged 0.81±0.04 (P<.0001). Repetitive extrasystole threshold increased by 44%, from 32±2 to 46±2 mA (P<.01).

Exercise training decreased the occurrence of VF during myocardial ischemia by 100%, since all seven dogs survived the exercise and myocardial ischemia test (Fig 2). This protection remained significant (P<.05) in the six dogs that repeated the exercise and ischemia test at a higher workload, even though two of them had recurrence of VF.

Heart rate did not play a significant role in the outcome of these experiments (Fig 3). Although training resulted in a decreased heart rate measured at rest (from 84±5 to 65±3 beats per minute; P<.01) and at the highest workload of submaximal exercise (from 211±10 to 200±8 beats per minute, P<.01), no difference was observed at 30 seconds of ischemia (229±5 versus 230±9 beats per minute). Overall, the protocol of the study made it unnecessary to repeat the exercise and ischemia test while using atrial pacing to maintain the heart rate constant.

The three animals assigned to cage rest again developed VF 6 weeks later when exposed to a second exercise and ischemia test. Of this group, two animals subsequently assigned to 6 weeks of exercise training survived the third exercise and ischemia test. Their data have been presented above to form a single group of seven dogs tested after exercise training. The animal that had difficulty with exercise training and that was
reassigned to cage resting conditions again developed VF during a third exercise and ischemia test. The trained animals survived not because of the time elapsed from the first ischemic episode but because of the actual intervention, that is, exercise training.

Discussion

The mechanism most likely to be involved in the results documented here is a change in the cardiac autonomic balance producing an increase, or a relative dominance, of the vagal component. It has been long known that exercise training reduces resting heart rate, a change that mimics increased vagal activity. The observed changes in both HRV and BRS indicate an augmentation of both vagal tone and vagal reflexes. Several laboratory studies have demonstrated that this type of autonomic modulation can reduce the incidence of VF.\textsuperscript{15} Such a protective effect in the same conscious animal preparation used in the present study has been achieved after either direct vagal stimulation through a chronically implanted electrode\textsuperscript{16} or administration of muscarinic agonists.\textsuperscript{17} Conversely, 25% of the low-risk dogs survive the exercise and ischemia test because of the presence of powerful vagal reflexes as they develop VF after pretreatment with atropine.\textsuperscript{18} The heart rate changes induced by these interventions contribute to the outcome in less than 50% of cases, as indicated by the experiments performed with constant heart rate.\textsuperscript{16}

Time domain analysis of heart periods and BRS are not redundant\textsuperscript{19}; HRV represents primarily vagal resting tone, whereas BRS is a marker of vagal reflexes that is used to quantify the capability of the baroreceptor reflex feedback loop to activate cardiac vagal efferent activity in response to a physiological stimulus. The tight relationship between BRS and the activity of single vagal fibers directed to the sinus node has been demonstrated.\textsuperscript{20} HRV and BRS already have been proven effective in discriminating between post-MI patients destined to survive or to die in relatively large clinical studies.\textsuperscript{21,25}

Together with vagal augmentation, a simultaneous decrease in the arrhythmogenic sympathetic efferent activity\textsuperscript{26} may have contributed to these results. An increase in VF threshold, observed in exercise-trained rats exposed to acute myocardial ischemia, has been associated with reduced myocardial cAMP concentration.\textsuperscript{27} This effect on adenylate cyclase activity may reflect reduced sympathetic and/or augmented vagal tone. On the other hand, the brisk increase in heart rate during coronary occlusion despite exercise training suggests that the excitatory cardio-cardiac sympathetic reflex elicited by acute myocardial ischemia\textsuperscript{28} had not been blunted. The maintenance of adequate protection in dogs subjected to a higher workload indicates that the reduction in metabolic requirement produced by exercise training did not play a significant role in our results.

The major increases in BRS, a variable only moderately influenced by reductions in sympathetic activity,\textsuperscript{29} and in HRV suggest that the main and primary mechanism for the change in susceptibility to VF observed in the present experiments is an increase in both tonic and reflex vagal activity. This would act largely by antagonizing the sympathetic effects at the ventricular level.\textsuperscript{30} The possible contributing roles of diminished sympathetic activity and of undefined structural or metabolic cellular changes remain to be clarified. In summary, exercise training increased the resting level of vagal activity, increased the capability to reflexly augment vagal activity, and concomitantly increased cardiac electrical stability.

Regardless of the specific mechanism(s) involved, the present study documents for the first time that it is possible to lower substantially the risk of sudden death in healthy subjects through daily exercise. The most logical target population, healthy, middle-aged men, constitutes the novelty for this intervention that would decrease their likelihood of developing a lethal arrhythmia in the event of an acute ischemic episode. This finding has major health-related implications. In an era characterized by the disappointing failure of most antiarrhythmic drugs in preventing sudden cardiac death,\textsuperscript{31} these results provide a sound rationale for a feasible approach to this problem. Exercise training is an inexpensive, nonpharmacological intervention that is essentially devoid of negative side effects and virtually available to everyone. These results offer the unique possibility of a scientifically testable hypothesis for a mass program of primary prevention that is particularly suitable for middle-aged adults who have not yet experienced heart disease.

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References

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