Exercise Training After Experimental Myocardial Infarction Increases the Ventricular Fibrillation Threshold Before and After the Onset of Reinfarction in the Isolated Rat Heart

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Previous work has shown that exercise training increases the ventricular fibrillation threshold of the isolated perfused rat heart. The aim of our study was to determine whether exercise training that begins after myocardial infarction can similarly increase the ventricular fibrillation threshold. Rats that had suffered an experimental myocardial infarction were subject to a running training program. Thereafter, the ventricular fibrillation threshold was measured before and after the onset of acute reinfarction induced by a second coronary artery ligation. Ventricular fibrillation thresholds were significantly elevated in trained rats during normoxia (13.7±2.2 vs. 4.7±0.8 mA, p<0.01) and during acute ischemia (6.8±1.6 vs. 3.0±0.7 mA, p<0.02). The myocardial cyclic AMP level was lower in the nonischemic zone of the trained hearts (0.21±0.01 vs. 0.28±0.01 nmol/g, p<0.05), which also had lower cyclic AMP levels after epinephrine challenge (0.50±0.05 vs. 0.73±0.09 nmol/g, p<0.01; 1.41±0.11 vs. 1.85±0.09 nmol/g, p<0.02 after epinephrine 10⁻⁷ M and 5×10⁻⁶ M injection, trained vs. untrained). Both propranolol 10⁻⁶ M and epinephrine 5×10⁻⁷ M attenuated the difference in ventricular fibrillation thresholds before and after second coronary artery ligation and eliminated any difference in cyclic AMP content of both the nonischemic and ischemic myocardial tissue. We conclude that exercise training increases the ventricular fibrillation threshold of the previously infarcted isolated rat heart before and after the onset of reinfarction and that the training effect may be mediated by a decrease in myocardial sympathetic tone, an increase in parasympathetic tone, or both. (Circulation 1989;80:138–145)

Epidemiologic evidence shows an association between exercise and a reduced incidence of sudden cardiac death.¹⁻⁴ We have previously shown that the exercise-trained rat heart has an increased resistance to ventricular fibrillation during normoxia, hypoxia, and acute regional ischemia,⁵ suggesting that training may act directly on the myocardium to increase myocardial resistance to lethal cardiac arrhythmias.

The aim of our study was to determine whether exercise training in the presence of an established previous myocardial infarction can also influence myocardial resistance to ventricular fibrillation. Epidemiologic evidence⁶⁻⁷ suggests that exercise as part of a comprehensive rehabilitation program after myocardial infarction may reduce the incidence of subsequent sudden cardiac death. In conscious postinfarct dogs, when further temporary myocardial ischemia is applied during exercise, the risk of ventricular fibrillation is decreased by prior exercise training, suggesting that postinfarct training in humans could prevent sudden death.⁸ However, the underlying cellular biochemical mechanisms for the benefits of postinfarct training have not been clarified.

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The purpose of our study was to determine whether exercise training after experimental myocardial infarction influences the ventricular fibrillation threshold (VFT) of the isolated perfused rat heart. Groups of rats that had suffered a surgically induced acute myocardial infarction were randomly assigned to either an exercising or a nonexercising control group. After a 10-week period, isolated perfused hearts from both trained and untrained rats were subject to a second acute coronary artery ligation before and after which the VFT was measured.

Previous studies\(^5\)\(^-\)\(^10\) have suggested that the increased myocardial resistance to ventricular fibrillation after exercise training might be related to altered autonomic nervous system activity. Myocardial biochemical studies were performed to determine whether trained hearts had altered levels of cyclic AMP (cAMP). Myocardial cAMP concentrations served as an indicator of myocardial sympathetic activity. The additional effects of \(\beta\)-adrenergic antagonism and stimulation were also studied.

**Methods**

**In Vivo Coronary Artery Ligation**

Male Long-Evans rats (250–300 g) were anesthetized with intraperitoneal Ketalar (ketamine HCl 100 mg/ml, Parke Davis) (1 mg/g body wt). Lidocaine (10 mg) was sprayed onto the epiglottis to prevent laryngospasm during intubation. A modified laryngoscope was used to intubate the rats, which were ventilated with a Harvard apparatus rodent respirator (Protea Holdings) on a 2:1 oxygen-halothane mixture (Maybaker [SA]).

A skin incision approximately 5 cm long was made from the sternum to the left shoulder. The left pectoral muscle was incised to expose the ribs. Next, an incision was made through the rib cage, care being taken to avoid damaging the underlying lungs. A chest miniretractor was used to expose the heart, and the thymus gland was held to one side with a fine artery forceps. The pericardium was gently dissected away and the left atrium elevated to establish clearly the origin of the left main coronary artery. A 6-0 Ti-Cron suture (Davis and Geck) was inserted into the left ventricle halfway down the course of the left anterior descending coronary artery. After ligation, the ventricular mass below the ligature became pale, corresponding to the area of acute ischemia, which represented approximately 25–35% of the left ventricular mass.

The chest and skin were closed with 3-0 Ti-Cron (Davis and Geck). Ventilation was changed to room air, which was maintained until spontaneous breathing returned. Aseptic procedures were not used and postoperation sepsis was not noted. Neither antibiotic nor antiarrhythmic therapy was instituted, and preoperative ketamine provided adequate analgesia.

A mortality of approximately 25% resulted from the acute coronary artery ligation.

**Training Program**

After a 1-week convalescent period, the rats were randomly assigned to either an exercising or a nonexercising group. Exercising rats completed a 10-week training program on a Quinton Model 42-15 treadmill (Quinton Instruments, Seattle, Washington). The rats exercised 5 days a week at a speed of 1.3 km/hr (15% elevation) for an initial period of 10 minutes increasing to a maximum of 60 minutes at the end of 2 weeks. This duration was maintained for the remainder of the training program. The treadmill is designed to provide electrical shocks via an electrical wire grid at the back of the running lanes to those rats that do not maintain their running speeds. In practice, the rats were shocked less than one shock every few minutes.

The untrained rats were maintained at normal cage activity for the 10-week period. Both groups were housed under the same conditions and were given food and water ad libitum.

As the trained rats were subjected to intermittent electrical shocks during the training program, an untrained group was placed on the electrical wire and prevented from running. These rats received intermittent shocks of the same frequency and intensity as did the trained rats for an identical period of time. After 10 weeks, rats from the untrained, untrained but shocked, and trained groups (three groups) were killed for the experimental studies.

**Experimental Protocols**

**Measurement of "training effect." MAXIMUM OXYGEN CONSUMPTION (\(\text{VO}_{2\text{max}}\)).** Before the start of training and after 10 weeks of training, rats were subject to a running performance test using the apparatus and methods previously described from this laboratory.\(^{11}\) Rats ran in a bottomless Plexiglas chamber (9.5x32.5x11.5 cm) that was suspended on a custom-built single-lane treadmill. Ambient air was drawn through the chamber at a flow rate of 5.0–7.5 l/min (STPD), depending on the mass of the rat. The flow rate was calibrated before and after each test with a Tissot spirometer. Samples of the extracted air were directed to an O\(_2\) (Applied Electrochemistry S-3A/1) and a CO\(_2\) (Applied Electrochemistry P-61B) analyzer, which were interfaced with an Alpha microcomputer. Oxygen consumption was calculated every minute as previously described.\(^{11}\) Before and after each test, the \(\text{O}_2\) and CO\(_2\) analyzers were calibrated with gases of known \(\text{O}_2\) and CO\(_2\) composition.

Each \(\text{VO}_{2\text{max}}\) test was conducted after a day of rest according to the testing procedure previously described from this laboratory.\(^{11}\) The test protocol involved increasing the treadmill speed and elevation every 3 minutes until the rat could no longer maintain his position on the treadmill belt. The highest \(\text{VO}_2\) measured was recorded as the \(\text{VO}_{2\text{max}}\).
SUBMAXIMAL RUNNING ENDURANCE. The submaximal running endurance was determined by running the rats at a speed of 20 m/min with no inclination or, in a separate series, at an inclination of 15°. The time taken to reach exhaustion represented the submaximal running endurance. Exhaustion was determined as the inability of the rats to maintain their position on the treadmill belt.

Measurement of ventricular fibrillation thresholds. VENTRICULAR FIBRILLATION THRESHOLD MEASUREMENTS DURING CONTROL PERFUSIONS. The rats were anesthetized with ether in a glass vacuum bowl. When adequately sedated, 10 μl heparin (1,000 units/ml) was injected into the femoral vein. The thoracic cavity was opened, and the heart rapidly excised and immediately placed into ice-cold Krebs-Henseleit buffer. The perfusate was a modified Krebs-Henseleit buffer solution with a concentration of 144 mM Na⁺, 5.9 mM K⁺, and 1.1 mM CaCl₂ aerated with 95% O₂-5% CO₂. Insulin (NUSO Neutral Insulin Wellcome Foundation) was added at a concentration of 2 IU/l. Once the heart had stopped beating, the aorta was cannulated and retrograde perfusion was commenced within 90 seconds via an isolated Langendorff system at a perfusion pressure of 100 cm H₂O.

The VFT of the isolated rat heart was measured as previously described.13 The heart was mounted on the aortic cannula, and two thin platinum electrodes were inserted into the base and apex of the left ventricle. These electrodes recorded the electrocardiogram on an oscilloscope and delivered square-wave stimuli of 2-msec duration (Grass S88 Physiologic Stimulus Generator). The VFT was measured by applying a single train of 10 stimuli of 200-msec duration across the T wave starting 10 msec after the onset of the R wave. The heart was stimulated every 60 seconds unless ventricular fibrillation occurred, in which case the next stimulus was only applied after 120 seconds. The current strength was increased by 2 mA every 60 seconds until ventricular fibrillation consisting of six or more repetitive ectopies of irregular form developed. The VFT was defined as the lowest current that produced ventricular fibrillation on three occasions and did not produce fibrillation at a current of 0.5 mA lower.

The first VFT measurements were made after a 15-minute stabilization period during which both coronary flow and spontaneous heart rate were measured. At the completion of the experiment, heart mass and size of the in vivo infarct were measured.

VENTRICULAR FIBRILLATION THRESHOLD MEASUREMENTS DURING ACUTE ISCHEMIA. In a separate series of experiments, VFT measurements were made during acute ischemia. After cannulation (as previously described), a 6-0 Ti-Cron suture with an atraumatic needle was passed deep to the left main coronary artery as it emerges adjacent to the left atrium, according to the technique described by Kannengieser et al.14 This ligature was necessary for the development of acute ischemia (see below). Once initial control VFT measurements had been performed, acute regional ischemia was induced by abruptly tightening the ligature that had previously been placed around the left coronary artery.

Beginning 2 minutes after ligation, VFT measurements were made for a period of 15 minutes. Thereafter, disulphan blue was injected into the aortic cannula to perfuse the coronary arteries. This dye distinguishes between oxygenated and non-oxygenated tissue and was, therefore, used to differentiate normal from ischemic or infarcted myocardial tissue. The hearts were then freeze-clamped with Wollenberger tongs15 that had been precooled in liquid nitrogen. The frozen tissue was separated into normal and ischemic/infarcted tissue and stored in liquid nitrogen pending cAMP and biochemical analysis.

VENTRICULAR FIBRILLATION THRESHOLD MEASUREMENTS DURING ACUTE ISCHEMIA IN HEARTS PERFUSED WITH PROPRANOLOL 10⁻⁶ M AND EPINEPHRINE 5×10⁻⁷ M. An identical protocol was used for two further sets of experiments. Hearts from trained and untrained rats were perfused separately with propranolol 10⁻⁶ M (Inderal, ICI Laboratories) and epinephrine bitartrate 5×10⁻⁷ M (Petersen Ltd). VFT measurements were performed as before and the hearts were freeze-clamped after 15 minutes of ischemia for cAMP and biochemical analyses.

cAMP measurements after catecholamine stimulation. In these experiments, VFT measurements were not performed. Hearts from trained and untrained rats with previous myocardial infarction were mounted on the perfusion apparatus as previously described. After the 15-minute stabilization period, the aortic cannula was cross-clamped and a 1 ml bolus of epinephrine bitartrate was injected into the aortic perfusate over a period of 2 seconds. Epinephrine bolus concentrations of 10⁻⁸ M, 5×10⁻⁸ M, 10⁻⁷ M, and 5×10⁻⁸ M were used. Ten seconds later, the hearts were clamped and the noninfarcted tissue segments were stored for cAMP analysis.

Tissue Analysis

Measurement of acute ischemic zone and infarct size. Hearts were removed from the aortic cannula after the injection of disulphan blue into the aortic perfusate. The ischemic and infarcted tissues failed to stain with dye. Assessment of ischemic tissue was made after the scar tissue from the in vivo infarct had been excluded, and a zone of apparently normal perinfarct tissue was also excluded. Measurements of in vivo infarct size were performed in a separate series of experiments where no secondary ischemia was induced. The infarcted tissue was dissected out, and its mass was recorded as a percentage of the total left ventricular mass.

Myocardial biochemical and cyclic AMP measurements. The tissue contents of ATP, phosphocreatinine, glycogen, lactate, and cAMP were mea-
sured in freeze-clamped hearts homogenized under liquid nitrogen by standard methods, as previously described in a report from this laboratory.5

Statistical Methods

Data are presented as mean±SEM. A 2×2×4 factorial analysis of variance (three-way ANOVA) was used to analyze VFTs. A multifactorial analysis of variance with repeated-measures design and a Student’s unpaired t test modified for multiple comparisons were used for analysis of biochemical data.

Results

Effect of Training on Exercise Performance

Exercise training significantly increased mean VO$_{2\max}$ in trained rats (Table 1). Running time to exhaustion also increased significantly with training during the maximal test. Similarly, exercise training significantly increased the time taken to reach exhaustion during the submaximal running tests.

Effect of Training on Rat Mass, Heart Mass, Infarct Size, Spontaneous Heart Rate, Coronary Flow, and Ventricular Fibrillation Threshold

Trained rats had lower body mass than untrained rats (Table 2). Heart mass was not different between groups. True infarct size, spontaneous heart rate, and coronary flow were not affected by training.

Exercise training significantly increased mean VFT in trained rats. There was no difference in VFT values between shocked and unshocked animals.

Ventricular Fibrillation Threshold Measurements During Acute Ischemia

At all times during coronary artery ligation, the VFT was higher in hearts from trained rats (Figure 1). As in the previous experiment, trained rats were lighter but there were no differences in heart mass, spontaneous heart rate of the isolated heart, or total coronary flow (data not presented).

Ischemia caused tissue ATP, phosphocreatinine, and glycogen levels to fall, whereas lactate levels rose, cAMP levels rose in the ischemic tissue, but this increase was not significant. Tissue levels of ATP, phosphocreatinine, glycogen, and lactate were not different between the trained and untrained groups after 15 minutes of regional ischemia (data not presented).

Myocardial cAMP levels were lower in the normal zone of the hearts from trained than untrained rats, but cAMP levels in the ischemic zone were unchanged by training.

Ventricular Fibrillation Threshold Measurements During Acute Ischemia in Hearts Perfused With Propranolol 10$^{-6}$ M or Epinephrine 5×10$^{-7}$ M

Hearts perfused with propranolol 10$^{-6}$ M. Propranolol significantly elevated the VFT value prior

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**TABLE 1. Effect of Training on Exercise Program**

<table>
<thead>
<tr>
<th>Test</th>
<th>Untrained (n=6)</th>
<th>Trained (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_{2\max}$ (ml O$_2$/kg/min)</td>
<td>68.5±2.0</td>
<td>74.8±1.7*</td>
</tr>
<tr>
<td>Run time to exhaustion during submaximal test (min)</td>
<td>19±4</td>
<td>69±7†</td>
</tr>
<tr>
<td>Run time to exhaustion during maximal test (min)</td>
<td>15.0±0.6</td>
<td>26.4±0.8†</td>
</tr>
</tbody>
</table>

Mean±SEM.

*pt<0.05.
†pt<0.01.

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**TABLE 2. Measurement of Rat Mass, Infarct Size, Heart Rate, and Coronary Flow During Control Perfusions of Hearts From Untrained Ligated, Trained Ligated, and Untrained Ligated Shocked Rats**

<table>
<thead>
<tr>
<th>Rats (n=8)</th>
<th>Rat mass (g)</th>
<th>Heart mass (g)</th>
<th>In vivo infarct size* (% LV)</th>
<th>Spontaneous heart rate (beats/min)</th>
<th>Coronary flow (ml/min)</th>
<th>VFT (mA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untrained, ligated</td>
<td>503±24†</td>
<td>2.05±0.07</td>
<td>27.3±3.2</td>
<td>261±19.5</td>
<td>18±2.6</td>
<td>4.9±0.8‡</td>
</tr>
<tr>
<td>Trained, ligated</td>
<td>462±19</td>
<td>2.11±0.15</td>
<td>27.0±1.7</td>
<td>274±8.0</td>
<td>17±1.1</td>
<td>13.7±2.2</td>
</tr>
<tr>
<td>Untrained, ligated, shocked</td>
<td>512±16†</td>
<td>2.08±0.04</td>
<td>28.0±2.4</td>
<td>273±11.0</td>
<td>19±2.5</td>
<td>4.8±0.8‡</td>
</tr>
</tbody>
</table>

Mean±SEM.

*For limitations of method, see Anversa et al.31
†pt<0.05 vs. trained, ligated.
‡pt<0.01 vs. trained, ligated.
TABLE 3. Tissue ATP, Phosphocreatine, Glycogen, Lactate, and Cyclic AMP in Nonischemic and Ischemic Zones of Hearts From Trained and Untrained Rats With a Prior Myocardial Infarct Perfused With no Drug, Propranolol 10^{-6} M, and Epinephrine 5 \times 10^{-7} M After 15 Minutes of Ischemia

<table>
<thead>
<tr>
<th>Group</th>
<th>ATP (μmol/g)</th>
<th>Phosphocreatinine (μmol/g)</th>
<th>Glycogen (μmol glucose Eq/g)</th>
<th>Lactate (μmol/g)</th>
<th>Cyclic AMP (nmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trained and no drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=8)</td>
<td>2.46±0.26*</td>
<td>4.56±0.35*</td>
<td>24.23±2.09*</td>
<td>4.35±0.46*</td>
<td>0.21±0.01†</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>1.19±0.13</td>
<td>2.24±0.28</td>
<td>14.70±2.25</td>
<td>10.44±2.07</td>
<td>0.26±0.04</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.29±0.25</td>
<td>1.77±0.22</td>
<td>10.31±1.37</td>
<td>9.79±2.22</td>
<td>0.29±0.02</td>
</tr>
<tr>
<td>Untrained and no drug</td>
<td>2.83±0.20*</td>
<td>4.61±0.36*</td>
<td>20.86±1.44*</td>
<td>3.73±0.60*</td>
<td>0.28±0.01</td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>1.29±0.25</td>
<td>1.77±0.22</td>
<td>10.31±1.37</td>
<td>9.79±2.22</td>
<td>0.29±0.02</td>
</tr>
<tr>
<td>Ischemic</td>
<td>3.91±0.17*</td>
<td>4.46±0.19*</td>
<td>23.38±1.63*</td>
<td>5.22±0.57*</td>
<td>0.28±0.01</td>
</tr>
<tr>
<td>Trained and propranolol</td>
<td>3.64±0.13</td>
<td>1.19±0.22</td>
<td>15.44±1.16</td>
<td>10.62±1.24</td>
<td>0.29±0.13</td>
</tr>
<tr>
<td>10^{-6} M (n=8)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nonischemic</td>
<td>3.90±0.18*</td>
<td>4.43±0.37*</td>
<td>23.56±1.39*</td>
<td>6.11±1.48*</td>
<td>0.28±0.01</td>
</tr>
<tr>
<td>Ischemic</td>
<td>3.04±0.32</td>
<td>1.38±0.13</td>
<td>15.63±1.45</td>
<td>13.51±3.20</td>
<td>0.32±0.02</td>
</tr>
<tr>
<td>Untrained and propranolol</td>
<td>3.00±0.16*</td>
<td>4.59±0.25*</td>
<td>17.16±2.60*</td>
<td>6.00±0.27*</td>
<td>0.71±0.03*</td>
</tr>
<tr>
<td>10^{-6} M (n=8)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>1.37±0.15</td>
<td>1.68±0.40</td>
<td>5.31±1.09</td>
<td>15.14±2.09</td>
<td>0.52±0.04</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.81±0.13*</td>
<td>5.14±0.63*</td>
<td>11.57±1.50*</td>
<td>6.39±0.65*</td>
<td>0.71±0.07*</td>
</tr>
<tr>
<td>Trained and epinephrine</td>
<td>1.18±0.18</td>
<td>1.24±0.18</td>
<td>4.43±1.05</td>
<td>15.10±2.54</td>
<td>0.46±0.06</td>
</tr>
<tr>
<td>5 \times 10^{-7} M (n=8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>2.81±0.13*</td>
<td>5.14±0.63*</td>
<td>11.57±1.50*</td>
<td>6.39±0.65*</td>
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</tr>
</tbody>
</table>
rats without myocardial infarction,5 was sufficient to produce a training effect. This was shown by the increased VO$_{2\text{max}}$ and increased running times to exhaustion during submaximal and maximal exercise in trained rats (Table 1). More important, this study establishes that training of rats after previous experimental myocardial infarction elevates VFTs before and after the onset of acute regional ischemia produced by a second coronary artery ligation. Trained hearts also had lower cAMP levels in the nonischemic left ventricular zone and in the normal myocardium after catecholamine stimulation. Both propranolol $10^{-6}$ M and epinephrine $5 \times 10^{-7}$ M attenuated this difference in VFT before and after second coronary artery ligation and eliminated any difference in cAMP content of both the nonischemic and ischemic myocardial tissue.

The present study, therefore, extends our previous work5 in which we showed that exercise training increased the VFT of isolated hearts from normal rats. Our data are in agreement with two additional animal studies. Verdouw and Schaffer10 found that exercise-trained noninfarcted pigs had a reduced incidence of ventricular fibrillation after acute myocardial ischemia during an open-chest anesthetized procedure, whereas Billman et al16 found that conscious dogs who were exercise trained after a previous myocardial infarction had a reduced incidence of ventricular fibrillation during subsequent acute ischemia, also in the conscious state.

In combination with ours, these studies provide strong experimental evidence that in very different experimental systems, exercise training increases myocardial resistance to lethal arrhythmias that occur either spontaneously8,10 or in response to electrical stimulation either before or after coronary artery ligation5 or after reinfarction as shown by this study.

It should, however, be noted that there are some apparent differences between the findings of our present and the previous study.5 In the present study, there is a lower level of cAMP in the nonischemic tissue of the trained rats, whereas the previous study showed lower concentrations of cAMP in the ischemic regions. Possible interpretations of these findings might relate to the difference in protocols in the two studies. In the present study, the rats were trained after myocardial infarction, whereas in the previous study healthy rats were trained. However, in both studies, mean cAMP levels are lower in both regions of the myocardium of trained rats, although not all values are significantly lowered. Furthermore, in the previous study, cAMP rose significantly in the ischemic zone in untrained rats, whereas in this study it did not (the increase was not significant). Because cAMP had not risen in the ischemic zone, training could not have been expected to reduce it.

Our findings of the effect of propranolol and epinephrine on the VFT also support the hypothesis that exercise training decreases myocardial sympathetic drive with a consequent increased resistance to the development of ventricular fibrillation. Trained and untrained hearts perfused with either propranolol or epinephrine had similar ventricular fibrillation thresholds and similar myocardial cAMP levels. Possibly the effects of propranolol or of epinephrine were to eliminate training-induced differences in myocardial sympathetic balance.

Lubbe et al16 also found that propranolol attenuated the decrease in the VFT of the isolated perfused rat heart during ischemia. Vulnerability to ventricular fibrillation in early myocardial ischemia was related to changes in cAMP content of the ischemic myocardium and appeared to be independent of the depletion of myocardial high-energy phosphate stores. Additional studies support this conclusion.17,18 Nonetheless, propranolol acted without decreasing myocardial cAMP levels.

In addition, hearts from trained rats had lower myocardial cAMP concentrations in nonischemic tissue after an epinephrine challenge. However, there was no difference in cAMP concentrations in the nonischemic tissue between hearts from trained and untrained rats subject to epinephrine stimulation and acute myocardial ischemia. It, therefore, appears that while exercise attenuates the increase in myocardial cAMP after catecholamine stimula-

FIGURE 3. Myocardial cyclic AMP concentrations 10 seconds after epinephrine stimulation. Mean±SEM, n=8. *p<0.01. **p<0.02.
tion, this effect is not present during both epinephrine stimulation and acute myocardial ischemia.

**Possible Role of Altered Autonomic Function**

The mechanism for this protective effect of exercise is presently unclear. One possibility is that exercise training alters the myocardial response to sympathetic stimulation. Enhanced sympathetic activity increases myocardial predisposition to ventricular fibrillation.28-29 Acting at a cellular level, high circulating catecholamine concentrations are considered to be potently arrhythmogenic and to cause lowering of the ventricular fibrillation threshold in the isolated rat heart.13 The proposed intracellular messenger of the arrhythmogenic effect is cAMP.22 The chronic effects of exercise on the sympathetic nervous system are well documented.23-25 In particular, there is decreased activity of the sympathetic nervous system, so that at comparable workloads the heart of a trained subject is exposed to lower levels of sympathetic stimulation.26,27 A training-induced reduction in myocardial catecholamine “sensitivity” is, therefore, a possible explanation for the higher VFT measured in hearts from trained subjects.

In this and our previous study,5 training was associated with a reduced concentration of cAMP in the nonischemic myocardium. In the present study, we also show that hearts from trained rats had lower myocardial cAMP levels after catecholamine stimulation. Lower cAMP levels could be explained either by chronically reduced whole-body catecholamine levels at rest or by alterations in the density or sensitivity of the β-adrenergic receptors. Although the isolated rat heart was used without an intact autonomic nervous system, the decreased levels of cAMP in the hearts from trained rats could indicate decreased myocardial sympathetic tone. A training-induced alteration in baroreceptor reflex control of heart rate and in autonomic actions paralleled the increased protection against ventricular fibrillation.8,28,29

The training effect found by Billman et al8 could be explained by an increase in parasympathetic activity, a decrease in sympathetic activity, or both. The importance of changes in baroreflex control is emphasized by two recent studies. In one, mortality in postinfarct patients was associated with decreased baroreflex sensitivity.24 In the other study, dogs with a prior myocardial infarction were subject to acute ischemia during exercise; ventricular fibrillation developed more easily in dogs with a low baroreflex sensitivity.29 We did not assess baroreflex sensitivity but measured myocardial cAMP levels as an end-point of cardiac autonomic activity. The level of cAMP, the second messenger of adrenergic stimulation, is influenced by additional hormone systems, in particular, the parasympathetic nervous system in which acetylcholine may counteract the catecholamine effect both before and after the adrenergic synapses. Postsynaptic acetylcholine may act both directly and indirectly via raised cGMP levels to reduce cAMP levels.30 Increased parasympathetic activity could, therefore, decrease cAMP levels. An alternative interpretation of the above findings would be that training elevates VFT by increasing parasympathetic activity. However, this conclusion would not explain the reduced cAMP response to epinephrine infusion (Figure 3).

**Limitations to Study**

There are three important limitations to this study. First, we used the rat model of electrically induced ventricular fibrillation rather than the development of spontaneous ventricular fibrillation. Limitations inherent in the Langendorff model of retrograde perfusion include a denervated isolated heart with low afterloads and coronary artery perfusion pressures that are not in the physiologic range of an intact preparation.

A second limitation concerned the inaccuracies inherent in the measurement of the ischemic zone, the infarct size, and coronary flow. Although coronary flow rates were similar in hearts from trained and untrained rats, the smaller reduction in VFT during acute ischemia in the trained rats could possibly reflect an improved collateral circulation so that the ischemic insult was smaller. Accurate measurement of infarct size in the rat model requires careful morphometric techniques, similar to those developed by Anversa et al.31 We cannot exclude that exercise training altered ultimate infarct size.

Third, the measurements of cAMP on freeze-clamped hearts could have been on a mixture of infarcted and noninfarcted tissue, as well as of ischemic and nonischemic tissue. Hence, the differences shown in Table 3 could have been influenced by a considerable sampling error. It remains true that a comparison of the values of ATP, phosphocreatine, glycogen, and lactate found between ischemic and nonischemic tissue shows that the separation technique was at least sufficiently adequate to achieve major differences.

**Conclusions**

The data obtained support the hypothesis that altered autonomic activity occurs with training, specifically, that the reduced sensitivity of the myocardium to catecholamines could improve the myocardial resistance to ventricular fibrillation. These data, therefore, provide experimental support for the possibility that exercise training after myocardial infarction might be associated with a reduced incidence of sudden death in humans.32

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References


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