Physical Training Increases Ventricular Fibrillation Thresholds of Isolated Rat Hearts During Normoxia, Hypoxia and Regional Ischemia

TIMOTHY D. NOAKES, M.D., LOUISE HIGGINSON, AND LIONEL H. OPIE, M.D.

SUMMARY  The effect of exercise training on cardiovascular mortality is controversial. The purpose of this study was to determine the effect of a period of treadmill training on the ventricular fibrillation threshold of the isolated rat heart. Trained hearts had higher threshold values during standard, control perfusion conditions, and when exposed to hypoxia, hypoxia plus isoproterenol infusion, or when subjected to coronary artery ligation. Myocardial metabolic studies failed to define the mechanism for the effect of running training. However, in coronary ligated hearts, the content of the arrhythmogenic substance 3',5' cyclic adenosine monophosphate (cyclic AMP) was reduced in the ischemic zone of hearts from trained rats. Cyclic AMP levels were also lower in trained hearts during control perfusions. We conclude that running training increases the resistance of the heart to ventricular fibrillation by mechanisms that are largely unknown, although they may involve cyclic AMP.

THE RELATION between exercise and ischemic heart disease remains controversial. Although even extreme exercise, such as marathon running, does not give total protection against coronary atherosclerosis or sudden cardiac death, there is strong epidemiologic evidence for an association between high levels of physical activity either at work or in leisure time and a reduced incidence of coronary heart disease and, in particular, sudden death. Paffenbarger et al. concluded that low levels of work energy output are a risk factor as powerful as cigarette smoking, a history of heart disease and high blood pressure, and more influential than obesity, abnormal glucose tolerance or high blood cholesterol.

Another possibility is that exercise training specifically protects against sudden coronary death. Thus, in the longshoreman studies reported by Paffenbarger and Hale, high energy output at work provided greater protection against sudden death than against death occurring 6 hours after the onset of symptoms. Similarly, in studies of British civil servants, not only were the overall coronary mortality rates lower in those who reported vigorous leisure time activity, but sudden death mortality and mortality from the first and subsequent heart attack were also lower. These findings are compatible with a specific, training-related protection against rapidly fatal heart attack. Indeed, Paffenbarger et al. postulated that part of the myocardial adaptation to training may be a stabilization of cardiac rhythm, perhaps conferring a reduced risk of the development of that chain of events proceeding from ectopic ventricular activity to fibrillation and death.

Additional epidemiologic studies are required to settle these controversial issues; but further information can be obtained from animal models designed to investigate the effects of exercise training on the myocardial...
electrical stability during experimental interventions believed to mimic conditions present during myocardial infarction.

We chose the isolated perfused rat heart model to compare the ventricular fibrillation thresholds of hearts isolated from running-trained rats with those of hearts from control rats. We studied the effects of hypoxia and acute regional myocardial ischemia on the ventricular fibrillation threshold to determine whether exercise training could increase the myocardial electrical stability under these specified experimental conditions.

Materials and Methods

Three weeks after weaning, young male Wistar-Weissman rats were randomly assigned to either an exercising or a control group and were housed and fed under identical conditions. Rats assigned to the exercising group completed the following training program, which lasted at least 9 weeks. The rats exercised 5 days a week on a Quinton Model 42-15 treadmill (Quinton Instruments) set at a 15° incline. On the first and second training days, the rats ran for 15 minutes, on the third day for 30 minutes, on the fourth day for 45 minutes, and on the fifth day for 60 minutes. Thereafter, the running time was increased by 3 minutes daily until, at the end of the fifth training week, the rats were running for 2 hours daily, the first hour at up to 0.8 mph and the second at up to 1 mph. This exercise level was maintained until the rats were killed. This training program significantly increases myocardial myosin ATPase activity and the degree of myosin P light chain phosphorylation, but does not cause myocardial hypertrophy.

Untrained rats were kept at normal cage activity. All rats were exposed to a 12-hour day/night cycle and were fed rat cubes and water ad libitum.

After 9 weeks of training, rats from either the control or trained group were anesthetized with ether in a vacuum bowl and, when asleep, 10 μl of heparin (Pulrin, Glaxo-Allenbury (SA) Pty Ltd., 1000 U/ml) was injected into the femoral vein. The thoracic cavity was opened and the heart rapidly excised and immediately placed in ice-cold (4°C) Krebs-Henseleit buffer. As soon as the heart stopped beating, it was removed from the buffer and mounted on the isolated Langendorff-perfused heart system used in this laboratory. Hearts from trained and control rats were perfused alternatively so that an equal number of hearts from each group were studied on each experimental day.

The perfusate was a modified Krebs-Henseleit buffer solution with a CaCl2 concentration of 1.1 mM, aerated with either 95% O2 and 5% CO2 or with 95% room air and 5% CO2 during studies of hypoxia. The perfusate substrate was 11.1 mM D(+)-glucose (Merck) plus insulin (NUSO Neutral Insulin, Wellcome Foundation) at a concentration of 2 U/l. The perfusion pressure was always 100 cm H2O. In experiments in which myocardial glycolytic rates were measured, 3H-glucose (D-2-3H(N))-glucose (New England Nuclear) was added to the perfusate in a concentration of 100 μl/l.

Experimental Protocols

Ventricular Fibrillation Threshold Measurements During Control Perfusions

The technique for measuring the ventricular fibrillation threshold in the isolated perfused rat heart has been described in detail. After mounting the heart on the aortic cannula of the isolated perfusion system, thin platinum electrodes were inserted into the apex and base of the left ventricle with the anode at the apex, for the delivery of square-wave stimuli of 2 msec duration (Grass S88 physiologic stimulus generator). For hearts used in the studies of regional ischemia, a 5-0 silk suture with an atraumatic needle was passed deep to the left main coronary artery within 2 mm of where the artery emerges adjacent to the left atrium, according to the technique described by Kannengiesser et al. The ventricular fibrillation threshold was measured by applying a single train of 10 stimuli at 200-msec intervals across the T wave, starting 10 msec after the onset of the R wave. The heart was stimulated every 30 seconds unless ventricular fibrillation occurred, in which case the next stimuli were only applied after 60 seconds. The current strength was increased by increments of 2.5 mA until ventricular fibrillation, consisting of six or more repetitive ectopic cycles with irregular form, developed. The ventricular fibrillation threshold was defined as the lowest current that produced ventricular fibrillation on three occasions, and that did not produce fibrillation at a current of 0.5 mA lower.

The hearts stabilized for 15 minutes before measurement of heart rate, from the oscilloscope, and coronary flow rate by collection, in a graduated measuring cylinder, a timed sample of coronary effluent from the heated chamber below the heart. The ventricular fibrillation threshold was then measured, which was taken to represent the value for the control perfusion.

A separate series of nine trained and eight control hearts was frozen for biochemical analysis of ATP, phosphocreatine and cyclic AMP levels after 15 minutes of Langendorff perfusion but before determination of their ventricular fibrillation thresholds.

Ventricular Fibrillation Threshold Measurements During Acute Regional Ischemia

After the ventricular fibrillation threshold had been measured under control conditions, hearts from 12 trained and 14 control rats were exposed to acute regional ischemia by abruptly tightening the ligature surrounding the left main coronary artery. Beginning 5 minutes after ligation, ventricular fibrillation thresholds were measured every 30 seconds for 10 minutes in hearts from six trained and seven control rats, and for 15 minutes in another six trained and seven control rat hearts.

In the group perfused for 20 minutes of regional ischemia, the experiments were terminated by removing the hearts from the aortic cannula after injection of
disulphan blue dye into the perfusate through the aortic cannula. This technique differentiates the ischemic zone from the nonischemic zone of the left ventricle.\textsuperscript{15} The ischemic zone was then dissected out, weighed and recorded as a percentage of the total left ventricular wet weight.

In the group of hearts perfused for 15 minutes of regional ischemia, the experiments were terminated by freeze-clamping the hearts in Wollenberger tongs\textsuperscript{16} precooled in liquid nitrogen. Hearts were then individually stored in liquid nitrogen until biochemical analysis.

**Ventricular Fibrillation Threshold Measurements During Hypoxia and During Hypoxia with Catecholamine Stimulation**

After measurement of the control ventricular fibrillation thresholds, a further series of hearts from eight trained and eight control rats was exposed to 15 minutes of hypoxic perfusion, during which the ventricular fibrillation thresholds were measured every 30 seconds.

After the initial 15 minutes of hypoxic perfusion, 1 × 10\textsuperscript{-8} M isoproterenol (Isuprel, Winthrop Laboratories) was infused for 15 minutes while hypoxia was maintained. Ventricular fibrillation thresholds were again measured. The experiments were terminated by freeze-clamping the hearts in precooled Wollenberger tongs.

In these experiments, coronary effluent was sampled every 5 minutes and its \textsuperscript{3}H\textsubscript{2}O content was measured to calculate myocardial glycolytic rates.

**Biochemical Measurements**

The tissue contents of ATP, phosphocreatine, glycogen, lactate and 3',5' cyclic AMP were measured in freeze-clamped hearts homogenized under liquid nitrogen by methods previously described.\textsuperscript{13}

The coronary effluent \textsuperscript{3}H\textsubscript{2}O content of hearts perfused with D-2-\textsuperscript{3}H glucose was measured according to the methods of Neely et al.\textsuperscript{17} Ion exchange resin (Resin Dowex 1 × 4-200, Sigma Chemical Company) was prepared according to instructions provided by Professor M.J. Rovetto of the Department of Physiology, Jefferson Medical College of the Thomas Jefferson University, Philadelphia. After preparation, the resin was placed over glass wool in Pasteur pipettes to a column height of 2.5 cm. The resin was thoroughly rinsed with distilled water before being dried with compressed air. A 0.5-ml aliquot of coronary effluent was then carefully washed through the resin with 3 volumes of distilled water, 0.5 ml per passage, into 10 ml of scintillation fluid (Insta-Gel, Packard Instrument Company). Standards and blanks were prepared from aliquots of perfusate that had not passed through the heart. Standards were prepared by adding 0.5 ml of perfusate plus 1.5 ml of distilled water directly to the scintillation fluid without passage through the column, whereas blanks were prepared by the passage of the perfusate aliquot through the resin columns.

After the perfusate or coronary effluent had been washed through the column with distilled water, the resin columns were again dried with the passage of compressed air. The scintillation vials were then spun to ensure complete mixing, wiped clean, and their radioactivity was determined by counting in a liquid scintillation counter (Beckman Instruments).

**Statistical Methods**

Data are presented as mean ± SEM. An unpaired t test was used to compare means between groups. A p value of less than 0.05 was considered significant.

**Results**

**Ventricular Fibrillation Thresholds During Acute Regional Ischemia**

Figure 1 shows the ventricular fibrillation thresholds in trained and control hearts before and after coronary artery ligation. At all times after coronary artery ligation, the ventricular fibrillation thresholds were significantly higher in hearts from trained rats (p < 0.05).

Table 1 is a list of additional observations made in these experiments. There were no differences in heart rates or coronary flow rates either before or after coronary artery ligation, and the infarct sizes expressed as a percentage of total left ventricular wet weights were similar in both groups. However, ventricular fibrilla-
In hearts dorff zone significantly lower in control than ligated hearts. Values are mean ± sem; numbers in parentheses indicate the number of measurements. Rats weighed 230–330 g; fresh weights of perfused hearts were 0.5–0.6 g.

**Abbreviation: VFT = ventricular fibrillation thresholds.**

Table 2 is a list of the tissue levels of ATP, phosphocreatine, glycogen, lactate and cyclic AMP in trained and control hearts clamped after 15 minutes of regional ischemia. The only significant difference was that tissue cyclic AMP levels were lower in the ischemic left ventricular zone of hearts from trained rats (p < 0.02). In hearts clamped after 15 minutes of Langendorff perfusion before determination of ventricular fibrillation thresholds, cyclic AMP levels were also significantly lower in trained hearts (0.21 ± 0.02 vs 0.28 ± 0.03 nmol/g, p < 0.03), whereas ATP and phosphocreatine levels were not different.

**Ventricular Fibrillation Thresholds During Hypoxia and During Hypoxia with Catecholamine Stimulation**

The ventricular fibrillation thresholds were significantly higher in hearts from trained rats during the control perfusions, during hypoxia, and during hypoxia combined with isoproterenol infusion (fig. 2).

Table 3 is a list of additional observations made during these experiments. There were no significant differences between trained and control rats in heart rates or coronary flow rates during either the control perfusions or during hypoxia or during hypoxia combined with isoproterenol infusion. There were also no significant differences in any metabolic measurements between hearts from trained and control rats (table 4).

**Ventricular fibrillation thresholds in trained hearts were significantly higher during control perfusions in this, but not in the first experimental series (fig. 1).** The rats used in this series of experiments had been trained for 12–16 weeks, whereas in the first study, the rats had been trained for 9–12 weeks. However, regression analysis failed to show a significant correla-

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**Table 1. Heart Rates, Coronary Flow Rates, Times to Decrease in Ventricular Fibrillation Thresholds and Infarct Sizes of Hearts from Trained and Control Rats Exposed to Acute Regional Ischemia**

|                  | Time to fall in VFT (min) | Control heart rates (beats/min) | Heart rates after 20 min regional ischemia (beats/min) | Control coronary flow rates (mL/min) | Coronary flow rates after 20 min regional ischemia (mL/min) | Infarct sizes (%)
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<tbody>
<tr>
<td>Trained rats</td>
<td>11.5 ± 1.0</td>
<td>185.3 ± 5.6</td>
<td>172.5 ± 8.4</td>
<td>7.9 ± 0.4</td>
<td>5.3 ± 0.4</td>
<td>36.9 ± 1.8</td>
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<tr>
<td>Control rats</td>
<td>8.4 ± 0.8</td>
<td>180.6 ± 6.1</td>
<td>172.4 ± 6.1</td>
<td>8.4 ± 0.6</td>
<td>5.1 ± 0.6</td>
<td>39.3 ± 3.3</td>
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<tr>
<td><em>p</em></td>
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<td>&lt;0.05</td>
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**Note:** The heart rates, coronary flow rates and infarct sizes are not different between trained and control hearts, but the mean time to the initial fall in VFT is significantly longer in trained hearts.

Values are mean ± sem; numbers in parentheses indicate the number of measurements. Rats weighed 230–330 g; fresh weights of perfused hearts were 0.5–0.6 g.

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**Table 2. Tissue ATP, Phosphocreatine, Glycogen, Lactate and Cyclic AMP Levels in Normal and Ischemic Zones of Hearts from Trained and Control Rats After 15 Minutes of Regional Ischemia**

<table>
<thead>
<tr>
<th></th>
<th>ATP (μmol/g)</th>
<th>PCr (μmol/g)</th>
<th>Glycogen (μmol glucose Eq/g)</th>
<th>Lactate (μmol/g)</th>
<th>cAMP (nmol/g)</th>
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<tr>
<td>Normal tissue</td>
<td></td>
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<tr>
<td>Trained rats</td>
<td>4.0 ± 0.1</td>
<td>5.8 ± 0.4</td>
<td>21.0 ± 1.1</td>
<td>1.4 ± 0.5</td>
<td>0.36 ± 0.1</td>
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<tr>
<td>Control rats</td>
<td>4.3 ± 0.5</td>
<td>6.1 ± 0.8</td>
<td>20.2 ± 1.2</td>
<td>2.1 ± 0.5</td>
<td>0.41 ± 0.1</td>
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<tr>
<td><em>p</em></td>
<td>NS</td>
<td>NS</td>
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</tbody>
</table>

**Ischemic tissue**

<table>
<thead>
<tr>
<th></th>
<th>ATP (μmol/g)</th>
<th>PCr (μmol/g)</th>
<th>Glycogen (μmol glucose Eq/g)</th>
<th>Lactate (μmol/g)</th>
<th>cAMP (nmol/g)</th>
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</thead>
<tbody>
<tr>
<td>Trained rats</td>
<td>2.9 ± 0.2</td>
<td>2.5 ± 0.5</td>
<td>18.1 ± 1.5</td>
<td>15.1 ± 2.0</td>
<td>0.38 ± 0.1</td>
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<tr>
<td>Control rats</td>
<td>3.5 ± 0.3</td>
<td>2.7 ± 0.6</td>
<td>17.4 ± 1.7</td>
<td>16.6 ± 3.2</td>
<td>0.48 ± 0.1</td>
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<tr>
<td><em>p</em></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Cyclic AMP levels are significantly lower in the ischemic left ventricular zone of trained hearts. Values are mean ± sem; numbers in parentheses indicate the number of measurements.

**Abbreviations:** PCr = phosphocreatine; cAMP = cyclic AMP.
during control perfusions, during hypoxia and during acute regional ischemia. The only previous report that has relevance to this study is that of Ammann et al., who reported that in response to acute circumflex coronary artery ligation, eight of eight untrained dogs developed ventricular fibrillation, whereas only eight of 16 trained dogs did so.

In this study, the increased thresholds in trained hearts during either acute regional ischemia or during hypoxia could not be explained on the basis of differences in heart rates, in coronary flow rates, or in tissue levels of high-energy phosphates, glycogen or lactate. There was also no evidence that, in this model, exercise training caused reduced infarct sizes in response to coronary artery ligation, as reported by McElroy et al., or increased coronary flow responses to hypoxia, as reported by Spear et al.

Cyclic AMP accumulation in the ischemic left ventricular zone was, however, significantly less in trained hearts, a finding consistent with the work of Kleitke et al., who reported that in response to acute global ischemia, hearts from swimming-trained rats had significantly lower cyclic AMP levels than those from control rats. In view of the hypothesis linking myocardial cyclic AMP levels and ventricular fibrillation thresholds in this model, decreased formation of myocardial cyclic AMP in response to coronary artery ligation in trained animals would explain the beneficial effects on ventricular fibrillation thresholds caused by exercise training.

Cyclic AMP levels were significantly lower in trained hearts during the control perfusion. Although in absolute terms these changes were small, changes of a similar magnitude have been used to explain the antiarrhythmic effects of amiodarone in the same isolated heart preparation. The possibility that cyclic AMP is compartmentalized within the heart cell could explain why relatively small changes in cyclic AMP might have relatively large effects. On the other hand, cyclic AMP changes could not explain the differences in ventricular fibrillation thresholds between trained and control rats when the hearts were exposed to hypoxia and isoproterenol infusion, although these values, measured after 30 minutes of hypoxic perfu-

**Discussion**

These studies show that ventricular fibrillation thresholds are increased in hearts from trained animals

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**Figure 2.** Effect of hypoxia and hypoxia combined with isoproterenol infusion on ventricular fibrillation thresholds of trained and control hearts. At all times, ventricular fibrillation thresholds are higher in trained hearts.

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**Table 3.** Heart Rates and Coronary Flow Rates of Hearts from Trained and Control Rats During Control Perfusions and During Hypoxia

<table>
<thead>
<tr>
<th></th>
<th>Control heart rates (beats/min)</th>
<th>Heart rates during hypoxia (beats/min)</th>
<th>Heart rates during hypoxia plus isoproterenol infusion (beats/min)</th>
<th>Control coronary flow rates (ml/min)</th>
<th>Coronary flow rates during hypoxia (ml/min)</th>
<th>Coronary flow rates during hypoxia plus isoproterenol infusion (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trained rats</td>
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<tr>
<td></td>
<td>187.4 ± 6.9</td>
<td>198.3 ± 12.4</td>
<td>274.8 ± 17.7</td>
<td>7.5 ± 0.5</td>
<td>15.7 ± 0.8</td>
<td>21.7 ± 0.8</td>
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<tr>
<td>Control rats</td>
<td>198.8 ± 8.5</td>
<td>184.8 ± 11.3</td>
<td>252.4 ± 11.3</td>
<td>8.4 ± 0.5</td>
<td>16.0 ± 1.7</td>
<td>21.1 ± 1.2</td>
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<td><em>p</em></td>
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</table>

Values are mean ± SEM; numbers in parentheses indicate number of measurements.
sion, may not have been representative of the levels that were present after 20 minutes of perfusion, when ventricular fibrillation thresholds were lowest (fig. 2).

The mechanisms whereby exercise training reduces the resting levels of cyclic AMP and its accumulation during ischemia could include reduced catecholamine turnover at rest and in response to ischemia, increased parasympathetic activity, or alterations in the density of β-adrenergic receptors. Ostman et al.23 found that the rates of myocardial noradrenaline turnover measured both at rest and during exercise in hearts of swimming-trained rats were half those of control rats, but similar studies have not been performed under ischemic conditions. An increase in parasympathetic tone has been found in some athletes, to such an extent that varieties of conduction abnormalities have been reported.24 Radioligand binding studies have shown that there is no alteration in either β-adrenergic or muscarinic cholinergic receptor numbers or affinities after swimming training;25 no data are available on running rats.

Whatever the mechanism for the reduced levels of cyclic AMP in trained hearts during ischemia, a consequence may be reduced calcium ion entry by the slow calcium current.26 Thandroyen27 showed that calcium ions may be important in the genesis of ventricular fibrillation. Further investigations on the effects of running training on calcium ion flux in the ischemic heart are warranted. Under conditions of maximal heart work, we found indirect evidence for increased trans-sarcolemmal calcium entry10,11 in trained hearts.

The finding that exercise training increased myocardial resistance to ventricular fibrillation in this model may not be applicable to man, in whom ventricular fibrillation occurs spontaneously and not in response to exogenous electrical stimulus. Nevertheless, these data from animal studies give experimental support for the epidemiologic data linking exercise training with decreased sudden cardiac death.3-5,7,8

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The Response to Procaainamide During Electrophysiologic Study for Sustained Ventricular Tachyarrhythmias Predicts the Response to Other Medications

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SUMMARY We evaluated 126 patients with inducible sustained ventricular tachyarrhythmias to assess whether the response to procaainamide during electrophysiologic study could predict responses to other conventional antiarrhythmic agents and combinations of agents. Thirty of 42 patients in whom ventricular tachycardia was not inducible after the administration of procaainamide and 69 of 84 patients in whom ventricular tachycardia was inducible after procaainamide underwent serial electrophysiologic studies. Forty-three of 67 antiarrhythmic regimens (64%) tested in the patients in whom ventricular tachycardia could not be induced after procaainamide prevented induction of ventricular tachycardia, compared with 10 of 145 regimens (7%) tested in the patients in whom ventricular tachycardia could be induced after procaainamide. Sixty of the 69 patients in whom ventricular tachycardia remained inducible after procaainamide had ventricular tachycardia induced on all other conventional antiarrhythmic regimens tested. By comparison, of the 30 patients in whom ventricular tachycardia became noninducible after procaainamide, 25 had no ventricular tachycardia inducible on at least one other antiarrhythmic regimen tested. Thus, the response to procaainamide accurately predicted the response to other conventional antiarrhythmic agents during electrophysiologic study.

Programmed ventricular stimulation can be used to guide antiarrhythmic drug therapy in patients with sustained ventricular tachyarrhythmias. However, repeated testing of multiple antiarrhythmic agents may be required to design effective therapy. These repeated studies are expensive, time consuming and difficult for patients.

Procaainamide is a frequently used antiarrhythmic drug for treating ventricular arrhythmias. High doses are often required to control sustained ventricular tachyarrhythmias. Previous studies in our laboratory have demonstrated that procaainamide is the most successful of standard agents for preventing inducible ventricular tachycardia. The present study was therefore undertaken to determine whether the response to procaainamide could predict the response to other conventional antiarrhythmic agents using electrophysiologic studies in patients with inducible sustained ventricular tachyarrhythmias.

Methods

Patients The patient population consisted of 107 men and 19 women, ages 16-77 years. Cardiac diagnoses included atherosclerotic heart disease in 107 patients, 102 of whom had prior myocardial infarction, 57 with left ventricular aneurysm. Other diagnoses included cardiomyopathy in six patients, tetralogy of Fallot in one patient, mitral valve prolapse in three patients, arrhythmogenic right ventricular dysplasia in one patient, sarcoidosis with left ventricular aneurysm in one

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Physical training increases ventricular fibrillation thresholds of isolated rat hearts during normoxia, hypoxia and regional ischemia.

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Circulation. 1983;67:24-30
doi: 10.1161/01.CIR.67.1.24

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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