Effects of Physical Training in Dogs with Coronary Artery Ligation

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SUMMARY
This experiment was designed to determine whether physical conditioning can be achieved in the presence of acute myocardial infarction and whether such an exercise program is harmful. For this purpose the effects of a 5-weeks' treadmill-exercise program and inactivity were compared in two groups of dogs in which acute myocardial infarction was produced by coronary artery ligation.

The exercised group of animals tolerated the training program well, and neither arrhythmia nor sudden death occurred. At the end of the training program the exercised group of animals displayed the characteristic changes of physical conditioning, namely, reduction in exercise heart rate, cardiac output, and blood lactate levels; rise in circulating epinephrine levels with exercise was also suppressed by conditioning.

Postmortem examination revealed neither ventricular dilatation nor aneurysm formation.

Additional Indexing Words:
Acute myocardial infarction
Enzyme changes

PATIENTS with coronary artery disease are often encouraged to engage in physical activity and even to participate in exercise programs in the belief that this may improve coronary circulation and reduce the frequency and severity of anginal attacks. However, patients with acute myocardial infarction are customarily kept at rest during the acute phase of the illness because it is assumed that physical exertion may provoke ventricular arrhythmias and congestive heart failure or predispose to ventricular aneurysm formation and myocardial rupture. Jetter and White\(^1\) reported a high incidence of cardiac rupture in patients with unrecognized myocardial infarction who were inmates of a mental institution and who remained active during the acute attack. In addition, there are several case reports suggesting that exertion may precipitate myocardial infarction, arrhythmias, and even sudden death.\(^2-5\)

There is a paucity of experimental studies evaluating the effects of exercise in the presence of acute myocardial infarction. In a small series of dogs subjected to coronary artery ligation, Sutton and Davis\(^6\) noted that daily exercise led to ventricular aneurysm formation. However, this conclusion was based on five animals, four being exercised within 3 days of ligation. On the other hand, Thomas and Harrison\(^7\) have suggested that early exercise is without hazard and compared to complete rest may even be beneficial. They studied the effect of activity level...

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upon mortality in rats that had been subjected to thermal injury of the myocardium. Control and exercised rats showed the same mortality, whereas complete restriction of activity in a small cage led to a significantly higher death rate. Other experimental studies suggest that the coronary circulation may be improved by an exercise program. Eckstein has shown that physical training enhances collateral flow in the presence of regional ischemia. The studies of Tepperman and Pearlman and of Stevenson and associates indicated that chronic exercise stimulates growth of the coronary vascular tree even in the absence of ischemia.

Further understanding of the influence of physical exertion upon the course of myocardial infarction must take into account the known effects of physical training. In the normal person, physiological adaptations ensue that operate to decrease the work load of the heart. For a given level of external work performance, physical training results in a progressive reduction in heart rate, cardiac output, and oxygen consumption.

Thus, physical training may possibly benefit the individual with myocardial damage by increasing coronary collateral blood flow, by accelerating the healing process, and by reducing the work load of the remaining healthy myocardium. A few recent reports have indicated that physical conditioning programs for patients who have had myocardial infarction are feasible and safe. However, such programs are begun usually within a month or more after the acute episode.

The present experimental study in animals was designed to determine whether physical conditioning is possible in the presence of acute myocardial infarction, and whether such an exercise program has any adverse effects.

Methods

Experiments were conducted in two groups of animals: 25 mongrel dogs, weighing between 14.5 and 23 kg, and 15 pedigreed coonhounds, weighing between 17.5 and 22 kg. The study consisted of four phases: (1) coronary artery ligation; (2) preliminary exercise testing with allocation of the animals into control and trained groups; (3) daily exercise for half of the animals (trained group) and inactivity for the other half (control group); and (4) final studies carried out in the two groups 5 weeks after the coronary ligation. These last studies included an exercise test, hemodynamic evaluation, coronary angiograms, and postmortem examination.

Coronary artery ligation was carried out as follows: Dogs were anesthetized with 30 mg/kg of pentobarbital and ventilated with a Harvard pump through a cuffed endotracheal tube. The chest was opened through the fourth intercostal space, and the anterolateral aspect of the heart was exposed. A 2.6-mm outer diameter polyvinyl catheter was introduced into the main pulmonary artery via the right ventricular outflow tract. The catheter was fixed to the myocardium by sutures, brought out through the thorax, and thence passed through a subcutaneous tunnel to an exit point in the nape of the neck, where it was secured by a dressing. The left anterior descending coronary artery was exposed and ligated 2.0 cm distal to its origin by the two-stage procedure. This procedure ordinarily results in infarction of about 15 to 30% of the left ventricle. In most animals procaine amide (300 mg) and lidocaine (150 mg) were given in divided doses during the ligation procedure. After operation the electrocardiogram was monitored for 24 hours. Blood was drawn from the pulmonary artery for determination of serum lactic dehydrogenase (SLDH) before and 24 hours after the operation. Both total and heat-stable fraction of SLDH were measured by the method of Bell. A complete electrocardiogram (ECG) was recorded daily for 1 week and once a week thereafter. Eleven animals died during the operation and in the immediate postoperative period. The remaining 29 animals entered the second phase of the experiment.

Two days after the operation all dogs were tested briefly on a Collins high-speed treadmill. Three animals would not run on the treadmill, and so were excluded from the study. The remaining 26 dogs entered the third phase of the experiment.

During the first week after coronary ligation all animals participated in a preliminary exercise test. In 19 animals this was carried out on the third day after ligation, but in seven animals this was delayed for technical reasons until the sixth day after ligation. Exercise consisted of running on the treadmill for 30 minutes at a speed of 4 miles per hour (mph), and at an incline of 10%. During this test all animals were in the postabsorptive state. Blood was drawn before and 5 minutes after exercise for determination of total and heat-stable SLDH. A Sanborn plate electrode and cable system was attached...

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to the animals, and the ECG was monitored on an oscilloscope screen before, during, and after the exercise. Tracings were recorded at fixed time intervals during the entire procedure.

After the exercise test the animals were divided randomly into the trained and control groups. Control animals were kept in cages and were not exercised. The trained group was exercised twice daily, 6 days a week, for a period ending 5 weeks after the coronary occlusion. Each exercise period again consisted of running on the treadmill for 30 minutes at a speed of 4 mph, and at an incline of 10%. The ECG was monitored during exercise once weekly, and on the same day blood was drawn for SLDH determination before and after exercise. Two animals in the trained group and one animal in the control group were dropped from the study during this period for intercurrent disease unrelated to the heart.

Five weeks after coronary ligation the 12 control dogs were once again subjected to the treadmill exercise test, and their performance was compared with the trained group. All animals were again in the postabsorptive state. A number 14 intracath was introduced through the right external jugular vein into the superior vena cava. The ECG was once again monitored throughout the entire exercise test, and tracings were recorded at fixed time intervals. Blood was drawn from the pulmonary artery catheter for the determination of SLDH and plasma epinephrine and norepinephrine before and at the end of the exercise. The method of Anton and Sayre was used for the determination of plasma catecholamines. Blood samples were also drawn for measurement of lactic acid prior to and at 2, 5, 10, and 30 minutes of exercise. Lactic acid was measured by the method of Barker and summerson. In 13 animals cardiac output was determined before and during the exercise by the dye-dilution technique. Indocyanine-green dye was injected into the superior vena cava, and blood was withdrawn from the pulmonary artery catheter through a densitometer. Cardiac output measurements were carried out in triplicate at rest prior to exercise, and every 5 minutes during exercise.

On the day following the final exercise test all animals were anesthetized with 30 mg/kg of pentobarbital. Ventilation was maintained by means of a Harvard pump. Number-7F Courand catheters were introduced into the left ventricle, thoracic aorta, and right atrium. Pressures were monitored† and recorded. A number-7F fiber-optic catheter was introduced into the thoracic aorta for cardiac output determination by the dye-dilution technique. The following were measured: heart rate, aortic and right atrial pressures, cardiac output, the peak of the first derivative of left ventricular pressure (dp/dt), and left ventricular end-diastolic pressure (LVEDP). Peripheral vascular resistance (PVR) was calculated from the formula:

\[
PVR \text{ in dynes sec cm}^{-5} = \frac{\text{aortic mean pressure in mm Hg} - \text{right atrial mean pressure in mm Hg}}{80/\text{cardiac output in L/min}}
\]

Cardiac index was calculated by correcting cardiac output for body surface area (BSA) by the formula:

\[
\text{BSA in m}^2 = (0.112)(\text{weight in kg})^{2/3}
\]

After the hemodynamic studies were completed a number-7 Sones catheter was introduced into the aortic root, and three or more selective left coronary cineangiograms were carried out. Three cubic centimeters of 60% Hypaque were injected each time, and films were taken at 30 frames per second. The animals were then sacrificed, and the heart, lungs, and liver excised. The coronary arteries were injected at 150 mm Hg with gelatin barium sulfate, and postmortem coronary angiograms were made. The organs were then fixed in Formalin and examined macroscopically and microscopically. The pathologist who examined the specimens was not aware whether they came from trained or control animals.

Data in the text and tables are expressed as mean ± SEM. Statistical analyses were carried out with the t-test of Student.23

**Results**

The entire study was completed on 23 animals, 11 in the trained group and 12 in the control group. The trained group contained four coonhounds, and the control group five. These pedigreed animals gave results similar to those of the mongrel dogs, and the data on the two types of animals are combined.

All animals that survived the operation and the postoperative period developed typical enzyme and ECG changes of acute myocardial infarction. The preoperative level of SLDH in the 29 surviving animals was 18 ± 3 units, rising 24 hours after coronary ligation to 139 ±

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*Gilford Instruments Co.

†Sanborn 267BC pressure transducers.

‡Electronics for Medicine model DR-8 recorder.

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after exercise. However the heat-stable fraction changed only from 6 ± 1 to 12 ± 2 units (fig. 1). This rise in SLDH in the trained group became less marked within 2 weeks after the first exercise test, approximating the changes observed in this laboratory in normal sham-operated dogs under similar exercise loads. At the end of the experimental study, during the final exercise test, the SLDH rise was similar in the two groups: Resting levels were 19 ± 3 units in the trained group and 17 ± 3 units in the controls, rising with exercise to 36 ± 6 units and 46 ± 6 units, respectively. The trained group completed the exercise program without complications. Fatal arrhythmias never occurred. There was no mortality in either group related to the coronary ligation or the training program. At the end of the conditioning period the trained animals displayed physiological adaptations to chronic exercise in the three parameters studied, which were heart rate, cardiac index, and blood levels of lactic acid. Differences between the two groups were observed also in the response to exercise of blood epinephrine levels.

Heart Rate

There was no difference between the 11 trained and the 12 control dogs in their response to exercise before the training period. However, at the end of the exercise program, trained dogs had a lower heart rate than the controls, both at rest and during exercise. As shown in figure 2, resting heart rate was 92 ± 3 in the trained and 112 ± 3 in the control group (P < 0.01), and during exercise the values were 174 ± 6 and 207 ± 6, respectively (P < 0.01). This reduction in heart rate with training was a gradual process (fig. 2).

Cardiac Index

Cardiac index was measured during the final exercise test in eight trained and five control dogs (fig. 3). Resting values were not significantly different. However, during exercise cardiac index in the trained dogs was significantly lower than that in the controls (8.65 ± 0.16 and 11.25 ± 0.55 L/min/m², respectively; P < 0.01).

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**Figure 1**

Total and heat stable SLDH in 23 dogs at rest and immediately after treadmill exercise, carried out 3 to 6 days after coronary artery occlusion.

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14. Heat-stable SLDH rose from 7 ± 2 to 58 ± 12. The ECG showed pathological Q waves in leads I, II and aVL, and in the left chest leads in every animal.

On the first day of exercise all animals successfully completed the 30-minute period on the treadmill without evident distress. Arrhythmias, collapse, and sudden death did not occur. However, a transient phase of ventricular irritability developed immediately after cessation of exercise. The only other observation suggesting a possible deleterious effect from exercise was a marked rise in total SLDH, which increased from a resting level of 20 ± 3 units to 126 ± 33 units immediately after exercise.
Figure 2
The response of heart rate in 11 trained and 12 control animals is compared during various phases of the experiment. While the resting heart rate (R) and rate during exercise (E) is unaltered in the control group, there is a progressive reduction in both rates in the trained group.

Figure 3
Cardiac index at rest and during treadmill exercise in five control and eight trained dogs 5 weeks after coronary artery occlusion.

Lactate Production
At rest prior to the final exercise test there was no significant difference between blood levels of lactate in 10 control and 11 trained dogs studied. The pattern of change in lactate level during exercise was identical in both groups, showing an immediate rise to a peak at 2 minutes of exercise, and thereafter dropping to a lower level as exercise proceeded (fig. 4). However, control dogs showed a significantly greater rise in lactate during exercise than the trained animals, the...
peak levels being $2.97 \pm 0.73$ mM/L in the control group and $1.30 \pm 0.24$ mM/L in the trained group ($P = 0.05$).

**Catecholamines**

Resting plasma levels of epinephrine and norepinephrine were the same in the nine trained and the seven control dogs studied. Exercise caused a rise in both amines (fig. 5). Changes in norepinephrine were comparable in both groups; however, the rise in epinephrine was significantly greater in the control dogs (from $0.16 \pm 0.06$ micrograms/L to $0.96 \pm 0.10$ micrograms/L) than in the trained animals (from $0.15 \pm 0.02$ micrograms/L to $0.22 \pm 0.07$ micrograms/L; $P < 0.01$).

While these physiological studies in the awake animal showed differences between the trained and the control dogs in almost all parameters investigated, the hemodynamic studies subsequently performed under anesthesia and the angiographic and pathological evaluations did not. The results of these hemodynamic measurements are summarized in table 1. Anesthesia produced sinus tachycardia and abolished the difference in resting heart rate in the two groups. The mean value for LVEDP was higher in control animals than in trained animals, but this difference was not significant ($0.05 < P < 0.10$). However, three of the control animals had LVEDP values of 23.5, 14.3, and 14.8 mm Hg, whereas the highest value observed in a trained animal was 10.3 mm Hg. Aortic pressure, cardiac index, right atrial pressure, peripheral vascular resistance, and dp/dt did not differ in the two groups.

Selective coronary cineangiography of the left coronary artery showed a marked collateral flow from the posterior descending artery to the distal end of the ligated vessel.
This was seen in all animals, and no difference was found between the two groups (fig. 6).

On examination of the postmortem coronary angiograms and the macroscopic and microscopic specimens, the pathologist could not detect any difference between the trained and the control dogs. All animals showed collateral channels from the posterior descending coronary artery to the distal end of the ligated vessel. A few connecting arteries were observed coming from the right coronary artery branches in three dogs (two trained and one control). The scar was well formed and appeared the same in the two groups. The mean size of the infarct was 9.0 g (range 3.0 to 22.0) in the trained dogs and 8.8 g (range 2.0 to 18.0) in the controls. These figures cannot, however, be taken to represent the amount of myocardium originally infarcted, since considerable shrinkage occurs over a period of several weeks. There was a difference of borderline significance between total heart weight in the two groups. In the trained dogs this was 7.86 ± 0.30 g/kg, and in the control group 6.97 ± 0.21 g/kg (0.05 < P < 0.10).

Discussion

The results of this study show that animals with acute myocardial infarction can undergo physical conditioning without deleterious effects, when such conditioning is begun 3 days or more after ligation of the left anterior descending coronary artery. During the exercise program, arrhythmias were not observed and sudden death did not occur. Despite the presence of acute myocardial necrosis, the characteristic adaptations of physical training were observed, namely, reduction of heart rate, cardiac index, and blood levels of lactic acid during exercise.

Lindhard24 and Dawson25 showed that physical training is associated with slowing of the heart rate, both at rest and during exercise; this was confirmed in the extensive literature that followed these early reports.13, 26-30 Whether this reduction in pulse is beneficial in the presence of coronary insufficiency is uncertain; however, it may indicate that the oxygen requirement of the heart is reduced. Fried31 and Bohnenkamp and associates32 studied the oxygen consumption of the frog heart and found it to be closely correlated with rate. The amount of oxygen consumed by the myocardium during a single beat has been shown to depend upon a variety of hemodynamic factors.33, 34 With large changes in heart rate, such as occur in exercise, myocardial oxygen consumption, as shown by Sheffield and Reeves, is determined primarily by the rate.35 Thus, rate reduction from physical training may reflect an oxygen-sparing effect on the heart both during body rest and exercise.

The mechanism by which slowing of the pulse is achieved is not fully understood. Kauf46 suggested that increased vagal tone with physical training may be important. Indirect support for this thesis may be found in case reports describing the Wenckebach phenomenon appearing in the recovery period after physical exertion in trained individuals.47, 48 A reduction in the activity of the sympathetic nervous system may also occur, as suggested by the diminished blood epinephrine levels following exercise observed in the trained dogs in the present series (fig. 5).

There is general agreement concerning the effects of physical training on lactic acid production. Bock and associates30 and Dill and associates39 found that lactate production is higher in untrained than in trained individuals for the same exercise load. This has been confirmed both in clinical and experimental studies.40, 41 Published reports concerning the cardiac output response to physical training are more contradictory. Lindhard24 and Collet and Liljestrand42 suggested that physical training reduces the cardiac output for a given exercise load. This was later substantiated13, 26 as well as contradicted.28, 50 In a recent study, Varnauskas and associates41 subjected nine coronary patients to a physical training program. All patients improved clinically, and all showed a marked reduction in lactate production and cardiac output during...
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exercise as compared to levels reached before training.

The alterations produced by physical training in lactate production and cardiac output during exercise imply a reduction in energy requirements by the whole body. In fact, it has been demonstrated that physical conditioning reduces total body oxygen requirement for a given amount of exercise.\textsuperscript{11} Although oxygen consumption was not measured in the present study, reductions in cardiac output response and blood levels of lactate with exercise in trained animals are consistent with this observation.

A rise in urinary catecholamines with physical exertion was described by Hartman and associates\textsuperscript{43} and later confirmed by Raab\textsuperscript{44} and by von Euler.\textsuperscript{45} Gray and Beetham\textsuperscript{46} found a similar rise in blood catecholamines with exercise, but only blood norepinephrine levels increased consistently; the response in athletic and sedentary individuals was similar.\textsuperscript{46} The observations recorded in the present study in dogs are unique. Both epinephrine and norepinephrine blood levels increased with exercise; however, epinephrine levels rose much higher in controls than in trained animals, whereas the norepinephrine response was similar in the two groups. The significance of these findings is uncertain, but may indicate reduction in sympathetic nervous system activity with training.

Physical exertion in normal individuals is known to raise the serum levels of lactic dehydrogenase, including the heat-stable fraction, along with other enzymes such as malic dehydrogenase, creatine phosphokinase, and the transaminases.\textsuperscript{47–50} These changes are transient, are related to the severity of the exercise, and become less pronounced after a period of physical training.\textsuperscript{47, 50} In the present study, elevation of SLDH was also observed following exercise; however, the very marked increases in SLDH noted when exercise was carried out shortly after ligation were most probably related to the coronary occlusion. Within 2 weeks after coronary ligation the exaggerated response disappeared, and at the time of the final exercise test, both trained and untrained animals showed a modest rise in SLDH comparable to that seen in normal animals. The tissue source of this excessive rise in enzymes shortly after ligation is unknown. Evidently, it is not from heart muscle, since the heat-stable fraction of SLDH rose only slightly. It may reflect ischemia or congestion of other organs such as liver or skeletal muscle.

The complete hemodynamic studies performed under anesthesia and the angiographic and pathological studies indicate that the dogs with coronary artery ligation were not harmed by the training program in any detectable way. In fact, it was impossible to differentiate between the two groups in any of these studies. Detection of elevated LVEDP in three of the control dogs may possibly indicate that physical training hastens recovery of abnormalities in left ventricular function following coronary ligation.\textsuperscript{51}

The studies of Eckstein\textsuperscript{8} and others\textsuperscript{9, 10} indicate that exercise promotes the formation of collateral vessels and improves collateral flow in the presence of myocardial ischemia due to coronary artery stenosis. The present study employed the technique of complete coronary occlusion, which resulted in extensive collateral formation in both control and trained animals. It was not possible to demonstrate either by selective cineangiography or by postmortem coronary injections any differences in the two groups. Thus, it appears that exercise may not enhance collateralization when a large vessel is totally occluded.

The training program did not produce thinning of the healed scar or formation of aneurysms, such as those previously described.\textsuperscript{6} The pathologist could not differentiate grossly or microscopically between the hearts or other organs of trained and control animals.

Current practice is to keep all patients with acute myocardial infarction at complete inactivity for varying periods of time. There is no evidence that such restriction in exercise is either necessary or beneficial. It is inviting to extrapolate from the results of animal experiments, such as reported here, to the human condition. However, the healthy
animal with an artificially induced acute occlusion at only one locus in a coronary vessel is hardly comparable to the patient whose disease has progressed over years and with a diffuse process usually involving the entire coronary tree. Furthermore, species differences in anatomy of coronary vasculature and the speed and extent of collateral formation prevent translation of these results to clinical practice. They emphasize, however, the need for further critical examination of the role of activity in various stages of coronary artery disease.

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References

25. DAWSON, P. M.: Effect of physical training and practice on the pulse rate and blood pressures.
during activity and during rest, with a note on certain acute infections and on the distress resulting from exercise. Amer J Physiol 50: 443, 1920.
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