Effect of Exercise on Acute Myocardial Infarction in Rats

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Infarct expansion, the time-related thinning and dilation of an acute transmural infarct, leads to aneurysm formation and cardiac rupture in humans. In this study, the effect of exercise on acute infarct expansion early after myocardial infarction was examined in 129 rats. Ninety rats were exercised on a treadmill for 1.5 hours daily for 1 week beginning on the day of coronary artery ligation; the remaining 39 rats remained in their cages. There was no effect on the prevalence or extent of expansion; specifically, infarct wall thickness, left ventricular diameter and expansion grade (0 to 4+) were similar in the exercise and control rats. There was no difference in infarct size or the number of animals with aneurysmal shape changes in the exercise and control groups. There was no significant difference between the two groups in the histologic finding of intramural hemorrhage, a feature that has been associated with cardiac rupture, and no complete rupture was seen. However, there was a nonsignificant trend toward higher mortality in the exercised group.

Thus, the findings of this study suggest that moderate exercise early after myocardial infarction produces no significant detrimental effect on infarct size or left ventricular topography in the rat model.

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The treatment of patients with coronary artery disease has changed dramatically from the traditional program of prolonged bed rest for patients after myocardial infarction to the current trend toward early ambulation, rehabilitation exercise programs and early exercise testing before hospital discharge. The conservative treatment of the past was based on retrospective autopsy series showing increased incidence of aneurysm formation and rupture in ambulatory patients (1–3), increased incidence of arrhythmias and experimental evidence in dogs of aneurysm formation with exercise (4). This latter study, however, included only five exercised dogs, and a subsequent study failed to demonstrate aneurysm formation in exercised dogs (5).

Recent studies have shown no change in mortality of patients after infarction who have undergone supervised low level activity (6–9) and no increase in mortality with early exercise testing (10,11). However, the safety of exercise after infarction is controversial and the effect of exercise on alterations in shape of the left ventricle that occur early after infarction, such as acute infarct expansion and aneurysmal dilation, have not been examined. To study this, we used a rat model of myocardial infarction known to produce extensive transmural myocardial infarction with an incidence of infarct expansion and aneurysm formation that is similar to that of humans (12–14) with transmural infarction.

Methods

Infarct model. Infarction was produced by left coronary artery ligation in female Sprague-Dawley rats weighing 200 to 300 g by a modification of previously described methods (12,15,16). The rats were anesthetized with 35 mg/kg body weight methohexital sodium (Brevitol) administered intraperitoneally. A left thoracotomy was performed in the fifth or sixth intercostal space. Intermittent positive pressure ventilation with 95% oxygen and 5% carbon dioxide was accomplished. A pericardiotomy was performed and the left main coronary artery was occluded by snaring and tying a band of myocardium within 2 to 3 mm to the left of the aorta and ligating it with 5-0 silk sutures. Because the left main coronary artery is an intramyocardial structure (15), the snared myocardium did not always include a coronary artery. Those animals in which ligation was unsuccessful were used as controls. The chest was closed with a 4-0 silk purse-string suture and 100,000 U of benzathine penicillin...
granulation and scar tissue. Infarct size data were analyzed using two formulas. The histologic sections were projected on a sheet of paper at 10× magnification, and infarcted and noninfarcted left ventricular areas were traced. The areas of the traced images were determined by planimetry using a digitizing computer program (Hewlett-Packard 9810A calculator with a 9864A digitizer). The mass of infarcted and noninfarcted myocardium was obtained by multiplying cross-sectional area by slice thickness; the value was expressed per kilogram of body weight. Body weight was similar in all groups and did not change significantly before and after exercise.

The following two formulas were used to calculate infarct size in all animals:

**Formula 1:**

$$\text{100%} \times \left( 1 - \frac{\text{Noninfarcted LV mass/kg body wt}}{\text{Control* LV mass/kg body wt}} \right)$$

**Formula 2:**

$$\text{100%} \times \left( \frac{\text{Infarcted LV mass}}{\text{Infarcted and noninfarcted LV mass}} \right)$$

where LV = left ventricular and wt = weight. Fourteen rats without an infarct in the exercise group (see later) were used to establish norms of left ventricular mass for the exercise group. Four rats without an infarct in the unexercised group (see later) and 20 rats from a previous series were used to establish norms for the unexercised group. Hearts were included in the control* (no infarct) group if they had no necrosis or only minimal epicardial necrosis at the suture site.

**Left ventricular diameter measurements** were made at the point of maximal dilation perpendicular to the septum in each slice (Fig. 1) as previously described (13), and normal values were established for the 14 exercised and 20 unexercised rats without an infarct. The percent change from control left ventricular diameter was calculated for each section in all experimental animals, and the slice with the largest percent increase was used for each animal in the analysis. The final apical slice was excluded, because the control left ventricular diameter was so small and variable that percent changes were markedly exaggerated. Infarcted free left ventricular wall thickness was measured at the thinnest representative point in one mid-left ventricular slice, and septal thickness was measured in the same slice. The degree of infarct expansion also was graded by a method previously described (12): 0 = none; 1+ = mild thinning; 2+ = mild thinning and dilation; 3+ = moderate thinning and dilation; and 4+ = marked thinning and dilation. Interoobserver variation did not exceed one expansion grade and was 95% concordant.

*In this formula, control left ventricular mass represents the left ventricular mass of rats that had no myocardial infarct.
Statistical analysis. Infarct size, left ventricular free wall and septal thickness and percent increase in left ventricular diameter were compared using the unpaired Student's t test. Regression analysis was used to assess left ventricular infarcted wall thickness to infarct size ratio for both groups, and the exercise and unexercised control group slopes and intercepts were compared.

The distribution of grades of expansion for small, moderate, large and all infarcts were compared using chi-square analysis. Mortality data and prevalence of specific histologic findings in the control and exercise groups were compared using chi-square analysis.

Results

Study groups. One hundred ninety-three rats underwent attempted coronary artery ligation. The operative mortality rate was 6%. Twenty-three rats developed infection at the suture site, resulting in purulent epicarditis with or without abscess formation, and were excluded from the analysis. Eighteen rats were found at sacrifice to have no infarct (unsuccessful coronary ligation): 14 in the exercise group and 4 in the control group. Ninety-nine rats with an infarct were exercised and 41 rats with an infarct were not exercised and served as controls. Nine exercise rats (9%) died, four of them less than 24 hours after infarction and five (5%) later than 24 hours. Two control rats (5%) died, both less than 24 hours after infarction (p = NS). Of the five exercised animals that died later than 1 day after infarction, three died on the treadmill, two with a large transmural infarction and one with diffuse contraction band necrosis.

Morphologic observations. Of the 39 control rats, 2 (5%) had an infarct that was nontransmural, compared with 5 (6%) of 90 in the exercise group (p = NS). At Day 7 all infarcts had central necrotic fibers surrounded by granulation tissue. Histologic infarct extension was present in 8 (9%) of the 90 exercised rats and 1 (3%) of the 39 control rats. These differences were not significant although there was a trend toward more extension in the exercised groups. Extension was characterized by contraction band necrosis at the margin of the infarct that appeared younger than the age of the infarct.

Intramural hemorrhage was seen in 22 (24%) of the 90 exercised rats and 8 (21%) of the 39 control animals (Fig. 2). Two animals in the exercise group had histologic findings similar to Fig. 2.

Figure 3. Distribution of expansion grades (0 to 4+) for control (top) and exercise (bottom) group rats. Number within each bar indicates number of animals with that expansion grade.

Table 1. Infarct Size (% left ventricle)

<table>
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<tr>
<th></th>
<th>Control Group</th>
<th>Exercise Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated by formula 1</td>
<td>25.1 ± 3.9</td>
<td>22.4 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Calculated by formula 2</td>
<td>25.2 ± 1.8</td>
<td>21.6 ± 1.1</td>
<td>NS</td>
</tr>
</tbody>
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Values are expressed as mean values ± SEM.

Figure 2. Myocardial infarct (7 days) in an exercised rat showing intramural hemorrhage (arrows) and necrotic myocardial fibers (M) surrounded by granulation tissue. This infarct is 2+ expanded. (Hematoxylin-eosin stain; original magnification × 40; reduced by 50%.)
consistent with "prerupture," or striking fiber splits with intramural hemorrhage. No animal sustained cardiac rupture.

**Infarct size (Table 1).** Infarct sizes calculated by measuring infarcted mass as a percent of left ventricular mass, or residual myocardium as a percent of control (hearts with no infarct) left ventricular mass were the same, suggesting that neither the net tissue resorbed nor residual myocardial hypertrophy was significant enough to affect the calculations. If there was tissue resorption exactly proportional to hypertrophy of uninfarcted myocardium, the two methods of infarct size calculations would fortuitously produce the same values. The infarct size derived from the former method was used in the subsequent analyses. Mean infarct size was the same in the control and exercised animals, showing that there was appropriate randomization. There was no difference in the percentage of hearts showing expansion (67% of exercise group versus 72% of control group), and there was no difference in the extent to which the infarcts expanded (0 to 4+). Exercise and control subgroups also were classified according to infarct size: small = 10% or less of the left ventricle, medium = 10 to 25% of the left ventricle and large = 25% or more of the left ventricle. There was no difference between the exercise and unexercised groups in the prevalence or extent of expansion in any subgroup (Fig. 4).

**Mean infarcted wall thickness** of control rats was 0.9 ± 0.5 versus 1.1 ± 0.6 mm of exercised rats (p = NS). Mean percent increase in left ventricular diameter was 28 ± 28% for control rats versus 19 ± 21% for exercised rats (p = NS). There was a small but statistically significant difference between noninfarcted septal wall thickness in the control group (1.7 ± 0.5 mm) and the exercise group (2.0 ± 0.5 mm) (F = 1.07, p < 0.001), possibly representing some hypertrophy of residual uninfarcted myocardium in the latter.

Because the degree of expansion is related to infarct size (12), we plotted a regression line for infarcted wall thickness in the exercise and control groups as a function of infarct size (Fig. 5). There was no significant difference between

![Figure 4. Distribution of expansion grades according to infarct size (small, moderate and large) for control (top) and exercise (bottom) group rats.](image-url)
Effect of exercise on acute infarction in rats.

Figure 5. Relation of infarcted left ventricular (LV) wall thickness to infarct size (% LV) for the control (A) and exercise (B) groups. The slopes and intercepts are similar for the two groups.

Discussion

Effect of exercise after infarction. Acute infarct expansion has been shown to lead to an increase in functional infarct size, overall cardiac dilation, aneurysm formation and cardiac rupture (13,14,19,20). Insofar as exercise increases heart rate, contractility (21) and wall stress, we sought to determine whether moderate exercise early after infarction might aggravate the regional dilation and thinning of the infarct zone that characterize expansion. Accordingly, we subjected rats to 1.5 hours of exercise daily on a treadmill for the first week after infarction. The findings demonstrated no difference in infarct size or in the prevalence or degree of infarct expansion or aneurysmal shape changes at 1 week after infarction. We assessed the effect of exercise on the extent of expansion, infarct wall thickness and changes in left ventricular diameter. As extent of infarct expansion is related positively to infarct size (12), we compared the relation of thickness of the infarcted wall (an index of expansion) and the distribution of expansion grades for exercised and unexercised animals as a function of infarct size, and still none of these variables were different between the two study groups. In addition, exercise did not increase infarct size.

No hearts ruptured and the two groups had a similar incidence of intramural hemorrhage, a histologic finding that may be associated with infarct rupture (1,22). Two hearts in the exercise group did have marked fiber splitting, separated by pools of blood suggesting partial rupture. There was a trend toward higher mortality in the exercise group, with 5 of the 94 exercised rats dying between days 1 and 7, and none of the unexercised rats dying during this period. Of note, three animals died during exercise while using the treadmill. The number of deaths, however, was small and not significantly different in the exercise and control groups and the mechanism of death unclear. Although 140 animals were studied, the mortality was low. It is possible that with
larger numbers of animals the difference in mortality might reach statistical significance; therefore, it cannot be conclusively stated that early exercise does not increase mortality after myocardial infarction.

Comparison with previous studies. Previous animal studies on the effect of exercise on left ventricular shape have shown conflicting results. Sutton and Davis (4), using treadmill exercising of dogs, showed that aneurysms only formed in animals not given a rest period between coronary ligation and exercise. However, in their study only five dogs were exercised and there were no control dogs. Thompson et al. (5) showed no effect of treadmill exercise on aneurysm formation in dogs. One must be aware, however, that dog infarcts produced by simple coronary ligation are extensively transmural and have a low rate of aneurysm formation (23), whereas rat infarcts expand and form aneurysms spontaneously (13). In another study (24,25) that used swimming exercise, exercised rats were shown to have thinner infarcted walls than those of the control animals, suggesting greater infarct expansion. The difference observed in our study may be related to differences in the severity, type or timing of exercise after infarction. Treadmill exercise and swimming also impose different forms of cardiovascular stress. Ordinarily, swimming rats periodically sink to the bottom and struggle up to resume swimming in response to hypoxia, imposing both a hypoxic and psychological stress as well as a major catechol stimulation on the heart. A greater depletion of creatine kinase (CK) from myocardium has been demonstrated (26) in rats confined to small cages, suggesting an important role of stress in infarct size. That study, using treadmill exercise, showed that mild exercise had no effect on CK depletion, but that moderate exercise (similar intensity but shorter in duration than this protocol) was associated with greater CK depletion.

We chose to begin exercise on the same day as the coronary ligation because previous studies have shown that expansion begins at that time (12) and that most infarcts that will expand have done so within the first 24 hours. The prevalence and severity of expansion and aneurysmal dilation has also been shown to reach a plateau by Days 5 to 7 (12,13) and, therefore, Day 7 was chosen to examine the hearts.

Implications. It is possible that we did not observe an effect of exercise on infarct expansion because the rats were subjected to only moderate exercise. By design, however, the animals were untrained and unaccustomed to exercise. In addition, they had undergone coronary ligation through a thoracotomy under general anesthesia on the first day of exercise. The level of exercise chosen was based on the observation that the majority of rats could not tolerate faster speeds (that is, they exhibited respiratory distress or refused to run). Our protocol was similar to the level of exercise employed in rat training protocols (17,18,21). Therefore, because the level of exercise could be viewed as modest at the least, our findings suggest that moderate degrees of exercise after infarction have no effect on acute infarct expansion, aneurysmal dilation or infarct size. It should be noted that this infarct model is one of single vessel disease; caution should be exercised in applying the results from a rat model of single vessel coronary disease to human beings, who often have multivessel disease.

It is encouraging that we did not observe significant left ventricular shape changes in exercised rats with infarcts. This study supports the observation that moderate exercise early after myocardial infarction is safe with regard to infarct size and cardiac shape, but further investigation is needed to clarify the effect of activity on cardiac rupture and on alterations in left ventricular function and arrhythmias, particularly before applying these and other similar animal data to humans.

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References


