Altered Left Ventricular Remodeling With β-Adrenergic Blockade and Exercise After Coronary Reperfusion in Rats

Byung-Hee Oh, MD, PhD; Shiro Ono, MD; Elizabeth Gilpin, MA; and John Ross Jr., MD

Background. β-Adrenergic blockade is known to improve the survival of patients after acute myocardial infarction and to reduce myocardial infarct size in experimental coronary occlusion. However, the effects of β-blockade on global and regional left ventricular (LV) remodeling have not been characterized after coronary occlusion with reperfusion. In rats subjected to coronary occlusion and reperfusion, we have demonstrated beneficial effects of reperfusion in sedentary rats with a hypertrophic response to exercise in the surviving outer wall of the infarcted zone, and in this study we investigated whether such remodeling is modified by β-blockade in both sedentary and exercised rats.

Methods and Results. Female Sprague-Dawley rats were randomized into groups at 5 days after 45 minutes of left coronary artery occlusion followed by reperfusion to produce nontransmural infarction. Animals completing the experiment included a propranolol-treated sedentary group (750 mg/l drinking water) (n=20) and a propranolol-treated exercised group (n=19), and these groups were compared with two groups of simultaneously randomized rats (which were also part of a separate study): an untreated sedentary group (n=21) and an untreated exercised group (n=20). After 3 weeks of intervention, global and regional LV morphological changes were analyzed in 78 completed experiments from midventricular transverse slices of hearts after perfusion fixation. Compared with sedentary untreated rats, propranolol-treated sedentary rats showed significantly increased LV cavity area (41.6 versus 31.5 mm²; p<0.001) and reduced wall thicknesses in the noninfarcted (1.77 versus 1.95 mm, p<0.01) and infarcted regions (1.29 versus 1.36 mm, p<0.01) (two-way ANOVA). In the propranolol-treated rats, exercise further increased the LV cavity area (44.6 versus 39.1 mm², p<0.001), reduced the noninfarcted wall thickness (1.62 versus 1.81 mm, p<0.01), and increased the LV dimension/wall thickness ratio in the noninfarcted region (4.7 versus 3.95 mm, p<0.001). Whereas exercise in the reperfused group in the absence of β-blockade significantly increased the viable subepicardial area of the infarcted zone, as reported elsewhere, propranolol treatment prevented this exercise-induced increase of subepicardial area (7.8 rest versus 7.7 mm² exercise, NS), and there was a significant reduction of total myocardial area in the propranolol-treated exercised group compared with the untreated exercised group (p<0.05). Corresponding trends in LV weights were not statistically significant.

Conclusions. These findings provide evidence for altered LV remodeling, including LV cavity dilation and reduced wall thickness, after 3 weeks of propranolol treatment in sedentary rats after coronary artery occlusion and reperfusion to produce nontransmural infarction. In addition, after 3 weeks of exercise together with propranolol treatment, morphological changes were consistent with suppression of exercise-induced myocardial hypertrophy globally and in the viable outer wall of the infarcted region, accompanied by further LV cavity dilation. (Circulation 1993;87:608–616)

Key Words • left ventricular remodeling • receptors, β-adrenergic blockers • reperfusion • exercise • myocardial infarction, nontransmural
left ventricle in this setting. However, permanent coronary occlusion in the rat is known to produce transmural infarction, whereas in species that develop a coronary collateral circulation, such as the dog and some human subjects in the setting of spontaneous or induced thrombolysis, nontransmural infarction occurs. Therefore, because of the limited applicability of the rat model of permanent coronary occlusion to the setting of reperfusion after coronary occlusion, we have developed and characterized a model of nontransmural myocardial infarction in rats by subjecting them to 45 minutes of coronary occlusion followed by reperfusion. In this model, substantial epicardial sparing was demonstrated in sedentary rats compared with those with permanent coronary occlusion, and swimming exercise induced additional hypertrophy of the outer wall in the infarcted region.

In addition to attenuating compensatory hypertrophy after experimental transmural myocardial infarction, \( \beta \)-blockade also can suppress isoproterenol-induced myocardial hypertrophy and hypertrophy in spontaneously hypertensive rats. However, the effects of \( \beta \)-blockade on LV remodeling in the setting of experimental coronary occlusion with reperfusion have not been examined. Accordingly, in this study, the effects of \( \beta \)-adrenergic blockade with propranolol on LV morphology were investigated in the rat model of coronary artery occlusion followed by reperfusion. In addition, since exercise training is used in rehabilitation after acute myocardial infarction and has been shown in the rat reperfusion model to produce regional hypertrophy, we also undertook to study the influence of \( \beta \)-blockade on the effects of exercise in reperfused hearts.

**Methods**

The animals in this study were handled according to the animal welfare regulations of the American Heart Association and the University of California San Diego, and the experimental protocol was approved by the Animal Subjects Committee of this institution.

**Animal Model and Surgical Preparation**

Female Sprague-Dawley rats weighing 250–300g were anesthetized with a mixture of ketamine hydrochloride (100mg/kg body w t i.p.), xylazine (10mg/kg i.p.), and morphine sulfate (5mg/kg i.p.). Forty-five minutes of coronary occlusion followed by reperfusion was performed as described elsewhere. Briefly, after adequate anesthesia, all animals were placed in the supine position on a table heated by circulating warm water, intubated, and ventilated under positive pressure with a rodent ventilator (model 683, Harvard Apparatus). Under a dissecting microscope, a left thoracotomy was performed in the fourth intercostal space, and the pericardium was opened. The left coronary artery (which is intramural) was encircled together with a band of myocardium between the left atrial appendage and right ventricular outflow tract with a curved needle and 6-0 silk suture. The artery was then occluded, and reperfusion was performed after 45 minutes by cutting the ligature around the left coronary artery. A small piece of plastic foam was tied between the ligature and myocardium to minimize direct injury to the myocardium and artery and to facilitate cutting of the ligature. A distinct color change of the myocardium upon reperfusion, the appearance of reperfusion arrhythmias, or both were considered to indicate reperfusion. The chest was then closed in layers and the pneumothorax evacuated.

**Experimental Protocol**

After surgery, animals were caged in proportion to size, given water and standard rat chow ad libitum, and housed in a climate-controlled environment subjected to 12-hour light/dark cycles. Five days after coronary reperfusion, 87 rats were randomly assigned to one of the following four groups: propranolol-treated sedentary rats (\( n=20 \)), propranolol-treated exercised rats (\( n=21 \)), untreated sedentary rats (control group) (\( n=21 \)), and untreated exercised rats (swimming) (\( n=25 \)). The latter two groups are also reported as part of another study, which also included preparation of sham-operated animals and animals with permanent coronary ligation. Propranolol (Sigma Chemical Co., St. Louis, Mo.) was administered ad libitum in drinking water at a concentration of 750 mg/l, and the water bottle was changed three times weekly.

Dose–response tests of isoproterenol on heart rate were performed in 14 rats (eight untreated, six propranolol-treated) just before termination of the experiments to confirm adequate \( \beta \)-adrenergic blockade. Under anesthesia, the right jugular vein was cannulated with a polyethylene catheter (PE 50), and an ECG was monitored and recorded (Gould Brush 200 recorder). After heart rates were recorded during a control period with saline infusion, isoproterenol was given continuously with an infusion pump at increasing doses of 0.05, 0.1, 0.25, 0.5, 1, and 4 \( \mu \)g/min. Dose–response curves from untreated and propranolol-treated groups showed a competitive antagonist effect with significant difference between the two groups (\( p<0.05 \), ANOVA) (Figure 1).

The swimming exercise began 5 days after surgery with a single 15-minute swimming period daily. The duration of the exercise period was increased by 5 min/day up to 60 minutes and then continued 7 days a week for 3 weeks. Rats swam in groups of five to 10 animals in a 50-cm-deep plastic tub containing water heated to 33–35°C.

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**Figure 1.** Isoproterenol dose–heart rate response curves in eight untreated and six propranolol-treated sedentary rats showing competitive antagonism of \( \beta \)-adrenergic receptor blockade by propranolol. The curve is shifted downward significantly in propranolol-treated rats compared with untreated rats (\( p<0.05 \), ANOVA). C, control group; S, saline infusion. *\( p<0.05 \) vs. control group using repeated-measures ANOVA with Tukey's test.
The experimental protocol after randomization was completed in 83 of 87 rats (three rats in the untreated exercised group and one in the propranolol-treated exercised group died during swimming exercise).

Postmortem and Histological Preparations

Twenty-six days after surgery, the rats were anesthetized with the same anesthesia as described above for the initial surgery and euthanized as described elsewhere. After the thorax was opened, the heart was perfused retrogradely from the aorta at a constant pressure of 60 mm Hg and a cavity LV pressure of 10 mm Hg and fixed for 20–30 minutes with 10% phosphate-buffered formalin.

After hardening, the heart was excised and immersed into 10% buffered formalin solution, and 24 hours later, the right and left ventricles including the interventricular septum were dissected, separated, and weighed. The heart weights were normalized by the length of tibia, as well as by body weight as described elsewhere.

After 2 days or more in 10% buffered formalin solution, the whole left ventricle was embedded in paraffin. Transverse serial sections 25 μm thick were cut, and every 40th section from the apex to the base (every 1 mm) was mounted and stained with Milligan’s trichrome.

Morphometric Analyses

Measurements were performed on two midventricular transverse slices (5 and 6 mm from the apex) and averaged, since those measurements have been shown to reflect data from all slices. All slides were analyzed blindly, and interobserver variation for such measurements was also demonstrated to be acceptably small. The slides were projected with a microprojector (Jena, Germany) with magnification of ×17.3, and measurements were made by computerized planimetry. The endocardial and epicardial outlines of the LV slice were traced on paper, and the area of the infarcted zone, including the scarred area and spared epicardial and endocardial areas, the area of the LV cavity, the area of the total myocardial ring, and the average thicknesses of noninfarcted septal and infarcted anterior walls, was measured as described elsewhere.

The percent infarct size on each slice was estimated from the ratio of the infarct area to the total area of the LV ring and expressed as percentage of total ring area. Transmurality of the infarct was defined as the ratio of the infarct area to the area of the total infarct region, which was subtended by radii touching the lateral margins of the infarct (sum of infarct, epicardial, and endocardial areas). The thickness of the interventricular septum was considered representative of the noninfarcted wall. The ratios of the LV dimension to the average thickness of the infarcted and the noninfarcted walls were calculated to estimate relative changes of regional LV diastolic wall stress according to the law of Laplace, since the hearts were fixed at a common distending pressure.

Statistics

All values are expressed as mean±SD. A two-way ANOVA was used to examine the effects of propranolol (untreated versus treated) and exercise (sedentary versus exercise) on variables related to heart weight and measures of morphological features. If there was a significant interaction between drug treatment and non-treatment or between exercise and non-exercise, further examination of selected pairwise comparisons was undertaken. We hypothesized that propranolol treatment would reduce or prevent the morphological changes shown in another study to be induced by exercise, and the Newman-Keuls test was used to test for such differences. When there was no interaction effect, it can be assumed that any significant effect of exercise was the same in treated and untreated animals. Values of p<0.10 were considered significant for interaction effects, and values of p<0.05 were considered statistically significant for main effects and for post hoc tests.

Results

Of the 83 rats that completed the experimental protocol, one heart in the untreated sedentary group, one in the untreated exercised group, one in the propranolol-treated sedentary group, and two in the propranolol-treated exercised group were excluded when it appeared that minor infarction (<5%) was due to suture injury and not to experimentally induced occlusion. Therefore, 78 hearts were used for the analysis. Data from the untreated animals randomized to sedentary and exercise groups, to which the propranolol-treated rats are compared, have been analyzed in detail elsewhere and compared with sham-operated animals and with rats with permanent coronary occlusion.

Effects of Propranolol on Heart Weights

The left and right ventricular weights and their values normalized by tibial length are summarized in Table 1. Although trends can be noted for LV weights and LV/tibial length ratios to be slightly lower at rest and after exercise with propranolol, neither treatment nor exercise had statistically significant effect on any of these measurements, and there were no significant interactions.

Effects of Propranolol and Exercise on LV Remodeling

Representative trichome-stained slices of the left ventricle from single untreated sedentary and exercised rats and from propranolol-treated sedentary and exercised rats are shown in Figure 2. Treatment with propranolol resulted in an increased LV cavity area (Figure 3) and increased LV dimension in both sedentary and exercised groups (Table 2). Treatment also reduced the thickness of the noninfarcted and infarcted walls (Figure 3) and increased LV dimension/wall thickness ratios (Table 2). Total myocardial areas were decreased by propranolol in both sedentary and exercised groups (Table 2).

Comparing exercised versus sedentary animals in both treated and untreated groups, exercise further increased LV cavity area and LV dimension, reduced wall thickness in the noninfarcted wall, and increased LV dimension/wall thickness ratio in that wall. For these four measurements, there was no significant drug/exercise interaction, so it can be assumed that exercise had about the same effect in treated and untreated animals.

Significant drug/exercise interactions suggested that a differential effect occurred between the untreated exer-
cised and propranolol-treated exercised rats for total myocardial area, the viable epicardial area of the infarct region, and the total infarct area (epicardial plus endocardial). By the Newman-Keuls test, propranolol-treated exercised animals had a significantly lower total myocardial area than untreated exercised animals, and the epicardial-infarct, endocardial-infarct, and epicardial-plus endocardial-infarct areas were also lower. This difference was particularly marked in the epicardial area of the infarct zone (Figure 4). All of these variables were at or below those in propranolol-treated sedentary rats, indicating lack of exercise-induced regional hypertrophy (Table 2).

The absolute infarct (scar) area was not significantly different in the four groups (Table 2), and the scatter was closely similar (Figure 5). However, since the nonscarred areas of the infarcted wall were reduced in propranolol-treated animals (in both sedentary and exercised groups), the percent transmurality was significantly increased in the treated groups (Table 2). Also, since the total myocardial areas were reduced by propranolol in both groups, the percent infarct size was increased (Table 2).

**Discussion**

The findings in the present study indicate that β-adrenergic blockade with propranolol can cause global LV dilation with thinning of both infarcted and noninfarcted walls in reperfused hearts. In addition, propranolol suppressed exercise-induced regional myocardial hypertrophy in the infarcted region. Thus, in nontransmural myocardial infarction, it may be hypothesized that potentially deleterious effects can be produced by β-adrenergic blockade through inhibition of compensatory and exercise-induced myocardial hypertrophy, leading to LV chamber dilation.

**β-Blockade and LV Remodeling**

LV dilation, scar thinning, and reduced myocyte hypertrophy in noninfarcted regions were reported by Fishbein et al8 with 5 weeks of propranolol administration commencing 1 day after permanent coronary occlusion in rats. Our study addressed the effects of 3 weeks of β-adrenergic blockade begun somewhat later (5 days) in hearts subjected to coronary artery reperfusion and then randomized to sedentary and exercised conditions to simulate the clinical settings of thrombolysis or acute percutaneous transluminal coronary angioplasty. In this reperfusion model, the transmurality of infarction was found to be much less than with permanent coronary occlusion.12 Nevertheless, β-adrenergic blockade caused dilation of the left ventricle, with thinning of infarcted and noninfarcted walls, both in sedentary and exercised animals, suggesting that such treatment might have suppressed not only exercise-induced hypertrophy but also compensatory hypertrophy in sedentary animals. Evidence for such hypertrophy in both infarcted and noninfarcted regions has been reported in other studies from this laboratory in sedentary dogs. In those studies, myocardial cell hypertrophy greater than that observed in noninfarcted regions was found in surviving cells of the infarced region at 3 weeks after 2 hours of coronary occlusion with reperfusion.17

LV dilation after acute myocardial infarction is known to be the net result of expansion of the infarcted area and dilation of noninfarcted regions.18 but the exact mechanism of LV dilation produced by β-adrenergic blockade after infarction remains to be elucidated. Volume overload and increased diastolic wall stress stimulate eccentric LV hypertrophy,18–20 and augmented LV diastolic volume, thinning of the wall, and increased wall tension could result from the decreased contractility and slowed heart rate produced by propranolol. Thinning of the infarcted and noninfarcted walls in our reperfusion model caused by blunted hypertrophy with propranolol might also contribute to elevated wall stress and further chamber dilation.

Attenuation of cardiac hypertrophy without significant change in blood pressure after chronic β-adrenergic blockade has been reported in adult spontaneously hypertensive rats,14,21 but β-blockers administered from the time of conception in such rats failed to alter either the progressive rise in arterial pressure or the development of LV hypertrophy.15 β-Adrenergic blockade with practolol also was reported not to attenuate experimentally induced LV hypertrophy in abdominal aorta-banded rats.22 However, myocardial hypertrophy after myocardial infarction tends to be of the eccentric type, compared with the concentric type caused by pressure overload, in which β-adrenergic blockade has shown variable results. Although the myocardial infarction was transmural and therefore different from those in this study, Fishbein and coworkers8 reported suppression of myocardial hypertrophy with longer-term propranolol treatment, with reduced myocyte cross-sectional area and volume. In this study, we report indirect evidence of

**TABLE 1. Heart Weights and Tibial Lengths 26 Days After Coronary Occlusion and Reperfusion in Four Groups of Rats**

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Exercised</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Propranolol</td>
</tr>
<tr>
<td></td>
<td>(n=20)</td>
<td>(n=19)</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>281±17</td>
<td>282±21</td>
</tr>
<tr>
<td>LV (mg)</td>
<td>817±88</td>
<td>788±64</td>
</tr>
<tr>
<td>RV (mg)</td>
<td>181±39</td>
<td>184±53</td>
</tr>
<tr>
<td>TL (mm)</td>
<td>40.0±0.6</td>
<td>40.0±0.8</td>
</tr>
<tr>
<td>LV/TL (mg/mm)</td>
<td>20.4±2.3</td>
<td>19.7±1.5</td>
</tr>
<tr>
<td>RV/TL (mg/mm)</td>
<td>4.5±1.0</td>
<td>4.6±1.4</td>
</tr>
</tbody>
</table>

**Note:** LV, left ventricular weight; RV, right ventricular weight; TL, tibial length; untreated, untreated control rats; propranolol, propranolol-treated for 3 weeks; exercised, swimming exercise for 3 weeks. All values are mean±SD.
blunted myocardial hypertrophy after nontransmural myocardial infarction based on reduced areas of viable myocardium in the infarct zone and reduced total myocardial area. The lack of significant reductions in LV weights after propranolol at rest and after exercise compared with untreated animals (Table 1) may be

FIGURE 2. Color photographs of transverse left ventricular slices at 26 days after coronary occlusion and reperfusion. Top panel: Sedentary rats, untreated and treated; bottom panel, exercised rats, untreated and treated. Milligan's trichrome stain. Original magnification at 1 cm scale shown.
related in part to regional nonuniformity of the observed changes. However, relatively small changes in total LV weight also have been observed in normal rats with longer periods of exercise than those used in this study and in our sham-operated rats.

**β-Blockade and Exercise**

The effect of exercise to further dilate the left ventricle after reperfusion was demonstrated in a previous report concerned with the untreated animals used in this study, and a similar change but with additional dilation was observed at β-blockade in the present study. Exercise had other significant interactions with propranolol, including a reduction in the total myocardial area in the propranolol-treated exercised group compared with the untreated exercised group; thus, whereas total myocardial area tended to be increased by exercise in untreated rats, it failed to increase and was actually significantly lower than in the propranolol-treated sedentary group (Table 2). Also, propranolol entirely prevented the exercise-induced increase in epicardial and endocardial areas in the infarcted region compared with the untreated group (Table 2, Figure 4).

The finding that propranolol blocked the effects of exercise to produce an increased myocardial area of the infarcted region has not been reported previously. This indirect evidence for inhibition of exercise-induced regional hypertrophy by propranolol in the present study suggests a possible link between increased sympathetic tone (or β-adrenergic tone) and myocardial hypertrophy in this model. Considering the potential contribution of myocardial hypertrophy of surviving myocardium in noninfarcted regions to regional and global functional recovery after myocardial infarction, β-adrenergic blockade might cause potentially deleterious effects on the recovery of global and regional LV function. Moreover, the combination of β-adrenergic blockade with exercise after myocardial infarction might be even more detrimental, with exaggeration of the LV dilation caused by propranolol in the sedentary state.

**Mechanisms for Inhibition of Hypertrophy**

Possible mechanisms for potential suppression of myocardial hypertrophy with β-adrenergic blockade remain uncertain. It is known that stretch of myocardial cells, which relates to increased wall stress, is a stimulus to activation of the hypertrophic gene program, and increased systolic stress also has been suggested to be an initiating factor for the development of myocardial hypertrophy. Our finding of increased diastolic cavity size and LV dimension/wall thickness ratios with propranolol treatment in both the infarcted and nonischemic walls (suggesting increased wall stress) provides indirect evidence that diastolic wall stress was elevated. On the other hand, decreased myocardial contractility and lowered blood pressure with chronic β-blockade, which are particularly prominent during exercise, may have reduced peak systolic wall stress. In addition, reduced myocardial blood flow caused by propranolol in nonischemic regions after coronary occlusion might have contributed to diminished hypertrophy. Suppression of a direct regulatory effect of cardiac β-receptors on myocardial hypertrophic events has also been suggested, and recently a possible relation between myocardial hypertrophy and β-adrenergic stimulation was suggested by Iwaki et al, who reported that immediate early gene expression was induced by β-adrenergic stimulation of neonatal rat myocardial cells. Both α- and β-adrenergic stimulation appear to induce expression of protooncogenes as well as to increase assembly of an individual contractile protein (MLC-2) into organized sarcomeric units.

**Methodological Considerations**

Several methodological issues should be mentioned. Because of the complexity of the protocol, we did not attempt to obtain hemodynamic measurements at rest or during exercise in this study. It would be even more...
TABLE 2. Topographic Changes of the Left Ventricle 26 Days After Coronary Occlusion and Reperfusion in Four Groups of Rats

<table>
<thead>
<tr>
<th></th>
<th>Sedentary Untreated (n=20)</th>
<th>Propranolol Untreated (n=19)</th>
<th>Exercised Untreated (n=21)</th>
<th>Propranolol (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV cavity area (mm²)</td>
<td>33.5±8.9</td>
<td>41.6±9.7*</td>
<td>39.1±6.5§</td>
<td>44.6±7.6*§</td>
</tr>
<tr>
<td>LV dimension (mm)</td>
<td>6.43±0.87</td>
<td>7.20±0.86*</td>
<td>7.01±0.61§</td>
<td>7.50±0.64*§</td>
</tr>
<tr>
<td>Total myocardial area (mm²)</td>
<td>48.6±6.1</td>
<td>46.8±4.4*</td>
<td>50.7±5.1</td>
<td>44.1±5.0*</td>
</tr>
<tr>
<td>Non-inf area (mm²)</td>
<td>31.2±6.0</td>
<td>28.8±5.3†</td>
<td>30.5±6.2</td>
<td>26.6±4.8†</td>
</tr>
<tr>
<td>Infarcted area (mm²)</td>
<td>6.6±2.2</td>
<td>7.0±2.1</td>
<td>6.3±1.6</td>
<td>6.7±2.1</td>
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<tr>
<td>Epi-inf area (mm²)</td>
<td>7.5±3.2</td>
<td>7.8±2.8</td>
<td>9.9±3.9</td>
<td>7.7±3.3</td>
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<tr>
<td>Endo-inf area (mm²)</td>
<td>3.3±1.2</td>
<td>3.2±1.2</td>
<td>4.0±1.3</td>
<td>3.1±1.2</td>
</tr>
<tr>
<td>Epi+endo area (mm²)</td>
<td>10.8±4.0</td>
<td>11.0±3.6</td>
<td>13.9±3.3</td>
<td>10.8±4.0</td>
</tr>
<tr>
<td>Percent infarct size (%)</td>
<td>13.8±5.0</td>
<td>15.2±5.1‡</td>
<td>12.6±3.6</td>
<td>15.3±4.8‡</td>
</tr>
<tr>
<td>Transmurality (%)</td>
<td>38.3±8.6</td>
<td>39.7±9.6‡</td>
<td>31.6±7.1</td>
<td>39.2±10.0†</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninfarcted wall</td>
<td>1.95±0.29</td>
<td>1.77±0.33†</td>
<td>1.81±0.23§</td>
<td>1.62±0.19†$</td>
</tr>
<tr>
<td>Infarcted wall</td>
<td>1.36±0.29</td>
<td>1.29±0.23†</td>
<td>1.51±0.34</td>
<td>1.25±0.26†</td>
</tr>
<tr>
<td>LV dimension/wall thickness ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninfarcted wall</td>
<td>3.40±0.83</td>
<td>4.25±1.06*</td>
<td>3.95±0.69§</td>
<td>4.70±0.79*§</td>
</tr>
<tr>
<td>Infarcted wall</td>
<td>4.99±1.55</td>
<td>5.78±1.23*</td>
<td>4.91±1.35</td>
<td>6.25±1.43*</td>
</tr>
</tbody>
</table>

Unstudied, untreated control rats; propranolol, propranolol-treated for 3 weeks (750 mg/l drinking water); exercised, swimming exercise for 3 weeks; LV, left ventricle; non-inf area, area of noninfarcted region; infarcted area, area of scar; epi-inf area, epicardial area in the infarcted region; endo-inf area, endocardial area in the infarcted region; epi+endo area, sum of epicardial and endocardial areas in the infarcted region. All values are mean±SD. Statistics (p values) were obtained by two-way ANOVA.

*p<0.001, †p<0.01, ‡p<0.05, main effect propranolol-treated vs. untreated (ANOVA).

§p<0.05, main effect exercise vs. sedentary (ANOVA).

$|p<0.05 for exercised untreated vs. exercised propranolol-treated groups (Newman-Keuls test).

It is desirable to obtain measurements of LV global and regional function, at least under resting conditions, and experimental studies concerned with such analyses in this animal model are now under way. As discussed elsewhere,12 we did not examine cell size because of the morphometric method used and because with only 3 weeks of exercise large numbers of animals would probably be needed to detect cell size differences.12 Other than reduction of hypertrophy, the other potential mechanism for the observed reductions in regional areas of viable myocardium from those in the absence of β-blockade is wall thinning caused by LV dilation, although the total myocardial area was diminished by propranolol in sedentary animals and further reduced by exercise. The apparent differences in the degree of response between slice areas and ventricular weights could be related to the regional nature of major responses (predominantly in the infarct zone) as well as to the possibility that events occurred in large part at the minor equator and were insufficient to promote proportional changes in total ventricular weight. The observed striking decrease in epicardial area in the infarct zone without change in infarct size might relate in part to global thinning of the LV wall, but it seems more likely...
that subendocardial scar formation prevented substantial stretch of the outer wall of the infarct region, because the infarcted wall was not significantly thinner after exercise. Therefore, the probable explanation for our findings is that propranolol inhibited the regional hypertrophic response to exercise observed in the untreated animals.

It should be pointed out that we fixed the hearts at a common LV filling pressure of 10 mm Hg to compare LV morphologies in different groups. It is likely, however, that the filling pressures were higher in vivo, particularly after β-blockade with exercise, and if the hearts had been fixed at in vivo pressures, the changes in chamber size and wall thickness probably would have been even larger.

**Potential Clinical Implications**

The results of this study cannot be directly compared with the clinical setting in patients who have received reperfusion therapy for acute myocardial infarction. The beneficial effects of long-term β-blocker treatment after acute myocardial infarction to reduce mortality and nonfatal reinfarction in many large clinical trials1-6 may appear discordant with our findings, which postulate a detrimental effect, but thrombolyis was not carried out in the large clinical trials on β-blockade after acute myocardial infarction, and the beneficial effects occurred primarily in high-risk patients.1-6 In the presence of thrombolyis, β-blockade has been reported to have no effect on LV function but to reduce early mortality by prevention of cardiac rupture.32 In a report from the Thrombolysis in Myocardial Infarction II-B study, in which thrombolysis was used in combination with β-blockade in patients with acute myocardial infarction,7 no decreases in mortality or incidence of cardiac rupture were demonstrated with β-blockade, nor was there an effect on LV function; however, some benefit was noted on recurrent chest pain and reinfarction in the first week.7 Our animal model of nontransmural myocardial infarction with reperfusion might be considered to resemble the setting of the low-risk patient undergoing reperfusion of an occluded vessel without disease in other coronary arteries.

Exercise training after myocardial infarction combined with β-blockade use might cause detrimental effects by limiting exercise-induced hypertrophy in the normal and infarcted regions, leading to further LV dilation, as in our animal model. However, clinical studies in a similar patient population would be needed before such an extrapolation could be made, and many other factors such as the duration of training, timing and dose of β-blockade therapy, and presence or absence of coronary disease in other coronary arteries would require consideration.

**Acknowledgments**

We thank Denice J. Brannigan and Abdul-Wahaab Farid for their expert assistance and Sharon Perry and Noa Katrin for manuscript preparation.

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Circulation. 1993;87:608-616
doi: 10.1161/01.CIR.87.2.608

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