Effect of Oral Propranolol on Rest, Exercise and Postexercise Left Ventricular Performance in Normal Subjects and Patients with Coronary Artery Disease

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with the technical assistance of Chuck Rue

SUMMARY  The effect of \( \beta \)-adrenergic blockade with oral propranolol on resting, exercise and postexercise ventricular performance was evaluated using multiple-gated equilibrium cardiac blood pool images in normal volunteers and patients with coronary artery disease. Propranolol produced no detectable effect on basal left ventricular function in normal subjects at doses producing intermediate (160 mg propranolol/day) and maximal (434 ± 99 mg propranolol/day) \( \beta \) blockade and in patients with coronary artery disease at clinically effective antianginal doses (162 ± 47 mg propranolol/day). During exercise, a dose-related, negative inotropic effect was observed in normal subjects: 160 mg propranolol/day produced a small but statistically insignificant decline in exercise left ventricular performance, whereas maximal \( \beta \) blockade significantly depressed the left ventricular response to exercise. In patients with coronary artery disease, propranolol’s effect on exercise ventricular performance depended on the presence or absence of ischemic dysfunction during exercise. In patients with an ischemic functional response to exercise, propranolol significantly improved regional and global performance during and after exercise; in coronary artery disease patients with a normal response to exercise, propranolol had no significant effect on exercise and postexercise ventricular function. These results imply increased sensitivity to the effects of \( \beta \) blockade in ischemic myocardium. In coronary artery disease patients with an abnormal response to exercise and in normal volunteers during \( \beta \) blockade, propranolol’s effect on exercise left ventricular performance was independent of changes in ventricular preload and afterload related to heart rate and blood pressure.

BETA-ADRENERGIC BLOCKADE with propranolol has been shown to relieve symptomatic ischemic heart disease\(^1-3\) and limit experimental infarct size.\(^4-6\) Presumably, these effects are achieved by improvement in the balance of oxygen supply and demand by inhibition of catecholamine-mediated increases in heart rate, blood pressure and inotropic state. Because an improved balance in oxygen supply and demand would result in reduced regional ischemia, \( \beta \)-adrenergic blockade with propranolol might actually improve mechanical performance in ischemic zones despite its negative inotropic effect on nonischemic myocardium. Supportive evidence for this possibility has been obtained from studies evaluating the effect of \( \beta \)-adrenergic blockade on regional ischemic function in experimental preparations.\(^7-11\) However, in humans, evaluation of the effect of propranolol on global left ventricular function during acute myocardial ischemia or infarction has yielded contradictory results.\(^12-14\) To date, no studies have been published in man evaluating the effect of \( \beta \)-adrenergic blockade on mechanical performance in regionally ischemic myocardium.

The present study was designed to evaluate the effects of \( \beta \)-adrenergic blockade with oral propranolol on resting, exercise and postexercise regional and global left ventricular performance as evaluated by multiple-gated equilibrium cardiac blood pool imaging. The goals of the study were to compare the effects of \( \beta \)-adrenergic blockade on ischemic and nonischemic myocardial performance and to evaluate the relative contributions of propranolol’s negative inotropic, chronotropic and anti-hypertensive effects on mechanical performance of normal and ischemic myocardium.

Methods

Study Population

The study population consisted of seven normal volunteers (all male) and 18 patients with coronary artery disease (16 males and two females). The mean age of the volunteers was 24 ± 4 years (±SD) (range 19–29 years); the mean age of the coronary artery disease patients was 54 ± 12 years (range 37–82 years).

The diagnosis of coronary artery disease was based on the presence of at least one of the following crite-
ria: (1) previous documented myocardial infarction with characteristic serum enzyme and electrocardiographic changes; (2) an abnormal ECG or thallium-201 exercise stress test; (3) angiographically proved, significant coronary arterial stenosis (greater than 70% decrease in luminal diameter). Nine patients with coronary artery disease were evaluated by coronary arteriography, and 16 patients had a positive exercise stress test. All of the patients with coronary artery disease were being treated with propranolol to relieve chest pain; 16 patients had classic exertional angina pectoris and two patients had angina at rest. Five patients had a history of acute transmural myocardial infarction occurring at least 2½ months before entry into the study. No patient had a history of congestive heart failure and no patient was taking digitalis. Patients were allowed to use nitrates for relief or prophylaxis of chest pain except for the 3 hours preceding the radionuclide studies.

The normal volunteers were clinically normal as assessed by a rest and exercise ECG, physical examination, and a cardiac history. Informed consent was obtained from each subject before entry into the study.

Radionuclide Technique

Multiple-gated equilibrium cardiac blood pool images were acquired 5–10 minutes after i.v. administration of 20 mCi of technetium-99m labeled in vitro to autologous red blood cells. Imaging was performed with an Anger scintillation camera (Ohio Nuclear Series 420 Mobile Gamma Camera) equipped with a high-resolution, low-energy, parallel-hole collimator. The detector was positioned in the left anterior oblique projection with a 10–15° caudal tilt. The position of the detector was adjusted until the interventricular septum was optimally visualized on the persistence oscilloscope.

Images were acquired with a dedicated nuclear medicine computer (Ohio Nuclear VIP 450). The RR interval was determined by averaging five beats immediately before data acquisition. The average RR interval was then divided into 16 equal frames with framing intervals ranging from 83 msec for the lowest resting heart rate to 20 msec during peak exercise. Cardiac cycles with RR intervals not within 20% of the original RR interval as well as the subsequent beat were rejected by the computer and did not count toward total imaging time. Data were acquired for 4 minutes at rest and for 3 minutes during exercise to generate composite images of the entire cardiac cycle. The average number of counts in the left ventricular region of interest for the background-corrected end-diastolic frame from studies acquired for 3 minutes during exercise was 14,500 ± 6600 (107 ± 43 counts/pixel).

Data Processing

Global left ventricular ejection fraction, mean normalized systolic ejection rate, regional ejection fractions and relative changes in end-diastolic volume were determined from left ventricular time-activity curves constructed from rest and exercise multipled-gated equilibrium cardiac blood pool images. Background activity was subtracted before identification of the left ventricular region of interest by placing a crescent-shaped region along the inferolateral border of the left ventricle in end-diastole. A variable region of interest was assigned manually over each of the first 14 frames of the cardiac cycle. The last two frames were excluded from analysis due to artifacts produced by small changes in sinus rate not rejected by the computer. Ejection fraction was calculated from the background-corrected relative volume curve from the formula (maximal counts−minimal counts)/maximal counts. Left ventricular ejection fraction calculated by this technique has been shown to correlate well with contrast angiography (in our laboratory \( r = 0.9, n = 21 \)). Mean normalized systolic ejection rate was also determined from the relative ventricular volume curve by fitting the ejection phase to a weighted, least-squares straight line.

Our technique for determining regional ejection fractions is similar to that reported by Caldwell et al.19 (fig. 1). After manual assignment of regions of interest to the left ventricle in each frame of the cardiac cycle, the computer determined the long axis and geometric center of the end-diastolic frame. A line through the geometric center parallel to the long axis and two lines at 120° to the first also passing through the geometric center were then constructed by the computer, effectively dividing the ventricle into apical, lateral and septal regions. Although defined only in the end-diastolic frame, these axes were used without alteration through the entire cardiac cycle. Regional time-activity curves were generated from each region and

![Diagram of the method used to divide the left ventricle into apical, lateral and septal regions.](http://circ.ahajournals.org/)

**FIGURE 1.** Diagram of the method used to divide the left ventricle into apical, lateral and septal regions.
the corresponding regional ejection fraction was computed in a manner similar to global left ventricular ejection fraction.

Relative changes in end-diastolic volume during exercise were computed directly from counts in the background-corrected end-diastolic frame. Because each cardiac cycle was divided into 16 equal frames, the reciprocal change in framing interval and heart rate during exercise assured that image time per frame remained constant throughout each radionuclide exercise evaluation. To analyze relative volume changes at rest between radionuclide evaluations, the areas (expressed as the number of pixels marked) of the left ventricular region of interest were compared.

Data processing was done by two independent observers, and the average of their results was used for data analysis. Interobserver variability for both rest and exercise evaluations was ± 0.048 for global left ventricular ejection fraction and ± 0.42 sec−1 for mean normalized systolic ejection rate. For regional ejection fractions, the interobserver variability was ± 0.65, ± 0.51 and ± 0.09 for lateral, apical and septal ejection fractions, respectively. The reproducibility of detecting relative changes in end-diastolic volume was ± 13.2% and ± 14.9% as detected by relative count changes and number of pixels marked, respectively. Except for lateral ejection fraction, for which intraobserver variability was ± 0.08, variability for a single observer processing the data twice separated by a 3–6-month interval was either equal to or less than the variability between observers.

Study Protocol

In the normal volunteers, oral propranolol therapy was instituted at 160 mg/day administered in four equal doses. The dosage was then increased by increments of 160 mg/day every 2–5 days until maximal β blockade was achieved. The degree of β blockade was evaluated by observing the decline in maximal heart rate during peak exercise on a treadmill at least 48 hours after each increment in dosage. Complete β blockade was considered present when there was a plateau in the decline of maximal heart rate over two successive increments in the dose of propranolol. Radionuclide imaging was performed before propranolol administration, after at least 48 hours of propranolol at the initial dosage of 160 mg/day, and at maximal β blockade.

In patients with coronary artery disease, oral propranolol therapy was instituted at 40-80 mg/day. The dose was then increased by increments of 40-80 mg every 2–7 days until maximal clinical improvement or drug intolerance occurred. Multiple-gated equilibrium cardiac blood pool images were obtained before propranolol therapy and after at least 48 hours at the peak propranolol dose. In the normal volunteers and the coronary artery disease patients, studies were obtained 2–3 hours after oral drug administration.

Supine bicycle exercise was performed using a bicycle ergometer (Collins Pedal Mode). After the rest study, bicycle exercise was begun at a work load of 25 W and was increased every 4 minutes in 25-W increments. Multiple-gated equilibrium cardiac blood pool images were acquired during the final 3 minutes at each work load, and 5 minutes after cessation of exercise. Exercise was continued until 3+4+ chest pain, shortness of breath or fatigue occurred. Blood pressure (measured by a standard cuff sphygmomanometer) and heart rate (determined from the ECG) were recorded during the final minute at each work load.

The study protocol was designed to evaluate the effect of propranolol on basal left ventricular performance, the response of the left ventricle to exercise, and on postexercise recovery of the left ventricle (fig. 2). Propranolol’s effect on exercise left ventricular performance was evaluated both at peak exercise and at an equivalent heart rate-blood pressure product. To evaluate the response of the left ventricle to exercise in patients with coronary artery disease before and during propranolol therapy at an equivalent heart rate–blood pressure product, left ventricular function was evaluated before propranolol therapy at a work load that produced a heart rate–blood pressure product comparable to that obtained during peak exercise on propranolol (fig. 3). In normal volunteers, left ventricular function was evaluated before propranolol and on 160 mg propranolol/day at work loads producing heart rate–blood pressure products comparable to that at peak exercise during maximal β blockade.

To compare the response of the left ventricle to exercise before and after administration of propranolol, exercise and postexercise values for all functional variables were expressed as the percentage change from the corresponding rest state. The paired t test was used to determine whether control and propranolol evaluations differed significantly.

Results

In patients with coronary artery disease, the mean dose (±sd) of propranolol was 162 ± 47 mg/day (range 80–240 mg/day). In the normal volunteers, maximal β blockade was produced by 434 ± 99 mg propranolol/day. Fifteen of 18 patients with coronary artery disease experienced improvement in their anginal syndrome of at least one New York Heart Association functional class. Exercise tolerance was significantly improved in coronary artery disease patients, with the control peak exercise work load increasing from 51 ± 30 to 61 ± 26 W with propranolol (p < 0.05). Also, the number of patients who stopped exercise due to chest pain decreased from 15 to nine. Propranolol did not affect exercise capacity in normal volunteers, with peak exercise work load averaging 100 ± 14, 100 ± 14 and 100 ± 14 W during the control, 160 mg of propranolol/day, and maximal β-blockade evaluations, respectively.

Effect of Propranolol on Heart Rate and Blood Pressure

Table 1 details the effect of propranolol on heart rate and blood pressure at rest and during exercise. In normal subjects, 160 mg of propranolol/day and doses producing maximal β blockade significantly depressed
resting, peak exercise and postexercise heart rates, with the greatest reduction occurring at the higher doses. Although propranolol had no effect on resting blood pressure, peak exercise values declined significantly as the dose was increased. Similarly, in patients with coronary artery disease, propranolol significantly reduced resting heart rate, peak exercise heart rate and blood pressure and postexercise heart rate. For normal subjects and coronary artery disease patients, mean values for heart rate alone and blood pressure alone were not significantly different during peak exercise on the maximal propranolol dose when compared with the values obtained at work loads producing comparable heart rate–blood pressure products before propranolol and in normal subjects taking 160 mg/day.

**Figure 2.** Diagram of study protocol. In normal subjects, radionuclide measures of left ventricular performance (LVP) were evaluated before propranolol, on 160 mg of propranolol/day, and at maximal $\beta$ blockade. In patients with coronary artery disease (CAD), left ventricular function was evaluated before propranolol and at clinically effective antianginal doses. During each study period in both groups, left ventricular performance was evaluated at rest, during exercise and 5 minutes after exercise. Before propranolol and on 160 mg/day in normal subjects, exercise left ventricular function was evaluated at peak exercise and at work loads producing heart rate–blood pressure products comparable to that obtained during peak exercise at maximal $\beta$ blockade. Before propranolol in the coronary artery disease patients, exercise ventricular performance was evaluated at peak exercise and at work loads producing heart rate–blood pressure products comparable to that at peak exercise on clinically effective antianginal propranolol doses. $=HR \times BP =$ equivalent heart rate–blood pressure products; Prop = propranolol.

**Figure 3.** Response of the left ventricle to exercise as measured by global left ventricular ejection fraction (LVEF) before propranolol, on 160 mg/day and at maximal $\beta$ blockade in a normal volunteer. Stars indicate work loads before propranolol and on 160 mg/day that produced heart rate–blood pressure products ($HR \times BP$) comparable to that at peak exercise during maximal $\beta$ blockade. In this subject, in contrast to the depressant effect of doses producing maximal $\beta$ blockade, 160 mg/day appeared to have little effect on exercise left ventricular ejection fraction.
**TABLE 1. Effect of Propranolol on Heart Rate, Blood Pressure and Exercise Capacity**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak exercise</th>
<th>Equivalent HR X BP</th>
<th>After exercise</th>
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</thead>
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<tr>
<td></td>
<td>HR</td>
<td>BP</td>
<td>HR</td>
<td>BP</td>
</tr>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>83</td>
<td>100</td>
<td>155</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>±9</td>
<td>±6</td>
<td>±16</td>
<td>±12</td>
</tr>
<tr>
<td>160 mg propranolol/day</td>
<td>69</td>
<td>92</td>
<td>123</td>
<td>136</td>
</tr>
<tr>
<td>Maximal β blockade</td>
<td>±11*</td>
<td>±11</td>
<td>±13*</td>
<td>±9§</td>
</tr>
<tr>
<td>CAD patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>76</td>
<td>116</td>
<td>117</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>±13</td>
<td>±17</td>
<td>±13</td>
<td>±20</td>
</tr>
<tr>
<td>Peak propranolol dose</td>
<td>±9†</td>
<td>±14</td>
<td>±11†</td>
<td>±19§</td>
</tr>
</tbody>
</table>

*p < 0.025.
†p < 0.001.
‡p < 0.02.
§p < 0.05.
¶p < 0.01.

Abbreviations: HR = heart rate; BP = mean systolic blood pressure; HR X BP = heart rate-blood pressure product; CAD = coronary artery disease.

**Effect of Propranolol on Left Ventricular Performance in Normal Subjects**

**Basal Performance**

In normal subjects, neither 160 mg of propranolol/day nor doses producing maximal β blockade had a significant effect on resting global left ventricular ejection fraction, mean normalized systolic ejection rate, or regional ejection fractions (table 2). Similarly, neither dose of propranolol had significant effect on basal end-diastolic volume as estimated by the number of pixels identified in the left ventricular region of interest.

**Exercise and Postexercise Ventricular Performance**

During the control period, global left ventricular

**TABLE 2. Rest, Exercise and Postexercise Hemodynamic Variables in Normal Subjects**

<table>
<thead>
<tr>
<th></th>
<th>LVEF</th>
<th>MNSER (sec⁻¹)</th>
<th>LEF</th>
<th>SEF</th>
<th>AEF</th>
<th>No. of pixels marked or % change in EDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.63 ± 0.05</td>
<td>3.8 ± 0.8</td>
<td>0.69 ± 0.07</td>
<td>0.56 ± 0.05</td>
<td>0.70 ± 0.07</td>
<td>143 ± 22</td>
</tr>
<tr>
<td>Equivalent HR X BP exercise</td>
<td>0.72 ± 0.06</td>
<td>6.0 ± 1.5</td>
<td>0.78 ± 0.1</td>
<td>0.62 ± 0.08</td>
<td>0.80 ± 0.08</td>
<td>−5 ± 12%</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>0.73 ± 0.05</td>
<td>6.8 ± 1.9</td>
<td>0.80 ± 0.05</td>
<td>0.66 ± 0.05</td>
<td>0.81 ± 0.08</td>
<td>−2 ± 10%</td>
</tr>
<tr>
<td>After exercise</td>
<td>0.67 ± 0.05</td>
<td>4.6 ± 0.8</td>
<td>0.75 ± 0.03</td>
<td>0.59 ± 0.08</td>
<td>0.76 ± 0.06</td>
<td>−7 ± 8%</td>
</tr>
<tr>
<td>Propranolol, 160 mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.61 ± 0.05</td>
<td>3.5 ± 0.8</td>
<td>0.69 ± 0.07</td>
<td>0.56 ± 0.05</td>
<td>0.68 ± 0.07</td>
<td>143 ± 24</td>
</tr>
<tr>
<td>Equivalent HR X BP exercise</td>
<td>0.69 ± 0.05</td>
<td>5.1 ± 0.7</td>
<td>0.74 ± 0.01</td>
<td>0.65 ± 1.9</td>
<td>0.74 ± 0.9</td>
<td>7 ± 12%</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>0.70 ± 0.05</td>
<td>5.5 ± 0.7</td>
<td>0.76 ± 0.04</td>
<td>0.65 ± 0.08</td>
<td>0.77 ± 0.08</td>
<td>10 ± 11%</td>
</tr>
<tr>
<td>After exercise</td>
<td>0.68 ± 0.06</td>
<td>4.4 ± 0.7</td>
<td>0.74 ± 0.08</td>
<td>0.62 ± 0.08</td>
<td>0.77 ± 0.09</td>
<td>−5 ± 10%</td>
</tr>
<tr>
<td>Maximal β blockade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.65 ± 0.05</td>
<td>3.7 ± 0.4</td>
<td>0.72 ± 0.07</td>
<td>0.57 ± 0.05</td>
<td>0.72 ± 0.05</td>
<td>145 ± 17</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>0.67 ± 0.05</td>
<td>4.5 ± 0.7</td>
<td>0.74 ± 0.1</td>
<td>0.63 ± 0.06</td>
<td>0.72 ± 0.06</td>
<td>19 ± 11%</td>
</tr>
<tr>
<td>After exercise</td>
<td>0.69 ± 0.05</td>
<td>4.3 ± 0.6</td>
<td>0.74 ± 0.1</td>
<td>0.62 ± 0.04</td>
<td>0.72 ± 0.06</td>
<td>−9 ± 10%</td>
</tr>
</tbody>
</table>

*p < 0.05.

Abbreviations: LVEF = left ventricular ejection fraction; MNSER = mean normalized systolic ejection rate; LEF = lateral ejection fraction; SEF = septal ejection fraction; AEF = apical ejection fraction; EDV = end-diastolic volume; HR X BP = heart rate–blood pressure product.
EFFECT OF ORAL PROPRANOLOL ON LV PERFORMANCE/ Marshall et al. 577

**Figure 4.** The effect of propranolol (Prop) doses producing intermediate and maximal β-blockade on left ventricular ejection fraction (LVEF) and mean normalized systolic ejection rate (MNSER) at peak exercise, at work loads producing comparable heart rate–blood pressure products (HR × BP), and 5 minutes after exercise.

Ejection fraction and mean normalized systolic ejection rate increased with exercise in all seven normal volunteers (figs. 3 and 4). Compared with control, the intermediate dosage of propranolol produced a small but statistically insignificant decrement in exercise left ventricular performance (fig. 4). Maximal β-blockade, on the other hand, significantly depressed the response of the left ventricle to exercise. At peak exercise during maximal β-blockade, the decline was statistically significant for both left ventricular ejection fraction and mean normalized systolic ejection rate compared with control peak exercise (p < 0.02 and p < 0.025, respectively) and to a level of control exercise producing a comparable heart rate–blood pressure product (p < 0.025 and p < 0.05, respectively).

The effect of propranolol on regional function during exercise is shown in figure 5. Propranolol's effect on apical and lateral ejection fraction during exercise was similar to that seen for global left ventricular function. Compared with control, the intermediate dosage of propranolol produced a small but statistically insignificant decrease in exercise apical and lateral ejection fractions. In contrast, maximal β-blockade produced a significant decline in both apical and lateral ejection fractions. The difference for both regions was significant at the p < 0.02 level when compared with control peak exercise and at the p < 0.025 level when compared with control exercise producing a comparable heart rate–blood pressure product. Propranolol had no significant effect on septal ejection fraction at either dose. Assuming synergistic contraction in these young, normal volunteers, the most likely reasons that septal ejection fraction did not reflect

**Figure 5.** The effect of propranolol doses producing intermediate and maximal β-blockade on regional ejection fraction at peak exercise, at work loads producing comparable heart rate–blood pressure products (HR × BP) and 5 minutes after exercise. C = control; P = 160 mg propranolol/day; M = maximal β-blockade.
global performance are that values for septal ejection were less reproducible between observers and that values for septal ejection fraction represent a combination of opposing septal contraction and heart motion during systole.

During the control evaluation, end-diastolic volume did not change significantly with exercise (table 2). Compared with control, the intermediate dose of propranolol produced a small but statistically insignificant increase in exercise end-diastolic volume. Maximal β blockade, however, was associated with a significant increase in exercise end-diastolic volume. At peak exercise during maximal β blockade, the increase was statistically significant compared with control peak exercise (p < 0.05).

After exercise, neither dose of propranolol produced a significant effect on global left ventricular ejection fraction and mean normalized systolic ejection rate (fig. 4), regional ejection fractions (fig. 5) or end-diastolic volume (table 2).

Effect of Propranolol on Left Ventricular Performance in Patients with Coronary Artery Disease

Effect of Propranolol on Basal Ventricular Performance

During the control period, 17 of 18 patients had normal basal global left ventricular function (LVEF ≥ 0.5). Of the 54 segmental ejection fractions, control resting regional function was normal in 48 and abnormal in six (abnormal resting regional function defined as 2 standard deviations or more below the control mean values in normal subjects). As in the normal subjects, propranolol had no significant effect on basal global left ventricular ejection fraction, mean normalized systolic ejection rate, or regional ejection fractions (table 3). Although basal end-diastolic volume tended to increase with propranolol, the difference between the control and propranolol evaluations did not reach statistical significance (p < 0.1).

Effect of Propranolol on Exercise Ventricular Performance

Before propranolol therapy, a variable response of left ventricular performance during exercise was noted. In four patients, the absolute value for left ventricular ejection increased by at least 0.05 from rest to peak exercise; in six patients, the absolute value did not change by more than 0.05; and in eight patients left ventricular ejection fraction declined by at least 0.05 in absolute value.

The effect of propranolol on left ventricular performance during exercise was also variable, in part depending on the presence or absence of control exercise-induced ischemic dysfunction as manifested by the failure to exhibit a “normal” increase in exercise left ventricular ejection fraction. A normal exercise functional response was defined as an increase from rest to peak exercise of at least 0.05 in the absolute value for left ventricular ejection fraction. Although arbitrary, this value is similar to that used by previous investigators evaluating the utility of exer-

![Figure 6](http://circ.ahajournals.org/)

**FIGURE 6.** The effect of clinically effective antianginal doses of propranolol (Prop) on left ventricular ejection fraction (LVEF) (A) and mean normalized systolic ejection rate (MNSER) (B) at peak exercise, at work loads producing comparable heart rate–blood pressure products (HR x BP), and 5 minutes after cessation of exercise in patients with coronary artery disease and an abnormal response to exercise.
normal response was defined as an increase of less than 0.05 in absolute value from rest to peak exercise. As septal ejection fraction did not reflect global left ventricular ejection fraction in normal subjects and had a higher interobserver variability, the septum was not analyzed unless there was an absolute value change of greater than 0.1 with a directionally reciprocal change in the value for lateral ejection fraction.

Of the 54 segments in the 18 patients with coronary artery disease, 26 segments showed an abnormal response to exercise, 13 showed a normal response, and 15 of the septal segments were not analyzed. Of the 26 segments with an abnormal response to exercise, propranolol improved exercise performance in 21. At peak exercise, the improvement in exercise regional performance was significant ($p < 0.005$) (fig. 8). Comparing regional function at peak exercise on propranolol with values obtained at a level of control exercise producing a comparable heart rate–blood pressure product, a significant improvement was observed ($p < 0.025$). In contrast, propranolol did not have any statistically significant effect during peak exercise on the 13 normally responding segments when compared with control peak exercise and control exercise producing a comparable heart rate–blood pressure product.

During the control period, end-diastolic volume increased in 16 of 18 patients. Propranolol produced no significant effect on the average increase in end-diastolic volume during exercise (table 3).

**Effect of Propranolol on Postexercise Ventricular Performance**

As with the results obtained during exercise, the effect of propranolol on postexercise ventricular performance depended on the presence or absence of stress-induced ischemic dysfunction during the control period. In patients with an abnormal response to exercise, both left ventricular ejection fraction and mean
TABLE 3. Rest, Exercise and Postexercise Hemodynamic Variables in Patients with Coronary Artery Disease

<table>
<thead>
<tr>
<th>Control—abnormal response</th>
<th>LVEF</th>
<th>MNSER</th>
<th>LEF</th>
<th>SEF</th>
<th>AEF</th>
<th>No. of pixels marked or relative change in EDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>0.57</td>
<td>±0.08</td>
<td>2.9</td>
<td>±0.8</td>
<td>0.66</td>
<td>0.51</td>
</tr>
</tbody>
</table>
| Equivalent HR × BP        | 0.51 | ±0.1  | 2.9 | ±0.8 | 0.61 | 0.45 | 0.51 | ±0.12 | 34  | ±26%
| Peak exercise             | 0.48 | ±0.11 | 3.0 | ±0.8 | 0.57 | 0.37 | 0.49 | ±0.10 | 26  | ±24%
| After exercise            | 0.55 | ±0.07 | 2.9 | ±0.9 | 0.63 | 0.48 | 0.55 | ±0.13 | 5.4 | ±17%

<table>
<thead>
<tr>
<th>Propranolol—abnormal response</th>
<th>LVEF</th>
<th>MNSER</th>
<th>LEF</th>
<th>SEF</th>
<th>AEF</th>
<th>No. of pixels marked or relative change in EDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>0.58</td>
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<td>2.7</td>
<td>±0.8</td>
<td>0.67</td>
<td>0.51</td>
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</tbody>
</table>
| Equivalent HR × BP            | 0.58 | ±0.08 | 3.2 | ±1.1 | 0.67 | 0.48 | 0.57 | ±0.16 | 29  | ±33%
| Peak exercise                 | 0.63 | ±0.04 | 3.1 | ±0.8 | 0.69 | 0.54 | 0.64 | ±0.17 | -9.1| ±13%
| After exercise                | 0.56 | ±0.02 | 2.6 | ±0.2 | 0.63 | 0.51 | 0.58 | ±0.14 | 129 | ±13 |

<table>
<thead>
<tr>
<th>Control—normal response</th>
<th>LVEF</th>
<th>MNSER</th>
<th>LEF</th>
<th>SEF</th>
<th>AEF</th>
<th>No. of pixels marked or relative change in EDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>0.56</td>
<td>±0.02</td>
<td>2.6</td>
<td>±0.2</td>
<td>0.63</td>
<td>0.6</td>
</tr>
</tbody>
</table>
| Equivalent HR × BP            | 0.64 | ±0.04 | 3.9 | ±0.4 | 0.72 | 0.6  | 0.6  | ±0.06 | 26  | ±33%
| Peak exercise                 | 0.67 | ±0.04 | 4.3 | ±0.5 | 0.75 | 0.7  | 0.7  | ±0.06 | 18  | ±34%
| After exercise                | 0.0  | ±0.04 | 3.1 | ±0.4 | 0.69 | 0.66 | 0.66 | ±0.04 | -9.1| ±13%

<table>
<thead>
<tr>
<th>Propranolol—normal response</th>
<th>LVEF</th>
<th>MNSER</th>
<th>LEF</th>
<th>SEF</th>
<th>AEF</th>
<th>No. of pixels marked or relative change in EDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>0.55</td>
<td>±0.03</td>
<td>2.5</td>
<td>±0.2</td>
<td>0.62</td>
<td>0.6</td>
</tr>
</tbody>
</table>
| Peak exercise                 | 0.64 | ±0.03 | 3.8 | ±0.5 | 0.7  | 0.67 | 0.67 | ±0.04 | 25  | ±37%
| After exercise                | 0.63 | ±0.04 | 3.1 | ±0.5 | 0.69 | 0.67 | 0.67 | ±0.03 | -9.0| ±10%

Abbreviations: LVEF = left ventricular ejection fraction; MNSER = mean normalized systolic ejection rate; LEF = lateral ejection fraction; SEF = septal ejection fraction; AEF = apical ejection fraction; EDV = end-diastolic volume; HR × BP = heart rate–blood pressure product.

normalized systolic ejection rate remained lower than resting values 5 minutes after cessation of exercise before propranolol (fig. 6). Propranolol significantly improved recovery of left ventricular performance in 13 of the 14 patients. Unlike the control state, average postexercise global performance was increased compared with the basal values. The difference between postexercise left ventricular performance before and after propranolol therapy was highly significant for both left ventricular ejection fraction (p < 0.005) and left ventricular ejection rate (p < 0.01) (fig. 6). In contrast, in patients with a normal response to exercise, control postexercise left ventricular ejection fraction and left ventricular ejection rate were increased over resting values, and propranolol had no significant effect on recovery ventricular performance (fig. 7). Analysis of regional function during the recovery period showed results similar to those obtained for global left ventricular performance. In the regions that developed ischemic dysfunction during exercise, propranolol significantly improved recovery regional ejection fraction in 24 of 26 segments. The average difference was significant at the p < 0.005 level (fig. 8). In the normally responding regions, propranolol had no significant effect on postexercise regional ventricular performance.

Discussion

Effect of Propranolol on Basal Left Ventricular Performance

Investigations into the effect of propranolol on resting left ventricular function have yielded conflict-
The Effect of Propranolol on Ventricular Performance During Exercise in Normal Subjects

The effect of propranolol on left ventricular function during exercise in normal man has been evaluated in three previous investigations. Sonnenblick et al.22 analyzed force-velocity-length curves to evaluate the effect of i.v. propranolol on exercise ventricular performance in patients undergoing postoperative catheterization after closure of an atrial or ventricular septal defect. Ehrhardt et al.29 investigated the effect of i.v. propranolol on exercise left ventricular ejection fraction determined from multiple-gated equilibrium cardiac blood pool images. Port et al.34 used sequential first-pass radionuclide angiocardiograms to evaluate the effect of oral propranolol on global left ventricular ejection fraction and regional wall motion during exercise. Although it is difficult to compare doses due to different routes of administration, there was strong physiologic evidence for significant \( \beta \) blockade in each study. In all three reports, propranolol significantly depressed left ventricular performance during peak exercise. In addition, Sonnenblick et al.22 and Ehrhardt et al.29 found that the effect on exercise ventricular function of propranolol was independent of its effects on heart rate. In contrast, in the study of Port et al.,34 propranolol exerted no effect on left ventricular ejection fraction compared with values during control exercise, producing a heart rate comparable to that at peak exercise with propranolol.

The results of the current study are similar, in that large doses of propranolol depressed exercise ventricular function. In addition, the current results support the contention of Sonnenblick et al.22 and Ehrhardt et al.29 that the depressant effect of propranolol is independent of its effect on heart rate. The failure of 160 mg of propranolol/day to affect exercise ventricular performance significantly has not been reported. However, the presence of a small decrement in each of the radionuclide measures of exercise systolic performance, in addition to the small increase in end-diastolic volume during exercise, argues against excluding a depressant effect of moderate doses of propranolol. The data suggest that the negative inotropic effect of 160 mg/day was too small to be detected by the techniques used to evaluate ventricular function in this study.

The marked suppression of peak exercise heart rate produced by 160 mg of propranolol/day contrasts with the lack of a significant effect on exercise left ventricular function. Although part of this difference might have been due to limitations inherent in the radionuclide evaluation of ventricular performance, this observation implies different sensitivities of inotropic and chronotropic receptors to the effects of \( \beta \) blockade.24, 40, 41
the severely ischemic segment is unclear. Similar to the current results, the beneficial effect of \( \beta \) blockade on marginally ischemic function was independent of changes in heart rate. In a recent study evaluating the effect of i.v. propranolol on chronic ischemia produced by an ameroid constrictor, \( \beta \) blockade improved ventricular function during exercise. The improvement of exercise ventricular performance resulting from propranolol, independent of changes in ventricular preload and afterload related to heart rate and blood pressure, suggests that \( \beta \) blockade can improve regional ischemia by reducing sympathetic stimulation of the myocardial inotropic state. Mechanistically, an improvement in the balance of oxygen supply and demand could result from reduced oxygen demand associated with decreased inotropic stimulation or from diversion of blood flow from non-ischemic myocardium. In a recent study of the effect of propranolol on regional function in experimental myocardial infarction, \( \beta \)-adrenergic blockade increased blood flow to marginally ischemic myocardium. However, other investigators have not observed an effect of propranolol on blood flow in experimental myocardial ischemia, suggesting that decreased oxygen demand is the basis for reduced regional ischemia. Because extrapolation of results from experimental infarction in another species to clinical ischemia must be done cautiously, further clinical as well as experimental investigations must be performed to elucidate the mechanism by which \( \beta \) blockade improves regional ischemia in man.

Ideally, in any drug intervention study, observers should be blinded as to which part of the study they are processing. However, technical and strategic concerns related to data processing did not allow this to be a part of our experimental design. Therefore, observer bias might have affected our results. However, the excellent agreement between independent data processors on the effect of propranolol in 16 of 18 coronary artery disease patients in whom a highly variable response to the drug was observed suggest that observer bias was not an important contributing factor.

Propranolol at a dose of 160 mg/day produced no significant effect on exercise regional and global ventricular function in patients with coronary artery disease and a normal functional response to exercise or in the normal volunteers. The depressant effect of moderate doses of propranolol might be too small to be detected by the methods used in this study. Insensitivity and physiologic variability of the functional variables evaluated might have masked subtle changes in exercise ventricular function. In addition, technical aspects of radionuclide imaging and analysis adversely affecting interobserver reproducibility further reduces our ability to detect subtle changes in ventricular performance. Although the interobserver variability for left ventricular ejection fraction reported here is comparable to or even less than that in previous investigations, the greater variability in the detection of relative changes in end-diastolic volume suggests that alterations in end-diastolic volume to compensate for the negative inotropic and chronotropic effects of propranolol might not have been detected in the current study. However, in patients with exercise-induced ischemic dysfunction, the same considerations apply and yet a significant improvement in exercise ventricular performance was observed on an average daily dose of 160 mg of propranolol. Although age-related altered sensitivity to the effects of \( \beta \) blockade might have accounted for this difference in normal volunteers and patients with stress-induced ischemia, the demonstration that nonischemic regional and global performance in patients with coronary artery disease were also unaffected by moderate doses of propranolol suggests that ischemia renders the myocardium more sensitive to the effects of \( \beta \) blockade. This observation implies that the improved exercise global performance in ventricles with ischemic and nonischemic zones might, in part, be due to regionally altered sensitivity to the effect of propranolol.

In conclusion, \( \beta \) blockade with propranolol had no detectable effect on basal ventricular performance in normal subjects at doses producing intermediate and maximal \( \beta \) blockade and in patients with coronary artery disease at clinically effective antianginal doses. During exercise in normal subjects, a dose-related depression of regional and global exercise left ventricular performance was detected. In patients with coronary artery disease and an abnormal functional response to exercise, clinically effective antianginal doses improved exercise and postexercise regional and global left ventricular function; in patients with coronary artery disease and a normal response to exercise, propranolol had no significant effect on exercise ventricular function. These results imply that ischemic myocardium is more sensitive to the effects of \( \beta \) blockade. In normal subjects and patients with an abnormal ventricular response to exercise, propranolol’s effect on exercise left ventricular performance was independent of changes in ventricular preload and afterload related to heart rate and blood pressure.

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References


Effect of oral propranolol on rest, exercise and postexercise left ventricular performance in normal subjects and patients with coronary artery disease.
R C Marshall, G Wisenberg, H R Schelbert and E Henze

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