SUMMARY
The success of propranolol in treating the symptoms of angina pectoris has raised questions about the effects of beta-adrenergic blockade on the hemodynamic functions, myocardial mechanics, energetics, and metabolic functions. Five milligrams of propranolol was given intravenously to 27 human subjects, 18 with and nine without angiographically proven coronary atherosclerosis. The drug produced a decrease in externally measured indices of myocardial mechanical effort and consequently a fall in myocardial oxygen demands. The hemodynamic changes and resultant increases in myocardial oxygen consumption and coronary flow during supine leg exercise were also attenuated. Propranolol produced different changes in myocardial arteriovenous oxygen extraction depending upon whether the coronary circulation was normal or diseased. Although the data suggest that coronary vasoconstriction occurred in patients with atherosclerotic lesions, no significant change in myocardial lactate exchange was noted after administration of propranolol. Beta-adrenergic blockade caused a decline in cardiac filling pressures and volumes at the dose level used in this study, presumably by decreasing venous return.

Additional Indexing Words:
Coronary blood flow  Myocardial O₂ consumption
Myocardial lactate-pyruvate exchange  Left ventricular volume  Physical exercise
Beta-adrenergic blockade  Left ventricular pressure

PROPRANOLOL selectively blocks beta-adrenergic receptors.¹ This action has provided a new and potent approach to the therapy of a variety of cardiovascular disorders. It has proved particularly effective in treatment of the symptoms of angina pectoris.²-⁴

It is now well established that propranolol decreases many of the measurable external parameters of myocardial mechanical effort, such as heart rate, cardiac output, and external left ventricular work. Concomitant with these changes, coronary flow and myocardial oxygen consumption have been shown in man to be reduced below control values.⁴ The drug presumably decreases the severity of angina by lowering myocardial oxygen demand in a variety of circumstances.

Some issues remain unclear, however. What are the effects of propranolol upon coronary vasomotion? Does propranolol block the increase in myocardial oxygen demands associated with the usual cardiac response to exercise? What are the effects of propranolol upon myocardial lactate metabolism? What are the effects upon left ventricular filling pressure and volume at beta-receptor blocking doses?

Methods
Twenty-seven patients were studied by diagnostic cardiac catheterization and selective coronary cinearteriography for evaluation of chest pain. None had symptomatic congestive heart failure. Coronary arteriographic studies revealed that 18 had coronary occlusions or stenosis involving greater than 50% of the arterial lumen.
Nine had morphologically normal coronary arteries, with no irregularity of the vessel walls to suggest intramural atherosclerosis.

The group of patients with normal coronary arteries was composed of seven males and two females; their average age was 34.9 years. The group with coronary atherosclerosis was composed of 16 males and two females whose average age was 48.2 years. Hypertension, defined as blood pressure consistently exceeding 140/90 mm Hg, was present in three patients with coronary disease and two subjects with normal coronary arteries.

The informed consent of all patients was obtained for the study, which was carried out after all diagnostic procedures were completed. The study began a minimum of 20 min after completion of angiography. This period has been described as adequate for recovery from the hemodynamic effects of injected contrast material.

Catheters were placed in the coronary sinus, brachial artery, and left ventricle (LV). Pressures were measured at these sites with a Statham P23-D manometer and were recorded on a Sanborn 560 Polybeam recorder. Cardiac output was measured by the indocyanine green dye-dilution method.

Coronary flow was calculated in milliliters per 100 g of LV muscle per minute from a semi-logarithmic plot of the activity of the radioactive gas krypton in serial blood samples taken from the coronary sinus after LV injection. This technic is rapid, nontraumatic, and reproducible. Unfortunately, however, it yields only an average value for coronary flow per 100 g of LV muscle per minute. The washout curve is dominated by fast flow components. In a segmental disease such as coronary atherosclerosis, this is represented primarily by the blood supply to normally perfused zones of myocardium.

Coronary sinus and arterial blood samples were analyzed manometrically for oxygen content. LV volume was determined by cineventriculography in the right anterior oblique projection following injection of 30 to 40 cc of 75% sodium diatrizoate, under power, into the LV in nine subjects. Cine film was then exposed at 60 frames/second. The cine system, its calibration, and the calculation of volume have been described previously.

These data were recorded before, and 20 min after, intravenous infusion of 5 mg of propranolol.† Left ventricular and arterial pressures, cardiac output, coronary flow, and arterial and coronary sinus O₂ content were also measured at rest and during supine bicycle leg exercise in six patients. This stress was sufficient to raise total body O₂ consumption to an average of 2.25 times control. The patients, three with normal and three with diseased coronary arteries, were then given propranolol, and the rest-exercise sequence and data collection were repeated. The data from the four states were analyzed by the single classification analysis of variance. Comparisons were made among means by a sequential method.

The following aspects of LV performance were calculated from the following formulas:
1. Stroke index (SI) in ml/beat/m² as

\[ SI = \frac{CI}{HR} \]

where CI = cardiac index in ml/min/m² and HR = heart rate in beats/min.

2. Mean systolic ejection rate (MSER) in ml/sec/m² as

\[ MSER = \frac{SI}{sep} \]

where sep = systolic ejection period in sec/beat.

3. Left ventricular work index (LVWI) in kg/min/m² as

\[ LVWI = \frac{1.36 \times (LVSP - LVEDP) \times (CI)}{100} \]

where LVSP = mean left ventricular systolic pressure; LVEDP = mean LV end-diastolic pressure, both in mm Hg.

4. Pressure-time per minute (PTM) in mm Hg sec as

\[ PTM = LVSP \times SEP \]

where SEP = systolic ejection period time/min.

The state of the coronary vascular bed was evaluated by the following measurements in 20 patients, 12 with and eight without coronary disease:
1. Myocardial arteriovenous (A-V) oxygen extraction was calculated as the percentage of arterial content from the fraction:

\[ \frac{\text{Arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}{\text{Arterial } O_2 \text{ content or } (A - V)} = A \]

2. Myocardial oxygen consumption (qO₂) was calculated in ml/100 g/min as the product of coronary flow* and the arteriovenous O₂ difference.

*The coronary flow measurement was technically unsatisfactory in one patient. Therefore, myocardial qO₂ and dependent measurements could be calculated in only 19 subjects.
3. Mean coronary vascular resistance (CVR) in dynes sec cm\(^{-5}\) was determined from the equation:

\[
\frac{BA_m - CS_m}{CF} \times 80,000,
\]

where \(BA_m\) = brachial arterial mean pressure in mm Hg, \(CS_m\) = coronary sinus mean pressure in mm Hg, and \(CF\) = coronary flow* in ml/100 g/min.

The distribution of age, sex, and incidence of hypertension in this subgroup with studies of coronary blood flow was not different from the group as a whole. Paired simultaneous blood samples were drawn for lactate and pyruvate determination from the brachial artery and from sites within the coronary sinus. The samples were collected and analyzed as reported previously.12 Five patients, all with coronary artery disease, were studied. None complained of chest pain at any time during the study. Paired samples were obtained from the artery and from two sites in the coronary sinus in one instance and three sites in the coronary sinus in another case. Thus, a total of eight paired samples was obtained during the control state and after propranolol. After beta-adrenergic blockade was established, an additional five pairs of samples were obtained during isoproterenol infusion at a rate averaging 8 \(\mu\)g/min. This rate was sufficient to overcome the blockade as judged by the ultimate induced increase in average heart rate. Pain was not produced in any patient by infusion of isoproterenol.

The lactate and pyruvate data were analyzed in two ways: (1) Arterial and coronary sinus lactate concentrations were compared to detect myocardial lactate extraction or production.13 (2) Since lactate concentrations in both arterial and coronary sinus blood are dependent to a large degree upon the available pyruvate, and since pyruvate is found in such small amounts in arterial blood that precise calculations based on pyruvate concentration are subject to substantial errors, the data were expressed as ratios of lactate to pyruvate (L/P).14 and only the difference between arterial and coronary sinus L/P ratios was analyzed (that is whether the arterial-coronary sinus L/P ratio is greater or less than unity). Under normal circumstances, the arterial L/P ratio exceeds the L/P ratio in coronary sinus blood.

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*The coronary flow measurement was technically unsatisfactory in one patient. Therefore, myocardial \(qO_2\) and dependent measurements could be calculated in only 19 subjects.

Circulation, Volume XL, October 1969

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Results

Myocardial Oxygen Consumption (\(qO_2\))

At Rest

The average myocardial \(qO_2\) for the 20 subjects fell from 11.4 to 9.1 ml/100 g of LV/min after infusion of propranolol (\(P < 0.001\)) (table 1). The oxygen consumption per beat decreased slightly from 0.15 to 0.13 ml/beat.

This decrease occurred simultaneously with a decline in the mechanical effort of the left ventricle (table 2). Systemic arterial systolic mean pressure, heart rate, cardiac index, ventricular work, and pressure time per minute all decreased significantly. There was little change in stroke volume or mean arterial pressure. Average LV end-diastolic pressure decreased from 14.6 to 12.0 mm Hg (\(P < 0.01\)). Average left ventricular end-diastolic volume fell from 97 to 87 ml/m\(^2\), but the series was too small (nine studies) for statistical significance.2 No difference was observed between the hemodynamic responses of the 19 patients with coronary disease and the eight subjects with normal vessels.

During Exercise

An identical level of leg exercise elevated the average myocardial \(qO_2\) in six patients from 10.3 to 17.4 ml/100 g LV/min before propranolol was given, and from 9.1 to only 14.0 ml after propranolol administration (\(P < 0.05\)) (fig. 1).

Concomitantly, mean heart rate, left ventricular external work, pressure-time per minute, and cardiac index all increased to a lesser degree after the administration of propranolol than prior to blockade (\(P < 0.05\)) (fig. 2).

Coronary Flow

At Rest

Concomitant with reduced myocardial oxygen consumption, average coronary flow decreased from a control value of 98.1 to 80.2 ml/100 g/min after propranolol (\(P < 0.001\)) (table 1).

During Exercise

As with myocardial oxygen consumption, beta-adrenergic blockade reduced the level of coronary flow induced by supine leg exercise.
### Table 1

**Coronary Hemodynamic Effects of Propranolol**

<table>
<thead>
<tr>
<th></th>
<th>CF (ml/100 g LV/min)</th>
<th>qO₂ (ml/100 g LV/min)</th>
<th>A-V O₂ diff. (ml/100 g LV/min)</th>
<th>A-V/A (X 100)</th>
<th>CVR (X 10⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>P</td>
<td>C</td>
<td>P</td>
<td>C</td>
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<tr>
<td><strong>Normal coronary arteries</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>L.S.</td>
<td>88</td>
<td>94</td>
<td>10.0</td>
<td>9.2</td>
<td>11.4</td>
</tr>
<tr>
<td>D.T.</td>
<td>66</td>
<td>63</td>
<td>8.4</td>
<td>6.4</td>
<td>12.8</td>
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<tr>
<td>E.R.</td>
<td>99</td>
<td>73</td>
<td>15.2</td>
<td>8.5</td>
<td>15.3</td>
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<td>G.P.</td>
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<td>110</td>
<td>11.1</td>
<td>9.1</td>
<td>10.6</td>
</tr>
<tr>
<td>E.R.</td>
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<td>113</td>
<td>10.9</td>
<td>10.6</td>
<td>10.5</td>
</tr>
<tr>
<td>R.E.</td>
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<td>51</td>
<td>8.7</td>
<td>6.4</td>
<td>10.2</td>
</tr>
<tr>
<td>E.G.</td>
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<td>92</td>
<td>18.0</td>
<td>10.7</td>
<td>12.3</td>
</tr>
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<td>J.S.</td>
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<td>57</td>
<td>10.0</td>
<td>7.4</td>
<td>10.7</td>
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<td>Mean</td>
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<td>81.6</td>
<td>11.5</td>
<td>8.5</td>
<td>11.7</td>
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<tr>
<td>±SE</td>
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<td>8.5</td>
<td>1.2</td>
<td>0.6</td>
<td>0.60</td>
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<td>12.5</td>
</tr>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>13.4</td>
</tr>
<tr>
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<td>10.4</td>
<td>7.9</td>
<td>11.4</td>
</tr>
<tr>
<td>B.K.</td>
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<td>16.1</td>
<td>9.3</td>
<td>12.9</td>
</tr>
<tr>
<td>A.M.</td>
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<td>10.0</td>
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<td>11.7</td>
</tr>
<tr>
<td>R.N.</td>
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<td>17.2</td>
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<td>11.7</td>
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<td>7.7</td>
<td>7.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Mean</td>
<td>97.8</td>
<td>79.1</td>
<td>11.2</td>
<td>9.6</td>
<td>11.6</td>
</tr>
<tr>
<td>±SE</td>
<td>7.15</td>
<td>4.0</td>
<td>0.93</td>
<td>0.42</td>
<td>0.31</td>
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</table>

**Total**

<p>| | | | | | |</p>
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<th></th>
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<th></th>
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<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Mean</td>
<td>98.1</td>
<td>80.2</td>
<td>11.4</td>
<td>9.1</td>
<td>11.64</td>
</tr>
<tr>
<td>±SE</td>
<td>5.2</td>
<td>4.1</td>
<td>0.71</td>
<td>0.36</td>
<td>1.44</td>
</tr>
</tbody>
</table>

| *P*      | <0.001 | <0.001 | NS | NS | <0.025 |

**Abbreviations:** CF = coronary flow (ml/100 g LV/min); qO₂ = myocardial O₂ consumption (ml/100 g LV/min); A-V O₂ diff. = myocardial arteriovenous O₂ difference (ml/100 ml); \( \frac{A-V}{A} \times 100 \) = percentage of myocardial O₂ extraction; CVR = coronary vascular resistance (dynes sec cm⁻⁵); C = control; P = propranolol.

* P <0.025, t-test for paired observations.

During the identical amount of exercise average coronary flow for the six patients studied was 115 ml/100 g LV/min after blockade compared with 140 ml/100 g LV/min before blockade \( (P<0.05) \) (fig. 1).

**Effects on Coronary Vascular Bed**

**At Rest**

Mean coronary vascular resistance was increased by propranolol \( (68 \times 85 \times 10^3 \text{ dynes sec cm}^{-5}; \ P < 0.025) \) (table 1). The change induced in the two groups of patients with either normal or diseased coronary arteries was not statistically different.

No change in average arteriovenous oxygen difference \( (11.6 \text{ to } 11.7) \) and average myocardial oxygen extraction \( (66 \text{ to } 67\%) \) was produced by propranolol. Analysis in terms of the underlying disease, however, revealed significant differences between the patients with,
Table 2

Effects of Propranolol

<table>
<thead>
<tr>
<th>Hemodynamics (N = 27)</th>
<th>Mean ±se</th>
<th>Control</th>
<th>Propranolol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean brachial arterial systolic pressure (mm Hg)</td>
<td>118 ± 2.5</td>
<td>115 ± 3.2</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Mean brachial arterial pressure (mm Hg)</td>
<td>103 ± 3.1</td>
<td>97 ± 2.7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>14.6 ± 1.5</td>
<td>12 ± 1.6</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>79 ± 3.4</td>
<td>71 ± 2.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Systolic ejection rate (ml/sec/m²)</td>
<td>112 ± 5.6</td>
<td>103 ± 4.4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.5 ± 0.08</td>
<td>2.1 ± 0.09</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>31.8 ± 1.7</td>
<td>29.3 ± 1.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Left ventricular work (kg/min/m²)</td>
<td>3.8 ± 0.44</td>
<td>3.0 ± 0.16</td>
<td>&lt;0.02</td>
<td></td>
</tr>
<tr>
<td>Pressure time/min (mm Hg sec/min)</td>
<td>2780 ± 93</td>
<td>2380 ± 94</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1

Effects of propranolol on myocardial energy needs during physical exercise. Coronary flow and myocardial oxygen consumption (qO₂) were lower after beta-adrenergic blockade during identical levels of supine leg exercise (P < 0.05). The stress imposed increased total body qO₂ to an average of 2.25 times the rest level both before and after propranolol administration.

Figure 2

Attenuation of the hemodynamic response to exercise by propranolol. Mean heart rate (HR), cardiac index (CI), pressure-time per minute (PTM) and left ventricular external work index (LVw) were significantly lower (P < 0.05) than before propranolol at identical levels of supine leg exercise after beta blockade.
and the patients without, coronary artery disease, despite similar declines in myocardial oxygen consumption and coronary flow.

In 10 of the 12 patients with coronary artery disease, the arteriovenous oxygen difference or the myocardial oxygen extraction or both increased. This was significant for the group \( (P < 0.025) \) (table 1, fig. 3). Of the patients with normal coronary arteries five of eight showed decreased myocardial oxygen extraction, and six showed decreased arteriovenous oxygen differences. Although statistical significance could not be established, the changes in mean A-V \( \text{O}_2 \) difference (11.7 to 10.8) and \( \text{O}_2 \) extraction (68 to 65%) were opposite in direction from those seen in coronary patients (fig. 3). These normal subjects, therefore, responded to decreased myocardial mechanical demands by extracting less oxygen from the blood delivered to the myocardium, as well as by a decrease in coronary flow. The same pattern of response was recorded during exercise (see below).

**During Exercise**

The mean myocardial \( \text{O}_2 \) extraction of both normal subjects and those with coronary artery disease increased with exercise both before and after beta-adrenergic blockade. In relation to each control state (rest or exercise), however, mean oxygen extraction in the normal patients was lower after propranolol administration. Conversely, the subjects with ischemic heart disease showed a higher oxygen extraction in both states after beta-blockade (table 3).

**Myocardial Lactate and Pyruvate Metabolism**

Propranolol caused little change in the mean arterial lactate level (0.61 to 0.55 mM/L) or in mean myocardial lactate extraction (14 to 16%). Lactate production was demonstrated during the control period in two paired samples. Following blockade, lactate production disappeared in one case, and production decreased in the other. In the remaining six pairs lactate extraction occurred during the control state. In four of the six, increased lactate extraction was observed after propranolol administration. In one, a small decrease in

![Figure 3](https://circ.ahajournals.org/)

**Figure 3**

Coronary vascular actions of propranolol. Coronary flow and myocardial \( q\text{O}_2 \) fell in both normal subjects and patients with coronary artery disease (CAD). In normal subjects the A-V \( \text{O}_2 \) difference and per cent \( \text{O}_2 \) extraction were decreased after propranolol was given. In the diseased vascular bed, however, both values increased (table 1). The increase in percentage of oxygen extraction was significant \( (P < 0.025) \).

![Figure 4](https://circ.ahajournals.org/)

**Figure 4**

Effect of propranolol on myocardial lactate metabolism. The percentage of lactate extraction in eight paired instantaneous arterial and coronary sinus samples is portrayed at rest, after propranolol, and then (five pairs) during isoproterenol infusion. No significant change in myocardial lactate extraction is manifest, although six of eight pairs are shifted toward increased extraction. Isoproterenol, given in high doses (averaging 8 \( \mu \text{g/min} \)) to overcome the blockade, consistently caused the opposite effect.

Circulation, Volume XL, October 1969
Table 3

Myocardial Oxygen Extraction (Per Cent) During Exercise

<table>
<thead>
<tr>
<th>Normal</th>
<th>Control</th>
<th>Propranolol</th>
<th>Exercise</th>
<th>Rest</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>4</td>
<td>63</td>
<td>65</td>
<td>65</td>
<td>69</td>
</tr>
</tbody>
</table>

Figure 5

Effect of propranolol on ratios of myocardial lactate to pyruvate. Since lactate concentrations are determined to a large extent by available pyruvate, the ratio of lactate to pyruvate (L/P) may be a better index of myocardial oxygenation than lactate alone (see text). $A = \text{arterial } L/P \text{ ratio; } V = \text{coronary } L/P \text{ ratio.}$

Three were examined during isoproterenol infusion after beta-blockade and no change was recorded in relation to the propranolol state.

Documentation of Beta-Adrenergic Blockade

As shown in figure 6, propranolol markedly attenuated the hemodynamic response to isoproterenol. Although a greater dose of isoproterenol was infused after propranolol administration, most parameters measured were not significantly changed from pre-infusion values. The remainder, although increased, were not elevated above the control levels.


Discussion

Coronary Vasomotion

Coronary flow is proportional to the net perfusion pressure (primarily the aortic diastolic pressure) opposed by the resistance of the small vessels in the coronary vascular bed. Changes in myocardial mechanical effort, by altering oxygen demand, affect coronary flow through a variety of mechanisms. It has, therefore, proved necessary to discuss coronary vasomotion in terms of the relationship between oxygen supply and demand. The myocardial arteriovenous oxygen difference (A−V) and the per cent of arterially supplied oxygen extracted by the heart (\( \frac{A-V}{A} \)) have been suggested as indices of this relationship.

Thus, a primary vasodilator should decrease the A−V O₂ difference and per cent O₂ extracted by the heart as evidence that it increased coronary flow to a greater extent than any simultaneous effects upon oxygen demand. Such an agent would be hydralazine, or isoproterenol. Norepinephrine, on the other hand, does increase coronary flow but appears to be a primary vasoconstrictor. Both the A−V O₂ difference and the percent O₂ extracted by the heart (\( \frac{A-V}{A} \)) are increased by this agent.

The rise in coronary flow is related primarily to increased coronary perfusion pressure, secondarily to augmented myocardial contractile effort and metabolic rate produced by this agent, but the demand for oxygen, nevertheless, is elevated beyond the increment in coronary flow.

In patients with normal coronary vasculature, both the myocardial A−V O₂ difference and the O₂ extraction fraction tended to decrease. Six of eight showed a smaller A−V O₂ difference and five of eight showed a lower percentage of O₂ extraction during beta-blockade than in the control state. This response has been reported by Nayler and associates on using propranolol in normal dogs. Scott and Balourdas found similar results following chronic sympathectomy in dogs.*

These findings are consistent with one of two situations:

1. Propranolol has nonspecific beta-adrenergic-stimulating or alpha-blocking actions. Experimental data have been reported which also suggest that the distinction between alpha and beta-adrenergic functions is not yet completely clarified for the coronary vascular bed. Berne has shown a biphasic change in coronary flow when norepinephrine and epinephrine are infused directly into coronary arteries in dogs. An initial decrease, followed by a prolonged increase in coronary blood flow was seen, the latter phase being associated with an increased A−V O₂ difference. Mendez and Kabela confirmed these findings and showed identical results with isoproterenol. Both phases in their study were abolished by beta blockade.

2. Little or no beta-adrenergic activity exists to be abolished in the basal normal coronary circulation, but significant beta-receptor-mediated vasodilatation exists at rest in patients with coronary disease. The latter possibility is supported by the fact that patients with coronary artery disease showed both an increased A−V O₂ difference and a reduced coronary flow after propranolol. This "vasoconstrictor" response can probably be explained by a different basal "set" of the vascular bed in the diseased subject, who may well have chronic coronary vasodilation in the normally perfused areas of myocardium. The coronary sinus oxygen saturation is often unusually high in patients with coronary atherosclerosis. The sinus oxygen concentration predominantly reflects the major portion of coronary flow which has perfused normal zones of the heart.

Coronary vasoconstriction appears to be an anomalous effect of an anti-anginal agent. It

*McKenna and co-workers have described coronary vasoconstriction by the criteria used above when propranolol was given to resting dogs. Their data are hard to interpret, however, as the dose used in their study was 2 mg/kg (more than 10 times that utilized by the other investigators cited).
is possible, however, that this action of propranolol may result in a more equitable distribution of coronary flow. This would occur if collateral vessels supplying ischemic zones arose proximal to the arteriolar resistance bed and did not contain adrenergic receptors. Under these circumstances, the collaterals would be given a selective advantage regarding perfusion when undiseased arterioles were constricted due to unopposed alpha effects after propranolol. If this occurred and if flow to ischemic zones were improved but did not reach "normal" levels, the proportion of highly unsaturated blood from these areas might increase. The result might be a decrease in coronary sinus oxygen content, as observed in this study.

In both normal subjects and patients with coronary disease, propranolol produced increased coronary vascular resistance. This probably represented contraction of the vascular bed in response to decreased needs.26

Myocardial Energy Needs at Rest and During Stress

Propranolol has previously been shown to decrease myocardial oxygen demands at rest in both animals and man. It has also been shown to diminish the mechanical response of the heart to stresses such as exercise.2,23,27,28

In this study, a significant decrease in myocardial oxygen demands has been documented after administration of propranolol both at rest and during the stresses of isoproterenol infusion or supine leg exercise. This attenuation occurred pari passu with similarly muted hemodynamic response to these challenges. Thus, it would appear that the anti-anginal effects of propranolol can be attributed to decreased oxygen demand not only at rest, but also under circumstances of catecholamine stress or physical exercise.

Effects on Left Ventricular Filling Pressure and Volume

In this series and in previously reported experiences,4 propranolol has reduced left ventricular end-diastolic pressure, right atrial pressure, and probably left ventricular volume in man. Several investigators have reported different results from ours, that is, increased left ventricular end-diastolic pressure suggesting an increase in left ventricular volume. Without exception, these studies27-30 have been performed with larger doses of the drug than were used herein.

The effects of propranolol on ventricular filling pressure and volume may vary, however, because two opposing pharmacologic actions are involved:

1. Propranolol's net cardiac actions may be partially due to peripheral venodilation and a consequent fall in venous return. Isoproterenol has been shown in one study to cause venoconstriction in canine preparations.31 Nayler's group,31 utilizing dogs on total cardiopulmonary bypass, has studied the effects of propranolol upon flow through the major vascular beds. Perfusing the animals at a constant arterial pressure, they noted dilatation of the inferior and superior venae cavae, draining the pelvis and lower extremities, and the upper extremities and head, respectively. This was evidenced by increased flow and decreased vascular resistance in these segments. Splanchnic, renal, and coronary flow fell. The net result was a fall in total venous return independent of any cardiac effects of propranolol.

In our study, the uniform reduction in left and right-s'ided filling pressures4 at the dose of blocker given suggests that beta-blockade decreases venous return in the intact human being as well.

2. Tending to offset reduction in filling pressure secondary to decrease in venous return would be negative inotropic actions of propranolol, which are unrelated to its beta-blocking properties, but probably allied to its local anesthetic effects.32 These have been shown to be minimal in normal subjects.28 Patients with congestive heart failure, however, depend on adrenergic stimulation of the myocardium even at rest. Thus, beta-adrenergic blockade might depress the heart and elevate end-diastolic pressure in patients with severely impaired cardiac reserve. Propranolol, however, has proved to be safe in patients with medically controlled heart failure.33 No patients
with symptomatic congestive failure were included in this study.

The effects of propranolol upon ventricular filling pressure and volume are the sum of interacting factors. Since it is, in any event, a competitive beta-antagonist, it is not surprising that varying its dose changes its observed effects.

**Metabolic Effects**

Propranolol caused no significant change in mean myocardial lactate extraction (14 to 16%), thus, despite a reduction in coronary blood flow and an increase in myocardial oxygen extraction, no evidence for increased myocardial glycolysis, such as was suggested by Robin and associates, could be added.

High doses of the agonist (isoproprenal) overcame the beta-blockade as judged by increases in heart rate. This resulted in either decreased extraction or frank production of lactate as evidence of myocardial glycolysis occurring with augmented mechanical activity in patients with coronary artery disease.

**Comparison with Physical Training**

Programs of physical training and conditioning have been utilized as therapy for selected patients with angina pectoris, often producing considerable amelioration of their symptoms. Hemodynamic and metabolic observations in patients with coronary artery disease have shown that physical conditioning reduces the response of cardiac output and left ventricular external work to physical exercise. While total body oxygen consumption is unchanged, the mixed A−V oxygen difference widens. Nonetheless, arterial lactate concentrations fall. In every respect, these effects are shared by propranolol, indicating that both interventions may owe their impact on angina to decreases in myocardial oxygen demands for any given amount of physical effort.

Studies of the effects of training in normal subjects have not always shown a fall in cardiac output with submaximal effort. They have consistently suggested, however, that changes in this or other factors (such as heart rate or tension-time index after conditioning) tend to reduce myocardial oxygen requirements for any given work load.

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