Propranolol in the Treatment of Acute Myocardial Infarction

Effect on Myocardial Oxygenation and Hemodynamics

By Hiltrud S. Mueller, M.D., Stephen M. Ayres, M.D., Anna Religa, M.D., Ph.D., and Robert G. Evans, B.A.

SUMMARY

Improvement of myocardial oxygenation is a major goal in the treatment of ischemic heart disease. Propranolol, 0.1 mg/kg intravenously, was administered to 20 patients in the acute state of myocardial infarction without clinical evidence of left ventricular failure. The most important hemodynamic response was a substantial decrease in myocardial contractility. This was reflected by a fall in cardiac index (average of 0.6 L/min/M², \( P < 0.001 \)) and of arterial mean pressure (average of 16 mm Hg, \( P < 0.001 \)) with little change in systemic vascular resistance. Decrease in cardiac index was due mainly to decrease in stroke volume. Heart rate, not strikingly increased at the control state in the majority of patients, decreased an average of 7 beats/min (\( P < 0.001 \)). Pulmonary wedge pressure rose an average of 2 mm Hg (\( P < 0.05 \)). It remained unchanged or decreased in three patients. These varying but small changes in wedge pressure in the presence of decreased contractility may be related to improved left ventricular compliance, produced by propranolol. Propranolol markedly improved myocardial metabolism. Arterial coronary sinus oxygen difference decreased an average of 0.72 ml/100 ml (\( P < 0.001 \)); coronary sinus oxygen tension increased an average of 2 mm Hg. Myocardial lactate production shifted to extraction (average of \(-8\%\) to \(14\%\)) or the rate of lactate extraction increased (average of \(20\%\) to \(29\%\)). Coronary blood flow decreased an average of 13 ml/100 g/min (\( P < 0.001 \)). Both decrease in mean aortic pressure and decrease in myocardial oxygen requirements probably contributed to the fall in coronary blood flow. The finding, that myocardial metabolism improved, suggests that reduction in myocardial oxygen demand outweighed the decrease in coronary blood flow. None of the 20 patients developed left ventricular failure or other complications related to beta-adrenergic blockade. Severe chest pain, unresponsive to conventional therapy in four patients, was relieved by propranolol. These findings demonstrate that acutely administered propranolol improves myocardial oxygenation in patients with uncomplicated acute infarction without endangering perfusion of other vital organs.

Additional Indexing Words:
Coronary blood flow  Myocardial lactate metabolism  Beta-adrenergic blockade

CLINICAL AND EXPERIMENTAL OBSERVATIONS, made during the past decade, support the belief that myocardial infarction develops in a stepwise manner and that myocardial tissue may be salvaged by techniques designed to interrupt this progressive necrotic process.¹⁻⁴ Beta-adrenergic blockade,⁵⁻⁷ peripheral vasodilatation,⁹⁻¹¹ cardiac assistance,¹²⁻¹⁸ and early coronary artery surgery¹⁹⁻²¹ have all been proposed as therapeutic interventions which might salvage myocardial tissue and decrease mortality from acute myocardial infarction. Our early observations that beta-adrenergic stimulation produced metabolic deterioration in different stages of coronary artery disease,¹⁴,²² together with parallel studies revealing the frequent occurrence of augmented myocardial free fatty acid uptake in complicated infarction,²³ suggested that beta-adrenergic blockade might be useful in limiting infarct size. Further evidence supporting this is the clinical finding that beta-adrenergic blockade decreases chest pain in both angina pectoris and acute myocardial infarction²⁴⁻³³ and the observation of Maroko et al.⁴ that beta-adrenergic blockade reduces the size of experimentally produced myocardial infarcts.

We recently presented evidence indicating that
myocardial metabolic changes might be a sensitive indicator of infarct size. If this is the case, improvement in myocardial oxygenation with beta-adrenergic blockade would be an important preliminary step in evaluating the clinical value of the drug. The present paper presents observations of myocardial metabolic measures in 20 patients treated with propranolol during the early stages of acute transmural myocardial infarction without evidence of left ventricular failure. The study demonstrates that beta-adrenergic blockade is capable of acutely reversing the metabolic abnormalities associated with acute myocardial ischemia.

**Methods**

Patients were considered for the present study if the criteria for an acute transmural myocardial infarction were met by development or presence of Q waves, of acute elevation of ST segments, and by a history characteristic of acute myocardial infarction. The patients were admitted to the coronary care unit either directly from the coronary ambulac or from the emergency room immediately after the diagnosis of acute myocardial infarction was obtained. The study was performed an average of six to eight hours after admission to the hospital. The patient was not included in the study if one or more of the following findings were observed: 1) previous history of cardiac failure; 2) symptoms of present cardiac failure such as cardiac enlargement, dyspnea, or bibasilar rales; 3) pulmonary venous congestion on chest radiograph; 4) systolic arterial cuff pressure of less than 110 mm Hg; 5) heart rate below 65 beats per minute; 6) atioventricular or intraventricular conduction delay; 7) history of asthma or bronchitis.

The protocol for hemodynamic and metabolic evaluation and for intravenous administration of propranolol was approved by the hospital research committee. Informed consent was obtained from the patient after having explained the purpose of the evaluation, the effects of the medication, and the placement of catheters. Most patients were medicated with morphine, meperidine, or lidocaine at the time of admission, but received no further medication 50-60 minutes before the control evaluation.

A *16 polyethylene catheter was advanced into the brachial artery via puncture of the surgically-exposed radial artery. A *7 Goodale Lubin catheter was placed into the coronary sinus via cutdown of the left medial basilic vein. A *6 teflon catheter was placed into the right atrium (12 patients), a *5 Swan Ganz catheter into the pulmonary artery (eight patients) via puncture of the right femoral vein, using the Seldinger technique. Cardiac output was determined in eight patients by the direct Fick method. Coronary blood flow was measured by a modification of the method of Krasnow, using *10 antipyrene as the indicator. Details about techniques, determination of blood concentrations of oxygen, lactate, pyruvate, and glucose, of plasma pH, oxygen and carbon dioxide tension, and of blood concentration of free fatty acids were previously published. After control evaluation 0.1 mg/kg propranolol was given intravenously in three divided doses at 5 min intervals. Ten minutes after the last administration of propranolol, measurements of hemodynamics, coronary blood flow, and myocardial metabolism were repeated.

**Calculation**

Time-tension index per minute, TTM, (mm Hg-sec/min) = mean systolic arterial pressure times systolic ejection period times heart rate. Systolic ejection rate, SER, (ml/sec/M²) = stroke index divided by systolic ejection period. Coronary vascular resistance, CPR, (dynes-sec-cm⁻⁵/1000) = mean diastolic arterial pressure minus mean right atrial pressure times diastolic filling period per min times 1332 divided by coronary blood flow times 0.75. Myocardial oxygen consumption, MVO₂, (ml/ 100 g/min) = arterial−coronary sinus oxygen difference times coronary blood flow. Myocardial respiratory quotient, MRQ = coronary sinus−arterial CO₂ difference divided by arterial−coronary sinus O₂ difference. Myocardial extraction ratio, Ex, (%) = arterial−coronary sinus difference divided by arterial content.

**Results**

Twenty patients, 19 men and one woman, were studied 6-8 hours following hospital admission for acute transmural myocardial infarction. The average age was 55 years and ranged from 36 to 74 years. The electrocardiogram revealed anterior wall infarction in five, anterior-lateral wall infarction in eight, and inferior wall infarction in seven patients. In three instances, the acute inferior wall infarction was associated with severe anterior-lateral wall subendocardial ischemia. Peak creatine phosphokinase averaged 1085 units/ml (range 146-2650); initial arterial free fatty acid concentration averaged 987 μ M/L (range 100-1450), of lactate 1.73 mM/L (range 0.69-3.44), glucose concentration averaged 184 mg% (range 118-304). All 20 patients tolerated the intravenously administered propranolol well. None developed dyspnea or other clinical findings of left ventricular failure. Perfusion of skin and urine output remained adequate. Two patients complained of fatigue after propranolol. These symptoms occurred in presence of a cardiac index of 2.70 and 2.22 L/min/M² and are probably not related to poor organ perfusion. None of the patients developed atioventricular or intraventricular conduction delays. Anginal pain, unresponsive to meperidine or morphine therapy, disappeared in four patients after propranolol. All patients survived and left the hospital.

**Initial Results of Hemodynamics and Myocardial Oxygenation in Acute Myocardial Infarction**

Mean values are shown in tables 1 and 2, individual measurements in figures 1, 2, and 3. Heart rate varied from 57 to 110 beats per minute and arterial pressures ranged from 104–202 mm Hg systolic, 66–103 mm Hg diastolic and 68–138 mm Hg mean (fig. 1). Right atrial pressure varied from 2 to 10 mm Hg and pulmonary wedge pressure, measured in eight patients, ranged
from 8 to 20 mm Hg. Cardiac index and arterial-pulmonary artery oxygen difference, also measured in eight of the patients, varied between 1.68–3.2 L/min/M² and 3.5–5.8 ml/100 ml respectively (fig. 2).

Coronary blood flow averaged 77 ml/100g/min (range 56–96), myocardial oxygen consumption 9.20 ml/100g/min (range 7.24–13.8), and myocardial oxygen extraction ratios were between 53 to 80% (fig. 3). Coronary sinus oxygen tension varied from 20 to 37 mm Hg. Five patients revealed myocardial lactate production and five had abnormally low myocardial lactate extraction (below 15%). Lactate extraction was normal in the remaining ten patients (fig. 3). Free fatty acid extraction ranged from 0% to 50%; six patients had free fatty acid extractions in excess of 15%.

### Table 1

**Effects of Propranolol on Hemodynamics and Arterial Substrate Contents**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean ± Standard Deviation</th>
<th>% Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>N = 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>80 ± 15</td>
<td>73 ± 14</td>
<td>− 9</td>
</tr>
<tr>
<td>Arterial systolic pressure (mm Hg)</td>
<td>130 ± 30</td>
<td>107 ± 23</td>
<td>−18</td>
</tr>
<tr>
<td>Arterial diastolic pressure (mm Hg)</td>
<td>72 ± 13</td>
<td>62 ± 11</td>
<td>−14</td>
</tr>
<tr>
<td>Arterial mean pressure (mm Hg)</td>
<td>92 ± 18</td>
<td>76 ± 16</td>
<td>−17</td>
</tr>
<tr>
<td>Time-tension index (mm Hg sec/min)</td>
<td>2481 ± 735</td>
<td>1054 ± 531</td>
<td>−21</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>6.6 ± 3.0</td>
<td>6.1 ± 3.8</td>
<td>−8</td>
</tr>
<tr>
<td>Arterial lactate content, mM/L</td>
<td>1.65 ± 0.65</td>
<td>1.92 ± 0.62</td>
<td>+16</td>
</tr>
<tr>
<td>Arterial free fatty acid content (μM/L)</td>
<td>933 = 416</td>
<td>873 = 454</td>
<td>−7</td>
</tr>
<tr>
<td>N = 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index, L/min/M²</td>
<td>2.6 = 0.46</td>
<td>2.0 = 0.38</td>
<td>−23</td>
</tr>
<tr>
<td>Stroke index, ml/beat/M²</td>
<td>32 = 6.56</td>
<td>28 = 5.71</td>
<td>−13</td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mm Hg</td>
<td>12 = 4.3</td>
<td>14 = 2.9</td>
<td>+27</td>
</tr>
<tr>
<td>Arterial - pulmonary artery O₂ difference (ml/100 ml)</td>
<td>5.0 = 1.47</td>
<td>5.5 = 0.96</td>
<td>+10</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne-sec-cm⁻¹)</td>
<td>1451 = 547</td>
<td>1635 = 578</td>
<td>+13</td>
</tr>
<tr>
<td>Systolic ejection rate (ml/sec/M²)</td>
<td>115 = 34</td>
<td>97 = 29</td>
<td>−16</td>
</tr>
</tbody>
</table>

**Effect of Propranolol on Systemic Hemodynamics**

Figure 1 shows that heart rate decreased following propranolol administration in all but three patients; the mean changed from 80 to 73 beats per minute. All indices of arterial blood pressure decreased; peak systolic pressure fell from an average of 130 to 107 mm Hg, diastolic pressure from 72 to 62 mm Hg, and mean arterial pressure from 92 to 76 mm Hg (fig. 1 and table 1). Pulse pressure decreased from an average of 58 to 45 mm Hg. Time-tension index per minute (TTM) decreased from 2481 to 1954 mm Hg.

### Table 2

**Effect of Propranolol on Coronary Blood Flow and Myocardial Metabolism**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean ± Standard Deviation</th>
<th>% Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>N = 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary blood flow, ml/100g/min</td>
<td>77 = 11</td>
<td>64 = 8.5</td>
<td>−17</td>
</tr>
<tr>
<td>Coronary vascular resistance (dynes-sec-cm⁻¹/1000)</td>
<td>67 = 14</td>
<td>70 = 15</td>
<td>+ 4</td>
</tr>
<tr>
<td>Myocardial O₂ consumption (ml/100g/min)</td>
<td>9.20 ± 1.94</td>
<td>7.20 ± 1.28</td>
<td>−22</td>
</tr>
<tr>
<td>Arterial - coronary sinus O₂ difference (ml/100 ml)</td>
<td>11.93 = 1.34</td>
<td>11.21 = 1.68</td>
<td>−6</td>
</tr>
<tr>
<td>Coronary sinus O₂ tension (mm Hg)</td>
<td>27 = 4.9</td>
<td>29 = 3.9</td>
<td>+ 7</td>
</tr>
<tr>
<td>Myocardial O₂ extraction (%)</td>
<td>65 = 5.8</td>
<td>62 = 7.0</td>
<td>− 5</td>
</tr>
<tr>
<td>Myocardial lactate extraction (%)</td>
<td>14 = 15</td>
<td>26 = 12</td>
<td>+ 86</td>
</tr>
<tr>
<td>Myocardial pyruvate extraction (%)</td>
<td>14 = 18</td>
<td>14 = 27</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial free fatty acid extraction (%)</td>
<td>14 = 12</td>
<td>16 = 10</td>
<td>+ 14</td>
</tr>
<tr>
<td>Myocardial glucose extraction (%)</td>
<td>0.4 = 6.3</td>
<td>3.0 = 9.4</td>
<td>+650</td>
</tr>
<tr>
<td>Myocardial respiratory quotient</td>
<td>0.81 = 0.09</td>
<td>0.91 = 0.15</td>
<td>+12</td>
</tr>
</tbody>
</table>
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sec/min. Peripheral vascular resistance remained essentially unchanged or increased slightly, averaging from 1450 to 1645 dynes-sec-cm\(^{-6}\).

Cardiac index decreased in all of the eight patients in whom it was measured, averaging 2.60 L/min/M\(^2\) before propranolol and 2.05 L/min/M\(^{2}\) after the intervention (fig. 2, table 1). This decrease in cardiac index was associated with a widening of the arterial-

### Figure 1

![Hemodynamic effects of propranolol in individual patients. Control values are shown at the left, results after propranolol at the right of the vertical axis. Heart rate (HR), mean arterial pressure (AP\(_{\text{mean}}\)), and time-tension index per minute (TTM) uniformly decreased after propranolol. ***P < 0.001; **P < 0.01; *P < 0.05.](http://circ.ahajournals.org/)

### Figure 2

![Hemodynamic effects of propranolol in individual patients. Control values are shown at the left, results after propranolol at the right of the vertical axis. Cardiac index (CI) and systolic ejection rate (SER) decreased after propranolol. Pulmonary artery wedge pressure (PAW) increased an average of 2 mm Hg. In the three highest initial values, wedge pressure decreased or remained essentially unchanged. ***P < 0.001; **P < 0.01; *P < 0.05.](http://circ.ahajournals.org/)

### Figure 3

![Effects of propranolol on myocardial perfusion and metabolism. Control values are shown at the left, results after propranolol at the right of the vertical axis. Coronary blood flow (CBF) and myocardial oxygen consumption (MV\(_{\text{O}}\)) decreased after propranolol. Myocardial lactate utilization improved. Lactate production (EXL) shifted to extraction or the rate of lactate extraction increased. ***P < 0.001; **P < 0.01; *P < 0.05.](http://circ.ahajournals.org/)
14% to 26% ($P < 0.001$). All of the five patients who initially produced lactate shifted to lactate extraction after propranolol (from an average of −8% to 14%). In five other patients, initial lactate extraction was below 15%, averaging 10%. Propranolol increased the rate of lactate extraction to an average of 18% in these patients. Lactate extraction increased or remained unchanged in the ten patients whose initial lactate extraction was normal (above 15%).

The interrelationships between lactate and free fatty acid extraction are shown in figure 6. Free fatty acid extraction was either unchanged or decreased in the five patients who produced lactate prior to propranolol (narrow dark lines). Four of the five patients who had reduced lactate extraction (dotted lines) increased free fatty acid extraction as well as lactate extraction with propranolol.

Dependency of Propranolol Effect on Initial Conditions

Heart rate decreased an average of 9% following propranolol. Figure 7 shows that there was a fair relationship between initial heart rate and change after propranolol; patients with a higher initial heart rate tended to have a greater decline ($P < 0.01$). Indices of arterial blood pressure decreased considerably more than heart rate and the decrease in these measurements was better correlated with initial values ($P < 0.001$) (fig. 8) than was the case with heart rate. The behavior of coronary blood flow and myocardial oxygen consumption was closer to that of arterial blood pressure than to heart rate. Both blood flow and oxygen consumption decreased an average of 22% and the decrease was closely correlated with the initial levels ($P < 0.001$) (fig. 9).

Discussion

Salvage of jeopardized myocardial tissue should be the main goal in the treatment of acute myocardial infarction. Experimental studies have shown that coronary reperfusion as long as three hours after occlusion can reestablish viability of ischemic tissue, demonstrating that salvage of myocardial tissue...
showed that, in the majority of patients, oral pronethalol increased the amount of upright bicycle exercise that could be performed before angina pectoris occurred. Subsequently, a multicenter double blind study demonstrated that pronethalol produced significant symptomatic improvement in patients with angina. The finding that pronethalol produced sarcomatous changes in mice, however, made it unsuitable for clinical use.

After initial disappointing results with propranolol, it soon became clear that, if used in high doses, it significantly relieved anginal pain and reduced the amount of nitroglycerin required. Subsequent studies confirmed the beneficial effect of propranolol on both the patient’s symptoms and his capacity to perform exercise before anginal pain occurred. Robinson demonstrated a remarkably constant relationship between development of chest pain and time-tension index per minute, a rough index of myocardial oxygen consumption. Decrease of time-tension index by nitroglycerin or propranolol significantly increased the exercise tolerance of the patients. Wolfson and Gorlin found a striking improvement of anginal pain by propranolol in 90 out of 104 patients, all with angiographically documented coronary artery disease.

The experience with propranolol in human myocardial infarction is rather limited. In 1965, Snow first reported a substantial reduction of mortality in acute myocardial infarction in patients who had received propranolol. These results, however, were based on a relatively small number (52 treated patients were compared to 55 control subjects) and the studies were performed without placebo control. Several randomized double-blind studies were then initiated. An average of 40-80 mg/24 hrs propranolol, ad-
administered orally in about 250 patients with acute myocardial infarction, did not reveal any definite results or conclusions. Interest in the possible use of propranolol in acute myocardial infarction was revived by observations pointing to the harmful effects of isoproterenol administration in acute myocardial infarction. We demonstrated that isoproterenol produced marked deterioration of myocardial oxygenation in shock following acute myocardial infarction in man and other investigators showed that isoproterenol increased while propranolol decreased infarct size in the experimental animal. The data presented above demonstrates that acute administration of propranolol is able to improve myocardial oxygenation in patients with uncomplicated acute myocardial infarction and that peripheral perfusion, although reduced, remained adequate.

The most important hemodynamic response to propranolol in our patients appeared to be a substantial decrease in myocardial contractility. This decrease was reflected by the fall in cardiac output and arterial pressure with little change in systemic vascular resistance. The fall in cardiac output was mainly due to a fall in stroke volume since heart rate changed surprisingly little, an average decrease of 7 beats per minute. Recent studies in acute myocardial infarction in man by Amsterdam et al. demonstrated similar decreases in cardiac index with propranolol. In both patient groups, the initial cardiac index averaged 2.6 L/min/M² and decreased after propranolol to 2.1 and 2.0 L/min/M² respectively. The mechanism of decrease, however, was different. In Amsterdam's study, cardiac index decreased mainly by fall in heart rate, in our study mainly by decrease in stroke volume. Much of this different behavior may be related to the difference in initial heart rate and propranolol dosage. In our patient group, initial heart rate averaged 80 beats/min; in Amsterdam's patients it averaged 99 beats/min. We gave 0.1 mg/kg propranolol i.v.; Amsterdam 0.03–0.05 mg/kg i.v. Further evidence that propranolol reduced contractility in our patients was the increase in pulmonary wedge pressure from an average of 12 to 14 mm Hg. The reduction in contractility and increase in end-diastolic volume may have been greater than that suggested by the observed increases in wedge pressure because of associated alterations in ventricular distensibility.

Variable relationships among left ventricular pressure, volume, and compliance complicate the interpretation of changing pulmonary wedge pressure in ischemic heart disease. Ross, in his Sir Thomas Lewis Lecture of 1969, reviewed the evidence indicating that sudden decreases in ventricular compliance were responsible for the appearance of prominent left ventricular "a" waves in patients with angina pectoris. Scheidt et al. reported similar findings in patients with angina pectoris, observing in some instances that acute elevations of left ventricular end-diastolic pressure preceded changes in heart rate and arterial pressure. Direct volume measurements made by Pepine and Wiener demonstrated that end-diastolic volume was unchanged while end-diastolic pressure increased during pacing-induced angina, clearly indicating that myocardial ischemia produced substantial decreases in ventricular compliance.

Our observations that propranolol produced but little change in pulmonary wedge pressure while contractility decreased might be interpreted in light of the compliance changes discussed above. Similar findings were reported by Forrester et al. They noted that propranolol decreased pulmonary wedge pressure from an average of 13 to 12 mm Hg in 14 patients with acute myocardial infarction; cardiac index fell from 5.2 to 3.8 L/min/M² and systolic blood pressure fell from 135 to 120 mm Hg. Alderman et al. demonstrated in patients with coronary artery disease without acute infarction that propranolol increased end-diastolic volume and compliance of the severely diseased left ventricle, but not of the ventricle with normal function. Our findings, together with those of Forrester et al. and Alderman et al., suggest that beta-adrenergic blockade may increase left ventricular compliance in patients with myocardial ischemia, possibly by improving myocardial oxygenation.

The response of myocardial metabolism to propranolol depends upon the effect of beta-adrenergic blockade on the determinants of myocardial oxygen consumption: contractility, heart rate, and wall tension. Decreasing contractility and heart rate decrease oxygen consumption. Opposing this is the observation that, in some patients, propranolol increases ventricular volume and fiber length, increasing wall tension and oxygen consumption. Our studies, demonstrating a 22% decrease in oxygen consumption per minute and a 14% decrease in oxygen consumption per beat, indicate that decreases in contractility and heart rate outweigh any increase in wall tension. Further evidence that these decreases in oxygen consumption represent decreased oxygen demand is the narrowing of the arterial— coronary sinus oxygen difference and the striking improvement in myocardial lactate metabolism. Stated differently, in the patient group described above, the oxygen-sparing effect of decreased contractility overshadowed any oxygen-wasting effect of increased cardiac size.

Direct measurements of ischemic zone metabolism,
recently obtained in our laboratory following coronary branch ligation, have confirmed the oxygen sparing effect of propranolol in ischemic tissue. Following ligation the metabolic pattern was characteristic of severe myocardial hypoxia: increase in myocardial glucose extraction, excessive lactate production, and decrease in coronary venous pH. These metabolic abnormalities could be reversed by propranolol. Lactate production of -63% shifted to extraction of 21% (P < 0.001); glucose utilization decreased and coronary venous pH improved. Similar observations have been reported by Haneda, Lee, and Ganz.

Coronary blood flow, the most important determinant of myocardial oxygen supply, decreased in all but one of our patients after propranolol administration. This response, previously observed in experimental myocardial infarction, might suggest propranolol to be harmful in ischemic heart disease. The over-all response of the myocardium to any intervention, however, should be considered in terms of both oxygen supply and oxygen need. Our findings that myocardial lactate metabolism improved and oxygen extraction decreased indicate that reduction in myocardial oxygen demand outweighed the decrease in coronary blood flow. The fall in mean aortic pressure from 92 to 76 mm Hg presumably played an important role in the decrease of coronary blood flow from 77 to 64 ml/100g/min. While the group average for coronary vascular resistance changed little with propranolol, coronary vascular resistance increased in 12 patients an average of 16% (P < 0.001). In this group both decreases in perfusion pressure and increases in resistance contributed to a decrease in coronary blood flow. Presumably, a decrease in oxygen demand improved myocardial oxygenation evoking an autoregulatory response.

Although our measurements of total coronary blood flow do not provide information relative to the distribution of blood flow within the myocardium, experimental studies demonstrate that beta-adrenergic blockade does not decrease blood flow in ischemic areas. Pitt et al. using different methods, showed that propranolol decreased regional perfusion in nonischemic areas of the myocardium; flow in ischemic regions was essentially unchanged. Labeled microsphere studies enabled Becker, Fortuin, and Pitt to demonstrate that propranolol reversed the maldistribution of coronary blood flow, produced by coronary ligation, improving the perfusion of subendocardial regions.

Our metabolic observations in human myocardial infarction, together with our animal studies and those of Haneda, Lee, and Ganz, demonstrate that beta-adrenergic blockade improved oxygenation of ischemic myocardium. Although these studies present effects following acute propranolol administration, the early use of propranolol in patients with uncomplicated acute myocardial infarction may interrupt the stepwise development of myocardial necrosis, salvage potentially viable myocardium, and improve both immediate mortality, and long-term ventricular function.

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_Circulation_. 1974;49:1078-1087
doi: 10.1161/01.CIR.49.6.1078
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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