The Effect of Delay in Propranolol Administration on Reduction of Myocardial Infarct Size After Experimental Coronary Artery Occlusion in Dogs

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SUMMARY  The effects of intravenous propranolol (2 mg/kg) on myocardial ischemic injury in relation to the influence of delay in therapy on gross infarct size (GIS) were determined in 39 closed-chest anesthetized dogs in which the left anterior descending coronary artery (LAD) was occluded at a fixed distance from its origin by a balloon catheter. Precordial ECG maps, hemodynamic variables and serum CK levels were monitored for 24 hours. After 24 hours, we estimated GIS from the measured areas of ischemic discoloration in serial sections of the left ventricle (LV). In nine dogs, propranolol administration was started before LAD occlusion, in another nine 3 hours and in 10 others 6 hours after occlusion; the remainder (n = 11) served as controls. In the dogs pretreated with propranolol, the GIS (14.0 ± 4.0 g or 10.0 ± 2.0% of LV weight) was 53% smaller (p < 0.01) than in the controls (29.0 ± 2.0 g or 22.0 ± 1.0% of LV weight); those given propranolol 3 hours after occlusion had 28% smaller (p < 0.05) GIS (19.0 ± 2.0 g or 15.0 ± 2.0% LV weight) than the controls. However, GIS in the dogs receiving propranolol 6 hours after occlusion (24.0 ± 3.0 g or 19.0 ± 3.0% of LV weight) was not significantly different from that in the controls. The beneficial effect of propranolol on GIS was accompanied by corresponding directional changes in the precordial ST-segment elevation and in the rate of decline of the R-wave amplitude of the ECG. Propranolol reduced the heart rate and cardiac output for 5–6 hours in pretreated dogs; in dogs given propranolol 3 and 6 hours after occlusion, heart rate was reduced for 3–4 hours, but the cardiac output remained low for the remainder of the 24 hours. The data in these studies indicate that the beneficial effect of propranolol on GIS varies inversely with the delay in drug administration after LAD occlusion, and that no effect is apparent when propranolol infusion is begun 6 hours after occlusion.
clinical reports suggesting that myocardial damage may be influenced favorably by certain pharmacologic interventions administered many hours after presumed coronary occlusion.

Of all the modalities experimentally evaluated, β-adrenergic blockade appears to be one of the most promising interventions that exerts a favorable influence on myocardial ischemic injury. Propranolol has been shown to reduce electrocardiographic and enzymatic, as well as histologic manifestations of myocardial ischemic damage. In the present study, we investigate the influence of delay in propranolol therapy on the degree of salvage of ischemic myocardium in dogs.

Methods

Mongrel dogs weighing 25–35 kg were premedicated with 1.5 mg/kg i.v. morphine sulfate, followed 30 minutes later by urethane 0.75 mg/kg i.v. Thereafter, further doses of urethane were given to maintain anesthesia at the minimal level necessary to suppress the corneal reflex. The animals were placed on their right sides, intubated and allowed to breathe spontaneously with room air.

After anesthesia, a #7 French thermodilution flotation catheter was placed in the pulmonary artery via the left external jugular vein. A 30-cm #5 French catheter, advanced through the jugular vein to the junction of the superior vena cava with the right atrium, was used to inject 5 ml of saline at room temperature. Catheters were also placed into the femoral vein to sample blood and into the femoral artery to record systemic pressure.

Coronary artery occlusion was produced by inflation of a balloon 5 cm from the left orifice of the left anterior descending coronary artery (LAD). From the left carotid artery, a #8 French Judkins angiographic catheter was inserted under fluoroscopic control into the orifice of the left main coronary artery (fig. 1). A #2 French balloon-tipped Fogarty catheter was then passed through the angiographic catheter into the LAD. The midpoint of the balloon of the Fogarty catheter was positioned 5 cm from the origin of the artery. The balloon was inflated with diluted (1:1) meglumine diatrizoate and the inflation maintained by a Hamilton syringe screw mechanism. After coronary artery occlusion, the angiographic catheter was withdrawn into the aorta while we advanced the shaft of the Fogarty catheter.

Hemodynamic Measurements

Pulmonary and systemic arterial pressures were monitored by fluid-filled catheters coupled to DB23 Statham transducers and an Electronics for Medicine recorder. Cardiac output (CO) was determined by thermodilution using triplicate injections and an Edwards Laboratories 9510 CO computer.

Precordial Electrocardiographic Measurements

We obtained a 12-lead precordial map by placing 12 subcutaneous unipolar electrocardiographic elec-

![Figure 1](http://circ.ahajournals.org/asset/1149.png)
trodes in a fixed grid pattern. The electrodes were arranged in two rows. We began the first row by placing an electrode over the point of maximum cardiac impulse, and completed it by placing other electrodes at 1-cm intervals parallel to the sternum — three cephalad to the initial one and two caudad. We positioned the second row of electrodes 3 cm posterior and parallel to the first. The electrodes were connected by a switch box to an amplifier and recorder. The ECG was recorded at 50 mm/sec paper speed and at a 2 cm/mV standardization.

The ST-segment elevation was measured 100 msec after the onset of QRS and the sum of ST-segment elevations (ΣST) was calculated. All records which had arrhythmias or intraventricular conduction defects (i.e., QRS width ≤65 msec) were excluded. The TQ interval was used as the reference level for estimation of ST-segment elevation. The R-wave voltage was measured as peak R-wave amplitude and individual values were added to give ΣR in mV. Lidocaine (40 mg i.v.) was given just before occlusion and repeated later if ventricular arrhythmias developed.

CK Determinations

Serum for CK activity was sampled in 10 mM EGTA. The CK activity was assayed by the Rosalki technique using a Worthington Stat Pack and a Gilford Autoanalyzer.

Determination of Anatomic Infarct Size

The dogs were sacrificed 24 hours after coronary occlusion. At autopsy, we confirmed the exact location as well as patency of the balloon and sought evidence for clot proximal to the balloon. In all cases, the site of occlusion was distal to the first diagonal branch of the LAD. The heart was washed in cold water, filled with cotton to fix its shape, and frozen at −56°C for 50 minutes. The ventricles were then sectioned into 7-mm slices perpendicular to their long axis. Each slice was weighed before and after removing the right ventricle. The zone of the macroscopically apparent infarcted area on both surfaces of the slice, as judged by a blinded observer by the pallor of the damaged myocardium, was measured by planimetry of the areas outlined on transparent paper. A computer program was used to determine the area and to reconstruct the volume of the infarcted myocardium (fig. 2). The demarcation zone of necrosis from viable myocardium at 24 hours was sharp in most instances. Concurrent studies (Kaplan L, Toshimitsu T, Van De Velde R, Corday E, Meerbaum S, Heng MK, Lang TW: unpublished observations) in our laboratories have indicated a high degree of correlation (r = 0.858)

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

**FIGURE 2. Method of delimiting and calculating gross infarct size (by gross inspection) in relation to the mass of the left ventricle. Gross infarct size was expressed in grams as well as a percent of the left ventricular weight. See text for details.**

\[
\frac{a + b}{2} \times \text{Weight of Slab (g)} = \text{Infarct Size of Slab (g)}
\]

(a) No of Slab

\[
(1) \quad \frac{a + b}{2} \quad \text{X Weight of Slab} = \text{Infarct Size of Slab (g)}
\]

(2) 

```
```

+ = \text{Infarct Size (g)}
between naked eye estimates of GIS and those determined by microscopic delineation of the infarct margin.

Statistical Analysis

We used Dunnet’s t test (a multiple comparison procedure) to test the significance of the differences in the effects of each treatment from control values, and we used Bartlett’s test to determine equality of variance among the four groups. The appropriate test statistics along with an adjustment factor required for unequal variance were computed. We then obtained the associated p value from Dunnet’s t distribution table.

We used the unpaired t test for single comparisons, i.e., testing for mean differences between two groups, and the paired t test for comparing mean values of a parameter at different stages of the experiment within a particular group. Standard linear regression analysis was used to determine the nature of the linear relationships between two variables.

Experimental Design

In all animals, a 12-lead precordial ECG map, heart rate (HR), systemic and pulmonary artery pressures, and CO were obtained before LAD occlusion. These measurements were repeated 15, 30, 45, 60, 90 and 120 minutes after occlusion and then hourly for the next 22 hours. Serum was sampled before conclusion and 30, 60, 75, 90, 105 and 120 minutes after coronary occlusion, and hourly for the next 22 hours. Four groups of dogs were studied. Dogs in group 1 (n = 11) served as controls, and underwent LAD occlusion without propranolol administration before or after coronary occlusion. The dogs in group 2 (n = 9) received propranolol 1 mg/kg i.v. over a 5-minute period commencing 10 minutes before LAD occlusion; two further doses of propranolol, each 0.5 mg/kg, were given at 2 and 4 hours after LAD occlusion. A total of 2 mg/kg of the drug was, therefore, administered to each dog in this group. Dogs were assigned alternately to groups 1 and 2.

The dogs in group 3 (n = 10) received propranolol 1 mg/kg 3 hours after occlusion and two further doses, 0.5 mg/kg each, 5 and 7 hours after occlusion. Propranolol 1 mg/kg was initially given to dogs in group 4 (n = 11) 6 hours after LAD occlusion and 0.5 mg/kg doses were repeated 8 and 10 hours after occlusion. Studies in groups 3 and 4 were undertaken concurrently, and the dogs were assigned alternately to each of the two experimental groups. All dogs were sacrificed 24 hours after LAD occlusion; those which did not survive 24 hours were excluded from analysis.

Results

There were no significant differences between the mean values for body weight, left ventricular weight, and the site of LAD occlusion for all dogs surviving 24 hours in all four groups. The incidence of ventricular fibrillation in all groups was similar (one and two for groups 1 and 4, respectively).

The Effects of Propranolol on Anatomic Infarct Size

The range of infarct sizes for each group is shown in figure 3. When expressed as percent of left ventricular

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

**Figure 3.** The effects of delay in propranolol administration on gross infarct size (GIS) after left anterior descending coronary artery (LAD) occlusion in closed-chest anesthetized dogs. The open circles indicate values for anatomic infarct size (AIS) expressed as percent of left ventricular (LV) weight. The closed circles with bar graphs represent mean ± SEM for control as well as treated groups. The groups given propranolol before LAD occlusion and 3 hours (but not those at 6 hours) after occlusion had significantly smaller (p < 0.05) GIS than the control series.
weight and compared with that in the control group, the mean infarct size was 53% smaller in the dogs pretreated with propranolol (group 2) (Dunnett's \( t = 4.63, p < 0.01 \)), but only 28% smaller (Dunnett's \( t = 2.43, p < 0.05 \)) in dogs given propranolol 3 hours after LAD occlusion (group 3). When propranolol administration was delayed 6 hours after coronary occlusion (group 4), the mean infarct size was 14% smaller than in the control group, but the difference was not statistically significant (Dunnett's \( t = 0.93, p = NS \)) (fig. 4).

When infarct size was expressed in absolute weight (g), Bartlett's test indicated unequal variance in the four groups, the result of the wider range of infarct sizes in dogs pretreated with propranolol (fig. 3). The mean data, analyzed by Dunnett's \( t \) test corrected for unequal variance, also showed significant differences in the infarct size in the pretreated dogs (Dunnett's \( t = 4.32; p < 0.01 \)) and in the dogs given propranolol 3 hours after LAD occlusion (Dunnett's \( t = 3.02; p < 0.01 \)) when compared with that in the control group. Once again, no significant difference was found between the mean infarct size in the control group and that in the dogs given propranolol 6 hours after LAD occlusion.

Effects of Propranolol on Hemodynamic Variables

The mean data for the hemodynamic changes in all four experimental groups are summarized in table 1. Propranolol had no significant effect on systemic and pulmonary arterial pressures.

The mean values for the basal HR and CO in all four groups were not statistically different. In the control series, the HR increased progressively for 24 hours after occlusion, reaching a mean value of 33 beats/min higher than the mean basal rate (\( p < 0.05 \)). In the pretreated dogs, changes in HR and CO were striking: HR fell by 20–30 beats/min over 4 hours and CO by 3.0 l/min, with a fall in stroke volume of about 15–20 ml/beat. The HR remained below the level of the control group for 24 hours. In dogs given propranolol 3 hours after occlusion (group 3), the effect on HR was less striking, a fall of only 12–15 beats/min (\( p < 0.05 \)), but the CO fell by 2.8 l/min and the stroke volume by 20 ml/beat. The effect on HR lasted less than 3 hours, while the effect on CO and stroke volume persisted until the dogs were sacrificed. In the dogs which were given propranolol 6 hours after occlusion (group 4), the reduction in HR, although 17 beats/min, was not statistically significant; the decreases in CO (average 3.5 l/min) and in stroke volume (average 15 ml/beat) were not only statistically significant (\( p < 0.05 \)) but, as in group 3, persisted until the end of the experiment.

The Effect of Propranolol on Precordial ECG in Relation to Anatomic Infarct Size

The data showing the time course of the electrocardiographic manifestation of ischemic myocardial damage for all groups in relation to anatomic infarct size are presented in table 2. The evolution of these changes relative to alterations in serum CK activity in a representative control dog is shown in figure 5. A close concordance was demonstrated between the onset and the time course of Q-wave evolution and serial CK release.

After LAD occlusion in the untreated dogs (group 1), \( \Sigma \)ST reached a peak value within 60 minutes,
Table 1. Effects of Propranolol on Heart Rate and Cardiac Output in Closed-Chest Anesthetized Dogs with LAD Occlusion

<table>
<thead>
<tr>
<th>Control</th>
<th>1/2</th>
<th>1</th>
<th>4</th>
<th>8</th>
<th>24</th>
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</thead>
<tbody>
<tr>
<td>A. Heart rate (beats/min)</td>
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<tr>
<td>Group 1 (n = 11)</td>
<td>119 ± 9</td>
<td>128 ± 9</td>
<td>129 ± 7</td>
<td>129 ± 8</td>
<td>140 ± 7</td>
</tr>
<tr>
<td>Group 2 (n = 9)</td>
<td>125 ± 7</td>
<td>104 ± 7</td>
<td>101 ± 6*</td>
<td>93 ± 6*</td>
<td>120 ± 5</td>
</tr>
<tr>
<td>Group 3 (n = 9)</td>
<td>111 ± 11</td>
<td>114 ± 9</td>
<td>115 ± 8</td>
<td>102 ± 6*</td>
<td>123 ± 11</td>
</tr>
<tr>
<td>Group 4 (n = 10)</td>
<td>120 ± 7</td>
<td>127 ± 7</td>
<td>124 ± 6</td>
<td>138 ± 9</td>
<td>126 ± 9</td>
</tr>
<tr>
<td>B. Mean arterial pressure (mm Hg)</td>
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<tr>
<td>Group 1 (n = 11)</td>
<td>110 ± 5</td>
<td>112 ± 7</td>
<td>114 ± 5</td>
<td>111 ± 5</td>
<td>115 ± 4</td>
</tr>
<tr>
<td>Group 2 (n = 9)</td>
<td>112 ± 7</td>
<td>108 ± 6</td>
<td>110 ± 7</td>
<td>109 ± 3</td>
<td>113 ± 8</td>
</tr>
<tr>
<td>Group 3 (n = 9)</td>
<td>109 ± 4</td>
<td>109 ± 6</td>
<td>113 ± 3</td>
<td>113 ± 7</td>
<td>114 ± 5</td>
</tr>
<tr>
<td>Group 4 (n = 10)</td>
<td>113 ± 6</td>
<td>107 ± 8</td>
<td>110 ± 8</td>
<td>108 ± 7</td>
<td>113 ± 7</td>
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<tr>
<td>C. Cardiac output (l/min)</td>
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<tr>
<td>Group 1 (n = 11)</td>
<td>6.3 ± 0.6</td>
<td>6.5 ± 0.5</td>
<td>6.5 ± 0.4</td>
<td>5.6 ± 0.4</td>
<td>5.8 ± 0.4</td>
</tr>
<tr>
<td>Group 2 (n = 9)</td>
<td>7.1 ± 0.5</td>
<td>4.5 ± 0.4*</td>
<td>4.6 ± 0.5*</td>
<td>3.9 ± 0.3*</td>
<td>5.2 ± 0.4</td>
</tr>
<tr>
<td>Group 3 (n = 9)</td>
<td>6.3 ± 0.8</td>
<td>6.2 ± 0.5</td>
<td>6.6 ± 0.5</td>
<td>3.5 ± 0.4*</td>
<td>3.8 ± 0.5*</td>
</tr>
<tr>
<td>Group 4 (n = 10)</td>
<td>7.7 ± 0.5</td>
<td>7.4 ± 0.5</td>
<td>7.2 ± 0.4</td>
<td>7.1 ± 0.5</td>
<td>4.6 ± 0.3*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM; n = number from which data were obtained. *p < 0.05; the statistical significance refers to differences between the values at stated times after LAD occlusion and control values.

Abbreviation: LAD = left anterior descending coronary artery.

generally by 15 minutes. Thereafter, variations in ΣST occurred with a trend toward lower values; by 24 hours, ΣST had reached a mean value of 59% of that at 15 minutes after LAD occlusion. ΣST in the pretreated dogs and in those given propranolol 6 hours after LAD occlusion was significantly lower compared with ΣST of controls (p < 0.05). No significant effect was apparent in the dogs that received the drug at 3 hours after LAD occlusion. The mean ΣST at 15 minutes after LAD occlusion was 45% lower (t = 10.83; p < 0.01) in the pretreated dogs (group 2) than in the control dogs (group 1).

Differences in precordial R-wave voltage in the four experimental groups were analyzed in terms of the actual R-wave magnitude (in mV), change in R-wave voltage (in mV), and percent reduction with reference to the precocclusion R-wave amplitude. It is evident from table 2 that there was no statistically significant difference between the four groups in the magnitude of the residual R-wave voltage at 24 hours. Dogs treated with propranolol 3 or 6 hours after occlusion (groups 3 and 4) were also not significantly different from the control series (group 1) with respect to the absolute or percent reduction in the R-wave amplitude. The dogs that were pretreated with propranolol (group 2) lost 11.7 mV (48%) of their precocclusion R-wave amplitude by 24 hours after LAD occlusion, while the corresponding decrement in the control group was 23.8 mV (68.5%) (p < 0.05). A weak but significant correlation was found between percent reduction in R-wave amplitude and anatomic infarct size in all dogs (r = 0.44, n = 39).

Table 2 shows the time course of the ΣQ-wave changes after LAD occlusion in control dogs and in dogs treated with propranolol. Although 8 hours after LAD occlusion the treated dogs (groups 2-4) had significantly lower ΣQ values (p < 0.05) than the control dogs, at 24 hours these differences were not statistically significant.

Discussion

These studies indicate that infarct size in closed-chest anesthetized dogs may be reduced significantly by propranolol if the administration of the drug in 2 mg/kg doses is begun before coronary artery occlusion or within 3 hours after occlusion. These findings are consistent with the work of Reimer and Jennings,10, 11 who found that pretreatment of dogs with propranolol reduced the extent of cellular necrosis from 46% to 16% of estimated papillary muscle mass after a 40-minute occlusion of the circumflex coronary artery. Our results show that the time of initiation of propranolol administration after LAD occlusion is critical for obtaining a beneficial response, since the degree of containment of infarct varied inversely with the delay in instituting adrenergic blockade. The maximal effect was apparent when propranolol was administered before coronary occlusion, and the reduction was slight and not statistically significant when drug administration was delayed 6 hours after occlusion; propranolol given 3 hours after occlusion had an intermediate effect on infarct size. In the present studies, infarct size was assessed 24 hours after coronary occlusion by inspection of the macroscopically identifiable anatomic damage relative to the change in
Table 2. The Effect of Propranolol on the Relationship Between Precordial ECG Changes and Anatomic Infarct Size in Closed-Chest Anesthetized Dogs with LAD Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1/4</th>
<th>1/2</th>
<th>3/4</th>
<th>1</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>24</th>
<th>Anatomic infarct size (g)</th>
</tr>
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<tbody>
<tr>
<td><strong>A. ST (mV)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Group 1</td>
<td>0.51 ± 0.19</td>
<td>5.48 ± 0.89</td>
<td>5.60 ± 0.87</td>
<td>5.05 ± 0.90</td>
<td>5.67 ± 1.14</td>
<td>5.40 ± 1.82</td>
<td>5.12 ± 1.39</td>
<td>3.08 ± 0.70</td>
<td>3.22 ± 0.51</td>
<td>28.8 ± 1.5</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.43 ± 0.66</td>
<td>3.15 ± 0.66</td>
<td>2.52 ± 0.51*</td>
<td>2.65 ± 0.56</td>
<td>3.31 ± 0.79</td>
<td>3.73 ± 0.97</td>
<td>1.60 ± 0.61*</td>
<td>1.13 ± 0.51</td>
<td>0.92 ± 0.43†</td>
<td>14.1 ± 3.8</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.34 ± 0.26</td>
<td>4.94 ± 1.19</td>
<td>5.88 ± 1.57</td>
<td>6.36 ± 1.69</td>
<td>6.79 ± 1.97</td>
<td>6.92 ± 1.82</td>
<td>3.50 ± 1.54</td>
<td>3.21 ± 0.93</td>
<td>2.21 ± 0.59</td>
<td>18.6 ± 1.7</td>
</tr>
<tr>
<td>Group 4</td>
<td>0.33 ± 0.15</td>
<td>3.06 ± 0.67</td>
<td>2.85 ± 0.62</td>
<td>2.83 ± 0.61</td>
<td>2.96 ± 0.69</td>
<td>2.47 ± 0.72</td>
<td>1.59 ± 0.60*</td>
<td>0.80 ± 0.41*</td>
<td>1.97 ± 0.47</td>
<td>24.0 ± 2.7</td>
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<tr>
<td><strong>B. SR (mV)</strong></td>
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<tr>
<td>Group 1</td>
<td>34.2 ± 3.7</td>
<td>40.5 ± 3.6</td>
<td>40.5 ± 3.3</td>
<td>38.1 ± 3.6</td>
<td>37.3 ± 3.5</td>
<td>24.9 ± 3.5</td>
<td>19.2 ± 5.9</td>
<td>14.2 ± 6.2</td>
<td>10.4 ± 2.9</td>
<td>28.8 ± 1.5</td>
</tr>
<tr>
<td>Group 2</td>
<td>26.5 ± 3.5</td>
<td>27.1 ± 2.8</td>
<td>25.0 ± 3.1</td>
<td>24.0 ± 2.9</td>
<td>22.8 ± 3.1</td>
<td>19.9 ± 3.3</td>
<td>17.3 ± 4.2</td>
<td>15.5 ± 3.2</td>
<td>12.8 ± 3.6</td>
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<td>Group 3</td>
<td>29.4 ± 3.0</td>
<td>34.3 ± 4.4</td>
<td>34.7 ± 4.8</td>
<td>32.9 ± 4.8</td>
<td>33.0 ± 4.8</td>
<td>26.4 ± 3.1</td>
<td>21.1 ± 4.4</td>
<td>11.6 ± 4.2</td>
<td>10.4 ± 1.9</td>
<td>18.6 ± 1.7</td>
</tr>
<tr>
<td>Group 4</td>
<td>31.4 ± 3.4</td>
<td>33.4 ± 3.2</td>
<td>33.2 ± 3.1</td>
<td>31.9 ± 3.1</td>
<td>30.8 ± 3.3</td>
<td>22.8 ± 3.2</td>
<td>18.8 ± 3.4</td>
<td>21.7 ± 8.4</td>
<td>12.4 ± 3.2</td>
<td>24.0 ± 2.7</td>
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<tr>
<td><strong>C. SQ (mV)</strong></td>
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<tr>
<td>Group 1</td>
<td>2.2 ± 0.5</td>
<td>2.9 ± 0.8</td>
<td>2.9 ± 0.7</td>
<td>2.9 ± 0.7</td>
<td>3.5 ± 0.7</td>
<td>8.9 ± 2.1</td>
<td>10.9 ± 3.1</td>
<td>11.5 ± 2.4</td>
<td>28.8 ± 1.5</td>
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</tr>
<tr>
<td>Group 2</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>1.6 ± 0.6</td>
<td>2.1 ± 1.0</td>
<td>4.1 ± 1.6*</td>
<td>7.6 ± 3.2</td>
<td>7.9 ± 1.8</td>
<td>14.1 ± 3.8</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.8 ± 0.5</td>
<td>2.1 ± 0.4</td>
<td>2.3 ± 0.6</td>
<td>2.4 ± 0.6</td>
<td>2.5 ± 0.7</td>
<td>2.8 ± 0.8</td>
<td>3.9 ± 1.9*</td>
<td>9.7 ± 3.0</td>
<td>10.4 ± 3.0</td>
<td>18.6 ± 1.7</td>
</tr>
<tr>
<td>Group 4</td>
<td>2.1 ± 0.5</td>
<td>2.4 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>3.4 ± 0.8</td>
<td>3.3 ± 0.8*</td>
<td>8.0 ± 2.4</td>
<td>10.6 ± 1.7</td>
<td>24.0 ± 2.7</td>
</tr>
</tbody>
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Data are mean ± SEM.  
*P < 0.05 (compared with control values).  
†P < 0.01 (compared with control values).  
Abbreviations: LAD = left anterior descending coronary artery; ST = sum of ST-segment elevations; SR = sum of peak R-wave amplitudes; SQ = sum of Q-wave amplitudes.
color of the infarcted myocardium. This zone of discoloration has been found to correlate well with histological changes, myocardial CK depletion, and loss of myocardial electrolytes. A zone of gross anatomic change may, therefore, be used as an index of infarct size in models of experimental infarction involving both circumflex as well as anterior descending coronary ligation.

The major criticism of the pathological technique of delimiting infarcted areas by visual inspection relates largely to the difficulty in clearly defining border zones of the infarct. However, since the errors inherent in the technique of tissue sampling were likely to be similar in all four experimental groups, they are not likely to affect the comparison between infarct sizes in treated and nontreated dogs.

Although serum levels of the drug were not measured in our studies, the dose of propranolol used must have produced substantial β-blockade, as indicated by the degrees of reduction in CO and HR, with little effect on blood pressure and left ventricular filling pressure.

However, high doses of propranolol (5 mg/kg) have been shown to influence neither tissue CK depletion nor the regional myocardial blood flow in this model of ischemia, although such a dose has been reported to have a salutary effect on histological appearances in the posterior papillary muscle of the dog after circumflex coronary occlusion. It is known that the posterior papillary muscle may remain relatively well preserved histologically despite a very low collateral perfusion. This has been related to the effect of ischemia producing decremental conduction with failure of contraction, resulting in a marked reduction in oxygen demand. Under these circumstances, even large doses of propranolol, as in the studies of Reimer and Jennings, are likely to have beneficial effects by further decreasing residual contraction in the papillary muscle. In contrast, the more complex model of ischemia secondary to LAD occlusion may exhibit differential effects to various doses of propranolol, the smaller doses being beneficial, the larger ones either ineffective or deleterious. It will thus be of interest to examine the effects of a range of doses of propranolol on tissue CK depletion and serum enzyme release rates after LAD occlusion.

The hemodynamic changes found in this study are comparable to those reported for the effects of block-
ing doses of intravenous propranolol in patients during the early hours of acute myocardial infarction.\textsuperscript{30} Although the peak decreases in HR and CO after propranolol administration were of similar magnitude in all three treated groups, changes in CO in pretreated dogs showed partial recovery toward control values. Since the effect of propranolol on infarct size in this group was also maximal, it is conceivable that the early reduction in ischemic injury might have contributed to a more favorable hemodynamic recovery than in the groups of dogs in which propranolol administration was delayed 3 hours and 6 hours after occlusion. In these dogs, the decreases in CO and stroke volume after propranolol infusion were maintained throughout, suggesting that the beneficial effect of the drug on ischemic injury was not sufficient to reverse completely the trend in hemodynamic depression resulting from the drug in the setting of substantial myocardial damage. The possibility also remains that a higher dose of propranolol may be necessary to influence infarct size favorably at 6 hours than is necessary when the drug is administered earlier in relation to coronary occlusion.

Furthermore, propranolol administered 6 hours after coronary occlusion may be beneficial, but the methods used in this study to assess infarct size may not have been sufficiently sensitive to detect smaller changes. However, this possibility needs to be balanced against the clinical findings. Although propranolol administered within 4 hours of the onset of presumed coronary occlusion leads to a significant reduction in serum CK release, further delay in its administration is not associated with a beneficial response.\textsuperscript{31}

Our data have indicated that propranolol does reduce anatomic infarct size after experimental coronary occlusion, yet the specific mechanisms through which it might act remain somewhat uncertain. The available data suggest that a number of its cardiovascular effects may contribute to its beneficial effects in ischemia. Perhaps the most important action in this regard is the reduction in the overall myocardial oxygen consumption (MVO\textsubscript{2}), since the drug reduces HR, contractility and systemic artery pressure, the major determinants of oxygen demand.\textsuperscript{32} Mueller et al.\textsuperscript{33} found that intravenous propranolol in the early stages of acute myocardial infarction in man decreased MVO\textsubscript{2} from 9.2 to 7.2 ml/100 g-min. In open-chest anesthetized dogs, Haneda et al.\textsuperscript{34} found that MVO\textsubscript{2} in the ischemic zone decreased from 3.5 to 2.5 ml/min after LAD occlusion. There was a further decrease to 1.7 ml/min after propranolol, associated with an increase in coronary venous oxygen saturation and a shift from myocardial lactate production to lactate extraction. These findings in experimental animals\textsuperscript{34} and in man\textsuperscript{33} indicate that decreases in MVO\textsubscript{2} after propranolol administration may, to an important extent, account for the observed beneficial effects of propranolol in myocardial ischemia. However, the possibility must also be considered that some of the beneficial actions of the drug may result from its effects on collateral blood flow or those acting directly on cellular metabolism. Propranolol reduces blood flow in the normal myocardium,\textsuperscript{35} but there are conflicting data\textsuperscript{33, 36} concerning its effect on the perfusion of ischemic myocardium. Becker et al.\textsuperscript{31} found an increase in the endocardial/epicardial ratio of tissue perfusion in the ischemic myocardium but no change in total regional blood flow. This finding has not been confirmed by subsequent studies,\textsuperscript{35, 36} although a recent report\textsuperscript{37} suggested that the drug may increase perfusion to the ischemic area in conscious dogs if the arterial pressure does not fall. Whether such apparently minor alterations in collateral blood flow do indeed play a role in ensuring tissue viability remains uncertain.

However, the possibility remains that minor changes in regional blood flow in ischemic areas may influence the concentration and distribution of drugs administered after coronary occlusion. The time uptake and distribution of propranolol in ischemia is not known, but it has been shown that the drug does depress regional contractility assessed by ultrasonic crystals in both ischemic as well as normal areas in the conscious animal subjected to coronary artery ligation.\textsuperscript{38} It is possible that the response to propranolol in terms of tissue viability may differ significantly in relation to the concentration of the drug reaching jeopardized areas of the myocardium, which may, in turn, be determined by alterations in regional perfusion.

While the relative roles of these potential mechanisms through which propranolol might be beneficial in ischemia may be debated, our experimental data are of clinical significance relative to the time delay in instituting therapy to salvage ischemic myocardium after occlusion in man. Although it still remains somewhat uncertain whether salvageable myocardium still exists 6 hours after coronary occlusion, the studies reported here indicate that in the dog, reduction of infarct size may not be possible if the administration of the test intervention is delayed to 6 hours after LAD occlusion. The overall findings are consistent with those of Smith et al.\textsuperscript{39} in primates, in which infarct size was reduced by reperfusion if reflow was established within 4 hours but not at 6 hours after coronary occlusion. Thus, our data are relevant to the design of trials to test the efficacy of therapeutic interventions to reduce infarct size after onset of infarction in man. If the behavior of the human coronary circulation and ischemic myocardium is similar to that in the experimental animal, containment of clinical infarct size may be critically dependent on early pharmacologic intervention, possibly within 6 hours of coronary occlusion. The data are in line with the preliminary clinical studies with propranolol\textsuperscript{40, 41} administered to patients within 4 hours of onset of symptoms of acute myocardial infarction.

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