Reduction by Propranolol of Myocardial Necrosis following Temporary Coronary Artery Occlusion in Dogs

By Keith A. Reimer, Margaret M. Rasmussen, and Robert B. Jennings

ABSTRACT
The effect of propranolol on the severity of myocardial necrosis following 40 minutes of temporary coronary artery occlusion was assessed in dogs. The circumflex coronary artery was occluded 1–2 cm from the aorta in open-chest dogs anesthetized with sodium pentobarbital. One group of dogs was untreated and a second group received propranolol (5.0 mg/kg, iv) 10 minutes prior to the occlusion. After 40 minutes the clamp was removed and arterial perfusion was restored. Dogs which survived this procedure were killed 2–5 days later for gross and histologic assessment of the necrosis. The relative area of necrosis (percent of fibers involved) in the posterior papillary muscle of each heart was quantified from stained histologic sections prepared from serial longitudinal slices of each posterior papillary muscle. Dogs treated with propranolol showed significantly less necrosis than did untreated controls, but the mechanism of the drug’s action remains unknown. During coronary artery occlusion, propranolol-treated dogs exhibited somewhat lower heart rates, systolic blood pressures, and S-T segment elevations than did untreated dogs. However, none of these latter differences between groups was significant.

KEY WORDS infarction heart quantification of infarct size ventricular fibrillation cell death

In the past few years much attention has been directed toward various therapeutic interventions which slow or prevent the development of myocardial cell death following an acute coronary artery occlusion. Sommers and Jennings (1) have suggested that propranolol in some way alters the course of ischemic injury. They observed that 17 of 31 untreated dogs subjected to a 20-minute temporary occlusion of the circumflex coronary artery showed foci of necrosis 24–48 hours later. Only 3 of 30 similar dogs treated prophylactically with propranolol showed any necrosis. The 20-minute occlusion, however, induced relatively mild injury even without treatment, since it caused only small islands of cell death in about half of the untreated dogs.

The present study was undertaken to provide a more severe test of propranolol’s efficacy against myocardial ischemic injury. A 40-minute period of temporary circumflex coronary artery occlusion was chosen for study; injury induced by this method causes necrosis in 100% of dogs in the absence of protective therapy, and the characteristics of this model have been described in considerable detail (2, 3). The posterior papillary muscle is in the center of the lesion and is the site of maximum, most predictable injury. The proportion of muscle fibers which become necrotic can readily be quantified and in a previous series of dogs was about 55% of the posterior papillary muscle projecting above the endocardial surface of the ventricle (4). Thus this model provides an appropriate injury in which either beneficial or deleterious interventions can be observed. In this study our purpose was to determine whether propranolol could reduce the number of cells which become irreversibly injured during 40 minutes of circumflex coronary artery occlusion.

Methods
Mongrel dogs of either sex generally weighing between 8 and 20 kg were fasted overnight and then anesthetized with sodium pentobarbital (30 mg/kg, iv). Additional pentobarbital was given during the experiment when necessary to abolish the corneal reflex. Each dog was intubated and ventilated with room air via a Harvard model 1063 respirator. Standard limb leads were attached, and lead II of the electrocardiogram was recorded continuously on a Grass model 5 polygraph. Clean surgical technique was used; the dog was draped with sterile towels and sterile gloves and instruments.
were used. A catheter was inserted through the right saphenous artery and attached to a strain gauge so that peripheral arterial blood pressure could also be recorded on the polygraph. The catheter was kept open with saline containing 50 units heparin/ml. The total dose of heparin per dog never exceeded 200 units. Control hematocrit and sedimentation rates were determined.

The chest was opened in the fourth left intercostal space, and the pericardium was opened. The heart was elevated by traction on the pericardium, and the circumflex branch of the left coronary artery was isolated under the left atrium. The isolated segment was usually 1–2 cm from the aorta and was distal to its arterial branch and proximal to any major ventricular branches. The blood pressure and the electrocardiogram were allowed to stabilize after dissection, and the artery was then occluded with a Goldblatt clamp. In all experiments the clamp was left in place for 40 minutes; then it was opened and removed to restore flow. Dogs which survived this procedure were allowed to live 2–5 days and were then reanesthetized. After an electrocardiogram had been recorded, the heart was excised for gross and histologic evaluation.

Two groups of dogs were studied. An untreated group underwent coronary artery occlusion but was not treated with propranolol. A treated group was given a single injection of propranolol HCl (5.0 mg/kg, iv) 10 minutes prior to occlusion. Dogs were assigned to the two groups randomly, and the treated and untreated dogs were interspersed throughout the experiment. The size of the necrotic lesion was assessed grossly and quantified histologically in each successful experiment. However, occasional dogs which did not have S-T segment elevation in lead II following coronary artery occlusion were rejected from the study. Dogs which died acutely during surgery or within the first 24 hours after surgery were also eliminated. In each case the site of occlusion was observed for evidence of thrombosis; when thrombosis was present, the dog was excluded from the study.

The left ventricle of each heart was opened, and the endocardial surface was photographed. The entire posterior papillary muscle was then cut into four or five longitudinal slices (2–3 mm thick) perpendicular to the surface of the heart. Each of these slices was also photographed and then fixed in 10% phosphate-buffered formalin for routine histologic sectioning. Three sections were cut from each slice for staining with (1) hematoxylin and eosin (H & E), (2) periodic acid-Schiff (PAS) for glycogen, and (3) Heidenhain's variant of Mallory's connective tissue method (CT). These slides were each examined for the presence of myocardial necrosis. The sections stained with H & E were used to identify areas of necrosis. Quantification of the area of involvement, however, was done using either the PAS (Fig. 1A) or the CT stain because the low-power contrast between necrotic and normal areas was much better with these stains. Either the PAS- or the CT-stained section from each slice of posterior papillary muscle was placed in a photographic enlarger, and a negative image was printed on two 8 x 10-inch sheets of photographic paper. The necrotic and surviving areas of each photograph were cut out and weighed, and the percent necrosis was calculated. By summing the areas from the four or five slices through the posterior papillary muscle, an estimate of the volume proportion of the muscle which was necrotic was obtained. Results were calculated from two reference bases. (1) The percent necrosis in that part of the posterior papillary muscle projecting into the left ventricular lumen (projecting posterior papillary muscle) was based on the muscle above the endocardial surface in each photograph, and (2) the percent necrosis in the anatomic posterior papillary muscle was based on the distribution of longitudinally oriented muscle fibers in the photograph (Fig. 1B).

Results

Fifty dogs underwent coronary artery occlusion. Of 27 untreated dogs, 16 died of ventricular fibrillation either during the 40-minute occlusion or at the time of release. Data were lost on 1 dog. The remaining 10 dogs were long-term survivors. Of 23 dogs treated with propranolol, 10 died of ventricular fibrillation during the operative procedure. An additional dog died at about 16 hours postoperatively. Two dogs had severe damage at the site of occlusion with thrombosis. The remaining 10 dogs were long-term survivors. Thus 10 dogs in each group were used for quantification of infarct size. The lower incidence of ventricular fibrillation in the propranolol-treated group was not statistically significant. Figures 2 and 3 show the changes in heart rate and systolic blood pressure which occurred in the 20 survivors prior to and during the period of coronary occlusion. Using the values for anesthetized closed-chest control dogs for comparison, it was evident that the surgical procedures themselves generally caused an accelerated heart rate but had little effect on blood pressure. Infusion of propranolol caused a significant long-term slowing of the heart rate when the rates were compared with open-chest control values in the same dogs. This reduction was maintained during the subsequent ischemia. Propranolol alone usually caused a minimal decrease in blood pressure. Circumflex coronary artery occlusion per se usually caused little change in heart rate, but it did cause marked decreases in systolic blood pressure. This hypotensive effect of occlusion was slightly greater in propranolol-treated dogs. The overall effect of propranolol treatment relative to the events in untreated dogs was therefore a mild but sustained reduction in both heart rate and blood pressure during occlusion. The heart rate and the systolic
Positive (A) and negative (B) prints of a longitudinal section through the posterior papillary muscle of a dog killed 2 days after 40 minutes of temporary coronary artery occlusion. A is oriented with the subendocardium uppermost and the apex of the posterior papillary muscle to the left. It is stained with PAS and shows loss of glycogen from the necrotic fibers in the subendocardium. Loss of glycogen is not accepted as a criterion for identifying cell death. However, close comparison of serial sections stained with PAS and H & E from each slice showed that in our studies there was a one-to-one correspondence between glycogen loss and necrosis seen in sections stained with H & E. The PAS stain could, therefore, be used to quantify necrosis with the advantage of high contrast between surviving and necrotic zones viewed at low power. B was made by placing the same PAS-stained slide in a photographic enlarger and printing the image directly on two 8 X 10-inch sheets of black and white photographic paper. Because B is a negative, the necrotic areas appear darker than the surviving areas. Necrotic fibers have been outlined by a dotted line. A dashed line drawn through the posterior papillary muscle demarcates the part of the muscle which projects (projecting posterior papillary muscle) above the endocardium into the ventricular cavity. This line is easy to draw but does not encompass the whole myocardium at risk. The solid line encompasses the anatomic posterior papillary muscle and is based on the longitudinal direction of fibers in the muscle vs. the radial arrangement of fibers in the left ventricular wall. This line is more difficult to draw but includes most of the posterior papillary muscle fibers at risk in this model. After cutting out the areas encircled by the various lines for each slice of posterior papillary muscle, the photographic paper was weighed and the percent necrosis was calculated using as a reference base the projecting and anatomic posterior papillary muscles for each heart. The scales in A and B represent 0.25 cm.
Mean heart rate in surviving dogs is expressed as percent of the rate after completing the surgical procedures but before coronary artery occlusion and is plotted vs. time after occlusion. The surgical procedure employed caused acceleration of the pulse in most dogs. Propranolol (P) slowed the preocclusion rate toward the resting level. Occlusion per se caused a slight, transient bradycardia primarily in untreated dogs. The differences between groups were not significant at any time. The open-chest control heart rate for the untreated group was 140 ± 9 (SE) beats/min, and for the propranolol-treated group it was 145 ± 7 beats/min.

Blood pressure midway through the 40-minute occlusion are shown for each dog in Table 1. The propranolol-treated dogs exhibited neither severe bradycardia nor severe hypotension, and the differences between the means of the two groups were not significant.

Figure 4 shows the average deviation from the lead II base line of the S-T segment with time in the untreated and the propranolol-treated groups. The S-T segment prior to occlusion was slightly depressed sometimes but became elevated within 30-45 seconds after occlusion. Usually this elevation reached a maximum by 5 minutes and then gradually returned toward normal and sometimes became depressed by the end of the 40-minute occlusion. The peak S-T segment elevation and the deviation of the S-T segment from the base line 38 minutes postocclusion are listed in Table 1 for each dog. When the clamp was released, the S-T segment became depressed within 1-5 minutes and then gradually returned toward the base line. The dogs in the group treated with propranolol showed a slightly lower initial S-T segment elevation which tended to return to the base line more quickly. Again the differences between groups were not significant. Despite the extensive subendocardial necrosis observed in the untreated dogs, Q waves were seldom observed in their electrocardiograms either acutely or at the time they were killed.

After coronary artery occlusion and release (2-5 days) surviving dogs were killed and each heart was opened to expose the endocardial surface of the left ventricle. Necrotic areas could be detected grossly by a yellow discoloration which was obvious when it was compared with the dark red color of the surrounding normal myocardium. The yellow lesion was always contained within the posterolateral wall of the ventricle and extended from the
The posterior papillary muscle was central to the area of yellow discoloration seen on the epicardium (Fig. 5). The area of yellow discoloration sometimes appeared uniform perpendicular to the endocardium, the area of necrosis or only small foci within the posterior papillary muscle. The surface area within which the lesion was confined was fairly constant and varied primarily according to the size of the circumflex bed. Within this area, however, the lesion appeared uniform in some untreated dogs (Fig. 5), but it was sometimes more focal. Dogs given 5.0 mg/kg of propranolol prophylactically showed lesions within the same surface area, but these lesions were usually distributed less uniformly. Sometimes no necrosis or only small foci within the posterior papillary muscle were visible (Fig. 6).

When the posterior papillary muscle of an untreated dog heart was cut into longitudinal slices perpendicular to the endocardium, the area of yellow discoloration sometimes appeared uniform throughout the muscle. More frequently, areas of surviving myocardium could be seen (Fig. 6). In dogs treated with 5.0 mg/kg of propranolol, the areas of sparing were usually larger, and some longitudinal slices showed no lesion at all.

The distribution of these yellow lesions seen grossly corresponded closely with the distribution of necrosis observed on H & E-stained sections. Necrotic areas were easily identified on H & E-stained sections. The distribution of these yellow lesions seen grossly corresponded closely with the distribution of necrosis observed on H & E-stained sections. Necrotic areas were easily identified on H & E-stained sections. Similar results were obtained with glycogen loss provided a precise definition of necrotic areas. Similar results were obtained with glycogen loss provided a precise definition of necrotic areas. Whereas the H & E stain allowed identification of necrotic areas according to accepted criteria of cell death, the other two stains provided much higher contrast and were most

**TABLE 1**

Cardiovascular Variables and Percent Necrosis following Temporary Coronary Artery Occlusion in Untreated and Propranolol-Treated Dogs

<table>
<thead>
<tr>
<th>Dog</th>
<th>20 Minutes postocclusion</th>
<th>36-Minute Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>1</td>
<td>145</td>
<td>105</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>140</td>
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<tr>
<td>4</td>
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<tr>
<td>8</td>
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<td>120</td>
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<td>9</td>
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<td>105</td>
</tr>
<tr>
<td>10</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>135 ± 9</td>
<td>122 ± 7</td>
</tr>
</tbody>
</table>

**Propranolol Treated (5.0 mg/kg, iv)**

<table>
<thead>
<tr>
<th>Dog</th>
<th>20 Minutes postocclusion</th>
<th>36-Minute Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>110</td>
<td>130</td>
</tr>
<tr>
<td>12</td>
<td>125</td>
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<td>13</td>
<td>140</td>
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<td>80</td>
</tr>
<tr>
<td>20</td>
<td>130</td>
<td>120</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>123 ± 5</td>
<td>113 ± 6</td>
</tr>
</tbody>
</table>

Nonpaired t = 1.15

| P    | NS | NS | NS | NS | <0.001 | <0.002 |

BP = blood pressure, HR = heart rate, PP = posterior papillary muscle, and NS = not significant.
Gross photographs of a representative untreated dog (dog 9) 5 days after 40 minutes of temporary circumflex coronary artery occlusion. The left ventricle has been opened to show the endocardial surface in the top left corner. The posterior papillary muscle is on the left and the anterior papillary muscle is on the right. The dark color of the anterior papillary muscle is the color of normal myocardium. The lighter posterior papillary muscle and the surrounding ventricular wall were discolored yellow and represent dead myocardium. Such yellow areas show massive necrosis by light microscopy. The entire posterior papillary muscle was cut into longitudinal slices about 2 mm thick, and three of the four slices cut from this heart are shown. The endocardium is uppermost, and chordae tendineae are attached at the left. The necrotic muscle is confined to the inner half of the myocardium. Within this dead area, focal areas of surviving myocardium are present. Thirty-six percent of the anatomic posterior papillary muscle (Fig. 1) was necrotic by histologic quantification.

useful in quantifying the necrosis on low-power projections.

Histologic sections from each of four or five slices of the posterior papillary muscle were used to calculate the area of necrosis according to the methods described above. The areas from each section were summed, and the overall proportion of cells which were necrotic was expressed as a percent of the anatomic or the projecting posterior papillary muscle. Results for each dog and the means are presented in Table 1. The dogs treated with propranolol showed considerably less necrosis than did the untreated dogs. With either reference base, the difference was highly significant when it was analyzed with the nonpaired t-test.

There were no systematic differences between the groups. The sex ratio (six male to four female in each group), the dog weight (untreated 15.1 ± 1.5 kg, treated 13.7 ± 1.5 kg), the distance from coronary ostia to point of occlusion (untreated 1.7 ± 2 cm, treated 1.8 ± 2 cm), and the number of small branches proximal to the occlusion (untreated 3.3 ± 0.4, treated 3.6 ± 0.5) were all essentially identical.

Discussion

Our purpose in designing this study was to determine whether propranolol could prevent or reduce the extent of necrosis resulting from a 40-minute period of temporary ischemia. Previous studies in our laboratory had shown that necrosis following a 20-minute coronary artery occlusion could largely be prevented by treatment with propranolol (1). However, 20 minutes of coronary
artery occlusion induces a relatively mild injury in that the areas of necrosis are small and only 50% of untreated hearts show necrosis. The 40-minute time period was therefore chosen as a much more severe test of the efficacy of propranolol. Our present results clearly demonstrated that propranolol does have a significant effect in either preventing or delaying the onset of irreversibility during ischemic injury.

Our results are in general agreement with those of Maroko et al. (5) and Watanabe et al. (6), who showed that propranolol reduced the S-T segment elevation in epicardial leads and preserved myocardial creatine phosphokinase activity following ligation of the anterior descending coronary artery in dogs. Conversely, in another study in which propranolol was given to dogs with increased left atrial pressure during experimental infarction, the S-T segment elevation increased (7). The results of propranolol therapy in human myocardial infarction are controversial (8–10), and its use is generally avoided because of the possibility of inducing congestive heart failure (11).

In our studies we chose a maximum dose of propranolol to detect possible direct as well as indirect (β-blocking) effects on the area of necrosis. We did not measure left ventricular end-diastolic pressures in our dogs, but the peripheral blood pressure of treated dogs was usually well maintained. It is of interest, however, that the two propranolol-treated dogs with systolic blood pressures below 100 mm Hg developed the largest infarcts in this group (Table 1).

We have described an easy way of quantifying the distribution of necrosis in the posterior papillary muscle. This method is based on the following...
assumptions. (1) The lateral margins of the area of injury as seen on the endocardial surface of the heart are relatively fixed and are determined by the area supplied by the circumflex coronary artery in each dog. (2) The uniformity and the depth of necrosis within the ventricular wall are maximum within the posterior papillary muscle and are determined primarily by the severity of the injury. Our gross observations in the present study suggested that these assumptions were true. We have previously observed that permanent coronary artery ligations result in a similar endocardial surface distribution of necrosis but that the lesions extend deeper into the midmyocardium and the subepicardium. Thus, although our method measures only the uniformity and the depth of injury in the posterior papillary muscle, we believe that it is an accurate index of overall infarct size.

Before considering some of the possible mechanisms through which propranolol might act, it is relevant to consider changes occurring in the severely ischemic cells during the time in which the drug exerts its effects. Myocardium which has been injured by 40 minutes of ischemia but which has not had flow reestablished differs from normal myocardium in several ways: myocardial oxygen tension \((P_O_2)\) is very low, membrane potential is low, the cells are acontractile \((12)\), and, because of anaerobic glycolysis, the concentration of lactic acid is elevated \((13, 14)\). Fine structural changes include margination of nuclear chromatin, relaxation of myofibrils, glycogen depletion, some swelling of mitochondrial matrices, and appearance of small amorphous matrix densities \((15-17)\). When blood flow is restored to the injured myocardium, the cells undergo explosive swelling, develop contraction bands, and show sarcomere disruption. Mitochondria become greatly swollen and develop discrete densities of CaPO\(_4\) \((18)\) in addition to the amorphous matrix densities which are present prior to arterial reperfusion. The myocardium rapidly loses \(K^+\) and gains \(Na^+\), \(Ca^{2+}\), and water \((18, 19)\). These changes are readily apparent by 20 minutes after restoration of flow but more recently have been observed as early as 2 minutes after release of the occlusion \((20)\). We assume that propranolol exerts its protective effect during the 40-minute episode of ischemia and thereby prevents the cell swelling, CaPO\(_4\) accumulation, etc. It seems unlikely that the drug delivered to the ischemic tissue during reperfusion could act quickly enough to prevent the explosive swelling and cell death. However, our studies have concentrated on the late phase of this injury when cells are obviously necrotic and undergoing phagocytosis.

We also know that the distribution of necrosis is seldom uniform. There are often areas within the posterior papillary muscle which are spared even in the absence of propranolol. It is not known whether this effect represents differences in cellular response to a fairly uniform injury or whether there is variation in collateral flow from one cell to the next. It is well known, however, that ischemic myocardial cells do not all become irreversibly injured at the same time \((4)\). Thus there is a population of cells, some of which die early and some of which die only after longer periods of injury. Propranolol does not prevent necrosis but does reduce the size of the lesion. This effect is probably due to a prolongation of the duration of injury which can be tolerated by individual cells. In effect, the distribution curve of cell death vs. time is shifted so that at any given time after occlusion fewer cells have become irreversibly injured. We have not yet established whether the curve is shifted sufficiently to prevent cell death following permanent coronary artery ligations.

To date we have done no experiments to establish the specific mechanism of propranolol's protective action. However, it is possible to classify the possible mechanisms in broad terms as shown in Figure 7. Propranolol could work via direct cellular effects or via the more indirect effects of altered oxygen supply vs. demand. The reported effect of propranolol on myocardial oxygen consumption is usually a reduction via decreased heart rate and decreased rate of myocardial contraction offsetting increased ventricular size \((21-23)\). We calculated the cardiac effort index as the product of heart rate and mean systolic blood pressure for each dog at 20 minutes postocclusion (Table 1). Although this product does not account for changes in the inotropic state, it has shown good linear correlation with myocardial oxygen consumption \((24, 25)\). In the present study, the cardiac effort index was somewhat reduced after propranolol injection but the linear correlation between this index and the percent necrosis (projecting posterior papillary muscle) was not significant (linear correlation coefficient \(r = 0.25\)).

Within the ischemic muscle, contractile activity is severely depressed within seconds after coronary artery occlusion \((26-28)\), and it seems unlikely that propranolol could contribute to a significant reduction of the already low work load. It is not known whether propranolol reduces the rate of oxygen...
PROPRANOLOL AND CORONARY OCCLUSION

POSSIBLE MECHANISMS

1. Metabolic Requirements
   A. INDIRECT HEMODYNAMIC EFFECT
   B. DIRECT CELLULAR EFFECT

2. O₂ Supply
   A. COLLATERAL FLOW
   B. REFLOW

3. PRIMARY STRUCTURAL STABILIZATION
   A. MEMBRANE EFFECTS

Outline of several general mechanisms discussed in the text which might account for the protective action of propranolol in our model of myocardial ischemic injury.

consumption in nonfunctional ischemic myocardium. However, it has been shown that, at the subcellular level, propranolol reduces mitochondrial respiration by inhibition of NADH oxidase (29) and inhibits Ca²⁺ uptake by isolated sarcoplasmic reticulum (30).

Propranolol also alters myocardial substrate metabolism. For example, propranolol reduces the myocardial uptake and utilization of free fatty acids (31, 32) thereby making the heart more dependent on carbohydrates as a metabolic fuel (33). However, propranolol inhibits the β-adrenergic activation of phospholipase (34). What effect altered substrate utilization has in this model is unknown. Anaerobic glycolysis is essential for ATP production during anaerobiosis (35) but, on the other hand, lactate accumulation appears to be toxic (36).

Another possible mechanism through which propranolol could prevent the ischemia-induced subendocardial necrosis in our model is by providing improved collateral circulation to the subendocardium. Although total coronary flow usually decreases after propranolol administration (37, 38), the microsphere studies of Becker et al. (39), Becker and Pitt (40), and Pitt and Craven (41) showed that propranolol caused increased relative flow to the subendocardial area during ischemia. This area is the most severely injured in untreated animals, and, if this improved flow and oxygenation persists, it could explain the reduced incidence of cell death. Unfortunately, these studies dealt with 30-second intervals of coronary artery occlusion, and the long-term effect of propranolol on coronary flow distribution remains unknown. Propranolol also could improve perfusion following restoration of coronary flow. It is still uncertain, however, to what extent the “no-reflow phenomenon” described following cerebral ischemia (42) occurs in the heart (43).

Propranolol also could protect ischemic myocardium through primary stabilization of cellular structure. Propranolol decreases both the rate of rise and the height of the action potential possibly through decreased sarcolemmal sodium conductance (44). This so-called membrane-stabilizing effect of propranolol could be relevant to our results, since it has been hypothesized that injury of the sarcolemma occurs early in the pathogenesis of irreversible ischemic injury (45).

In summary, we have described a model for quantitative analysis of the efficacy of therapeutic agents against myocardial ischemic injury. We have tested propranolol in this model and have shown that, when it is given prophylactically in high doses prior to a 40-minute period of coronary artery occlusion, propranolol prolongs cellular viability. The necessary conditions for efficacy and the mechanism of action are still unknown.

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References


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