The Effect of Propranolol on Microvascular Injury in Acute Myocardial Ischemia

ROBERT A. KLONER, M.D., PH.D., MICHAEL C. FISHBIN, M.D., RAMZI S. COTRAN, M.D., EUGENE BRAUNWALD, M.D., AND PETER R. MAROKO, M.D.

SUMMARY The purpose of this study was to determine whether propranolol, which has been shown to reduce the extent of myocardial infarction, reduces microvascular injury which may play a role in exacerbating ischemia. Saline (10 dogs) or propranolol (2 mg/kg i.v., 7 dogs) was injected prior to a one hour occlusion of the left anterior descending coronary artery. Carbon black (1 mg/kg), which labels damaged and leaky vessels, was injected 5 min after release of the occlusion and allowed to circulate for two hours. By morphometric analysis of 1 μ thick sections, 75 ± 12% of vessels and 84 ± 7% of myocardial cells showed damage in untreated dogs; only 2 ± 1% of vessels and 9 ± 8% of myocardial cells showed damage in the propranolol-treated dogs (P < 0.001). The number of carbon black-labeled vessels/10 fields/biopsy from comparable areas of ischemic tissue was 55 ± 7 in untreated dogs and 27 ± 3 in propranolol-treated dogs (P < 0.001).

The results suggest that propranolol not only protects the ischemic myocardial cell, but also significantly decreases the ischemic microvascular changes.

beta-adrenergic blocking agent, propranolol, which has been shown to reduce the extent of myocardial infarction, decreases microvascular ischemic injury. The extent of vessel injury was studied by electron microscopy, morphometric analysis of 1 μ sections, and by quantitating the degree of vascular damage using the method of labeling with colloidal carbon as a marker of endothelial injury.

Methods

Studies were carried out in mongrel dogs of both sexes that weighed between 19 and 25 kg. They were anesthetized with sodium thiopental (25 mg/kg i.v.), and ventilated with a Harvard respirator following endotracheal intubation. Arterial pressure was recorded through a saline-filled catheter from the carotid artery (Statham P23Db pressure transducer) and lead aVp of the ECG was monitored continuously throughout the experiment on a polygraph (Brush Instruments, Cleveland, Ohio). A thoracotomy was performed in the fifth left intercostal space and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery was isolated from the adjacent tissues approximately 2–2.5 cm distal to the aorta. For carbon black injections, a catheter was placed into the left atrial appendage and tied into place with a purse string suture.

Two occlusions were carried out in each dog. The first occlusion lasted 15 minutes, a time period during which myocardial cell injury can be reversed, as determined by morphologic techniques. The first occlusion was performed to demonstrate that the site of occlusion selected resulted in grossly similar areas of ischemia between groups of dogs, as
determined by the area of epicardial cyanosis and electrocardiographic changes. After 15 min the occlusion was released and the dogs were reperfused for 30 min. Then they were randomly assigned to untreated or propranolol-treated groups. Ten minutes prior to the second occlusion, i.e., after 20 min of reperfusion, the dogs received either saline (10 dogs) or propranolol, 2 mg/kg (7 dogs), intravenously. The second occlusion lasted one hour and was followed by two hours of reperfusion and excision of the heart.

Prior to and 15 min after each coronary occlusion, epicardial electrocardiograms were obtained from 10–13 sites on the anterior surface of the left ventricle. Sites were chosen from within the area supplied by the occluded vessel, from distant regions (presumably nonischemic), and from the border zone, as defined by the border of epicardial cyanotic and noncyanotic tissue. The input impedance of the recorder amplifier was 100 megohms, and the frequency response of the system was ± 0.5 db from 0.14 to 70 Hz. The electrode was a 15 mm² copper cylinder with a saline-soaked wick (area of contact, 15 mm²) connected to the precordial "V" lead, held by a cable perpendicular to the electrode to minimize mechanical stress. Because of the area of the electrode, small variations in location did not change the configuration of the recording. The impedance of the electrode was maintained constant, as reflected in the reproducibility of the tracings.

The height of the ST segment was measured at the J point. A mean epicardial ST-segment elevation (ST) was determined for each dog by dividing the sum of ST-segment elevations by the number of sites. ST during the first occlusion was compared to ST during the second occlusion in each dog using the paired t-test. The percentage of all sites which exhibited ST elevation ≥ 2 mV (%NST) was also compared. The area of epicardial cyanosis (determined by placing a clear plastic sheet over the heart and tracing around the area of cyanosis) during the first occlusion was compared in the two groups of dogs.

Colloidal carbon black was used to label damaged and leaky myocardial vessels. Briefly, described, the method entails injecting 1 ml/kg of biologic Pelikan carbon black (300 Å particles; John Henschell Co., New York, NY) following filtration, via the left atrial catheter, 5 min after release of the second coronary occlusion. Two hours were then allowed for the carbon black to circulate and be cleared by the reticuloendothelial system.

The animal was then sacrificed and the heart rapidly removed; it was suspended in 10% formalin for five days and "breadloafed" into 1 cm sections in which the area stained by carbon black was determined as described below. Transmural biopsies corresponding to epicardial ECG mapping sites were obtained and slices were stained with hematoxylin and eosin.

The degree of carbon black labeling of damaged vessels was assessed both grossly and microscopically. To determine the percentage of the left ventricle exhibiting gross labeling, clear plastic sheets were placed over the 1 cm thick left ventricular slices and areas of gross blackening and non-blackening were traced, cut, and weighed. From the weighed plastic pieces, the percentage of left ventricle showing gross labeling was determined. To quantitate the number of labeled vessels, each transmural biopsy stained with hematoxylin and eosin was examined by light microscopy at a magnification of 400. Five nonoverlapping, randomly chosen fields from the inner, and five fields from the outer myocardial wall were examined for the number of labeled vessels. Carbon labeling was expressed as a number of labeled vessels/10 fields/transmural biopsy. The percentage of the left ventricle showing gross carbon black labeling and the number of vessels showing carbon labeling were compared in untreated and propranolol-treated groups, using the Student's t-test.

Immediately following excision of the heart, subendocardial biopsies were sampled for electron microscopy, from three sites beneath the area where cyanosis had been present and where ST segments had exceeded 2 mV during the first occlusion. Control samples were obtained from the subendocardium of nonischemic areas above the occlusion and from the posterior left ventricular wall.

For electron microscopy, 1 mm³ blocks of tissue were fixed in cold 1% osmic acid for one hour, passed through graded alcohol, propylene oxide and a 1:1 mixture of propylene oxide and Epon 812, overnight. The blocks were then placed in Epon 812 for three hours before embedding in Epon 812. One micron thick sections for light microscopy were stained with toluidine blue. Thin sections were mounted on plain copper grids, stained with uranyl acetate and lead citrate and examined under a Philips 200 electron microscope.

To obtain an estimate of the percentage of myocardial cells and vessels per block of tissue which showed the early changes of ischemic injury, a point counting technique was used. The thick sections were examined by light microscopy at a magnification of 400 under a grid. The intersections of crosslines in the counting grid can fall on myocardial cells, vascular elements, or the interstitial space. Each intersection or point was examined and the structure on which it fell was recorded. If a point fell on a myocardial cell, the degree of morphologic ischemic damage was graded and recorded from 0 to 4+ according to the following criteria:

0 = normal myocardial cell
1+ = nuclear chromatin clumping alone or with occasional vacuoles or relaxation, as manifest by I bands
2+ = the above plus intermyofibrillar edema and more vacuoles
3+ = the above plus numerous vacuoles and/or the sarcolemmal membrane lifted off the myofibrils
4+ = severe swelling and architectural disruption.

When each point falling on a myocardial cell had been assigned a numerical value of 0–4, a distribution of severity of ischemic damage per section was determined. A mean ischemic score (I) was calculated for each dog by calculating the average severity (0–4) of myocardial cell injury. Vessels were recorded as being normal or having ischemic changes, as reflected by intraluminal blebs, fibrin deposits, red blood cell stasis, and localized hemorrhage. I and the percentage of vessels showing ischemic changes were compared between groups using the Student's t-test.

Results

A number of measurements were made to assure that both groups of dogs were comparable prior to treatment (table 1).
The number of branches proximal to the coronary occlusion and the ratio of the distance from the origin of the vessel to the site of occlusion to the total length of the left anterior descending artery were similar in both untreated and propranolol-treated groups. Mean ST-segment elevations 15 min postocclusion were similar in the untreated (7.3 ± 1.0 mV) and propranolol-treated (9.2 ± 2.0 mV) groups during the first occlusion. There was no significant difference in %NST, as defined above, during the first occlusion between groups (table 1). The heart rate, systemic arterial pressure, and estimated areas of cyanosis during the first occlusion were similar in the two groups of dogs.

During the second occlusion mean ST-segment elevation was similar to the first occlusion in untreated dogs (6.0 ± 2.0 mV, NS) but was reduced in propranolol-treated dogs (3.0 ± 1.8 mV, P < 0.001). The change in heart rate between the first and second occlusions was +2 beats/min (NS) in untreated animals and -25 beats/min (P < 0.001) in propranolol-treated dogs. The change in blood pressure between the first and second occlusions was -7 mm Hg (NS) in untreated dogs and +6 mm Hg (NS) in the propranolol-treated group. Three dogs in the untreated group (one during the first occlusion, one during the second occlusion, and one after release of the second occlusion) and one dog in the propranolol-treated group (during the second occlusion) died of ventricular fibrillation. Results from these animals were excluded from this study.

Gross carbon labeling could be seen as confluent dark grey patches in the anterior wall of the left ventricle in the region supplied by the occluded left anterior descending artery (fig. 1). Gross and microscopic labeling were most prominent in the subendocardium of the ischemic zone, but extended into the middle and outer myocardium in many animals. The percentage of the entire left ventricle showing gross labeling was 14 ± 3% in untreated animals and 4 ± 1% in propranolol-treated animals (P < 0.02). By light microscopy, four basic types of labeling were seen: 1) carbon thrombi or plugs; 2) circumferential labeling; 3) a combination of 1 and 2 (fig. 2B–D), and 4) leaking of carbon into the interstitial space. Types 2–4 were commonly associated with microscopic foci of hemorrhage. The total number of labeled vessels/10 high power fields/biopsy taken from the area supplied by the occluded vessel, as determined by epicardial ST-segment elevation and cyanosis during the first occlusion, was 55 ± 7 in the untreated group and 27 ± 3 in the propranolol-treated group (P < 0.001). When the types of capillary labeling were analyzed separately, all four types were decreased in propranolol-treated animals (table 2).

In order to assess independently the severity of ischemic changes in the vasculature and in myocardial cells, morphometric analysis was performed on 1 µ thick toluidine blue sections. While 75 ± 12% of vessels showed ischemic changes in the untreated group, only 2 ± 1% (P < 0.001) showed ischemic changes in the propranolol-treated group. The mean ischemic score of the myocardial cells (I) was 1.7 ± 0.3 in untreated animals and 0.1 ± 0.1 (P < 0.001) in treated animals, showing that both the vascular and myocardial cell injury were decreased by propranolol.

Ultrastructure of nonischemic myocardium sampled above the occlusion and on the posterior ventricular wall revealed normal myocardial structure in both groups of dogs; myofilaments were in register and mitochondria showed tightly packed cristae. Glycogen was abundant and nuclear chromatin was distributed homogeneously; endothelial cells were intact with numerous pinocytotic vesicles (figs. 2A and 3A).

Myocardium from the ischemic anterior left ventricular wall, defined as that tissue subjacent to the area of cyanosis and ST-segment elevations, revealed marked changes in untreated animals (figs. 2B, 3B). Myocardial cells were markedly swollen with numerous vacuoles and intermyofibrillar edema. The sarcolemmal membrane often was lifted off the myofilaments. Contraction bands were numerous and myofilaments were frequently out of register. Mitochondria were swollen with disrupted cristae and intramitochondrial dense bodies. Nuclear chromatin clumping and margination were prominent and glycogen was absent. Endothelial cells showed a variety of alterations, ranging from focal swelling and apparent decreases of pinocytotic vesicles (fig. 3C) to outright endothelial degeneration (figs. 4A and 4B).

**FIGURE 1.** Section from the anterior left ventricular myocardial wall of a dog after 1 hour of left anterior descending coronary occlusion and 2 hours of reflow (untreated). Carbon labeling is most prominent in the subendocardium with patchy extension into the outer wall. White bar = 1 cm.

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**Table 1. Comparison of Untreated and Propranolol-Treated Groups During the First Occlusion**

<table>
<thead>
<tr>
<th></th>
<th>ST: first occlusion (mV)</th>
<th>%NST: first occlusion</th>
<th># of branches proximal to occlusion</th>
<th>Relative distance along LAD to occlusion*</th>
<th>Estimated area of cyanosis (1st occlusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>7.3 ± 1.0</td>
<td>59 ± 6%</td>
<td>1.7 ± 0.3</td>
<td>25.0 ± 1.3%</td>
<td>15.0 ± 1.6 cm²</td>
</tr>
<tr>
<td>Propranolol</td>
<td>9.2 ± 2.0</td>
<td>71 ± 10%</td>
<td>1.8 ± 0.5</td>
<td>25.8 ± 2.4%</td>
<td>15.3 ± 1.7 cm²</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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*(Distance between the bifurcation of the left coronary to the occlusion/length of left anterior descending coronary artery) × 100
Intraluminal blebs, occasional thrombi, foci of hemorrhage, and gaps due to focal degeneration (figs. 3C, 4, and 5) were also seen. When carbon plugs were present (fig. 4A), the endothelium often had gaps or was degenerated.

Circumferential labeling by light microscopy usually was secondary to carbon particles adhering to damaged endothelium or bare basement membrane (fig. 4B). Occasionally, carbon was found "intramurally," that is, between

<table>
<thead>
<tr>
<th></th>
<th>Carbon thrombus</th>
<th>Circumferential</th>
<th>Carbon thrombus + circumferential*</th>
<th>Leaking of the carbon into the interstitial space</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>44.9 ± 4.7</td>
<td>7.7 ± 2.5</td>
<td>1.6 ± 0.5</td>
<td>1.0 ± 0.2</td>
<td>55.0 ± 6.6</td>
</tr>
<tr>
<td>Propranolol</td>
<td>26.2 ± 2.8</td>
<td>0.3 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>26.5 ± 2.8</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Excluding those vessels from column #1 and #2.
damaged endothelium and an intact basement membrane or pericyte (fig. 4C). This also gave a circumferential appearance to the labeling by light microscopy. Carbon particles were also present in the interstitial space (fig. 4D). Carbon could sometimes be found within platelet or fibrin thrombi (fig. 5).

In the ischemic zone of propranolol-treated animals (defined as the myocardium subjacent to the area of cyanosis and ST-segment elevations during the first occlusion), most myocardial cells appeared normal and most vessels were intact (table 3, fig. 6). The mean ischemic score was significantly lower in propranolol-treated animals (0.1 ± 0.1) compared to untreated animals (1.7 ± 0.3, P < 0.001). The mean percentage of vessels showing ischemic change also was significantly lower in propranolol-treated animals (1.5 ± 1.1%) compared to untreated animals (74.7 ± 11.8%, P < 0.001). Occasional myocardial cells from propranolol-treated dogs showed swelling and loss of glycogen. Contraction bands were infrequent. Occasionally endothelial blebs and diffuse endothelial swelling were present. Foci of hemorrhage and endothelial gaps were rarely seen. When carbon labeling was seen, it usually took the form of a plug and was associated with damaged endothelium.

**Discussion**

Changes in the microvasculature during the early phase of experimental ischemic injury have been noted in kidney, brain, skeletal muscle, and heart. Several morphologic changes occur and the organs vary in their sensitivity to microvascular ischemic damage. In the kidney, endothelial swelling is usually diffuse and marked after one hour of ischemia. In brain and skeletal muscle, localized swelling as manifest by intraluminal blebs is more common. The brain appears to be the most sensitive organ to microvascular changes; after five minutes of ischemia, certain areas of rabbit brain can no longer be reperfused. Blebs and swollen glial cells appearing to compress adjacent capillaries are common.

In myocardial ischemia, early endothelial swelling may be concentrated in one area and include the formation of intraluminal blebs. Infrequently, the endothelium may be diffusely swollen. Endothelial gaps are present and are associated with extravascular fibrin deposits and red cells; red cell sludging is common. Arminger et al. described blanched endothelial cytoplasm as early as 10 min following coronary occlusion. Endothelial changes become ad-
vanced by 90 min after occlusion and may contribute to incomplete reperfusion following release of the occlusion.\textsuperscript{18, 19} Whether microvascular changes play a primary role in causing irreversible myocardial cell injury\textsuperscript{18} remains to be determined. Certainly, if damaged vessels are supplying downstream myocardial cells which are still salvageable (reversibly injured) then microvascular damage could exacerbate ischemia by interfering with collateral flow. In fact, during experimental coronary occlusion in the untreated dog, collateral flow to ischemic tissue has been shown to fall between 1.5 min and 6 hours after occlusion.\textsuperscript{7} This fall may be secondary to microvascular damage.

The use of colloidal carbon as a tracer for vascular injury is a well established technique which has been used in a variety of experimental models.\textsuperscript{8} Carbon labeling of vessels has been seen in tissue injured by heat, histamine and serotonin, ischemia, and bacterial toxins. Its value depends on the basic observation that when carbon is injected into an animal having areas of vascular damage and allowed to circulate, damaged vessels retain the colloidal carbon, while the remainder is cleared from the circulation by the reticuloendothelial system.\textsuperscript{8, 9} In the dog, occasional carbon plugs can be seen in presumably nonischemic myocardium but the amount of labeling is negligible compared to labeling in damaged tissue. This background labeling occurred in our study despite 1) the microscopic observations that carbon

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{The various types of carbon labeling occurring in ischemically injured myocardium in untreated animals are shown in this and figure 5. Panel A) A carbon plug is present in a lumen of an ischemically damaged capillary. The endothelium (e) is largely degenerated especially on the right hand side of the vessel. The myocardial cell is massively swollen with architectural disruption. $\times$ 12,250. Panel B) Carbon circumferentially labeling an ischemically damaged capillary. Red cell sludging and extravascular red cells (R) are present. The endothelium is degenerated. $\times$ 11,733. Panel C) Intramural carbon (arrow) between an endothelial cell and the endothelial basement membrane, presumably a sign of increased capillary permeability. $\times$ 21,000. Panel D) Extravascular carbon, i.e., carbon which has leaked out of a vessel, is present in the interstitial space mixed with fibrin tactoids, suggesting increased capillary permeability. $m$ = mast cell, $i$ = interstitial space. $\times$ 9,100.}
\end{figure}
was not clumped prior to injection; 2) filtering prior to injection; and 3) allowing two hours for clearing of carbon black by the reticuloendothelial system. This phenomenon has been observed in other models and the reason for it is not known. Microscopic quantitation of carbon labeling is a more sensitive technique than gross quantitation since ischemically damaged tissue from grossly unlabeled areas of myocardium sometimes showed microscopic carbon labeling.

This phenomenon of vascular labeling does not present itself uniformly. There are several ways by which carbon can label damaged vessels as observed ultrastructurally: 1) intramural deposits of carbon (fig. 4C), which were infrequently seen in this study, are thought to represent a separation of endothelial cells followed by intraluminal leaking of plasma and carbon particles which are then retained in the basement membrane; 2) another type of labeling, which was commonly observed occurred as a result of carbon particles adhering to an adhesive endothelial surface with or without an admixture of fibrin and platelets (fig. 4B); 3) a third type of labeling occurred as a carbon plug, which has been interpreted as occurring when endothelial injury is so severe that practically all of the plasma escapes from the lumen, and only tracer particles remain. This was the most common type of labeling seen in this study and in previous studies of ischemic rat skeletal muscle (fig. 4A); 4) actual leakage of the colloidal carbon as manifest by particles in the interstitial space was observed (fig. 4D). Endothelial phagocytosis of carbon has been described in some experimental models, but was not observed in this study. Overall, the present investigation supports the validity of the colloidal carbon technique: carbon labeling correlated with ultrastructural evidence of endothelial damage.

Although a number of pharmacologic interventions have been shown to decrease myocardial cell injury during ischemia, the effect of these agents on the microvasculature largely has been ignored. The major finding of this study was that propranolol, an agent known to decrease experimental infarct size, not only reduced myocardial cell injury, but reduced microvascular injury and the increased microvascular permeability for carbon as well. One might expect other pharmacologic interventions which reduce infarct size

**Table 3. Morphometric Analysis Comparing Untreated and Propranolol-Treated Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Mean ischemic score</th>
<th>Mean % of vessels showing ischemic change</th>
<th>Mean % of myocardial cells showing ischemic change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1+</td>
</tr>
<tr>
<td>Untreated</td>
<td>1.7 ± 0.3</td>
<td>74.7 ± 11.8</td>
<td>16.2</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.1 ± 0.1</td>
<td>1.5 ± 1.1</td>
<td>91.4</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*The cells from only one dog fell into the grade 3+ class. The other five dogs showed no cells with such severe ischemic changes.*

**Figure 5.** Untreated myocardium temporarily ischemic for one hour and two hours of reflow showing carbon mixed with a fibrin thrombus in a capillary (panel A) and carbon mixed with a platelet thrombus in a large venule (panel B); p = platelet. × 14,000 = A; × 4,500 = B.
also to reduce endothelial damage, but this remains to be determined. In addition, this investigation showed that colloidal carbon can be used as a tracer of microvascular damage and of increased microvascular permeability during the early phase of myocardial infarction.

Propranolol decreases myocardial infarct size during both permanent \(^{20-22}\) or temporary \(^{23-26}\) coronary occlusion. Although its mechanism of action is not completely understood, it may be related to the drug’s ability to reduce myocardial oxygen demand. Although some studies show that propranolol results in a relative improvement of the endocardial/epicardial ratio of coronary blood flow after a 30 second coronary occlusion, \(^{28}\) in other studies it was shown that absolute flow to the ischemic myocardium during a period of reversible injury as well as the endo/epicardial flow ratio was not improved. \(^{27}\) However, after 24 hours of continuous ischemia, the qualitative distribution of coronary flow as measured by a fluorescent dye (thioflavin S) was improved in animals that received propranolol. \(^{28}\) This may be related to propranolol’s protective effect on the microvasculature described in the present investigation. Preservation of myocardial cells by propranolol is probably not related primarily to the preservation of the microvasculature since propranolol decreases infarct size after short period of temporary occlusion, \(^{29}\) at which time vascular damage in the dog is minimal. \(^{19}\) It may be speculated that an increase in damage of the microvasculature may increase ischemic damage of myocardial cells, but data on this subject are lacking. If this were true, then propranolol may protect ischemic myocardium by the secondary process of preserving the microvasculature. Apart from this secondary process propranolol should reduce the amount of incomplete reperfusion following release of longer coronary occlusions.

That propranolol may exert a protective effect on ischemic vessels was also suggested by Diaz et al. \(^{29}\) in which it was shown in dogs that this drug significantly reduced the amount of gross hemorrhage which was seen after a three hour occlusion followed by 24 hours of reflow. This investigation and the observations described in the present paper point to a relationship between vascular injury during acute myocardial ischemia and degree of beta-adrenergic drive. Suppression of the drive by beta-blockade may actually decrease the severity of vascular injury and hence hemorrhage. Whether propranolol does this by decreasing oxygen demand of the endothelial cells themselves and whether other interventions which salvage ischemic myocardium have a similar effect on the microvasculature remains to be determined.

In conclusion, the present study adds additional data to support the concept that ischemic myocardium can be salvaged. \(^{4}\) Whereas previous studies have concentrated on infarct size, this study shows that the early morphologic changes of ischemic myocardial cells and vessels, as assessed by morphometric, ultrastructural and carbon labeling techniques, can be diminished by an intervention. The observation in this study that the microvasculature was preserved by propranolol has an additional important clinical implication, since a relatively patent microvasculature will facilitate the delivery of other drugs to a damaged area.
Acknowledgment

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References


Corrections

Conley et al.: Circulation 55: 158, 1977. On page 161, in table 9, the series from Peter Bent Brigham should read 171 patients with an operative mortality of 4.7%.

Chandraratna et al.: Circulation 55: 622, 1977. On page 624, table 1, the normal value for IVSE should read 0.4–1.0 cm.
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