The effect of streptokinase on intramyocardial hemorrhage, infarct size, and the no-reflow phenomenon during coronary reperfusion

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ABSTRACT The purpose of this study was to determine whether streptokinase (1) exacerbates intramyocardial hemorrhage during coronary reperfusion, (2) has any intrinsic effect on myocardial infarct size other than its ability to lyse proximal thrombi in coronary arteries, and (3) can abolish the no-reflow phenomenon. Anesthetized open-chest dogs underwent coronary occlusion for 3 hr followed by 3 hr of reperfusion. Area of infarct was assessed by tetracorization staining, anatomic zone of no-reflow by injection of the fluorescent dye thioflavin S at the end of the reperfusion period, regional blood flow during occlusion and reperfusion by the radioactive microsphere technique, and extent of gross hemorrhage by assessment of photographic enlargements of the heart slices. Area of infarction of the left ventricle was similar in control (13.4 ± 3.6%) and streptokinase-treated dogs (13.0 ± 2.9%; p = NS). Seven of eight dogs in the untreated group had anatomic perfusion defects as assessed by thioflavin S at the end of the reperfusion phase; seven of eight dogs in the streptokinase group had anatomic perfusion defects. There was no difference in the extent of gross hemorrhage between the two groups (6.5 ± 2.1% of left ventricle in controls and 5.7 ± 2.3% in streptokinase-treated dogs). Severe depression of regional blood flow during reperfusion was present within the infarcted tissue and was associated with an anatomic perfusion defect as defined by thioflavin S; there was moderate depression of flow within the noninfarcted, salvaged subepicardium. In a separate series of experiments, infarcts were assessed for hemoglobin content. Intramyocardial hemoglobin levels were not higher after fibrinolytic therapy plus reperfusion compared with reperfusion alone. In conclusion, streptokinase did not exacerbate myocardial hemorrhage after coronary reperfusion, had no effect on infarct size, and did not abolish the no-reflow phenomenon. The no-reflow phenomenon is unlikely to be caused by fibrin thrombi.


OVER THE LAST 4 to 5 years there has been intense interest in the concept of treating patients with acute myocardial infarction with fibrinolytic therapy.1–8 Several studies have shown that patients with acute myocardial infarction can safely undergo coronary angiography followed by intracoronary administration of streptokinase to lyse the intracoronary thrombus. Recent investigations show that intravenous streptokinase may also be effective.8 Approximately 80% to 85% of patients have successful thrombolysis with intracoronary streptokinase, which has been associated with amelioration of chest pain, improved electrocardiographic findings, and improved thallium perfusion, suggesting salvage of ischemic tissue. Some studies have shown improvement of left ventricular function after coronary reperfusion, while others have not.9,10 There are still several unknown factors concerning streptokinase. Since coronary reperfusion has been associated with hemorrhagic infarction11,12 and since streptokinase is fibrinolytic, it is conceivable that reperfusion with this agent could exacerbate hemorrhagic infarction and perhaps result in hemorrhage dissecting beyond the necrotic area. There is a lack of data concerning the effect of streptokinase on the morphology of the reperfused infarct.

Several pharmacologic agents have been shown to reduce the extent of myocardial infarction,13,14 there is even some suggestion that heparin may be capable of reducing myocardial infarction.15 Although studies have suggested that coronary reperfusion with streptokinase has reduced infarct size,1,2 it has been assumed that this was caused by the lysis of thrombi in the
proximal coronary arteries. Whether streptokinase has any intrinsic effect in reducing myocardial infarct size is unknown. It is conceivable that infarct size has been reduced by an action of streptokinase other than coronary thrombolysis.

After release of coronary occlusions of 90 min or longer, certain areas within the myocardium may not have restoration of normal myocardial blood flow as assessed by dye or carbon-black injections, despite removal of the coronary obstruction. This phenomenon has been termed the "no-reflow phenomenon" and has been observed in several organs subjected to ischemia, including skin, kidney, and brain. The etiology of the no-reflow phenomenon has been a subject of debate. Some investigators have postulated that it is primarily caused by ischemic contracture of myocardial cells after reflow, while others have suggested that it is caused by microvascular damage. Other studies have suggested that it is caused by fibrin thrombi, and a recent study suggested that it is the result of white blood cell plugging. One way to test whether the no-reflow phenomenon is related to fibrin deposits within the microvasculature is to assess whether it occurs in the setting of streptokinase. If streptokinase were to abolish the no-reflow phenomenon, this would suggest that the phenomenon is caused by fibrin thrombi. If streptokinase were unable to abolish the no-reflow phenomenon, this would suggest that the mechanism of no-reflow is related to factors other than fibrin thrombi.

Therefore the purposes of this study were threefold: (1) to determine whether streptokinase exacerbates intramyocardial hemorrhage during coronary reperfusion, (2) to determine whether streptokinase has any intrinsic effect on myocardial infarct size other than its ability to lyse proximal thrombi in coronary arteries, and (3) to determine whether streptokinase can abolish the no-reflow phenomenon.

Methods

Twenty-six mongrel dogs of either sex weighing 15 to 41 kg were anesthetized with pentobarbital (30 mg/kg iv), intubated, and placed on a Harvard respirator (Ealing Co., So. Natick, MA). A thoracotomy was performed through the fifth left intercostal space and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was dissected free from surrounding tissue proximal to the first large diagonal branch. A polyethylene catheter was placed into the left carotid artery to monitor blood pressure with a Statham P23Db transducer. A third catheter was placed into the left jugular vein for intravenous infusions.

After administration of lidocaine (1.5 mg/kg iv) the LAD was occluded with an atraumatic Schwartz vascular clamp. A second, similar dose of lidocaine was given 5 min after coronary occlusion. To measure regional myocardial blood flow, radioactive microspheres (2.0 × 10^6) 8 to 10 μm labeled with 46Sc, 111In, or 141Ce were injected into the left atrium 1 hr after coronary occlusion, and a reference blood sample was withdrawn from the carotid artery at the rate of 15.3 ml/min.

Dogs were then randomly assigned to two groups. One received streptokinase (10.714 IU/kg iv bolus over 30 min followed by an infusion of 1425 IU/kg/hr) from 60 min after the coronary occlusion until death; the other received saline. The high dose of streptokinase was similar to that used in human studies in which the drug was administered intravenously for the treatment of acute myocardial infarction.

At 3 hr after coronary occlusion, lidocaine was again administered and the occlusion was released by removing the Schwartz vascular clamp. Reperfusion was continued for 3 hr at which time regional myocardial blood flow again was measured. To visualize an anatomic zone of no reflow, thioflavin S (4%, 1 ml/kg), a fluorescent dye, was injected into the left atrium at the end of 3 hr of reperfusion (coronary clamp removed), and dogs were killed with potassium chloride. Thioflavin S has been used previously in several studies of heart, kidney, and spinal cord to assess the presence of anatomic reperfusion defect (no reflow). The heart was removed and the left ventricle was isolated by removing the right ventricle and structures above the atrioventricular ring. The left ventricle was then cut into 5 to 6 mm transverse slices and each slice was weighed. The presence or absence of an anatomic perfusion defect as assessed by thioflavin S was noted for each dog. The left ventricular slices then were incubated in triphenyltetrazolium chloride (TTC) for 10 to 15 min to visualize the infarcted zone. Several previous studies have shown that TTC is a reliable marker of irreversibly damaged myocytes in this time frame of ischemia. Upon removal of the slices from TTC, slices were traced on an acetate sheet to outline the areas of noninfarcted tissue, which stain dark red, and irreversibly damaged myocardial tissue, which does not stain. These tracings were then transferred to bond paper.

Photographic enlargements of the left ventricular slices were projected, and the outline of the slices and extent of hemorrhage were traced on bond paper. The percent of the left ventricle that was necrotic was determined as follows: the tracings of the heart slices and area of necrosis were cut out and the paper was weighed. The percent of the total necrotic area of the slice was determined from the weights of the paper. The weight (g) of necrotic area of the slice was determined by multiplying the percentage of the slice that was necrotic by the weight of the slice. The weight of the necrotic area of the total left ventricle was determined by adding the weight of the necrotic area from each slice. The percentage of the left ventricle that was necrotic was determined by dividing the total weight of the necrotic area by the total weight of all the slices. The percentage of the left ventricle that was hemorrhagic was calculated in the same manner.

Determination of regional myocardial blood flow was performed by dividing tissue into epicardial, midmyocardial, and endocardial thirds from both normal and necrotic areas. Regional myocardial blood flow was calculated from the formula

\[ C_s \times RBF \times C_{h-1} \]

where \( C_s \) is counts in the tissue sample, \( RBF \) is reference blood flow, and \( C_{h-1} \) is counts in the reference blood sample. Myocardial...
al blood flow was expressed in milliliters per minute per gram.

To assess whether there were qualitative differences in the appearance of necrosis or the extent of hemorrhage in infarcts reperfused with streptokinase compared with untreated reperfused infarcts, an entire transverse midpapillary left ventricular slice from each dog was fixed in formalin. The slice was dissected to encompass the whole infarct, which was processed for histologic examination.

To better quantitate the degree of hemorrhage after coronary reperfusion, a separate group of anesthetized open-chest dogs (n = 14) was also subjected to 3 hr of proximal occlusion of the LAD followed by 3 hr of reperfusion. At 50 min of ischemia the dogs were randomly assigned to control or streptokinase treatment. The investigators were blinded as to the treatment regimen. At the end of 60 min of coronary occlusion, treated dogs received an intravenous bolus dose of streptokinase (10,714 IU/kg infused over 30 min) followed by 1425 IU/kg/hr until death. Untreated dogs received an equivalent volume of saline. After 3 hr of reperfusion the heart was excised, cut into 5 mm transverse slices, and weighed. Two nonadjacent slices from the midpapillary region of the heart were placed aside for hemoglobin analysis. The remaining slices were incubated in TTC to visualize the zone of irreversible damage. The entire infarct from the slices used for hemoglobin analysis was dissected by using the opposite block faces of their adjacent slices as a guide to infarct location. The infarcted region of these two slices and remote noninfarcted tissue were then subjected to analysis of hemoglobin as previously described. An estimate of the extent of necrosis within the left ventricular slices used for hemoglobin analysis was determined by dividing the weight of the infarcted region by the total weight of the respective slice.

Differences in percent of hemorrhage and percent of necrosis in the left ventricle between the control and streptokinase groups were analyzed by Student's t test.

**Results**

Twenty-six dogs were entered into the study to assess the presence of an anatomic reperfusion defect, quantitate infarct size and hemorrhagic zone by gross analysis, and measure regional myocardial blood flow. Nine dogs were excluded because of ventricular fibrillation (VF); seven developed VF before randomization and two after. The two that had VF after randomization were both in the control group and both developed VF during reperfusion. One other dog was excluded because of respiratory failure. Of the 16 dogs remaining, eight were randomly assigned to the control group and eight to the streptokinase-treated group.

**Qualitative features.** After 3 hr of coronary occlusion and 3 hr of reperfusion the myocardial infarcts were well delineated as pale areas not stained by TTC. These zones of infarction were for the most part confined to the subendocardium and midmyocardium; the outer third of the ventricle was usually spared. Most of the infarcts had evidence of gross dark brown hemorrhage (figures 1 to 4). This hemorrhage was confined to the necrotic area and did not appear to extend beyond it. There was often a rim of nonhemorrhagic necrotic tissue surrounding the zone of hemorrhage.

**LUBORATORY INVESTIGATION–REPERFUSION**

The gross qualitative appearance of the infarcts and hemorrhagic zones did not differ between control and streptokinase-treated dogs.

The presence of an anatomic reperfusion defect was assessed by injection of thioflavin S dye just before the dog was killed, at a time when the coronary clamp was removed. Thioflavin S is known to stain endothelial cells fluorescent yellow-green when they are receiving flow16; cells are not stained when flow is very low. The anatomic reperfusion defects appeared as nonfluorescent tissue when the slices were viewed under ultraviolet light (figures 2 and 4). Seven out of eight dogs in each group had anatomic reperfusion defects. These reperfusion defects were similar to those termed "no-reflow phenomenon" in previous studies.16 The anatomic reperfusion defects were also confined to the necrotic area and did not appear to extend beyond it. They corresponded to approximately the same areas as gross hemorrhage.

**Quantitative analysis (table 1).** The percentage of the left ventricle that was infarcted was 13.4 ± 3.6% in control dogs and 13.0 ± 2.9% in streptokinase-treated dogs (p = NS). The zone of gross hemorrhage was in general smaller than the necrotic zone and averaged 6.5 ± 2.1% of the left ventricle in control dogs and 5.7 ± 2.3% of the left ventricle in streptokinase-treated dogs.

<table>
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<tr>
<th>Dog</th>
<th>% of LV necrotic</th>
<th>% of LV hemorrhagic</th>
<th>% of infarct hemorrhagic</th>
<th>Perfusion defect present</th>
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**Streptokinase**

<table>
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<th>% of LV hemorrhagic</th>
<th>% of infarct hemorrhagic</th>
<th>Perfusion defect present</th>
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<td>34.7 ± 8.0</td>
<td>7/8</td>
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</table>

p = NS p = NS p = NS
dogs. There was no significant difference in the gross assessment of hemorrhage between the two groups.

Regional myocardial blood flow data are shown in table 2. At 1 hr after coronary occlusion, regional myocardial blood flow in the nonischemic tissue averaged approximately 1.0 ml/min/g and did not vary between control or treated groups. Ischemic zone blood flow in the subendocardium of the control animals was reduced to 0.10 ± 0.04 ml/min/g and in the streptokinase-treated group was similarly reduced to 0.09 ± 0.05 ml/min/g (p = NS, control vs streptokinase). Blood flow in the midmyocardium was reduced to 0.24 ± 0.10 ml/min/g in the control group and to 0.18 ± 0.06 ml/min/g in the streptokinase-treated group (p = NS between groups). Blood flow in the subepicardium averaged 0.45 ± 0.19 ml/min/g in control animals and 0.41 ± 0.13 ml/min/g in streptokinase-treated animals; again no difference between groups was present during the period of ischemia.

With 3 hr of coronary reperfusion, regional myocardial blood flow in the normal tissue was approximately 0.9 ml/min/g and did not differ between the control and

FIGURE 1. Left ventricular slice from a streptokinase-treated animal. Hemorrhage appears as a dark-brown discoloration within the subendocardium and midmyocardium. This is surrounded by a rim of pale-yellow infarcted but nonhemorrhagic tissue. An outer rim of subepicardium is noninfarcted. The hemorrhage is not present in noninfarcted tissue.

FIGURE 2. Same left ventricular slice as in figure 1 viewed under ultraviolet light for thioflavin S fluorescence. Thioflavin S was infused during reperfusion and failed to stain a portion of the subendocardium and midmyocardium (no reflow); the subepicardium was stained. Streptokinase did not abolish the no-reflow phenomenon.

FIGURE 3. Left ventricular slice from a control animal. Hemorrhage appears as a brown-discoloration within the subendocardium and midmyocardium. A rim of pale infarcted but nonhemorrhagic tissue surrounds the hemorrhagic zone, and a portion of the subepicardium is not infarcted. There is no difference in gross pathologic appearance compared with figure 1.

FIGURE 4. Same left ventricular slice as in figure 3 viewed under ultraviolet light showing zone of no reflow (nonfluorescent region).
TABLE 2
Regional myocardial blood flow (ml/min/g)*

<table>
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<tr>
<th></th>
<th>Nonischemic</th>
<th>Ischemic</th>
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<tr>
<td></td>
<td>Control</td>
<td>Streptokinase</td>
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<tr>
<td>1 hr after occlusion</td>
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<tr>
<td>Subendocardium</td>
<td>1.06 ± 0.16</td>
<td>1.05 ± 0.15</td>
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<tr>
<td>Midmyocardium</td>
<td>1.07 ± 0.19</td>
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<tr>
<td>Subepicardium</td>
<td>0.93 ± 0.12</td>
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<td>3 hr reperfusion</td>
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<tr>
<td>Subendocardium</td>
<td>0.97 ± 0.08</td>
<td>0.86 ± 0.16</td>
</tr>
<tr>
<td>Midmyocardium</td>
<td>0.94 ± 0.11</td>
<td>0.83 ± 0.10</td>
</tr>
<tr>
<td>Subepicardium</td>
<td>0.85 ± 0.11</td>
<td>0.91 ± 0.18</td>
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*Data expressed as mean ± SEM. For all values, p = NS control vs streptokinase.

Regional myocardial blood flow within the previously ischemic zone remained significantly depressed compared with flow in the nonischemic zone even though the coronary occlusion had been removed. Blood flow in the subendocardium was 0.33 ± 0.06 ml/min/g in control dogs and similar at 0.38 ± 0.07 ml/min/g in streptokinase-treated animals. Blood flow in the middle third of the myocardium was also depressed after removal of the coronary occlusion at values of 0.25 ± 0.05 ml/min/g in control and 0.44 ± 0.11 ml/min/g in streptokinase-treated animals (p = NS between groups). Finally, regional myocardial blood flow in the ischemic subepicardium was less depressed than that in the subendocardium or midmyocardium after reperfusion but was still not normal at 0.54 ± 0.08 ml/min/g in control animals and 0.62 ± 0.12 ml/min/g in streptokinase-treated animals (p = NS between groups). Thus regional myocardial blood flow after removal of the coronary clamp was depressed not only in the midmyocardium and the subendocardium, where the myocardium had been infarcted and in which the anatomic reperfusion defect was present, but was reduced to a lesser extent in the subepicardial third of the myocardium in which the myocardial tissue was usually preserved.

Heart rate and blood pressure results are shown in table 3. There was no significant difference between control or treated animals either during occlusion or after coronary reperfusion.

Histologic analysis. Analysis of sections stained with hematoxylin and eosin revealed contraction band necrosis with foci of hemorrhage and vascular congestion (figures 5 and 6). There were no recognizable differences in the degree of hemorrhage or in morphologic appearance of the infarcts between control and streptokinase-treated animals. A prominent feature in both groups was early neutrophil infiltration (figures 5 and 6). Margination of neutrophils was prominent as well as the presence of neutrophils within the walls of blood vessels. This early neutrophil infiltration is in contrast to the findings of a previous report in which this type of infiltrate was less prominent in reperfused infarcts by 72 hr after reperfusion.25

Hemoglobin analysis. Fourteen additional dogs were entered into a study in which the hemoglobin content of the infarcts was assessed. Three dogs developed VF before randomization. One dog from the streptokinase-treated group failed to develop an infarct and was excluded from the study. Of the remaining 10 dogs, five were untreated and five received streptokinase.

The mean hemoglobin concentration in noninfarcted tissue was 10.1 ± 1.7 mg/g wet weight in untreated animals and 8.9 ± 1.3 mg/g wet weight in streptokinase-treated animals (p = NS; table 4). The mean hemoglobin concentration within the infarcted tissue was 26.0 ± 5.5 mg/g wet weight in untreated and 12.3
± 3.0 mg/g in streptokinase-treated animals (p = NS). Therefore there was no evidence that fibrinolytic therapy enhanced reperfusion hemorrhage; in fact, there was a trend for hemoglobin levels to be lower in the streptokinase-treated group, although this was not statistically significant.

The average extent of infarction in these slices was 28.0 ± 7.3% in control animals and 30.3 ± 6.8% in streptokinase-treated animals (p = NS).

Discussion

The results of this study suggest that (1) streptokinase has no intrinsic effect on reducing myocardial infarct size, (2) streptokinase does not exacerbate hemorrhage during reperfusion, and (3) the no-reflow phenomenon is not likely to be caused by fibrin thrombi.

There have been several studies that have examined the effects of hemorrhage in myocardial infarction. It is now clear that reperfused infarcts are more hemorrhagic than nonreperfused myocardial infarcts, although some hemorrhage may be present in infarcts created by permanent coronary occlusion. While some studies have suggested that hemorrhage and microvascular damage are not important exacerbating features for the development of myocardial necrosis, others have suggested that hemorrhage and increased capillary permeability could increase ischemic necrosis. A recent study from this laboratory

<table>
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<th>Table 4</th>
<th>Myocardial hemoglobin levels</th>
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suggested that hemorrhage associated with reperfusion could result in an altered leukocyte response following 3 days of reperfusion after a 4 hr coronary occlusion. However, no long-term impairment of healing was noted. One possible disadvantage of streptokinase is that it has the potential to cause bleeding problems. It was therefore conceivable that this agent could exacerbate hemorrhagic myocardial infarction and perhaps even result in dissection of hemorrhage outside of a necrotic zone. Our present results suggest that streptokinase does not exacerbate hemorrhagic myocardial infarction whether hemorrhage is assessed by gross pathologic analysis, microscopic analysis, or analysis of intramyocardial hemoglobin levels. In both control and streptokinase-treated infarcts the zone of hemorrhage was contained within the area of necrosis and there was no evidence of dissection of hemorrhage outside of that zone. The relative size of the areas of hemorrhage did not differ between control and streptokinase-treated animals, suggesting that reperfusion with streptokinase does not change the morphologic characteristic of the infarct or increase the amount of hemorrhage that occurs during release of coronary occlusion. The histologic results suggested that even within those zones of the reperfused infarct that are normally hemorrhagic, streptokinase did not worsen the hemorrhage.

The results of these studies suggest that streptokinase has no intrinsic effect on reducing myocardial infarct size other than its previously reported effect on inducing coronary fibrinolysis. Although many pharmacologic agents have been shown to reduce myocardial infarct size, there has been much debate over the efficacy of several of these, including β-blockers, nitroglycerin, and certain anti-inflammatory agents. Other reports suggest that heparin could reduce myocardial infarct size. If streptokinase had an intrinsic effect of reducing myocardial infarct size, it is conceivable that beneficial effects reported for this agent might not be solely due to its effect on proximal coronary thrombi but might be due to effects on distal microvasculature or even to direct myocardial effects. Such was not the case, however, and this study supports the concept that the primary beneficial property of strepto-

FIGURE 6. Histologic section from a streptokinase-treated animal showing hemorrhage into the myocardial infarct. No histologic difference between control and treated animals was observed. Arrows point to polymorphonuclear cells. (Original magnification × 1500.)
kinase in acute myocardial infarction is its ability to lyse proximal thrombi and that it does not produce any intrinsic effect on myocardial cells.

There has been considerable debate as to the cause of the no-reflow phenomenon. The results of this study suggest that thrombi may not be an important cause. The very high dose of streptokinase administered has been shown to lyse thrombi in humans, and it is therefore unlikely that thrombi per se contributed to the no-reflow phenomenon, since the perfusion defects were present in both control and streptokinase-treated dogs. It is much more likely that the no-reflow phenomenon, as defined by an anatomic perfusion defect, is related to microvascular damage within the zone of necrosis. In fact, the zone of no reflow often correlated very closely with the zone of gross hemorrhage. It is also conceivable that the early neutrophilic response contributed to the no-reflow phenomenon by white cell plugging.

In a previous study, the neutrophil response was reduced at 3 days of reperfusion compared with infarcts that had not been reperfused. It is likely that with reperfusion, neutrophil infiltrates peaks very early and then is diminished a few days later at the time it normally peaks in infarcts that have not been reperfused.

In this study there were areas of very low regional myocardial blood flow in the subendocardium and the midmyocardium after reperfusion; these were the same areas where the anatomic perfusion defects as defined by thioflavin S were noted. These areas have been associated with microvascular damage within frankly infarcted tissue and white blood cell plugs and previously have been referred to as the “zone of no reflow.” However, in this study there was also a reperfusion abnormality that was prominent in the reperfused, previously ischemic subepicardium. In this situation, the depression of regional flow 3 hr after release of the coronary occlusion was not as marked as that in the inner layers of the heart and was associated with tissue that was salvaged by coronary reperfusion and in which the microvasculature was intact. It is not clear whether this subepicardial reperfusion abnormality is caused by the same process as the subendocardial reperfusion abnormality associated with frank infarction. Flow during reperfusion in this subepicardial tissue was high enough to allow thioflavin S to penetrate the tissue but low enough that moderately reduced flow was detected by microspheres. Perhaps the reperfusion defect in this area should be referred to as “low reflow” rather than “no reflow.” In a previous study this phenomenon was not appreciated, since regional myocardial blood flow was not assessed with radioactive microspheres. However, we have seen a similar phenomenon in salvaged subepicardial myocardium subjected to 2 hr of coronary occlusion followed by reperfusion, in which regional flow remained slightly depressed in the outer ventricular wall.

Previous studies have suggested that with salvage of tissue by reperfusion there may be a delay in return of cardiac function and intramyocardial high-energy phosphates. This myocardium has been termed the “stunned myocardium.” It is likely that this abnormally functioning tissue has a lower oxygen demand and therefore regional myocardial blood flow is reduced. On the other hand, we cannot rule out the possibility that there is some primary abnormality in the delivery of blood flow to this tissue, which is then responsible for the depressed function and depressed high-energy phosphate levels. Regional myocardial blood flow in the nonischemic zone was slightly lower during reperfusion as well. This may have represented reduced myocardial oxygen demand secondary to reduced compensatory hypercontractility.

In summary, these results suggest that streptokinase administered during coronary occlusion and reperfusion does not exacerbate hemorrhage into the myocardium and does not have any intrinsic effect on infarct size other than reperfusion per se. Our findings suggest that the no-reflow phenomenon is not primarily caused by fibrin thrombi. While reperfusion is associated with marked reduction in flow, anatomic perfusion defects, and gross hemorrhage within the zone of infarction in the subendocardium and midmyocardium, reperfusion abnormality in the salvaged subepicardial tissue is not as severe and is not associated with infarct, hemorrhage, or anatomic reperfusion defect. It may be related to an autoregulatory phenomenon in which oxygen demand is reduced because of suppression of myocardial contraction.

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