Determinants of Myocardial Hemorrhage After Coronary Reperfusion in the Anesthetized Dog

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SUMMARY Intramyocardial hemorrhage often occurs with reperfusion in experimental acute myocardial infarction and is thought to be associated with extension of necrosis. To determine if hemorrhage was associated with extension of necrosis, 20 anesthetized dogs were reperfused after 6 hours of circumflex coronary artery occlusion and 10 others had control occlusion with no reperfusion. Fifteen of the 20 reperfused dogs had gross hemorrhage and none of the control dogs did. In 12 reperfused and 10 control dogs, radioactive microspheres were injected after coronary occlusion to quantify collateral flow and in the reperfusion group microspheres were injected to quantify reflow. Complete flow data were available in eight reperfused and 10 control dogs. Twenty-four hours after coronary occlusion, 1-g segments of infarct and control regions were analyzed for hemorrhage, collateral flow and creatine kinase activity. Serial microscopic examination was performed in eight additional dogs reperfused after 6 hours to determine if hemorrhage occurs into otherwise microscopically normal myocardium.

Pathologic examination indicated that hemorrhage did not occur into otherwise microscopically normal myocardium. In dogs with hemorrhage, the extent of hemorrhage was inversely related to myocardial creatine kinase concentration and collateral flow. Mean collateral flow in 47 hemorrhagic segments was 4.5 ml/100 g (4.2% of control). Mean creatine kinase in 36 hemorrhagic segments was 233 mIU/g (21% of control). No hemorrhage was found in areas with collateral flow more than 21% of control or creatine kinase more than 37% of control. Mean reflow in hemorrhagic segments was 78.5% of control flow. These studies indicate that hemorrhage on reperfusion is associated with severe myocardial necrosis and markedly depressed flow before reperfusion and thus occurs only into myocardium already markedly compromised at the time of reperfusion. There is no evidence for hemorrhage into areas that had normal or even moderately depressed flows before reperfusion.

THE BENEFITS of reperfusion after acute coronary occlusion are controversial. Extent of infarction is an important determinant of prognosis after coronary occlusion, and restitution of flow would appear to provide an effective means of rectifying ischemia and thus limiting infarct size. Jennings et al. demonstrated that reperfusion after 20 minutes of occlusion prevented the development of ischemic injury, while other studies using enzyme analysis, histologic examination and functional assessment have shown limitation of infarct size with reperfusion 3 hours after coronary occlusion. Other studies have not substantiated significant improvement after reperfusion. Bresnahan et al. demonstrated an increase in infarct size in seven of 16 dogs reperfused 5 hours after coronary occlusion. Other investigators have reported ventricular dysrhythmias accelerated morphologic changes of ischemia and exacerbation of functional and metabolic measurements of ischemia.

The deleterious consequences of reperfusion are often associated with extensive intramyocardial hemorrhage, supposedly because of the loss of structural and functional integrity of the microcirculation, resulting in the extravasation of blood into the extravascular space with restitution of blood flow. In the present study we examined the extent of hemorrhage on reperfusion and related it to the amount of collateral flow during the time of occlusion, the adequacy of reflow and the extent of myocardial necrosis.

Methods

Reperfusion Group

Mongrel dogs that weighed 15–20 kg were anesthetized with thiopental sodium (25 mg/kg) and anesthesia was maintained with 0.25% halothane. The heart was exposed by a left lateral thoracotomy through the fourth intercostal space and suspended in a pericardial cradle. A Biotronex electromagnetic flow probe was placed around the aortic root in four dogs to measure aortic flow. A microsphere withdrawal technique was used to measure cardiac output in the remaining dogs, and for this reason, a small plastic catheter was introduced into the ascending aorta through the left subclavian artery and sutured in place. Another plastic catheter used to inject microspheres was introduced into the left atrium through the left atrial appendage and sutured in place. The catheters and flow probe leads were brought to the back of the neck for monitoring and later injection and sampling of microspheres. After exposing the left circumflex coronary artery near its origin, a small bulldog clamp was used to occlude the vessel. The pericardium was left open, the chest closed and air evacuated from the pleural space. The dogs were pretreated with 100 mg...
of xylocaine plus a continuous infusion of 1–2 mg/min for the first 30 minutes after occlusion. Two hundred milligrams of propanamide were given intramuscularly 30 minutes before occlusion.

In 12 dogs, 1 hour after occlusion, 100–125 ml of blood were removed and tagged with 200 μCi of chromium-51 (51Cr) in the form of sodium chromate (Na2CrO4).11,12 After labeling the cells for 45 minutes at room temperature, an average of six washings was done to remove free sodium chromate. Samples were taken from the supernatant to assess the amount of free 51Cr obtained. At the last washing, the supernatant fraction contained less than 1% of the total 51Cr counts. Approximately 5 hours after occlusion, the packed, labeled red cells were reinjected into the dogs. Six hours after occlusion, anesthesia was again induced using the same anesthetics and the chest was reopened. Just before release of the occlusive clamp on the circumflex coronary artery, 15-μ curium (144Ce) microspheres were injected into the left atrium to quantitate collateral flow to the ischemic myocardial bed. After this injection, the clamp was released and reflow was assured by visual inspection. Five minutes after release, a second bolus of strontium (85Sr) microspheres was injected to assess adequacy of reflow. In one dog, technical problems precluded a valid injection of enough microspheres at the time of reperfusion, so the data were excluded; all other dogs had adequate microsphere injections. After reperfusion, the chest was closed and the dogs were allowed to recover.

Malignant ventricular dysrhythmias present at the time of reperfusion were treated with 1–2 mg/min of i.v. xylocaine after a 100-mg i.v. bolus. After 18 hours of reperfusion (24 hours after occlusion), when the recovery myocardial infarct was easily visualized, the dogs were killed with sodium pentobarbital. The heart was quickly excised, placed immediately on ice and, from this point on, the heart and pieces of myocardium to be analyzed were kept as cold as possible. A glass cannula 2 cm in diameter, which was attached to a perfusion reservoir and mercury manometer, was placed in the ascending aorta and tied securely. The heart was flushed with cold saline using pressures of 90–100 mm Hg for 15 minutes until return from the coronary sinus was clear. The heart was then sectioned from apex to base in 6–10-mm slices, and the slices with easily defined infarcted areas were traced on a plastic overlay. After quickly washing the heart with cold saline, approximately 1-g sections (0.5–1.0 g) were taken from control areas of the uninfarcted anterior left ventricle and from infarcted regions located in the distribution of the left circumflex coronary artery. Sections were selected from inner, middle and outer third of the ventricular wall after excluding the epicardium and associated coronary vessels. Segments from the ischemic zone were matched with segments from the control uninfarcted area of the same slice. Approximately 30 sections were taken for analysis in each heart. Each segment was blotted once, weighed, placed immediately in plastic counting tubes with 5 ml of cold buffer containing 0.5 M Tris (trihydroxymethylaminomethane), 0.001 M ethylene diamine tetraacetic acid and 0.001 M beta mercaptoethanol (pH 7.4) and then counted in a cooled autogamma spectrometer for 2 minutes with keV setting to measure 144Ce (as an indicator of collateral flow), 85Sr (as a measure of reflow) and 51Cr (as an assessment of contained red cells). Seven of the eight dogs that survived 24 hours had myocardial creatine kinase assessed as an index of necrosis.

After counting, the pieces were minced using a Virtis blender at medium speeds. The tissue was homogenized using two 30-second bursts separated by 1 minute to allow for cooling. The homogenate was diluted to a final volume of 20 ml with buffer and 5 μl were assayed for CK activity. The final activity was expressed as mIU/g of wet weight. Myocardial CK measurements in ischemic segments were expressed as a ratio of control segments in the same ventricle. Five control samples from two dogs were analyzed for CK immediately after sacrifice to examine extent of loss of CK activity during the counting of microspheres and 51Cr. In five dogs with gross myocardial hemorrhage, the amount of hemoglobin in each section was analyzed spectrophotometrically and expressed as mg/g wet weight. Thus, hemorrhage was quantitated both by spectrophotometric measurement of hemoglobin and assessed by the 51Cr counts per minute (cpm) per gram of wet weight. Chromium counts were expressed as multiples of 51Cr counts in control areas of the same ventricle.

In this study, 15 ± 5-μ microspheres (3M) labeled with 144Ce and 85Sr were used. The microspheres were suspended in 20% dextran and Tween 80 (polyoxyethylene sorbitan mono-oleate) solution. Each injection contained 2–4 × 10⁶ microspheres. The mean activity per microliter had been determined previously, taking into account the rate of decay so that the counts per minute injected were determined. Organ blood flow in dogs equipped with aortic flow probes was measured by the formula

\[
\text{tissue flow} = \frac{AF \times \frac{\text{tissue cpm/g}}{\text{cpm g/l}} \times 100}{\text{cpm I/g}}
\]

where AF = aortic flow (ml/min) and cpm I = cpm injected. The cpm I were determined by previous methods. In dogs not instrumented with aortic flow probes, the reference withdrawal method was used. Ten seconds before injection of microspheres, blood was withdrawn at a constant rate of 15 ml/min from the ascending aorta with a constant infusion pump for 90 seconds. Tissue flow was then determined from the equation \( F_R \times C_m/C_r \), where \( F_R \) = reference flow (ml/min), \( C_m \) = cpm in the unknown and \( C_r \) = cpm in the reference sample.

Myocardial hemorrhage as assessed by 51Cr counts was related to collateral flow before reperfusion, adequacy of reflow, and degree of myocardial necrosis, as assessed by myocardial creatine kinase activity. Collateral flow and reflow were expressed not only as
absolute values, but as fractions of matched control segments from the same ventricle. Autoradiographic sections were made from two dogs to demonstrate \(^{99}\)Cr-labeled red blood cells and to examine their location.

**Pathologic Analysis**

Eight other dogs were subjected to 6 hours of occlusion and 18 hours of reperfusion. These dogs were subjected to precisely the same occlusion and reperfusion technique. Radioactive microspheres were not injected in this group, but the fresh hearts were opened and samples of the anterior and posterior papillary muscles obtained for hemoglobin analysis. The hearts were then fixed in 10% neutral buffered formalin and later sliced from apex to base at 8–10-mm intervals. Three transverse, full-thickness blocks of left ventricular wall were taken at two levels, the junction of the apical and middle third and the junction of the middle and basal third of the ventricles. Each set of three blocks represented the entire infarct in that plane of section and included the central portion of the infarct and the lateral margins with adjacent noninfarcted myocardium. Five-micron-thick sections were cut from each block and stained with hematoxylin, phloxine and saffron for microscopic examination.

**Control Group**

Ten dogs, using a similar occlusion technique, acted as controls with no reperfusion. They were sacrificed 24 hours after occlusion and had infarct analysis for myocardial creatine kinase, tissue hemoglobin and \(^{141}\)Ce as a measure of collateral flow.

**Results**

**Incidence of Myocardial Hemorrhage**

Of the 20 dogs reperfused at 6 hours, 16 survived for 24 hours. One dog died at 10 minutes after reperfusion and was found to have no demonstrable hemorrhage at postmortem examination; two dogs died between 2 and 3 hours, one with gross hemorrhage, and one dog died between 8 and 18 hours with myocardial hemorrhage at postmortem limited to the tip of the posterior papillary muscle. Fifteen of the 20 dogs demonstrated some areas of gross hemorrhage, nine with hemorrhage into more than 15% of the left ventricle and six with hemorrhage limited to the tip of the posterior papillary muscle. Hemorrhage in all cases involved the posterior papillary muscle and extended in three cases to within 5 mm of the epicardium.

**Quantitative Assessment of Hemorrhage**

Five dogs with gross hemorrhage had hemoglobin content measured by a spectrophotometric technique in each section taken, and this was correlated with \(^{99}\)Cr counts in the same segment (fig. 1). In these five dogs, the correlation coefficient averaged 0.91 ± 0.03, indicating that \(^{99}\)Cr counts were a good assessment of the hemoglobin content. Autoradiographic sections of hemorrhagic myocardium demonstrated \(^{99}\)Cr-labeled red cells in the myocardial interstitial space (fig. 2).

**Association Between Hemorrhage and Collateral Flow**

Collateral flow was markedly diminished in all sections of myocardium with grossly visible hemorrhage. The mean collateral flow in 46 hemorrhagic segments from eight dogs averaged 4.5 ± 1.1 ml/100 g/min, which represented 4.2 ± 1.0% of flow to matched control segments (table 1). The relationship between \(^{99}\)Cr content and collateral flow in a representative dog with gross myocardial hemorrhage is shown in figure 3. Significant \(^{99}\)Cr counts were not observed in any samples with collateral flow greater than 60% of control and were apparent only in samples with flow reductions of more than 80%. Grossly visible hemorrhage was not present in any sample that had more than 20.9% of the flow in control areas, and 95% of the hemorrhagic sections had collateral flow less than 15% of the flow measured in control areas. Thus, hemorrhage occurred into sections already severely compromised at the time of coronary occlusion and before reperfusion.

**Association Between Hemorrhage and Myocardial Necrosis**

When myocardial creatine kinase as a fraction of control was related to the severity of myocardial hemorrhage (fig. 4), there was an inverse relationship. No uniformly hemorrhagic sample was obtained that did not have a very significant drop in myocardial creatine kinase. In 36 hemorrhagic segments from five dogs, the average was 232.9 ± 47.9 mIU/g wet weight, which represented 21.2 ± 4.0% of the myocardial creatine kinase in control segments (table 1). No hemorrhagic segment was identified with a creatine kinase greater than 37% of control areas, and 30 segments (83.3%) had a value less than 25% of control segments. There was less than a 5% difference be-
MYOCARDIAL HEMORRHAGE AFTER REPERFUSION/Higginson et al.

 Авторадиография кровоточащего миокарда. стрелки указывают на образовавшиеся серебряные зерна над красными кровяными клетками, которые расположены вне сосудистого пространства и находятся между миокардиальными клетками.

 BETWEEN SEGMENTS ANALYZED IMMEDIATELY AFTER SACRIFICE AND SIMILAR CONTROL PIECES ANALYZED AFTER GAMMA COUNTING, INDICATING ONLY A SMALL LOSS OF CREATINE KINASE ACTIVITY DUE TO THE PROCESSING.

 ASSOCIATION BETWEEN HEMORRHAGE AND MI myocardial reflow

 THE AVERAGE REFLOW IN 41 HEMORRHAGIC SEGMENTS FROM SEVEN DOGS WAS 78 ± 17 ml/100 g/min, WHICH REPRESENTED 78.5 ± 12.3% OF FLOW TO CONTROL-MATCHED AREAS.

 TABLE 1. SUMMARY OF DATA FROM EIGHT DOGS WITH HEMORRHAGE ON REPERFUSION

<table>
<thead>
<tr>
<th>Dog</th>
<th>N</th>
<th>CK (mIU/g)</th>
<th>%C</th>
<th>CF (ml/100 g/min)</th>
<th>%C</th>
<th>Reflow (ml/100 g/min)</th>
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<td>1</td>
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<td>†</td>
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<td>Average</td>
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<td>4.5</td>
<td>4.2</td>
<td>78.6</td>
<td>78.5</td>
</tr>
</tbody>
</table>

**Dog 1 did not have an assessment of CK; hemorrhagic segments had severe depression of CK, marked compromise of collateral flow and reflow averaging 78% of control areas. Dog 12 with severe depression in reflow had ventricular tachyarrhythmias at the time of measurement.**

* Technical problems with reperfusion.
† Died within 24 hours.

**Abbreviations:** N = number of hemorrhagic segments obtained; CK = myocardial creatine kinase in mIU/g wet weight; CF = collateral flow; %C = percent of control segments from the same ventricle.
areas. The tip of the papillary muscle was most subject to the decreased or no-reflow phenomenon and, in the dogs with myocardial hemorrhage, averaged 68 ± 18.1 ml/100 g/min. Cardiac output 5 minutes after reperfusion averaged 2.2 ± 0.2 l/min. All dogs except one were in normal sinus rhythm. One of the eight dogs with gross myocardial hemorrhage had very depressed reflow values, averaging 11.3 ml/100 g/min. This dog had a markedly depressed cardiac output (0.7 l/min) at the time of reflow measurement associated with ventricular dysrhythmia. No dog required electrical countershock.

The magnitude of reflow depends on when reflow is measured. For this reason, all measurements were taken at 5 minutes after reflow to ensure visually that the artery was being reperfused and to control ventricular dysrhythmias.

Control Animals and Microscopic Analysis

None of the 10 dogs with occlusion and no reperfusion had gross myocardial hemorrhage. Tissue hemoglobin from the tip of the posterior papillary muscle averaged 8.9 ± 1.7 mg/g, vs 30.3 ± 3.6 mg/g in five dogs with gross hemorrhage on reperfusion.

Pathologic analysis in eight dogs reperfused after 6 hours revealed transmural or almost transmural infarcts in the posterior wall of the left ventricle. The infarcts involved the posterior papillary muscle, a portion of the posterior septum and occasionally, the adjacent posterior free wall of the right ventricle. The infarcts extended from the apex to the base of the hearts and occupied 25–30% of the left ventricular muscle mass. Hemorrhage was most intense within the subendocardial third and less marked in the middle third of the left ventricular wall. A distinct perimeter of pallid or mottled necrotic tissue separated the hemorrhagic zone from the adjacent intact myocardium (fig. 5). Microscopically, the inner and middle zones of the infarcts showed coagulation necrosis and neutrophilic infiltration admixed with variable degrees of interstitial hemorrhage, the latter most prominent in the subendocardial portions of the infarcts. The peripheral zones of the infarcts showed coagulation and contraction band necrosis, usually extending in an uneven peninsular but well-defined fashion into the surrounding normal tissue. Extravasation of blood was rarely seen in the necrotic border zone and no hemorrhage was present in areas of intact myocardium in which there was no well-established necrosis.

Discussion

Reperfusion after 6 hours of coronary occlusion resulted in gross hemorrhage in 15 dogs (60%), including nine with hemorrhage into more than 15% of the left ventricle and six with hemorrhage localized to the tip of the posterior papillary muscle. These studies suggest that gross myocardial hemorrhage after reperfusion of the ischemic myocardium at 6 hours is associated with marked myocardial necrosis. However, under these circumstances, hemorrhage did not extend into normal tissue, but was limited to areas already severely compromised before the release of coronary occlusion. The results also show that in this preparation, reflow after 6 hours of coronary occlusion is significant and only moderately depressed over control flows.

Hemorrhage on reperfusion of the acutely ischemic myocardium has been demonstrated by several investigators and considered a detrimental aspect of reperfusion. Bresnahan et al., assessing infarct size by creatine kinase enzyme curves in the conscious
dog, reported extension of myocardial infarct size when reperfusion was performed 5 hours after coronary occlusion, and this was associated with extensive myocardial hemorrhage. Since then, Jarmakani et al. showed that serum creatine kinase analysis may be an inaccurate means of determining the extension of infarct size after reperfusion, because creatine kinase analysis is greatly influenced by flow through the ischemic zone and washout may influence the calculation of infarct size. Lang et al. noted in the anesthetized animal that reperfusion after 3 hours of occlusion exacerbated already abnormal potassium and lactate metabolism. These changes were often associated with accelerated necrosis and hemorrhage. Mathur et al. demonstrated that in the conscious dog, reperfusion after 2 hours produced severe ventricular dysrhythmia and metabolic and hemodynamic deterioration. Reperfusion was usually associated with a hemorrhagic infarct. Several other studies have reported the lack of benefit or deleterious effects of reperfusion on left ventricular function, metabolic state, and myocardial ultrastructure. Although early improvement after reperfusion may not occur, there may be beneficial effects on left ventricular function and infarct size when examined several days or weeks later compared with dogs with permanent coronary occlusions. Although the deleterious effects of reperfusion are often accompanied by myocardial hemorrhage, a cause-and-effect relationship has not been established. Little is known about the factors that determine the appearance of hemorrhage after coronary reperfusion. It has been suggested that sympathetic activation plays an important role and that propranolol and barbiturates may be used to reduce the incidence of hemorrhage.

Regional collateral circulation correlates with the eventual extent and severity of myocardial necrosis. In the present study, in all areas with gross hemorrhage, collateral flow dramatically decreased. Hemorrhage did not occur in areas with previously normal collateral flow, suggesting that although hemorrhage may increase necrosis within the compromised zone, it does not influence the perimeters of the ischemic area. However, these observations are predicated upon the sensitivity of the technique. If smaller samples had been taken, small areas near the border zone might have been discovered with extensive hemorrhage and near-normal collateral flows.

This is not the first study to suggest that hemorrhage on reperfusion occurs exclusively into myocardium which is already necrotic. Reimer et al. using a similar model of circumflex occlusion and reperfusion, showed that there was always a peripheral zone of myocyte necrosis and that hemorrhage occurred within the margins of the infarcted myocardium. Ultrastructural studies have similarly shown that microvascular injury associated with reperfusion does not occur without surrounding severely damaged myocardium, suggesting that hemorrhage does not occur in normal myocardium. Darsee and Klener while not specifically examining the phenomenon of hemorrhage on reperfusion, concluded that reperfusion does not increase the quantity of ischemic tissue that eventually becomes necrotic.

Work from this laboratory using scanning and transmission electron microscopy has shown that structural damage to coronary vessels occurs within 45 minutes of coronary occlusion and is characterized by slight swelling of endothelial nuclei and occasional cytoplasmic projections into the lumen. After 2 hours of occlusion, endothelial cell nuclei are markedly swollen, the lumen is filled with cytoplasmic projections and by 4 hours the vessel surface is partially denuded of endothelial cells. There is also evidence from these studies and others that the microvascularity is more resistant to ischemic damage than surrounding myocardial cells. Myocardial hemorrhage in the dog is less common when reperfusion occurs within 2 hours than at 6 hours after coronary occlusion, which suggests that microvascular integrity, intact at 2 hours, is compromised by 6 hours. In the presence of adequate reflow, the loss of vascular integrity in ischemic areas is thus probably responsible for the hemorrhage.

Restoration of flow in many organs of the body, including the heart, may result in nonuniform reperfusion of previously ischemic regions. Intra- and intercellular swelling after coronary occlusion is increased during the initial phase of reflow and is believed to be a primary factor in this no-reflow phenomenon. The severity of the no-reflow phenomenon in myocardial tissue depends on how long the coronary vessel is occluded. Willerson et al. showed that although reflow may not be compromised after 1 hour of coronary occlusion, by 2 hours there is a significant decrease in reflow, compared with reperfusion after 10 minutes of occlusion. In these and other experiments, reperfusion of the occluded circumflex artery in the dog at 6 hours resulted in an average reflow to the ischemic region of 71 ± 8 ml/100 g/min, whereas reperfusion at 24 hours resulted in a reflow of only 41 ± 6 ml/100 g/min. Reperfusion early after coronary occlusion may result
in a low incidence of hemorrhage because of the limited amount of vascular damage. Later, after the 6-hour ischemic period examined in the present study, there is adequate reperfusion and severe microvascular damage; thus, myocardial hemorrhage occurs with a distribution related to the extent of necrosis. Even later, although there is significant microvascular damage, hemorrhage may not occur to the same extent because of the decreased ability to reperfuse the necrotic myocardium.

Comparing experimental reperfusion to the clinical situation has obvious drawbacks. In the dog, the absence of other vessel involvement, the presence of collateral vessels and the different mechanism of infarct production all preclude a direct extension of these results to clinical ischemic heart disease. However, extensive myocardial hemorrhage has been reported in man associated with prolonged aorto-coronary bypass surgery, and because 5-10% of bypass reperfusion procedures are complicated by acute infarction, associated myocardial hemorrhage may be a problem. Lie et al. suggested that intraoperative infarction is more often associated with myocardial hemorrhage than infarction occurring later after surgery, suggesting the importance of the temporal relationship between acute infarction and reperfusion in the development of hemorrhage.

Collateral circulation during coronary occlusion and reflow after coronary release was quantitated by injecting 15-μm microspheres. Limitations of the microsphere technique have been reported. The problem of an inadequate number of spheres per sample was minimized by the injection of 3-4 x 106 microspheres. Buckberg et al. demonstrated marked variation in results when there were fewer than 400 spheres per sample. Using a sampling technique similar to the one in this study and injecting 800,000 to 1.1 million spheres per injection, found 3900 spheres within the inner half of the posterior papillary muscle. Streaming effects and inadequate trapping through arteriovenous shunting cannot be ruled out. Microsphere loss from infarcted tissue may contribute to falsely low blood flow measurements. The effect of microsphere loss on ischemic flow measurement is very small and does not greatly affect the interpretation of low ischemic flows.

In summary, myocardial hemorrhage on reperfusion of the acutely ischemic myocardium at 6 hours does not occur into tissue with normal coronary flow before reperfusion and is associated with severe myocardial necrosis. Reflow after 6 hours, although moderately depressed, still averages more than 70 ml/100 g, and this may be an important factor in the production of hemorrhage.

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Circulation. 1982;65:62-69
doi: 10.1161/01.CIR.65.1.62

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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