

The influence of residual coronary stenosis on size of infarction after reperfusion in a canine preparation

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ABSTRACT The effect of a residual coronary artery stenosis on size of myocardial infarction was studied in an open-chest canine preparation of coronary occlusion and reperfusion. Eighteen male mongrel dogs (16 to 26 kg) underwent left thoracotomy under general anesthesia; the circumflex artery was instrumented with a hydraulic cuff occluder, a screw clamp, and an electromagnetic flow probe. Animals were randomized to one of three groups: group I (n = 6) had a 6 hr circumflex occlusion, group II (n = 6) had a 2 hr occlusion followed by 4 hr of partial reperfusion through a residual stenosis adjusted to ~ 30% of baseline flow, and group III (n = 6) had full reperfusion for 4 hr after a 2 hr occlusion. Zones of risk, infarction, and no reflow were defined by staining with Evans blue, triphenyl tetrazolium chloride, and fluorescein, respectively. At 6 hr the hearts were excised and areas of risk, infarction, no reflow, and hemorrhage were determined by planimetry of serial transverse heart slices (5 mm thick). Infarction as a percent of the risk area was $96 \pm 1\%$ in group I, $90 \pm 2\%$ in group II, and $79 \pm 4\%$ in group III ($p < .001$), and the differences between each of the groups were significant. Gross hemorrhage was seen in none of the six dogs in group I, two of the six in group II, and five of the six in group III, but did not affect infarct size. We conclude that residual stenoses may exert a deleterious effect on the outcome of coronary reperfusion. In the clinical setting of coronary thrombolysis they may deserve aggressive treatment to maximize salvage of myocardium.
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NUMEROUS ANGIOGRAPHIC studies have demonstrated a high prevalence of coronary thrombi in the early hours of acute myocardial infarction.¹⁻⁶ Thrombolytic agents are now widely used in this setting in an effort to salvage myocardium through early reperfusion. Studies using intracoronary streptokinase have reported early recanalization rates of approximately 60% to 80%.²⁻⁶ Most patients in whom restoration of flow is achieved, however, are left with luminal narrowing at the site of previous coronary occlusion. In the series reported by Rutsch et al.,⁴ approximately three-fourths of patients who had "complete thrombolysis" had residual stenoses of 75% or greater luminal diameter narrowing. Similar findings were observed

by Urban et al.⁵ Such narrowings, whether due to atherosclerotic plaque, residual thrombi, or arterial spasm, may, if severe enough, impede flow and thereby reduce the effectiveness of thrombolysis in preserving myocardium. Alternatively, it is conceivable that these stenoses might have a protective effect by attenuating the degree of reflow and thus modifying the extent of any reperfusion injury.

The purpose of our study was to further define the significance of such residual stenoses by examining their effects in an open-chest canine preparation of coronary reperfusion.

Materials and methods

Preparation and instrumentation. Twenty-two male mongrel dogs weighing 16 to 26 kg were anesthetized with 3.6 mg/kg thiamylal sodium (Bio-tal) and 66 mg/kg chloralose, intubated, and ventilated with room air with the use of a volume-cycled ventilator. Supplemental infusions of chloralose were given as needed. Femoral arterial and venous cannulas were inserted for pressure monitoring and administration of drugs. Succinylcholine, 1 mg/kg, was given, a left thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial cradle. The circumflex artery be-

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tween the first and second obtuse marginal branches was freed of surrounding fat and any small atrial branches were ligated and divided. A hydraulic cuff occluder was placed around the vessel in this segment proximally, an electromagnetic flow probe (Biotronex laboratory Inc., Kensington, MD) was placed distally, and a plastic screw clamp was placed medially. Animals were treated with 1.5 mg/kg lidocaine followed by a constant infusion of 2 mg/min. No anticoagulants were given.

After baseline measurements of blood pressure, lead I of the electrocardiogram, resting circumflex flow, and maximal hyperemic circumflex flow after a transient arterial occlusion, the artery was occluded via the hydraulic cuff occluder in each dog for 2 hr. Animals were randomly assigned to one of three groups. In group I, the proximal occlusion was maintained for an additional 4 hr. In group II, the screw clamp was adjusted to reduce flow to approximately 30% of baseline, and the animals were monitored during a 4 hr reperfusion period. In group III there was no residual stenosis after release of the cuff occluder, and the animals were likewise monitored during a 4 hr reperfusion period.

Blood pressure, circumflex flow, and lead I of the electrocardiogram were recorded 15 sec before and 15 sec after 2 hr of circumflex occlusion, and thereafter at 20 min intervals.

Exclusions. Three animals died of ventricular fibrillation during the first 30 min of circumflex occlusion and were excluded from the study. One animal in group II died 1 hr after the start of reperfusion of cardiogenic shock complicated by refractory ventricular arrhythmias, and this dog was also excluded, leaving a total of six dogs in each group.

Myocardial staining

Area of risk. The risk area was defined by injection of 50 ml of 5% Evans blue dye into the left atrium with the circumflex occluded 6 hr after initial circumflex occlusion (area unstained equals area at risk).

Area of infarction. The animals were then electrically fibrillated, and the hearts were quickly removed and cut in 5 mm thick slices from apex to the atrioventricular groove. These ventricular slices were then weighed and immersed in a 1% solution of triphenyl tetrazolium chloride (TTC) in phosphate-buffered saline at room temperature for 20 to 30 min until tissue boundaries were well defined (infarcted tissue is unstained, noninfarcted tissue stains bright red).^{7, 8}

Area of hemorrhage. When there was gross evidence of hemorrhage the ventricular slices were placed in 25% ethanol for 5 min. After this the hemorrhagic area turned brown, while the TTC-stained areas remained red.

Area of no reflow. In three of six dogs in each of groups II and III, the areas of no reflow were defined by left atrial injection of

fluorescein immediately before final circumflex occlusion and examination of the ventricular slices under a Woods light.

Ventricular borders and regions of risk, infarction, hemorrhage, and no reflow were traced on sheets of clear plastic and their areas were determined by planimetry with the use of computerized graphics tablet. The mass of the tissue at risk was determined by multiplying the ventricular mass by the percent of total ventricular area within the risk zones.

Circumflex arteries. Each artery was dissected free and opened to inspect for thrombi at the site of instrumentation after removal of the hearts.

Statistical analysis. Numeric values are expressed as mean \pm SEM. Differences in means of continuous variables were compared between the three groups with a one-way analysis of variance, and where appropriate, between pairs of groups by a Mann-Whitney test. Differences in frequencies of nominal variables were tested by chi-square analysis. Pearson correlation coefficients were calculated for selected pairs of variables with standard techniques. Probability values of less than .05 were considered indicative of a significant difference. Programs of Statistical Analysis System were used for all data analysis.^{9, 10}

Results

Baseline data are presented in table 1. The three groups did not differ significantly in any of a number of baseline characteristics, including ventricular weight, heart rate, mean blood pressure, rate-pressure product, baseline circumflex flow, circumflex flow per gram of tissue at risk, and maximal hyperemic circumflex flow after transient arterial occlusion. The relatively rapid baseline heart rates are typical of the open-chest canine preparation.

Mean heart rate and mean arterial pressure as a function of time are presented in figure 1. The three groups did not differ significantly in mean heart rate, mean arterial pressure, or mean rate-pressure product during the final 4 hr of the study (reperfusion period for groups II and II) or during the first 2 hr of circumflex occlusion.

Electrocardiographic data. All animals developed prominent ST segment elevations shortly after circumflex occlusion, and in most cases these tended to re-

TABLE 1
Baseline data

	Group I (n = 6)	Group II (n = 6)	Group III (n = 6)	p value
Weight (kg)	20 \pm 1	20 \pm 1	21 \pm 1	NS
Ventricular weight (g)	107 \pm 10	104 \pm 5	119 \pm 7	NS
HR (beats/min)	155 \pm 4	145 \pm 6	158 \pm 9	NS
BP (mm Hg)	138 \pm 8	133 \pm 6	137 \pm 4	NS
HR \times BP	21440 \pm 1630	19300 \pm 1140	21880 \pm 1700	NS
CFX flow (ml/min)	57 \pm 10	67 \pm 11	72 \pm 9	NS
Hyperemic flow (ml/min) ^A	217 \pm 68	187 \pm 23	270 \pm 20	NS
Flow/tissue at risk (ml/min/g)	2.7 \pm 0.1	3.1 \pm 0.5	2.3 \pm 0.5	NS

HR = heart rate; BP = mean femoral arterial pressure; CFX = circumflex artery.

^AHyperemic flow refers to the maximal circumflex flow after a transient arterial occlusion.

solve during the remainder of the study, regardless of whether reperfusion occurred or not. All animals evolved pathologic Q waves. Short runs of ventricular tachycardia occurred in all animals during the occlusion and/or reperfusion periods in spite of prophylactic antiarrhythmic therapy, but only one dog in group I had hemodynamically significant ventricular tachycardia requiring cardioversion.

Coronary flow. Coronary flow data are presented in figure 1. Flow was 0 in all groups during the first 2 hr after occlusion, and remained 0 during the final 4 hr in all group I dogs. After release of the cuff occluder in group II, the residual stenosis generated by the screw clamp limited flow to approximately 30% (22% to

40%) of preocclusion baseline flow. No hyperemic flow response was observed in this group. There was a trend toward decreasing flow during the 4 hr reperfusion period, and circumflex flow eventually reached 0 in two of the six group II dogs. This decrease in flow was not due to proximal coronary thrombosis, however, because none of the animals in any group had evidence of thrombi in the instrumented segments on postmortem examination.

In group III there was a prompt and sustained hyperemic flow response after release of the cuff occluder. The mean peak reperfusion flow in this group (130 ± 34 ml/min) averaged $161 \pm 43\%$ of the preocclusion baseline flow and $50 \pm 8\%$ of the preocclusion hyperemic flow. The mean flow in group III did not reach baseline until approximately 1 hr after the occlusion period. Thereafter there was also a trend toward decreasing flow in this group, and flow reached 0 by the end of the reperfusion period in one of the six group III dogs.

Risk areas. As shown in table 2, the three groups did not differ significantly with regard to absolute size of the risk zones or the relative amount of ventricular tissue at risk, measured at the end of the study. The size of the initial risk zones (immediately after initial circumflex occlusion) was not determined by our techniques.

Infarct size. The mean infarct size relative to the area at risk differed significantly between the three groups ($p < .01$; table 2), with the largest relative infarctions in group I (0.96 ± 0.01), intermediate infarctions in group II (0.90 ± 0.02), and the smallest relative infarctions in group III (0.79 ± 0.04). The differences between each of these groups were significant.

As shown in table 2, there was considerable vari-

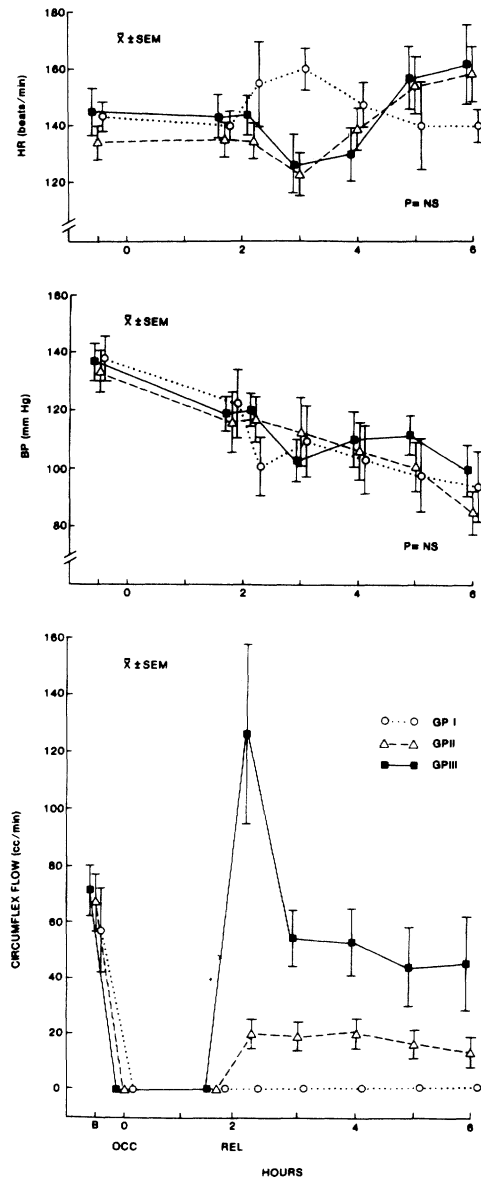


FIGURE 1. Hemodynamic and coronary flow data. HR = heart rate; BP = blood pressure; B = baseline; OCC = occlusion of cuff occluder; REL = release of cuff occluder (groups II and III).

TABLE 2
Infarct and risk areas

	Group I	Group II	Group III	p value
Tissue at risk (g)	27 ± 2	23 ± 2	33 ± 2	NS
Risk/Ventricle	0.24 ± 0.03	0.22 ± 0.03	0.29 ± 0.03	NS
Infarct/Risk	0.96 ± 0.01 (0.93–0.98)	0.90 ± 0.02 (0.83–0.95)	0.79 ± 0.04 (0.64–0.89)	<.001

Risk = risk area; Ventricle = ventricular muscle area; Infarct = infarct area. Areas determined by planimetry of serial 5 mm thick ventricular slices. Tissue at risk determined by multiplying Risk/Ventricle by ventricular weight.

ability in relative infarct size within the groups, especially among the animals undergoing reperfusion (groups II and III). This variability could not be attributed to different myocardial oxygen demands, however, because within individual groups there was no association between the mean rate-pressure product and the relative infarct size.

The most extensive necrosis was observed in the endocardial half of the risk zones. In group I there was little noninfarcted myocardium within the risk zones. What viable tissue remained was usually confined to the epicardial half of the zone, around its margin. On the cut surfaces these areas often appeared as "islands" or "peninsulas" of tissue projecting into the infarcted tissue. In groups II and III the areas of viable tissue within the risk zones were larger, but otherwise had a pattern similar to that in group I.

Hemorrhage and no reflow. Gross areas of myocardial hemorrhage (confirmed microscopically) were observed in none of the six dogs in group I, two of six dogs in group II, and five of six dogs in group III. The hemorrhagic regions were located in the central and subendocardial portions of the infarctions, and never extended beyond the infarct margins. In no case was noninfarcted tissue seen within the hemorrhagic zones. In the animals showing gross hemorrhage, the hemorrhagic areas averaged $60 \pm 6\%$ of the area of infarction in group II, and $46 \pm 21\%$ of the area of infarction in group III.

The areas of no reflow as determined by fluorescein staining generally corresponded to the areas of hemorrhage. In the few animals in which circumflex flow fell to 0 by the end of the reperfusion period, the zone of no reflow measured at that time encompassed the entire risk zone.

Discussion

This study demonstrates that a critical residual coronary stenosis has a deleterious effect on infarct size following reperfusion after a 2 hr period of ischemia in dogs. At the same time, the limited amount of flow provided through such stenoses does result, on average, in slightly smaller infarcts than those that develop with no reperfusion at all. The validity of these conclusions depends on the accuracy of our measures of infarct size and risk area.

Although several recent reports have questioned the specificity of TTC staining at 6 hr for predicting the long-term viability of myocardium,^{11, 12} these studies were conducted under conditions (e.g., lack of reperfusion, prolonged postmortem autolysis, and use of drugs that might introduce staining artifacts) that great-

ly limit the applicability of their findings to our investigation. Most studies have reported good correlations between estimates of infarct size based on TTC staining and light microscopic results^{13, 14} and support the continued widespread use of this technique as a histochemical marker of tissue viability.

Regarding the risk areas, we defined this area at the end of the study. Because of the possible changes in collateral flow, these may not have been the same as the risk areas before or immediately after circumflex occlusion. More importantly, the stimulus for collateral flow might have differed significantly between the three groups, leading to risk zones of different sizes. The studies of Bishop et al.¹⁵ have shown that while there are often some early increases in collateral flow in dogs after coronary occlusion, the amount of this flow is relatively small and does not increase until 24 hr after occlusion. In our study, the size of the risk zones and the fraction of the total myocardium at risk did not differ significantly between the three groups (table 2), and this argues against any major differences in collateral flow between these groups.

While we anticipated that a critical residual stenosis might result in larger infarcts than observed with full reperfusion, it was possible that these stenoses would attenuate reflow and thus limit any "reperfusion injury" and result in infarcts as small or smaller than those in the full reperfusion group. Several lines of evidence have been cited to support the existence of reperfusion injury as a pathophysiologic entity, and the subject has been discussed in several reports.^{16, 17} Early studies indicated that reperfusion could result in serious arrhythmias and extensive myocardial hemorrhage.^{18, 19} More recent investigations have described a variety of deleterious biochemical and ultrastructural consequences of reperfusion, both within the ischemic zone and in more distant nonischemic zones as well.²⁰⁻²³ None of these studies, however, have shown under any conditions that reperfusion actually leads to larger areas of infarction than observed without reperfusion, and for this reason the utility of the concept of reperfusion injury has been questioned.²⁴

Our study indicates that the limitation of reflow produced by a fixed critical residual stenosis has a deleterious effect on infarct size, as measured at 6 hr after coronary occlusion. While there was a trend toward more frequent hemorrhage in the full reperfusion group compared with the residual stenosis group, this did not affect infarct size, and there is now general agreement that hemorrhage is confined to areas of irreversibly injured tissue and does not itself lead to further tissue necrosis.^{11, 23, 25} In our study, hemorrhage

was confined to the central portions of the infarct zones and in no case were "islands" or "peninsulas" of viable tissue observed in the hemorrhagic zones.

Reperfusion arrhythmias are most frequent after relatively brief (20 to 30 min) periods of ischemia,²⁵ and may occur in the absence of any infarction. They are less frequent after more prolonged periods of ischemia. We did not observe any significant differences between the two reperfusion groups in frequency or severity of reperfusion arrhythmias. While all animals did receive prophylactic lidocaine, this drug is reported to have little effect on the vulnerability to malignant ventricular arrhythmias during coronary reperfusion and it is unlikely that its use masked any difference between the groups.²⁶

Relatively little previous experimental work has been done examining the effects of partial coronary occlusions on the outcome of myocardial reperfusion. Jolly and Lucchesi and their colleagues^{27, 28} have used both transient and continuous residual stenoses in their studies of coronary reperfusion to limit reperfusion arrhythmias and hemorrhage, but the specific effects of such stenoses on infarct size were not examined.

Karsch *et al.*²⁹ studied the effect of varying durations of thrombotic coronary occlusion on infarct size in a canine preparation that involved reperfusion through a fixed residual stenosis. They observed an inconsistent trend toward larger infarcts with longer periods of occlusion. Because their study did not include control groups with either full reperfusion or no reperfusion, it is difficult to compare their results to those of the present study. Interestingly, however, they found that only 50% of the left anterior descending or circumflex risk zone was infarcted after a 6 hr period of occlusion followed by a 2 to 3 hr period of partial reperfusion. This is substantially less than the percent infarction in any of our groups, including group I (full reperfusion after a 2 hr occlusion). While the reasons for this difference are not clear, they may relate, in part, to the lower rate-pressure products observed in their animals during the occlusion period. Maroko *et al.*³⁰ have shown that myocardial metabolic demands during coronary occlusion can influence infarct size. In Karsch's study, serious reperfusion arrhythmias were less frequent with longer occlusions. Hemorrhage was only noted following 6 hr of occlusion, and was present in all dogs undergoing reperfusion after an occlusion of this duration.

Clinical studies of coronary reperfusion with thrombolytic agents have reported a high prevalence of residual stenoses in human coronary arteries immediately after thrombolysis.¹⁻⁶ Follow-up angiograms obtained

days to weeks later show that these arteries may reocclude, may remain stenotic, or may become less stenosed with time.^{31, 32} Some have taken an aggressive approach to the management of such residual stenoses, and combined thrombolysis with angioplasty³³ or early coronary bypass grafting.³⁴ The clinical significance of these residual stenoses is still unclear and their optimal management thus remains undecided. Caution should always be exercised in applying data from animal studies to humans, but our study does provide some evidence that early efforts to reduce the severity of residual stenoses after reperfusion may salvage otherwise jeopardized myocardium and reduce infarct size in patients.

There are several limitations to the present study. The most significant of these, and one shared by all short-term studies of myocardial salvage, is that we have not proven that areas within the risk zone that are viable at 6 hr will remain viable, much less become functional, when examined after several days or several weeks. While we believe that tissues that are viable after a 4 hr reperfusion period will remain viable as long as reperfusion is maintained, the present study does not specifically answer this question. A second limitation is that our method of generating residual stenoses (screw clamp) differs from the actual situation in patients after thrombolysis in whom the stenosis is caused by underlying atherosclerotic plaque and possibly residual thrombus. While it seems unlikely that such stenoses would have less impact on infarct size than those in the present study, the possibility exists and must be considered before attempting to generalize from our results. Finally, we have not defined the distribution of reperfusion within the risk zones beyond grossly assessing the zone of no reflow. While such data would certainly be of interest and should be examined in future studies in which this preparation is used, they would not have an effect on the conclusions of the present investigation.

In summary, we have shown that residual coronary stenoses may exert a deleterious effect on the outcome of coronary reperfusion. While the applicability of these findings to clinical studies is unknown, they do provide some support for early mechanical treatment if critical stenoses remain after coronary thrombolysis.

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