Redistribution of Collateral Blood Flow from Necrotic to Surviving Myocardium following Coronary Occlusion in the Dog

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SUMMARY Early changes in collateral blood flow after acute coronary occlusion may be critical for survival of ischemic myocardium. We used 15-μm radioactive microspheres to study myocardial blood flow in thoracotomized dogs 10 minutes and 24 hours after occlusion of the left anterior descending coronary artery (LAD). The ischemic area was delineated by dye injected into the distal artery, and identification of potentially ischemic samples was confirmed by a newly developed technique in which microspheres were excluded from the normally perfused LAD. Layers were separated into necrotic or normal as defined by gross inspection and confirmed by histological examination and creatine phosphokinase assay. Infarction always involved endocardial layers and extended toward the epicardium. Average myocardial blood flow in 48 necrotic samples from 16 dogs either remained low (< 0.05 ml/min g⁻¹) or declined, falling from 0.11 ± 0.02 (SE) at 10 minutes to 0.05 ± 0.01 ml/min g⁻¹ at 24 hours (P < 0.001). In contrast, in the 32 normal-appearing samples which were ischemic at 10 minutes, flow increased from 0.24 ± 0.03 to 0.39 ± 0.04 ml/min g⁻¹ (P < 0.001). Flow in control myocardium was 1.43 ± 0.12 and 1.04 ± 0.07 ml/min g⁻¹, respectively. Peripheral mean coronary arterial pressure increased from 26 ± 3 to 35 ± 3 mm Hg, largely because of enlargement of collateral vessels; collateral conductance calculated from retrograde flow in 14 dogs increased from 0.023 ± 0.005 after occlusion to 0.051 ± 0.009 ml/min mm Hg⁻¹ 24 hours later (P < 0.001). Thus, coronary collateral blood flow is redistributed from necrotic endocardial layers to surviving epicardial ones. In combination with a developing collateral supply this process may be essential for sparing myocardium after coronary occlusion.

SURVIVAL of myocardium after coronary occlusion depends on a balance between supply and demand for oxygen. Measures which reduce myocardial necrosis by reducing oxygen demand must be coupled with an eventual increase in oxygen supply if function is to be restored to the ischemic myocardium. Thus, ultimate salvage of ischemic myocardium should depend on the development of an adequate coronary collateral supply. Numerous studies on animals have demonstrated the eventual development of coronary collaterals following gradual or abrupt coronary occlusions, but the changes in collateral blood flow in the early critical period after occlusion remain poorly understood. Several studies demonstrated no evidence for an increase in coronary collateral blood flow for several days after an acute coronary occlusion but others reported increases within 24 hours in peripheral coronary pressure, xenon clearance, and retrograde flow, or in myocardial flow measured with microspheres. However, even with rapid development of collaterals, necrosis or a "no reflow" phenomenon may alter the distribution of flow within the myocardium by the time sufficient flow is available to the ischemic myocardium. The present study was undertaken to examine in detail the changes in myocardial blood flow that occur in ischemic myocardium within 24 hours after an acute coronary occlusion.

Methods

EXPERIMENTAL PREPARATION

Twenty mongrel dogs weighing 11–22 kg (average, 15.2 kg) were anesthetized with sodium pentobarbital (27.5 mg/kg, iv). Additional pentobarbital was administered as...
required to maintain anesthesia. After intubation with a cuffed endotracheal tube the dogs were ventilated with an intermittent positive-pressure respirator with 100% oxygen. Under sterile conditions a thoracotomy was performed in the 5th left intercostal space. The heart was exposed by incising the pericardium parallel to the phrenic nerve, and the left anterior descending coronary artery (LAD) was isolated below its first diagonal branch (Fig. 1). After ligation of the artery a cannula was inserted distal to the occlusion and perfusion was continued through a polyvinyl bypass system with arterial blood from a large bore cannula placed in the left carotid artery. Initiation of this procedure interrupted perfusion for about 2-3 minutes. At the time of distal LAD-bypass the blood was anticoagulated with heparin, 5,000 U.

A first side arm in the bypass system near the inserted cannula permitted continuous measurements of either the perfusion or the peripheral coronary arterial pressure by means of a Statham P23Db pressure transducer. A second side arm permitted measurements of retrograde flow during back-bleeding through use of a graduated cylinder and a stopwatch. Two other side arms led to a 50-ml reservoir containing a balloon and arranged so that filling of the balloon resulted in a simultaneous emptying of the reservoir (Fig. 1). The balloon was large enough to remain flaccid even when it occupied the entire reservoir volume. Prior to assembly of the reservoir the balloon was tested for leaks by inflating it with saline. After assembly the saline remaining in the balloon was withdrawn through its connecting side arm so that no air remained trapped inside the balloon. The myocardium supplied by the distal LAD thus could be perfused with reservoir blood at the pressure transmitted to the outflow by distention of the flaccid rubber balloon (see below). Initially clamps A and B were closed and clamp C was open, thus permitting normal perfusion of the artery. Polyvinyl catheters were inserted into the left atrium through the appendage to permit measurement of left atrial pressure and injection of microspheres. Similar catheters inserted into the thoracic aorta via the right femoral artery permitted measurement of systemic blood pressure. Aortic, left atrial, and distal LAD perfusion or peripheral coronary pressure were recorded continuously on a Beckman type S11 multichannel oscillograph.

ADMINISTRATION OF MICROSPHERES

We used standard carbonized microspheres, 15 ± 5 µm in diameter, labeled with the nuclides 113Ce, 85Sr, and 99Cr (3M Company) to measure myocardial blood flows and cardiac output. The microspheres were suspended in a 63% glucose solution and were dispersed prior to injection by mechanical agitation and sonication for 5 minutes in an ultrasonic bath. Ten milliliters of the solution, containing 10^6 beads, were injected over a period of 20-25 seconds through the left atrial cannula which was subsequently flushed with 10 ml of physiologic saline. Usually the injection caused no observable hemodynamic changes but occasionally there was a 10-20 mm Hg decrease in aortic pressure for about 10-15 seconds. To calculate absolute tissue flows as well as the cardiac output, withdrawal of an arterial blood sample was started just prior to administration of microspheres and continued for 30 seconds beyond the end of injection by use of a Harvard pump with a withdrawal rate of 11.6 ml/min.

EXPERIMENTAL PROCEDURE

Immediately prior to the first microsphere injection, the stopcock at the top of the reservoir was opened and the reservoir was filled with arterial blood by opening clamp B (Fig. 1). The stopcock then was closed. Clamp A then was opened and clamp C closed, causing the empty balloon in the closed chamber to fill and displace reservoir blood into the distal LAD. Under these conditions pressures at the level of the LAD cannula were identical to the pressures prior to initiating perfusion from the reservoir and corresponded closely to aortic pressures. Mean perfusion pressure was within 2 mm Hg of aortic root pressure while phasic pressures transmitted through the carotid artery and perfusion system were similar to the aortic root pressures. During diastole the aortic root pressure exceeded perfusion pressure by only 5-10 mm Hg, and then only during a portion of diastole. Perfusion from the reservoir could be continued without reduction in pressures for at least 2½ minutes. Thus, all coronary arteries were perfused at similar pressures. Under these conditions blood flow in interarterial anastomoses should be minimal. At this time the first set of microspheres was injected into the left atrium and those destined for the LAD were collected in the balloon. Microspheres were deposited in the heart except in the area supplied by the distal LAD. Any myocardial samples subsequently obtained from the LAD area which were found...
to contain these microspheres must have contained some tissue that normally was perfused by blood delivered through adjacent arteries. Perfusion in this tissue presumably continues after LAD occlusion and this tissue, therefore, cannot properly be considered as ischemic tissue. In our view, only the tissue supplied by the LAD is made ischemic by LAD occlusion. Thus, the first set of microspheres in samples from the LAD area identifies adequately perfused tissue which “contaminates” tissue made ischemic by LAD occlusion. If blood flow in this contaminating tissue is equal to that in more distal samples from the area perfused by the circumflex artery the amount of normal tissue contaminating samples from the LAD area can be estimated from the first set of microspheres.

As was expected, samples obtained from near the border of the LAD area contained significant numbers of microspheres after the first injection; this indicates that tissue supplied by the LAD interdigitates to various degrees with adjacent normally perfused tissue and cannot easily be separated. Because the identity of these border samples is unclear only samples from the center of the ischemic area were used in this study. Even central samples showed a small amount of contamination with normally perfused tissue, averaging 1.8% for all 80 samples. Flow in the contaminating tissue which was equated to flow per unit of tissue in a control sample supplied by the circumflex artery was subtracted from the measured flow. The corrected flows reported here are therefore representative only of ischemic tissue, i.e., tissue normally supplied exclusively by the LAD. It has to be emphasized, however, that the results are not altered significantly by omitting this correction.

Two minutes after the injection of microspheres, the LAD was occluded by closing clamp B (Fig. 1). Ten minutes after occlusion a second set of microspheres was injected. These microspheres were carried into the ischemic area only through preformed coronary collateral vessels and provided a measure of myocardial blood flow in both the normal and ischemic areas.

After measurement of retrograde flow, 50 mg of protamine sulfate were administered. The cannula inserted in the LAD and the atrial catheter then were removed, and the pericardium and the chest cavity subsequently were closed. Air and fluid were evacuated from the chest cavity by a tube that remained under suction for about 4 hours. Premature ventricular beats and tachyarrhythmias occurring during the first 4 hours after coronary occlusion while blood pressure was monitored were suppressed by bolus injections of 50–100 mg of a 2% solution of lidocaine hydrochloride. Additionally each dog received 300–400 ml of physiologic saline intravenously during the first hours of recovery, a single dose of sodium ampicillin (500 mg) intramuscularly, and morphine sulfate in doses of 10 and 15 mg subcutaneously as often as required to ensure comfort.

On the next day the dogs received 10 mg of morphine sulfate intramuscularly followed by less than one-half of the initial dose of pentobarbital. This change in the procedure of anesthesia was necessary because irreversible cardiac arrests occurred when the full dose of pentobarbital was employed for the first two dogs of the series. The dogs were prepared as before, and after administration of 5,000 units of heparin, the LAD was recannulated at the site of ligation. Twenty-four hours after occlusion, the third set of microspheres was injected and measurements of peripheral LAD pressure and retrograde flow were repeated.

At the end of the experiment ventricular fibrillation was induced and a 5- to 8-ml bolus of a 2% solution of Evans blue dye was injected through the inserted cannula. The dye stained the area originally supplied by the LAD distal to the site of ligation. The heart then was removed and frozen quickly in a bath of dry ice and alcohol. In three cases the hearts were fixed by perfusing the coronary bed for 20 minutes with a 10% buffered formaldehyde solution at a constant pressure of 120 mm Hg.

**TISSUE ANALYSIS**

The hearts were cut into slices 4 mm thick from the apex to the base by an electric slicing machine. The Evans blue dye injected into the distal artery delineated the zone at risk from zones supplied by unoccluded vessels. Myocardium which was both normal in appearance and unstained was considered to be perfused adequately throughout the experiment. The dye injection led to a sharp separation between stained tissue, which appeared, for the most part, to be normal, and tissue within the LAD perfusion area, which remained unstained and was white-gray in color and often surrounded by a hemorrhagic border. This unstained tissue within the LAD area was considered to be necrotic. Pictures were taken of all the slices of each heart. Representative sections are shown in Figure 2.

A transmural, sector-shaped piece of myocardium then was cut out of the center of the ischemic area in each slice and divided into five equal layers from the endocardium to the epicardium (Fig. 3). Corresponding layers from each slice were pooled and the five samples so obtained were identified as "necrotic" or apparently "normal" according to the predominant type of tissue in each as determined by gross inspection. Since the exact boundary of the necrotic zone sometimes was unclear, and its position varied from section to section, the combined samples at the demarcation between necrotic and normal-appearing layers probably contained mixtures of both types of tissue. Control sections were taken out of normal unstained myocardium of the left ventricular free wall. The weight of the tissue samples from the ischemic area averaged 0.705 ± 0.056 g, whereas the control samples exceeded 1 g in weight in each case.

Gamma ray spectrometry was used to measure radioactivity in all tissue and the corresponding blood samples using a Searle analytic model 1185 three-channel gamma ray counter with a 2-inch crystal. The number of microbeads per gram of tissue averaged 627 ± 44 beads/g in the control samples but was substantially less in the ischemic tissue samples, averaging 92 ± 13 beads/g. The data were corrected for background and cross-over counts with a Digital PDP-11 computer; the tissue flows and cardiac outputs are expressed in absolute units.

In the three hearts fixed with formaldehyde solution, the pieces cut from the ischemic area were stained with hematoxylin-eosin and subjected to routine light microscopic examination to confirm the identification of necrosis based on gross inspection.

In addition, tissue creatine phosphokinase (CPK) enzyme activity was analyzed in 10 hearts by the method of Kjekshus et al. (1975).
and Sobel. Frozen tissue samples obtained as described above were placed in 20 ml of iced buffer and then disrupted in a Virtis homogenizer. The homogenate then was centrifuged at low speed. This procedure allowed complete recovery of the microspheres in the pellet for determination of myocardial flow, while corresponding CPK levels could be determined for the supernatant fluid.

All results were expressed as mean ± 1 se. Paired comparisons with Student's t-test were used to evaluate the significance of differences in the data.

Results

Of the 20 dogs that initially were studied, 16 recovered well from the first surgical procedure and were restudied successfully 24 hours after occlusion. Four dogs died before restudy was complete: one as a result of surgical complications, two with irreversible cardiac arrest following the second induction of anesthesia, as mentioned earlier, and one suddenly during the night. In addition, in two dogs the LAD could not be recannulated to measure retrograde flow and peripheral coronary pressure during the second study.

The general hemodynamic findings are summarized in Table 1. Compared to the values at the time of occlusion, heart rate increased from 144 ± 6 to 160 ± 7 beats/min 24 hours later at restudy (P < 0.025), cardiac output decreased from 2,537 ± 257 ml/min to 1,849 ± 119 ml/min (P < 0.001), and mean aortic pressure decreased from 119 ± 5 mm Hg to 88 ± 2 mm Hg (P < 0.001. Mean left atrial

FIGURE 3 Method of dissection. Evans blue dye was injected into the distal portion of the occluded left anterior descending coronary artery (LAD) to stain the tissue rendered ischemic. The heart was sectioned as shown and a transmural sector was cut from the ischemic area in each slice and divided into five layers. Corresponding layers from each slice were pooled to yield five samples from the ischemic area for each heart.
pressure rose significantly from 6 ± 1 to 10 ± 2 mm Hg (P < 0.05) apparently due to left ventricular failure caused by the infarcting myocardium. The observed hemodynamic changes may be explained in part by the differences in anesthesia, however, they are more likely the result of some pump failure due to damaged myocardium. In addition, a slight decrease in the intravascular volume also may have occurred even though the dogs received an infusion of saline to maintain blood loss, the hematocrit decreased from 38 ± 2% to 34 ± 1% (P < 0.001).

The area normally perfused by the LAD was well-delineated anatomically by the dark blue color imparted to it by injection of Evans blue dye into the distal portion of the occluded vessel (Fig. 2). This area was made ischemic, hence is referred to as the area jeopardized by LAD occlusion. The region that was stained with the blue dye appeared normal and involved mainly the layers near the epicardium. It extended to a much lesser degree into the endocardial layers surrounding the necrotic zones. The tissue undergoing frank necrosis was determined easily by inspection, because of its white and sometimes brown-gray and often slushy appearance. The blue dye did not appear to penetrate these zones. In several hearts, there was almost no blue-stained tissue appearing samples were found in the subepicardial layers in the subendocardial layer (Table 2).

In contrast, normal-appearing samples were found in the subepicardial layers in the subendocardial layer (Table 2). In contrast, normal-appearing samples were found in the subepicardial layers in the subendocardial layer (Table 2). The differentiation by gross inspection between necrotic hemorrhagic zones, and interstitial edema to predominantly focal necrosis with cellular reaction and wavy fibers in the less damaged parts of the tissue. Samples from the stained but normal-appearing area revealed nearly normal myocardium with only mild leukocytic infiltration, mainly at the epicardial surface, and with very mild interstitial edema. In a few normal-appearing samples some areas with wavy fibers and some small zones of focal necrosis were observed.

This differentiation was further confirmed by measuring the tissue content of CPK in the samples of ten hearts. CPK activity in samples identified as necrotic was 22 ± 2% of control values, compared to 42 ± 6% in the apparently surviving tissue from the ischemic zone. CPK activity in the control samples from the area perfused by the circumflex artery was 39.3 ± 4.6 IU/mg of protein, a value similar to those reported recently by others.14

Myocardial blood flow in the 48 samples of tissue that looked infarcted decreased significantly from 0.11 ± 0.02 ml/min·g⁻¹ at 10 minutes after occlusion to 0.05 ± 0.01 ml/min·g⁻¹ after 24 hours (P < 0.001). In contrast, the tissue flow in the 32 samples that were ischemic but ap-
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figure 4  Blood flow in ischemic myocardium following occlusion of left anterior descending coronary artery (LAD). Samples were identified as "infarcted" or "normal appearing" at the time of dissection, on the basis of visual inspection. Collateral blood flow appears to be redistributed from necrotic to surviving myocardium. Overlapped the values for samples that survived. The flows in the two groups were separated clearly only after 24 hours.

Myocardial blood flow, as determined by microspheres, in the normal tissue of the free wall of the left ventricle increased from epicardium to endocardium (Fig. 6). In the 16 dogs studied flow in the innermost layer averaged 1.63 ± 0.15 ml/min·g⁻¹ and decreased gradually toward the epicardial layers, where it reached a minimum of 1.22 ± 0.12 ml/min·g⁻¹. These absolute values obtained 10 minutes after occlusion tended to be higher than normal values before occlusion, suggesting a hyperemic response to coronary occlusion. The blood flow ratio of the endocardial half to the epicardial half was 1.15. Similar results for both absolute flows and flow ratios using microspheres have been reported by other investigators. The flow in the ischemic area decreased 10 minutes after acute coronary occlusion; in the innermost layer it fell to 0.08 ± 0.02 ml/min·g⁻¹, or 5% of control, and in the outermost layer to 0.27 ± 0.05 ml/min·g⁻¹, or 22% of control. The endocardial to epicardial ratio decreased to 0.43. Twenty-four hours after occlusion the flow in the innermost layer dropped even further, to 0.04 ± 0.02 ml/min·g⁻¹, or 2% of control, while the flow in the

figure 6  Myocardial blood flow across the heart wall. Average values for myocardial blood flow in each of the five layers dissected are shown for the control samples (normal tissue) and the ischemic samples 24 hours later. The position of the horizontal axis indicates the location within the heart wall. All the outermost ischemic samples were identified as normal in appearance, while infarction extended progressively outward as the infarct size increased. Thus, the intermediate layers represented averages of infarcted and normal appearing samples while the outer and innermost samples were more homogeneous (see Table 2). Flow in the ischemic endocardial layer appeared to decrease in the 24 hours following occlusion while epicardial flows returned toward normal.
outermost layer increased to 0.47 ± 0.06 ml/min·g⁻¹, or 55% of control. The endocardial to epicardial ratio, therefore, further decreased to 0.18. Thus, the reversal of the gradient of blood flow across the ventricular wall caused by a coronary occlusion became more pronounced with the passage of time. The change in flow gradient was conditioned by an apparent increase in resistance to flow in the infarcting inner layers and, as will be shown, by an increase in collateral vessel function. The average transmural blood flow across the wall in the center of the ischemic area increased from 0.12 ± 0.03 ml/min·g⁻¹ 10 minutes after acute coronary occlusion to 0.18 ± 0.03 ml/min·g⁻¹ 24 hours after occlusion (P < 0.001).

Even though mean aortic pressure decreased slightly during the 24-hour period of observation, peripheral coronary pressure increased from 26 ± 3 to 35 ± 3 mm Hg at restudy (P < 0.025). This increase probably was due largely to enlargement of collateral vessels; this was indicated by an increase in retrograde flow from 2.6 ± 0.5 ml/min after occlusion to 4.2 ± 0.6 ml/min at 24 hours (P < 0.001). Collateral conductance calculated by dividing retrograde flow by mean aortic pressure increased in all cases (Fig. 7), averaging 0.023 ± 0.005 ml/min·mm Hg⁻¹ after occlusion and 0.050 ± 0.009 ml/min·mm Hg⁻¹ at restudy (P < 0.001). This indicates a definite increase in collateral vessel function within the first 24 hours after acute coronary occlusion.

Discussion

Coronary occlusion often is followed by development of coronary collateral vessels so that myocardium which eventually survives is provided with a nearly normal arterial supply, at least at rest. This study demonstrates that blood flow in the surviving myocardium increases within 24 hours, while flow in the infarcting tissue decreases further. Thus, as coronary collaterals develop, collateral blood flow becomes increasingly heterogeneous within the ischemic area. These results suggest a dynamic redistribution of blood flow within the developing myocardial infarction. Following a coronary occlusion, blood flow is reduced more in the subendocardium and infarction occurs here first. Resistance to flow in the infarcting tissue increases and causes a redistribution of flow to adjacent surviving layers of myocardium which lie toward the epicardium. This process continues and, combined with the enlargement of collateral vessels, results in a sufficient flow to the epicardial layers so that they may survive. The border or so-called "twilight" zone in an infarct appears to be the epicardial layers, and the redistribution of collateral blood flow during the early critical period following an occlusion may be essential to its survival. A similar finding of a redistribution of coronary collateral flow from endocardial to epicardial layers has been presented in a preliminary report by Pasyk and Schaper from experiments performed on three chronically instrumented unanesthetized dogs after occlusion of the left circumflex coronary artery. This suggests that the results reported here are independent of which coronary artery is occluded or of the state of consciousness of the animal.

The key to these observations is the separation and correct identification of the tissue samples. If normal, ischemic but surviving, and necrotic samples were mixed, it is unlikely that the redistribution of collateral blood flow would be observed. This may account in part for the failure of others to observe similar reductions in flow. Tissue supplied by the occluded coronary artery interdigitates to various degrees with adjacent normally perfused tissue and makes it difficult to separate the normal and ischemic myocardium with confidence. Staining the area with dye shows that the boundary cannot be predicted from the epicardial topography and, even when samples are taken only from the center of the stained area, mixtures of normal and ischemic tissue occur. The microspheres injected while perfusing the LAD with unlabeled blood identified mixed samples which then were corrected for the amount of contamination so that the results truly would be representative of ischemic tissue alone.

The identification of infarcted and normal-appearing samples of myocardium was made visually at the time of dissection, and the boundary of the necrotic zone in general was discerned quite easily. The differentiation by gross inspection was well supported by histological studies as well as by assays of CPK. Similar differences in CPK depletion between subendocardial and subepicardial layers have been reported by Kjekshus et al. The reduction in CPK activity in the normal-appearing samples from the subepicardial layers confirms the suspicion that the combined samples at the demarcation between necrotic and normal-appearing layers contained mixtures of both type of tissue. Necrosis may occur in all parts of the ischemic zone but, being distributed more focally in the epicardial layers, they simply may have escaped unnoticed. Additional evidence of a mixture of necrotic and normal tissue in some samples is

![Figure 7](http://circres.ahajournals.org/)

**FIGURE 7** Collateral conductance following occlusion of left anterior descending coronary artery (LAD). Collateral conductance, which was calculated by dividing retrograde flow by mean aortic pressure, doubled in 24 hours following acute LAD occlusion. The open circles represent mean values and the vertical bars represent ±1 SE.
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provided by the flow data. Flow was reduced consistently in the samples identified as necrotic, and although flow usually increased in the normal-appearing samples, a few showed a decline in flow over the 24-hour period; this suggests that these samples also contained necrotic tissue.

Microspheres are used widely to measure both normal and ischemic myocardial blood flow, but evidence of the ability of microspheres to penetrate necrotic myocardium is lacking. Studies performed in this laboratory with *Rb and microspheres have shown that microspheres up to 50 μm in diameter are able to penetrate acutely ischemic myocardium as well as Rb ions (unpublished results). The interpretation (based on experiments using microspheres) that the resistance to flow in the necrotic tissue increased over the 24-hour period also is supported by the finding that Evans blue dye injected into the recannulated distal vessel did not penetrate the parts of the tissue undergoing necrosis. Thus, it appears that the vessels within the necrotic zone are damaged and prevent both antegrade and collateral flow from reaching the tissue. Although the increase in heart rate and the decrease in aortic blood pressure from the time of occlusion to 24 hours later at restudy would tend preferentially to reduce flow to the endocardial layers, the increases in total flow to the ischemic area and in flow to normal-appearing samples indicate that a true redistribution of flow occurs. Moreover, the 11% increase in heart rate is unlikely to cause the observed 2-fold decrease in flow to the necrotic samples and, although aortic pressure decreased, peripheral coronary pressure, which is the driving pressure for perfusion of the ischemic area, actually increased.

The cause of the redistribution of collateral blood flow is the increase in resistance to flow in the infarcting tissue. Disruption of the microvasculature in the area of severe ischemia has been reported by others and has been associated with the "no reflow" phenomenon. In this condition the ischemic myocardium cannot be perfused despite the presence of patent arteries and the absence of intravascular thrombosis. Intracellular and interstitial edema may occur as early as 30 minutes after acute coronary occlusion, and eventually severe capillary damage is observed within larger areas of irreversible myocardial cell injury. Once the no reflow phenomenon has developed, neither flow restored by bypass surgery nor flow provided by coronary collaterals can penetrate the necrotic area. Whether redistribution of collateral blood flow precedes and thus augments necrosis is a significant but unresolved question. If the former is true then treatments which promote a more uniform collateral blood flow may delay necrosis. Prevention of reduction in flow to necrotic tissue, however, may endanger the surviving tissue by delaying the restoration of sufficient flow in the "twilight" zones. From experiments with heated thermocouples and blocking agents Grayson has suggested that α-adrenergic vasoconstriction may cause a reduction in flow in ischemic myocardium. Although these observations have been questioned, our experiments also demonstrate a decrease in collateral blood flow within the ischemic myocardium. Studies performed in this laboratory, however, show that large changes in collateral blood flow do not take place for several hours (unpublished observations).

The increase in coronary collateral conductance observed in our experiments within 24 hours probably corresponds to changes Schaper has described as the early transformation of developing coronary collaterals during which the vessels appear to be greatly overstretched arterioles lacking a muscular coat. Rupture of the internal elastic lamina occurs and many vessels show evidence of damage and even signs of perivascular inflammation. These changes progress over a period of months and ultimately the vessels are transformed into almost normal arteries. Of course, the rate of change in collateral conductance reported here for the dog may not be applicable directly to other species. Within the necrotic zone the early reduction in flow reported here may be followed by a rerervascularization of the infarct during the process of infarct healing. dense vascuularization of infarcts has been recorded and flow in the infarct 1 week after occlusion is increased in relation to flow measured immediately after occlusion; this suggests a biphasic change in myocardial blood flow within the necrotic area. It is unlikely, however, that the vessels within the necrotic area serve as anastomotic channels.

A recent study by Downey et al suggests that a portion of the collateral flow to acutely ischemic subendocardial tissue may be derived from sources different from those that supply flow to the subepicardial areas, since during collection of retrograde coronary flow, subendocardial flow was reduced relatively less than subepicardial flow. If luminal or other microvascular connections to the subendocardial tissue are disrupted by necrosis, then it would not be accurate to characterize the present findings as a redistribution of the initial collateral blood flow since the flow to the endocardium may not be made available to the epicardium. On the other hand, as collateral vessels develop and flow in the ischemic area returns toward normal, the importance of the small residual flows reported by Downey et al diminishes, and to the extent that flow fails to penetrate necrotic tissue, collateral flow is made available to the surviving tissue. Therefore, the primary significance of our findings may relate to the redistribution of the emerging collateral blood flow rather than to the redistribution of flow immediately after coronary occlusion.

As early as 1918 Smith showed that the myocardium most likely to undergo necrosis after acute experimental coronary occlusion is in the subendocardial layers of the ventricular wall. Immediately after coronary occlusion, flow is reduced in the deeper layers to a much greater extent than in the superficial layers. Thus, ischemia is more severe and necrosis more likely in the subendocardium. The location of the interarterial anastomoses on the epicardial surface of the dog heart might account for the favored position of the epicardial layers, but it is more likely that the distribution of collateral blood flow across the heart wall is primarily influenced by the perfusion and intramyocardial pressure. Coronary collateral blood flow has been shown to occur primarily during diastole, so that the pressure perfusing the ischemic area is almost entirely the relatively low diastolic pressure in the peripheral coronary vessel. Intra-myocardial diastolic pressure, which is equal to ventricular diastolic pressure at the endocardial surface and decreases toward the epicardium, significantly reduces the net pressure
available to perfuse the endocardial layers. This view is
supported by the experiments of Kjekshus, who showed
that increasing ventricular diastolic pressure significantly
increased the ischemia of the endocardial layers in an area
supplied by collateral blood flow. In addition to a blood flow
gradient in the ischemic area, a lower oxygen tension of the
normal myocardium and a more rapid buildup of lactate in
the endocardial layers after a total coronary occlusion suggest
that the endocardium has a relatively higher oxygen
requirement when, which, combined with severe ischemia,
would result in initial necrosis in the subendocardium of the
ventricular wall.

Immediately after a coronary occlusion, blood flow
throughout the ischemic area may be insufficient to permit
prolonged survival of the entire involved tissue. We suggest
that as the process of necrosis evolves early redistribution of
a fixed collateral blood flow could result in sufficient flow to
a portion of the ischemic myocardium so that it may survive.
In this view, the fraction of the myocardium initially made
ischemic that would survive would be proportional to the
fraction of normal flow delivered by the coronary collateral
vessels. Surviving myocardium would be directly proportional
to the level of collateral blood flow immediately after
the occlusion. This is consistent with observations from this
laboratory that infarct size measured in hearts 1 week after
experimental occlusion varies inversely with coronary collat-
eral blood flow measured at the time of occlusion. The
degree to which this relationship can be altered would be a
test of the success of an agent which reduced infarct size.

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