Regional Myocardial Blood Flow during Acute Myocardial Infarction in the Conscious Dog

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SUMMARY Regional myocardial blood flow was studied in the conscious dog at periods of 5 minutes to 4 days after occlusion of a major branch of the left coronary artery. Dogs were instrumented with aortic electromagnetic flow probes, occlusive cuffs on either the anterior descending or circumflex branch of the left coronary artery, and a left atrial Silastic catheter for injection of microspheres (15 ± 5 μm) labeled with either 85Sr, 113Ce, or 14Cr. Microspheres were injected into 25 fully conscious dogs during three of the following time periods: control preocclusion and 0.1, 2, 6, 24, or 96 hours postocclusion. In the conscious dog, before occlusion, the endocardial half of the left ventricular myocardium received 28% more blood flow than the epicardial half. After sudden occlusion of a coronary artery branch, there was a marked reduction in blood flow as well as an alteration in distribution of blood flow within the ischemic tissue; blood flow was most severely reduced in the subendocardial center of the ischemic region, less so in the epicardial ischemic region, and least reduced in the marginal region of the infarct. Blood flow was increased to the nonischemic tissue. There was no change in this pattern of reduced blood flow by 6 hours postocclusion, but by 24 hours, flow was moderately increased to all areas except the central subendocardial core, and was further increased at 96 hours. Blood flow to the endocardial half of the left ventricular myocardium averaged 63 ml/100 g per min during the control period, was reduced to 12–18 ml/100 g per min at 0.1–6 hours in the ischemic region, increased to 29 ml/100 g per min at 24 hours, and to 48 ml/100 g per min by 96 hours. These findings indicate that there is a reversal of the flow ratio within ischemic myocardium with relative underperfusion of the endocardial half of the wall, which is not corrected by 4 days. There is a modest increase of collateral blood flow to ischemic tissue by 24 hours and this increase is considerably augmented by 96 hours, apparently as a result of the growth and enlargement of collateral vessels.

THE ABILITY of existing coronary collateral vessels to deliver blood to myocardial tissue acutely deprived of its primary source is a key factor in determining survival of the tissue. It has long been recognized that hearts with a well-developed collateral circulation are better protected from the effects of major coronary artery occlusion than those with poor collateral circulation. Numerous studies of naturally occurring ischemic heart disease in man and acute experiments on anesthetized dogs have demonstrated a subendocardial localization of the most severe ischemic necrosis. Few studies have attempted to quantify the development of changes in regional distribution of collateral blood flow to the myocardium after sudden occlusion of a coronary artery in the conscious animal. Previous studies have used methods which directly measured blood flow in the unoccluded artery or a collateral branch, or depended upon indirect means such as measurement of peripheral coronary pressure, isotope washout, retrograde flow, or anatomical evidence to estimate collateral blood flow.

Previous studies from our laboratory demonstrated anatomical enlargement of coronary collateral circulation by 4 days postocclusion along with an increase in peripheral coronary pressure and retrograde flow which suggested increased collateral flow to the ischemic tissue.
tion of radioactive tracer microspheres has provided a means to make repeated determinations of regional distribution of blood flow to the myocardium. The purpose of this study was to determine the regional distribution of blood flow to the subendocardial and subepicardial layers of ischemic myocardium, and to determine the time course of development of increased collateral flow during acute myocardial infarction in the conscious dog.

Methods

ANIMAL PREPARATION

Healthy adult mongrel dogs weighing 15–25 kg were maintained in standard laboratory cages or runs and fed a standard laboratory dog food. Anesthesia was induced with sodium thiamylal (25 mg/kg of body weight, iv) and maintained with halothane and oxygen using positive pressure ventilation. Under sterile conditions, a left lateral thoracotomy was performed and the aortic root was instrumented with a Biotronix electromagnetic flowmeter probe as previously described. An inflatable pneumatic latex cuff was placed around either the anterior descending or the circumflex branch of the left coronary artery approximately 2 cm distal to its bifurcation. In all dogs a Silastic catheter was placed in the left atrium through the left atrial appendage for injection of radioactive tracer microspheres. In six dogs a Silastic catheter also was placed in the descending thoracic aorta for measurement of systemic arterial pressure. The electromagnetic flowmeter leads, the latex cuff tubing, and the catheters were brought out through the thoracic wall, tunneled subcutaneously, and exited through the skin at the base of the neck. The chest cavity was closed in layers and the pneumothorax was evacuated. The catheters were filled with aqueous heparin (1,000 U/ml) and flushed three to five times weekly. Antibiotics were administered for 1 week after surgery and the dogs were allowed to recover from the surgical procedure for 1–3 weeks prior to the experimental study.

The dogs were trained to lie in right lateral recumbency on a padded table and were studied while fully conscious. Aortic blood flow was measured using a Biotronix BL-310 electromagnetic flowmeter amplifier. The flowmeters were calibrated by passing measured flows of whole blood between 0.8 and 2.0 × 10⁶ microspheres, labeled with either 86Sr, 141Ce, or 51Cr, were injected into the left atrium via the left atrial catheter. Aortic flow, aortic pressure, and a lead II electrocardiogram were recorded continuously during injection and for several minutes thereafter. At the dose range used in this study, no significant changes occurred in any of these variables. At the time of injection the microspheres were thoroughly mixed with a Vortex shaker. A sample was withdrawn into a 3.0-ml siliconized Wade-Hamilton gastight syringe with a Teflon plunger, diluted with approximately 3.0 ml of 10% dextran, and immediately injected into the dog over a 10- to 15-second period. The syringe and catheter were flushed with 10 ml of sterile saline.

We calculated the amount of radioactivity of the various microspheres injected in the following manner: For each microsphere batch, sample activity in counts per minute (cpm) per milliliter of microsphere suspension was obtained from the mean activity of multiple 5-µl pipette samples withdrawn directly from the well mixed sample vial and counted in the gamma spectrometer. The volume contained
in the injection syringe was calculated from its weight and the specific gravity of the suspension (1.03). The injection syringes were counted to determine residual radioactivity. Calculation of the amount of radioactivity injected took into consideration the residual activity in the syringe and the decay of the various isotopes from the time of injection to actual counting of the tissue samples.

The regional distribution of microspheres was determined by dividing the hearts into the following four regions: right ventricular free wall, interventricular septum, left ventricle supplied by the left anterior descending coronary artery including the anterior papillary muscle, and left ventricle supplied by the left circumflex coronary artery including the posterior papillary muscle. The region containing the infarct was subdivided on the basis of gross inspection into the following three zones: the ischemic zone, the marginal zone, and the nonischemic zone. The marginal zone included an approximately 1.0-cm rim of tissue at the periphery of the infarct and was selected to separate unquestionably ischemic tissue from clearly ischemic or nonischemic tissue. The marginal zone therefore contained variable amounts of nonischemic tissue in addition to ischemic tissue. Samples from 11 dogs in which a central core of the ischemic zone was clearly identifiable were analyzed separately. The left and right ventricular tissues were further divided into endocardial and epicardial halves and the interventricular septum into right and left halves (Fig. 1). A sample of tissue from each area was weighed (usually 4–10 g, minimum, 1.5 g) and distributed into plastic disposable tubes for counting in a Packard Autogamma spectrometer with a well-type counting chamber. Care was taken not to fill the tubes more than 2.5 cm from the bottom, because preliminary experiments showed nonlinearity of counts when tubes were filled to a greater depth. Energy windows on the spectrometer were set according to previously established keV for the photo peaks of the individual nuclides and the total energy spectrum cpm/g tissue for each nuclide was calculated according to the method described by Rudolph and Heymann. 14

Blood flow to the various regions of the myocardium was determined as a percentage of cardiac output (CO) for each isotope according to the formula: % CO = [[cpm/g tissue] x tissue weight]/cpm injected. When cardiac output had been obtained by the aortic flow probe, coronary blood flow (CBF) = [cpm/g tissue]/min was calculated by the formula: CBF = ([cpm/g tissue]/cpm injected) x CO (ml/min) x 100. Relative distribution of blood flow within the myocardium, e.g., endocardial to epicardial ratio, was determined by comparison of the cpm/g tissue for the respective zones. Results were analyzed by standard statistical techniques according to Snedecor. 21 Because only three differently labeled microspheres were available for the study, it was not possible to study each dog at each of the six time periods. Group means ± SEM are presented for all dogs at each time period. However, because data derived from the same animal at different time periods were included in three of six different groups, thereby weakening comparison of group means by nonpaired t-test or analysis of variance, paired t-tests were made between groups which included common dogs.

**CRITIQUE OF THE TRACER MICROSPHERE TECHNIQUE**

Several previous investigators have established the validity of the tracer microsphere technique to study regional distribution of myocardial blood flow. 15, 16, 22-24 Estimation of flow distribution to subendocardial and subepicardial regions depends on several factors. Domenech et al. 25 reported that large microspheres overestimate subendocardial blood flow in comparison to results obtained with diffusible indicators. 27, 28 Studies using tracer microspheres 7–10 µm in size in the anesthetized open-chest dog report endocardial to epicardial flow ratios close to unity. 27, 28 In the conscious dog, however, Cobb et al. 23 reported that, with microspheres of 7–10 µm, endocardial blood flow was 6–16% greater than epicardial blood flow, a difference which disappeared with anesthesia and thoracotomy.

In preliminary studies to investigate the effect of anesthesia and thoracotomy on microsphere distribution, we injected three sets of microspheres, 15 ± 5 µm in size, into the left atrium of five dogs anesthetized with fentanyl citrate-droperidol-pentobarbital, iv. 26 The heart was paced at 90, 145 (one dog each), or 250 (three dogs) beats/min and regional distribution of microspheres was determined. Since heart rate-dependent changes were not apparent in this small group, all five animals were considered as one group and the microsphere distribution ratios were compared to the distribution ratios in the conscious dogs (Table 1). The endocardial to epicardial flow ratios in anesthetized, open-chest dogs were close to unity in contrast to flow ratios of 1.28 ± 0.04 in conscious dogs (Table 1). These data confirm previous studies with 7–10-µm microspheres 22 to the effect that anesthesia and thoracotomy result in a redistribution of transmural blood flow from that present in the fully conscious dog. Although the use of microspheres 15 µm in size may slightly overestimate subendocardial perfusion in comparison to measurement with 7–10-µm microspheres, Utley et al. 24 have suggested that this difference is
Dium it is necessary either to have a reference flow system or to combine a measurement of cardiac output with determin-

less than 5–10%. Neill et al. have presented arguments supporting greater subendocardial than subepicardial blood flow in the normal myocardium.

The use of tracer microspheres to determine regional myocardial blood flow during acute myocardial infarction in the conscious dog requires the following conditions: (1) repeated injections of tracer microspheres result in reproducible values for flow distribution; and (2) spontaneous changes in heart rate, in the range which is present during myocardial infarction, do not alter regional myocardial blood flow. We therefore determined the distribution ratio of microspheres, in size, in 27 normal conscious dogs. In five dogs, two additional sets of microspheres subsequently were injected at 15-minute to 24-hour intervals after the initial injection. The distribution ratios between various regions of the heart are shown in Table 1. Repeated injections resulted in similar microsphere distribution ratios.

At spontaneous heart rates of 50 to 140 beats/min in conscious dogs, the percentage of cardiac output to the left ventricle and septum ranged from 1.50-3.80 (mean = 2.76) and to the right ventricular free wall from 0.37-1.0 (mean = 0.67). At heart rates less than 140/min there was no effect of heart rate on the percent of cardiac output to left or right ventricles. At spontaneous heart rates above 140, however, and ranging up to 210 in four dogs which became excited while restrained on the table, we calculated values up to 210 in four dogs which became excited

Results

MORTALITY

We occluded a major branch of the left coronary artery in 38 conscious dogs. Since there were no significant differences in infarct size, heart rate changes, mortality rate, or microsphere distribution ratios within the myocardium between dogs with occlusion of the anterior descending or circumflex branch of the left coronary artery, all dogs were considered as one group. Eight dogs were excluded from the study because of incomplete occlusion of the coronary artery or the finding of old scar tissue in the myocardium associated with implantation of the occluding cuff. Death occurred in two of eight dogs (25% mortality) with occlusion of the anterior descending branch of the left coronary artery at 15 minutes and 18 hours after occlusion. Of 22 dogs with complete occlusion of the circumflex branch of the left coronary artery, six died (27% mortality) between 5 minutes and 12 hours after occlusion. Five of these were excluded from the study because microspheres were not given to dogs with severe arrhythmias in the immediate postocclusion period.

FUNCTIONAL ALTERATION

Heart rate and cardiac output changes are illustrated in Figure 2. Heart rate increased after occlusion from a control rate of 90 ± 3 (SEM) beats/min to a maximum of 142 ± 6 beats/min at 6 hours. By 24 hours, heart rate had started to decline, although arrhythmias were frequent, and by 96 hours, was further decreased toward control values. Cardiac output did not change significantly from the mean control value of 2.4 ± 0.133 liters/min during the study period. As a result of the constant cardiac output but increased heart rate, stroke volume decreased from a control value of 27 ± 2 ml to 19 ± 2 ml at 0.1 hour and 18 ± 2 ml at 24 hours after coronary artery occlusion. Left atrial pressure did not change significantly from 6 ± 0.25 torr during control studies; nor, in six dogs with implanted aortic catheters studied at 0.1 and 24 hours postocclusion, did systemic mean arterial pressure change significantly from the control mean of 99 ± 1 torr.
GROSS LESIONS

The mean infarct size in 25 dogs included in the study was 15 ± 2% (median = 14%) of total ventricular mass, although individual values ranged from no detectable gross infarct in one dog up to 35% in another. Infarcts produced by occlusion of the circumflex branch were constantly centered around the posterior papillary muscle, tended to be sharply circumscribed, and the larger infarcts often had a pale central core area in the endocardial half of the ischemic tissue, which was separated from the adjacent ischemic tissue by a well delineated zone of darker tissue.

HISTOPATHOLOGY

Histological appearance of the ischemic myocardium 24 and 96 hours after occlusion of the coronary artery was similar to that described in previous reports. In the ischemic zone there was diffuse degeneration and necrosis of myocardial fibers, with extensive inflammatory cell infiltration (Fig. 3). In the center of the ischemic area there was frequently a central core region, sharply demarcated from the adjacent ischemic tissue by a zone of intense polymorphonuclear leukocyte infiltration (Fig. 4). The central core was characterized by a lack of edema, hemorrhage, or inflammatory cells. Myocytes in the core were eosinophilic, but often appeared very well preserved, with normal striations and nuclear morphology (Fig. 5). However, in other central core areas, myocytes were fragmented and had contraction bands, indicating eventual necrosis of the tissue. This central core extended to the endocardium in many sections, while in others there was necrotic tissue separating the core from the endocardium, depending on the level of the section.

REGIONAL MYOCARDIAL BLOOD FLOW

Myocardial blood flow is summarized for the nonischemic, marginal, ischemic, and central core regions of left
ventricular endocardium and epicardium in Figures 6 and 7,
and the ratios of blood flow between various areas in the left
ventricle in Table 2. During the control preocclusion period
there was greater blood flow to the endocardium (64 ± 2
ml/100 g per min) than to the epicardium (50 ± 1 ml/100 g
per min). During the period from 0.1 to 6 hours after occlu-
sion, myocardial blood flow was significantly increased to
both the endocardial and epicardial areas of nonischemic
tissue to 80 and 65 ml/100 g per min, respectively. At 24
and 96 hours there was continued increase in blood flow to
the nonischemic tissue, while the ratio of endocardial to epi-
cardial blood flow remained unchanged (Table 2). Blood
flow to the combined endocardium and epicardium of the
right ventricle was slightly, but not significantly, increased
after coronary artery occlusion from preocclusion control
values of 48 ± 3 ml/100 g per min to 56 ± 5 ml/100 g per
min at 24 hours postocclusion. There was an association be-
tween the size of the infarct and the increase in blood flow to
the nonischemic left ventricular tissue. In dogs with infarcts
which involved 15% or less of the left ventricle and septum,
the mean blood flow to combined endocardial and epicar-
dial nonischemic left ventricular tissue at 24 hours was 78 ±
6 ml/100 g per min, while in dogs with infarcts over 15%,
combined blood flow to nonischemic tissue was 129 ± 25
ml/100 g per min (P < 0.025). Dogs with larger infarcts also
had heart rates in the upper half of the distribution range
during the postocclusion period.

In the ischemic zone, blood flow was sharply decreased
during the 6 hours after occlusion to group means of 12–18
ml/100 g per min in the endocardium and to 30–38 ml/100
g per min in the epicardium. With increasing time there was
a gradual increase in blood flow to the ischemic tissue,
which by 96 hours had reached the control level of blood
flow in the epicardial tissue, but had not reached preocclu-
sion control blood flow in the endocardial tissue. However,
endocardial blood flow remained less than epicardial blood
flow in the ischemic region at all time periods studied as re-
lected by the reversal in the endocardial to epicardial flow
ratio. Furthermore, although epicardial blood flow reached
preocclusion control levels of absolute flow by 4 days, flow
was still significantly reduced compared to noninfarcted
tissue flow at all time periods.

The marginal zone, containing both ischemic and non-
ischemic tissue, had a similar, but less pronounced, pattern
of blood flow change. There was a reduction in blood flow to
the endocardial region and no change in epicardial flow
which resulted in equalization of the blood flow between
endocardium and epicardium. By 96 hours, blood flow to the
marginal region was equal to that in the nonischemic region.

For myocardial samples from the region identified grossly
as the central core, blood flow was between 2 and 11 ml/100
g per min at all times studied postocclusion (Fig. 6).

Preexisting collateral flow was better developed in some
dogs than others and resulted in marked variability of gross

![Figure 4](http://circres.ahajournals.org/)

**Figure 4** Photomicrograph of junctional area between peripheral region and central core of infarct 96 hours after coronary artery occlusion. There is a sharp demarcation between the two areas with a zone of intense neutrophil infiltration at the border. The peripheral tissue, in the upper half of the illustration, is characterized by intense inflammatory cell infiltration, edema, and myofiber necrosis. Hematoxylin and eosin stain.
infarct size (0–35%). Infarct size was inversely related to the ratio of ischemic to nonischemic endocardial blood flow at 24 hours postocclusion (Fig. 8).

Discussion

Sudden, complete occlusion of a major branch of the left coronary artery in the dog results in severe alterations in the pattern of blood flow within the affected region of myocardium. Although the major source is interrupted, there still is a variable amount of blood flow to the region through existing collateral channels. The regional distribution of the remaining blood flow to the ischemic zone, however, is markedly altered from that present when the circulation is intact. In the present study, using 15-μm microspheres in the fully conscious dog, blood flow to the endocardial half of the myocardium during preocclusion control periods was 28% greater than to the epicardial half of myocardium. This larger endocardial blood flow relative to epicardial blood flow in the conscious dog is real, because studies in our laboratory on the open-chest, anesthetized dog and using the same microsphere techniques, showed nearly equal ratios of endocardial to epicardial blood flow (see Methods and Table I). After coronary artery occlusion, there was significant reduction in blood flow to the affected region which was most marked in the central subendocardial core of the ischemic tissue, and least severe in the epicardial marginal zone. This alteration in blood flow distribution produced ischemic necrosis of the region, necrosis which, in general, was most severe in the endocardial half of the myocardial wall. These findings confirm results of previous studies by others.28, 29, 31-33

During the postocclusion period there was gradual recovery of blood flow to the ischemic region. Blood flow to the ischemic tissue did not change from 0.1 to 2 hours after occlusion in either endocardial or epicardial tissue and was only slightly increased in epicardial tissue at 6 hours. However, by 24 hours there was an increase of approximately 60% in endocardial blood flow, to 29 ml/100 g per min, and by 96 hours flow had increased to 48 ml/100 g per min, an increase of 160% from the immediate postocclusion period. By 96 hours after occlusion epicardial flow was approximately double that found immediately after occlusion. Thus, although total flow had increased to the ischemic region, there was no change in the ratio of endocardial to epicardial flow, and the endocardium remained underperfused relative to the epicardium.

An increase in blood flow to ischemic tissue during the postinfarction period may result from (1) opening of existing collateral channels, (2) reduction in tissue resistance, as by a decrease in tissue edema, (3) growth of existing vessels, or (4) development of new anastomotic blood vessels. Opening of existing channels is a very rapid response and presumably related to the release of adenosine from the ischemic myocardial cells. Although difficult to quantify for collateral channels, a 10-second temporary occlusion of a coronary vessel is sufficient to produce maximal dilation of

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**Figure 5** Higher magnification of the central core region illustrated in the lower half of Figure 4. There is very little edema or inflammatory cell infiltration, and myocyte nuclei and most cross-striations are well preserved. Focal areas of myolysis are evident, there is cellular fragmentation, and the cells were eosinophilic-staining. Hematoxylin and eosin stain.
Figure 6: Blood flow to various regions of endocardial half of left ventricle after occlusion of a left coronary artery branch. Numbers at the bottom of each bar represent number of dogs studied at each time period. Normal, marginal, ischemic and core refer to regions described in the text and in Figure 1. Statistical analysis is by paired test. $t = P < 0.05$ at 0.1-, 2-, 6-, and 96-hour time periods. $t = P < 0.05$ compared to control period values, $n = 6$. No paired values were available at the 0.1-hour time values, $n = 6$. No paired values were available at the 0.1-hour time values, $n = 6$.

The increase in flow to the ischemic tissue observed at 24 hours, without a change in endocardial to epicardial perfusion ratio, could be due to either a hemodynamic adjustment such as lowered vascular resistance within the ischemic tissue, to a metabolic substance or hemodynamic factor which produced further dilation of the collateral vessels, or to the early effects of cell growth in the vessel wall. The effects of tissue edema would be minimal at 0.1 hour and maximal at 24 hours and tend to reduce blood flow at the 24-hour time period. The studies of Schaper et al. have shown that during the early period of collateral vessel development there is a large lumen with a thin wall, suggesting that acute dilation of the vessels has occurred. Vessel dilation could explain the increased collateral flow seen at 24 hours in our present study.

Growth of tissue in response to ischemia, either for enlargement of existing vessels or development of new ones, is a slower process and requires several days for detectable increases to occur. Although cell growth is probably minimal by 24 hours, even a small increase in the number of cells in the vascular wall could account for a significant increase in lumen diameter and blood flow. Schaper et al. have demonstrated DNA synthesis and mitotic activity in collateral vessels by several days after gradual occlusion of a coronary artery branch, but the very early time course of development of new growth has not been studied. Our present study suggests that collateral vessel growth already may be started by 24 hours, and that by 96 hours has resulted in a considerable increase in functional capacity of the collateral bed.

In previous studies of the rate of return of coronary collateral flow to the ischemic region using either $^{133}$Xe washout, or measurement of retrograde flow, no evidence was found for increased flow until 3-4 days after sudden occlusion. Although in the present study we found a moderate increase in flow to the ischemic region at 24 hours, the major increase in blood flow did not occur until 4 days postocclusion. Previous studies from our laboratory as well as by others have demonstrated an increase in peripheral coronary artery pressure after occlusion of the coronary artery in the conscious dog; peripheral coronary pressure may provide indirect evidence for increased collateral coronary flow during the early postinfarction period. However, as previously discussed, the interpretation of peripheral coronary pressure has several limitations, and the correlation of this indirect index with true collateral flow has not been demonstrated satisfactorily.

Sudden occlusion of the coronary artery produced an immediate increase in heart rate while cardiac output and aortic pressure remained unchanged. From 0.1 to 6 hours postocclusion there was an increase of approximately 25% in blood flow per gram of tissue to the nonischemic left ventricle, and an increase of 15% in blood flow per gram to the right ventricle. By 1 and 4 days postocclusion, there was an even further increase in blood flow to the nonischemic tissue, while at the same time heart rate returned toward control levels. Previous studies on both conscious and anesthetized dogs have noted the increase in heart rate and stable cardiac output after acute coronary artery occlusion. Khouri et al. measured an increase in blood flow in the anterior descending branch of the left coronary artery after occlusion of the circumflex branch in conscious dogs, and suggested that, in addition to an increased workload of the nonischemic tissue, the increased flow was due to perfusion of an increased amount of tissue or collateral flow. In the present study, flow per gram of nonischemic tissue was increased, indicating increased oxygen demand by this tissue. Increased work by the nonischemic tissue recently has been demonstrated after acute coronary

Figure 7: Blood flow to various regions of epicardial half of left ventricle after occlusion of a left coronary artery branch. Identification as in Figure 6.
TABLE 2  Effect of Acute Myocardial Infarction on Left Ventricular Myocardial Blood Flow Distribution Ratios

<table>
<thead>
<tr>
<th></th>
<th>Hours after coronary artery occlusion</th>
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<tr>
<td></td>
<td>Control (n = 12)</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Endocardium/epicardium</td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>1.28 ± 0.05</td>
</tr>
<tr>
<td>Marginal</td>
<td>1.28 ± 0.05</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.20 ± 0.05</td>
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<tr>
<td>Ischemic/nonischemic</td>
<td></td>
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<tr>
<td>Endocardium</td>
<td>0.99 ± 0.06</td>
</tr>
<tr>
<td>Epicardium</td>
<td>0.91 ± 0.02</td>
</tr>
<tr>
<td>Marginal/nonischemic</td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>1.02 ± 0.04</td>
</tr>
<tr>
<td>Epicardium</td>
<td>0.98 ± 0.02</td>
</tr>
</tbody>
</table>

Values are group means ± SEM for all dogs studied at each time period.

— Paired t-test significantly different from 0.1-hour time period; n = 1 at 2-hour time, n = 7 at 6-hour time, n = 17 to 19 at 24-hour time, n = 11 at 96-hour time.  
† Paired t-test significantly different (P < 0.05) from control time. Paired samples at 2, 6, and 96 hours were not available, n = 10, 11, or 12 dogs at 0.1- and 24-hour time periods.

Increased heart rate is responsible for some of the increased oxygen demand, but since there was a greater percentage increase in blood flow to the left ventricle than to the right ventricle, increased work appears to be the major factor contributing to the increased oxygen demand and blood flow to the nonischemic tissue.

The central core region of the infarct produced by occlusion of the circumflex branch of the left coronary artery did not receive an increased blood supply over the time period studied. Histologically, the tissue in this central core area was well preserved in several of the larger infarcts, with little evidence of inflammatory cells. The presence of a central core also has recently been reported by Buja et al. This observation leads to some interesting speculations relative to the cause of cell death in the ischemic tissue. It long has been recognized that acute ischemia results in abnormal contractions of the affected tissue, and that the tissue bulges during systole. However, the ischemic tissue does contract during the late systolic period. This contraction, however ineffective, continues to utilize energy which must be supplied in the form of ATP, which in turn requires oxygen for its production in the amounts needed. If the energy requirements of the ischemic cell outstrip the production capability with the available oxygen, cell degeneration and necrosis would occur as a consequence of loss of energy-dependent membrane stabilization. In the central core, however, it is possible that if decremental conduction occurred through the ischemic tissue, the impulse may not reach the core and excitation and contraction would not occur. The tissue then would be in a noncontracting resting state. Oxygen requirements of resting myocardial tissue have been estimated at 1.0 to 1.5 ml/100 g per min. Assuming an oxygen extraction rate of 15 ml/100 ml of blood, the observed blood flow of 5–10 ml/100 g per min in the central core region would be sufficient to maintain viability of the noncontracting tissue. The sharp border between the well preserved central core and the necrotic ischemic region tissue, with an absence of reactive inflammatory cells in the central core, suggests that such a functional demarcation was present.

The dogs used for this study showed a remarkable variation in the presence of preexisting collateral circulation as evidenced by the wide range of infarct sizes produced by proximal occlusion of a major coronary artery branch. As would be expected, infarct sizes were smaller in those hearts with a greater amount of collateral flow to the ischemic region. There appears to be a genetic predisposition to the pattern of collateral development, since Schaper has noted differences in collateral development between purebred beagles and mixed breed or purebred Labrador retrievers, as well as differences among species. Factors which regulate the development of protective collateral circulation are poorly understood, although hypoxia clearly appears to have a stimulatory effect on cell growth in vascular walls, and will continue to be a major area of investigation.

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Circ Res. 1976;38:429-438
doi: 10.1161/01.RES.38.5.429

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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