Mechanisms of remote myocardial dysfunction during coronary artery occlusion in the presence of multivessel disease

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ABSTRACT  Myocardial dysfunction may occur in areas remote from an acutely occluded coronary artery if those areas are served by a critically stenosed vessel. Although subendocardial hypoperfusion of such remote myocardium has been demonstrated in experimental preparations of this situation, this study was undertaken to determine whether actual reductions in subendocardial perfusion below control levels were necessary for such dysfunction to occur. A 20 mg dose of pentobarbital was injected into the left anterior descending artery (LAD) in 14 anesthetized dogs to create a large anterior regional wall motion abnormality without drawing significant collateral flow from the circumflex vascular bed. Circumflex subendocardial flow was found to rise during injections of pentobarbital and occlusion of the LAD (1.12 ± 0.38 and 1.17 ± 0.34 ml/min/g, respectively, vs control 0.91 ± 0.23 ml/min/g; p < .05) in the absence of circumflex stenosis. In the presence of circumflex stenosis, circumflex subendocardial flow fell during left anterior descending occlusion (0.59 ± 0.21 vs 0.89 ± 0.19 ml/min/g control; p < .01) but did not change during pentobarbital injections in the LAD (0.77 ± 0.36 ml/min/g). In the absence of circumflex stenosis, circumflex segment shortening increased during injection of pentobarbital or occlusion of the LAD (14.3 ± 4.9% and 14.4 ± 3.5%, respectively, vs 12.3 ± 3.3% control). In the presence of circumflex stenosis, it did not change (12.5 ± 4.0% pentobarbital, 11.8 ± 3.6 LAD occlusion vs 13.1 ± 4.0% control). We concluded that the presence of large regional wall motion abnormalities may increase the oxygen consumption of remaining myocardium and that dysfunction of that myocardium may result from relative hypoperfusion if blood flow cannot increase appropriately.


A HIGH INCIDENCE of multivessel coronary disease has been found in patients sustaining an acute myocardial infarction.1 Electrocardiographic changes, wall motion abnormalities, and abnormal myocardial metabolism have been noted in regions remote from the acutely occluded coronary artery but served by a critically stenosed coronary artery.2–7 These observations suggest that occlusion of a coronary artery may have deleterious effects on remote myocardium supplied by a critically stenosed coronary artery. Schwartz et al.8 have measured circumflex coronary pressure and regional myocardial blood flow distal to a circumflex coronary artery stenosis during occlusion of the left anterior descending artery (LAD) in an experimental preparation of myocardial infarction in the setting of multivessel disease. They found that distal circumflex artery pressure and myocardial blood flow both fell when an occlusion of the LAD was superimposed on a circumflex artery stenosis. Gascho et al.9 confirmed these observations and further noted that the increase in circumflex wall thickening that usually occurs during occlusion of the LAD did not occur in the presence of a critical circumflex stenosis.

The explanation for this phenomenon is not clear. The abnormal functional response in this setting may reflect subendocardial hypoperfusion within the distribution of the circumflex coronary artery. An alternative hypothesis, however, is that the large regional wall motion abnormality induced by occlusion of the LAD increased the workload of circumflex bed myocardium resulting in increased oxygen consumption. If a critical circumflex stenosis prevents an increase in

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myocardial blood flow adequate to satisfy these requirements, myocardial ischemia and dysfunction may result.

This study was designed to test the hypothesis that the presence of a regional wall motion abnormality in myocardium perfused by the LAD by itself (unaccompanied by diversion of circumflex blood flow to LAD myocardium via collateral channels) might result in abnormal function of circumflex myocardium when that myocardium is supplied by a stenosed coronary artery. To test this hypothesis, pentobarbital was injected into the LAD to create a severe, transient regional wall motion abnormality without causing sufficient decreases in distal LAD pressure to draw collateral flow from the circumflex vascular bed.

Methods

Nineteen adult mongrel dogs were premedicated with morphine sulfate (1 mg/kg im), anesthetized with α-chloralose (100 mg/kg iv), and ventilated by a Harvard respirator with supplemental oxygen to maintain arterial pH, Po₂, and PCO₂ within the physiologic range. The right internal carotid artery was dissected free and two Millar micromanometer-tipped-catheters were inserted. One catheter was advanced to the left ventricle for left ventricular pressure monitoring and the second catheter was advanced to the proximal aorta. The left internal carotid artery was then dissected free and cannulated with large-bore silicone rubber tubing. This tubing contained an in-line electromagnetic flow probe (Gould Statham) and an injection port. The tubing terminated in a stainless-steel 14-gauge perfusion cannula. An additional 22-gauge stainless-steel cannula was bonded to the external surface of the larger perfusion catheter to permit measurement of distal intracoronary pressure. The distal tip of the pressure monitoring cannula extended 3 mm beyond the tip of the perfusion cannula (see figure 1). A polyvinylchloride fluid-filled catheter was then inserted into the right femoral artery and advanced to the ascending aorta to permit blood withdrawal. A thoracotomy was then performed in the left fourth intercostal space, and the heart was suspended in a pericardial sling. A polyvinylchloride fluid-filled catheter was inserted into the left atrium for microsphere injections. The proximal 1.5 cm of the left circumflex coronary artery was dissected free, and an electromagnetic flow probe and a hydraulic occluder were fitted around it. Pairs of ultrasonic microspheres were then inserted for measurement of circumferential segment shortening. One pair of crystals was placed in the center of the myocardium supplied by the LAD, and an additional pair was placed well within the area of myocardium supplied by the circumflex coronary artery. Pairs of crystals were placed 1.0 to 1.5 cm apart within the inner one-third of the left ventricular wall and oriented circumferentially. The proximal 1.5 cm of the LAD was then dissected free and 10,000 U of heparin was administered intravenously. The proximal LAD was then ligated, and the artery was cannulated with the previously described stainless-steel perfusion cannula, allowing perfusion of the LAD with blood from the left internal carotid artery. Less than 90 sec was required for cannulation of the LAD in each instance. After cannulation, the ability of the LAD to demonstrate reactive hyperemia was confirmed by a 10 sec occlusion of the silicone rubber perfusion tubing during monitoring of the LAD flow with the electromagnetic flowmeter.

The experimental protocol involved two identical series of interventions performed once in the absence of circumflex coronary artery stenosis and again with circumflex stenosis. Circumflex stenosis was achieved by inflating the circumflex occluder sufficiently to abolish reactive hyperemia but to reduce circumflex artery flow less than 20% below the baseline value. The order of the two series of interventions (stenosis present, stenosis absent) was randomized for each dog. During each series, baseline hemodynamic, ultrasonic dimension, and electromagnetic flowmeter data were recorded, and radioactive microspheres were injected into the left atrium for determination of regional myocardial perfusion. A 20 mg dose of pentobarbital was then injected into the LAD perfusion cannula, which was then flushed with 3 ml of normal saline. During introduction of the pentobarbital into the silicone rubber tubing, antegrade flow through the perfusion cannula was temporarily interrupted (4 to 5 sec) to prevent backflow into the carotid artery. Distal LAD pressure was monitored to ensure that it remained below aortic pressure at all times during this injection. The intracoronary dose of pentobarbital was sufficient to produce a severe regional wall motion abnormality (as assessed by the implanted ultrasonic microspheres), which was usually less than 90 sec in duration. Hemodynamic, ultrasonic microcrystal, and electromagnetic flowmeter data were recorded continuously throughout the intracoronary pentobarbital injection. Five seconds after intracoronary injection of pentobarbital, radioactive microspheres were injected into the left atrium for determination of regional myocardial perfusion.

Ten minutes was then permitted for stabilization of the preparation, after which repeat hemodynamic, ultrasonic dimension, and flowmeter data were recorded. The LAD perfusion cannula was then occluded for 60 sec. Twenty seconds after the onset of LAD occlusion, radioactive microspheres were injected into the left atrium for determination of regional myocardial perfusion. Hemodynamic, ultrasonic dimension, and flowmeter data were recorded throughout the period of coronary artery occlusion and for 2 min after reperfusion. Twenty minutes was then permitted for the preparation to stabilize and the series was repeated with the alternative protocol (circumflex stenosis present or circumflex stenosis absent). Thus all dogs underwent...
intracoronary pentobarbital injections and LAD occlusions both in the presence and absence of circumflex coronary artery stenosis.

In four dogs, dose-response curves for intracoronary pentobarbital were performed by injecting 3 ml of saline as control and serial injections of 0.1, 1.0, 5.0, 10.0, 15.0, and 20.0 mg of pentobarbital, each diluted with saline to a total volume of 3.0 ml, into the LAD perfusion cannula. The order of injections was randomized for each animal, and at least 3 min was permitted between injections for the preparation to return to baseline conditions.

In 13 dogs, 125I-labeled microspheres, 15 μm in diameter, were injected into the LAD cannula in a manner identical to that described for intracoronary pentobarbital injections. Microspheres were injected during stenosis of the circumflex coronary artery in four dogs and in the absence of circumflex coronary artery stenosis in four. In five additional dogs, the microsphere suspension was mixed with 20 mg of pentobarbital, and the two were injected simultaneously into the LAD in the presence of circumflex stenosis.

In all dogs, 5 ml of Evans blue dye was then injected into the LAD perfusion cannula to mark the perfusion boundaries of the LAD. This was done to ensure that the pairs of LAD microcrystals were located at least 1 cm within the perfusion boundary of the LAD as defined by blue-stained myocardium and that the circumflex crystal pairs were located at least 1 cm away from the perfusion boundary of the LAD. The dog was then immediately killed with an overdose of sodium pentobarbital and the heart was excised and fixed in 4% formalin. After fixation, the heart was weighed and sectioned into eight slices from apex to base. The endocardial and epicardial outlines of each slice, borders of Evans blue staining, and positions of each pair of ultrasonic microcrystals were traced on a transparency. Each slice was then subdivided into eight segments, and each segment was divided into three layers from epicardium to endocardium.

Myocardial blood flow was measured with microspheres labeled with gamma-emitting nuclides (125I, 141Ce, 51Cr, 85Sr, 99Nb, 113Sr, and 46Sc). Before injection, microspheres were agitated for at least 15 min in an ultrasonic bath. During each intervention, 3 × 10⁶ microspheres were injected into the left atrial catheter over 15 sec, and the catheter was flushed with 10 ml of isotonic saline. Beginning 5 sec before each microsphere injection and continuing for 90 sec, a reference sample of blood was withdrawn from the aortic catheter at a constant flow rate of 15.0 ml/min.

Myocardial and blood reference specimens were counted in a Packard Model 5912 gamma counting system with a multichannel analyzer at window settings corresponding to the peak energies of each radionuclide. The activity recorded in each energy window was corrected for background and for overlapping counts contributed to accompanying isotopes according to the method of Domenech et al. Blood flow to each myocardial specimen was computed as Qm = Qr·Cm/Cr, where Qm = myocardial blood flow (ml/min), Qr = reference blood flow rate (ml/min), Cm = counts/minute of the myocardial specimen, and Cr = counts/minute of the reference blood specimen. Blood flow was divided by the sample weight and expressed as milliliters per minute per gram of myocardium. For intracoronary injection of 125I-labeled microspheres, the corrected number of total counts per myocardial specimen was divided by specimen weight to provide a normalized number of counts per specimen.

Two groups of myocardial segments were then identified: LAD-perfused segments were identified on the basis of Evans blue dye staining, and circumflex-perfused segments were designated as those interposed between the circumflex crystal pairs.

All hemodynamic, ultrasonic dimension, and electromagnetic flowmeter data were recorded on a Hewlett-Packard Model 8800 direct-writing oscillograph. Circumflex flow measurements were obtained using the Gould Statham SP2202 electromagnetic flowmeter. The volume of antegrade circumflex coronary artery flow was determined by electrical integration of the electromagnetic flowmeter tracing. Ultrasonic microcrystals were activated with a Schussler and Associates Model 401 ultrasonic dimension system modified so as to be compatible with simultaneous electromagnetic flowmeter operation. End-diastolic segment length was measured at the initiation of the upstroke of the left ventricular pressure tracing, and end-diastolic length was measured 200 msec before peak negative dP/dt on the differentiated ventricular tracing. Percent segment shortening was defined as end-diastolic length minus end-systolic length divided by end-diastolic length.

Hemodynamic, blood flow, and microcrystal data from different interventions were initially compared by analysis of variance for repeated measures. When an overall difference was found, individual comparisons were made by Student's paired t test and the Bonferroni adjustment for multiple simultaneous comparisons. Linear regressions were performed with least-squares analysis. Values are presented as mean ± SD unless otherwise noted.

**Results**

Three dogs died of ventricular fibrillation, and in two dogs technical difficulties precluded measurement of regional flow by microspheres; thus data were available for 14 dogs.

**Hemodynamics.** In the absence of circumflex artery stenosis, both LAD intracoronary pentobarbital injections and LAD occlusions resulted in small nonsignificant decreases in aortic systolic pressure (table 1). In

**TABLE 1**

<table>
<thead>
<tr>
<th>Effect of intracoronary pentobarbital and LAD occlusion on hemodynamics (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic systolic pressure (mm Hg)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>No stenosis</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Pentobarbital</td>
</tr>
<tr>
<td>LAD occlusion</td>
</tr>
</tbody>
</table>

LVEDP = left ventricular end-diastolic pressure.

*p < .05 vs control.
the presence of circumflex stenosis, injections of pentobarbital into the LAD and occlusion of the LAD resulted in more pronounced decreases in aortic systolic pressure, which achieved statistical significance. There were no significant changes in heart rate or left ventricular end-diastolic pressure during intracoronary injections of pentobarbital or coronary artery occlusions either in the presence or absence of circumflex stenosis. The effect of intracoronary pentobarbital and LAD occlusion on distal LAD pressure and the gradient between the diastolic aortic and LAD pressure is summarized in table 2. Intracoronary pentobarbital was associated with a modest but significant decrease in distal LAD pressure and an increase in the aorta-LAD pressure gradient. During occlusion of the LAD there was a profound decrease in distal LAD pressure and an increase in the aorta-LAD pressure gradient.

Myocardial blood flow in the LAD perfusion zone is summarized in table 3. Intracoronary injections of pentobarbital resulted in a significant increase in both mean transmural and subendocardial myocardial blood flow to LAD-perfused myocardium in the absence of circumflex stenosis. In the presence of circumflex stenosis, results were qualitatively similar. After occlusion of the LAD there were marked decreases in both mean transmural and subendocardial myocardial blood flow in the LAD region both in the presence and absence of circumflex artery stenosis.

The effect of LAD occlusion and intracoronary injection of pentobarbital on circumflex coronary artery blood flow as determined by electromagnetic flowmeter is summarized in table 4. In the absence of circumflex stenosis, both intracoronary pentobarbital and LAD occlusions produced increases in circumflex coronary artery flow. In the presence of a circumflex coronary artery stenosis, however, circumflex flow was unchanged after both of these interventions.

The effect of intracoronary injection of pentobarbital and LAD occlusion on circumflex bed myocardial blood flow as determined by radioactive microspheres is summarized in table 5. In the absence of circumflex stenosis, LAD occlusions and intracoronary injections of pentobarbital resulted in significant increases in mean transmural circumflex myocardial blood flow. In the presence of circumflex stenosis, intracoronary pentobarbital and occlusion of the LAD resulted in nonsignificant decreases in mean transmural circumflex myocardial blood flow. However, application of the circumflex artery stenosis did restrict circumflex mean transmural flow during both LAD occlusion and pentobarbital injections when compared with similar conditions without stenosis (p < .01). The linear correlation between percent change in mean circumflex transmural blood flow (microsphere technique) and circumflex artery flow (flowmeter) during intracoronary injection of pentobarbital was fairly good (r = .85).

Circumflex subendocardial myocardial blood flow rose significantly during pentobarbital injections and

| TABLE 2 |
| Effect of intracoronary pentobarbital and LAD occlusion on LAD pressure and aorta-LAD pressure gradient (n = 11) |

<table>
<thead>
<tr>
<th>Distal LAD pressure (mm Hg)</th>
<th>Aorta-LAD gradient (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No stenosis</td>
</tr>
<tr>
<td>Control</td>
<td>80.4±15.4</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>65.9±15.2b</td>
</tr>
<tr>
<td>LAD occlusion</td>
<td>15.6±8.4b</td>
</tr>
<tr>
<td></td>
<td>5.9±10.3</td>
</tr>
<tr>
<td></td>
<td>12.5±11.6A</td>
</tr>
<tr>
<td></td>
<td>62.2±24.2b</td>
</tr>
</tbody>
</table>

*p < .05 vs control.

*p < .001 vs control.

| TABLE 3 |
| Regional myocardial blood flow to LAD-perfused myocardium with and without circumflex stenosis (n = 14) |

<table>
<thead>
<tr>
<th>Mean transmural flow</th>
<th>Subendocardial flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No stenosis</td>
</tr>
<tr>
<td></td>
<td>No stenosis</td>
</tr>
<tr>
<td>Control</td>
<td>1.00±0.11</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>1.68±0.11A</td>
</tr>
<tr>
<td>LAD occlusion</td>
<td>0.19±0.04A</td>
</tr>
<tr>
<td></td>
<td>0.92±0.10</td>
</tr>
<tr>
<td></td>
<td>1.51±0.12A</td>
</tr>
<tr>
<td></td>
<td>0.13±0.03A</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SE.

*p < .05 vs control.

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LAD occlusion in the absence of circumflex stenosis (table 5). In the presence of circumflex stenosis, there was a significant decrease in circumflex subendocardial myocardial blood flow during occlusion of the LAD (p < .001) but not during intracoronary injection of pentobarbital (p = .28). Again, circumflex subendocardial flow in the presence of circumflex artery stenosis was less than that in the absence of stenosis (p < .01).

Total occlusion of the LAD and injection of pentobarbital produced similar depressions of segment shortening in LAD-perfused myocardium. Segment shortening fell to \(-113.6 \pm 46.3\%\) of the baseline value after intracoronary injection of pentobarbital compared with \(-126.2 \pm 45.3\%\) during occlusion in the absence of circumflex stenosis and to \(-119.3 \pm 6.2\%\) of baseline after pentobarbital compared with \(-146.9 \pm 61.1\%\) during LAD occlusion in the presence of circumflex stenosis. Thus the severity of myocardial dysfunction in the LAD perfusion zone was similar during both interventions.

In the absence of circumflex stenosis, intracoronary injection of pentobarbital resulted in a modest but statistically significant increase in percent segment shortening in the circumflex perfusion zone (see figure 2). Circumflex segment shortening during LAD occlusion and intracoronary injection of pentobarbital was similar (\(14.4 \pm 3.5\%\) vs \(14.3 \pm 49\%\); p = NS); thus, the functional response of circumflex-perfused myocardium to dysfunction in the LAD perfusion zone was equivalent for both interventions. In the presence of circumflex stenosis, however, there was no increase in circumflex segment shortening during either pentobarbital injection (\(12.5 \pm 4.0\%\)) or occlusion of the LAD (\(11.8 \pm 3.6\%\)) (figure 3).

When the change in subendocardial blood flow was compared with the change in circumflex segment shortening in the presence of circumflex stenosis, fairly weak but statistically significant correlations were noted; function = 0.90 (flow) + 32.7, r = .76, p = .014 for LAD occlusion; function = 0.32 (flow) + 2.4, r = .64, p = .044 for intracoronary pentobarbital. However, less than half of the variance in circumflex segment shortening could be attributed to changes in subendocardial flow.

Figure 4 summarizes the dose-response relationship describing the effect of intracoronary pentobarbital on LAD segment shortening. Although there was substantial variability at higher doses, these were invariably accompanied by severe depressions in segment

### TABLE 4
Effect of intracoronary pentobarbital and LAD occlusion on circumflex artery flow

<table>
<thead>
<tr>
<th></th>
<th>Circumflex artery flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No stenosis</td>
</tr>
<tr>
<td>Control</td>
<td>52.0±26.2</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>58.0±26.3A</td>
</tr>
<tr>
<td>LAD occlusion</td>
<td>66.0±24.2A</td>
</tr>
</tbody>
</table>

* p < .05 vs control (n = 14).

* p < .01 vs same LAD intervention without circumflex stenosis.

### TABLE 5
Regional myocardial blood flow to circumflex-perfused myocardium with and without circumflex stenosis

<table>
<thead>
<tr>
<th></th>
<th>Mean transmural flow</th>
<th>Subendocardial flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No stenosis</td>
<td>Circumflex stenosis</td>
</tr>
<tr>
<td>Control</td>
<td>0.86±0.20</td>
<td>0.84±0.22</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>1.11±0.31A</td>
<td>0.86±0.25B</td>
</tr>
<tr>
<td>LAD occlusion</td>
<td>1.07±0.27A</td>
<td>0.69±0.15B</td>
</tr>
</tbody>
</table>

* p < .05 vs control (n = 14).

* p < .01 vs same LAD intervention without circumflex stenosis.
shortening. However, lower doses (0.1 to 1.0 mg) uniformly resulted in no detectable alterations in LAD segment shortening.

Table 6 summarizes normalized $^{125}$I counts in circumflex- and LAD-perfused myocardium, right ventricle, right and left atria, and kidney after injection of $^{125}$I-labeled microspheres into the LAD. The small amount of $^{125}$I counts noted in tissues outside the distribution of the LAD presumably resulted from arteriovenous shunting of minute numbers of microspheres not trapped in the myocardium. The higher mean value noted in the group with circumflex stenosis resulted from one dog that had substantially higher $^{125}$I counts in all tissues. In one dog receiving pentobarbital with circumflex stenosis, substantial counts were recorded in the kidney (but no other myocardial tissues), resulting in a high mean value for this group. The counts in the circumflex myocardium were not higher than those in other tissues either in the presence or absence of circumflex stenosis, indicating that significant collateral flow from LAD- to circumflex-perfused myocardium did not exist at the mild level of circum-

**FIGURE 3.** Percent circumflex segment shortening at baseline, during injection of pentobarbital into the LAD, and during occlusion of the LAD in the presence of circumflex stenosis. Bars represent mean ± SD.

**FIGURE 4.** Dose-response relationship for intracoronary pentobarbital and segment shortening. The dose of pentobarbital (mg) delivered to the LAD is shown on the X axis, and the change in percent LAD segment shortening (compared with saline injection) is shown on the Y axis. Doses of 0.1 to 1.0 mg of pentobarbital resulted in no depression of segment shortening.

**TABLE 6**

$^{125}$I activity (counts/g) after injection of microspheres into the LAD

<table>
<thead>
<tr>
<th>LAD myocardium$^a$</th>
<th>Circumflex myocardium$^b$</th>
<th>Left atrium</th>
<th>Right atrium</th>
<th>Right ventricle</th>
<th>Kidney$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis ($n = 4$)</td>
<td>100</td>
<td>0.008 ± 0.009</td>
<td>0.005 ± 0.005</td>
<td>0.007 ± 0.005</td>
<td>0.84 ± 1.66</td>
</tr>
<tr>
<td>Control stenosis ($n = 4$)$^d$</td>
<td>100</td>
<td>0.29 ± 0.55</td>
<td>0.23 ± 0.44</td>
<td>0.23 ± 0.45</td>
<td>0.61 ± 0.52</td>
</tr>
<tr>
<td>Stenosis with pentobarbital ($n = 5$)$^e$</td>
<td>100</td>
<td>0.003 ± 0.004</td>
<td>0.018 ± 0.025</td>
<td>0.002 ± 0.004</td>
<td>0.016 ± 0.011</td>
</tr>
</tbody>
</table>

$^a$All counts normalized to a value of 100 for LAD myocardium.
$^b$Mean value of circumflex myocardium for all 13 animals was 0.09% of LAD myocardium.
$^c$Mean value of both kidneys.
$^d$Microspheres alone injected into LAD.
$^e$Microspheres and 20 mg pentobarbital injected into LAD simultaneously.
blood flow nor the increase in segment shortening occurred during intracoronary pentobarbital injections, suggesting that the restricted arterial blood supply limited the functional response of the circumflex myocardium in this situation. The most likely explanation is that a large left anterior descending regional wall motion abnormality resulted in hemodynamic, metabolic, or reflex sympathetic responses or changes in cardiac geometry or regional mechanical interaction that increased oxygen consumption of the circumflex-perfused myocardium. When these increased oxygen requirements could not be met, dysfunction resulted. Thus several factors may contribute to distant ischemic wall motion abnormalities in the setting of myocardial infarction with multivessel disease: actual reductions in blood flow in the distribution of a nonoccluded critically stenosed vessel, and relative hypoperfusion caused by increases in oxygen demand of these tissues without commensurate increases in myocardial perfusion.

Several previous studies have documented increased circumflex coronary artery flow when the LAD is abruptly occluded.8, 13–15 This increased circumflex artery flow could have resulted from increased flow distributed to circumflex-perfused myocardium secondary to increases in oxygen consumption of that tissue or from an increase in collateral flow to the LAD-perfused myocardium.

The application of radioactive microsphere techniques to measure myocardial blood flow to circumflex-perfused myocardium permitted further resolution of this problem. Increased transmural blood flow8, 16, 17 or subendocardial flow9, 18 to nonischemic regions in response to acute coronary occlusion has been found by some but not all investigators.19 Thus occlusion of one vessel is associated with increased myocardial blood flow to distant nonischemic regions. The finding of increased circumflex subendocardial blood flow during injections of pentobarbital into the LAD in the current study indicates that the wall motion abnormality in LAD-perfused myocardium is the critical variable causing an increase in circumflex flow. Although oxygen consumption of nonischemic myocardium was not directly measured in this study, changes in coronary blood flow have been previously shown to be closely coupled to changes in myocardial oxygen consumption.20, 21 Thus the finding of increased myocardial blood flow to nonischemic regions during coronary artery occlusion and pentobarbital injections strongly suggests that distant myocardial oxygen consumption had increased.

Several previous studies have examined the effect of LAD occlusion on circumflex bed perfusion in the presence of a circumflex stenosis.8, 9, 19 As in the current study, subendocardial perfusion was found to diminish when LAD occlusion was superimposed on a critical circumflex stenosis. There may be several mechanisms contributing to this primary subendocardial hypoperfusion, including active vasoconstriction of resistance vessels, passive increases in stenosis resistance, reductions in coronary driving pressure caused by decreased aortic diastolic pressure or increased left ventricular diastolic pressure,22 and diversion of blood through collateral channels to the LAD-perfused myocardium. Gascho et al.22 in a similar preparation, have shown that decreases in aortic diastolic pressure may be sufficient to reduce circumflex flow in the presence of a fixed circumflex stenosis. The current preparation differed slightly in that the circumflex stenosis was modulated to maintain constant antegrade circumflex artery flow during LAD occlusion and pentobarbital injections. Thus there were no significant differences in circumflex mean transmural flow during either intervention.

In the absence of a critically stenosed coronary artery, regional function of distant nonischemic myocardium has been found to increase during coronary artery occlusion.9, 12, 17, 19, 23 Although not invariably,18 Lew et al.23 have demonstrated that the increased segment shortening occurs before the onset of left ventricular ejection; segment shortening during ejection is unchanged. Furthermore, β-blockade did not significantly attenuate the increased segment shortening, indicating that this was not a reflection of increased sympathetic stimulation. Although shortening in the absence of a load is accompanied by relatively small increases in oxygen consumption, left ventricular pressure rises during the preejection period so that shortening during that period would occur against a pressure load. Thus it is likely that the increased segment shortening of nonischemic myocardium is accompanied by increased myocardial oxygen consumption.

Altered functional responses of circumflex myocardium to occlusion of the LAD have been observed in the presence of a critical circumflex artery stenosis. Gascho et al.9 found that the increase in circumflex thickening that normally accompanies LAD occlusions failed to occur in the presence of a critical circumflex artery stenosis. Naccarella et al.19 applied a severe circumflex stenosis, sufficient to reduce circumflex shortening at rest, and found that circumflex function actually fell with occlusion of the LAD. In both studies abnormal circumflex functional responses were accompanied by actual decreases in subendocardial per-
fusion. Since myocardial oxygen consumption was not measured, the relative influences of primary decreases in subendocardial flow and increases in myocardial oxygen consumption without commensurate increases in flow could not be determined.

The altered functional response of circumflex myocardium to intracoronary injections of pentobarbital in the presence of circumflex stenosis noted in the current study occurred in the absence of a significant drop in subendocardial perfusion. This suggests that the abnormal functional response may reflect ischemia resulting from failure of circumflex flow to increase appropriately in the face of increased myocardial oxygen consumption and indicates that only relative subendocardial hypoperfusion is required to demonstrate this response. The mild (14%) and nonsignificant decrease in subendocardial perfusion observed was not associated with changes in mean transmural flow and may have reflected altered transmural distribution of circumflex flow resulting from reduced distal coronary perfusion pressures and loss of vasodilator reserve in endocardial layers during conditions of relative myocardial ischemia.

Other explanations for the observed results appear less likely. It is possible that pentobarbital injected into the LAD may have entered the circumflex vascular bed via collateral channels, resulting in direct depression of circumflex myocardial performance. This is extremely unlikely to have occurred in the absence of circumflex stenosis for two reasons: first, LAD pressure during pentobarbital injections was at all times less than the aortic diastolic pressure, and second, circumflex myocardial function actually increased during pentobarbital injections. In the presence of circumflex stenosis, however, distal circumflex pressure may have been sufficiently reduced to allow blood (and pentobarbital) to flow from the LAD vascular bed to the circumflex bed even when distal LAD pressure was less than aortic diastolic pressure. This is also unlikely for several reasons. First, the circumflex stenosis used in this study was not severe; it reduced resting circumflex flow by less than 20% in all cases and did not result in subendocardial hypoperfusion or resting circumflex dysfunction. Thus, although distal circumflex pressures were not measured in this study, they were unlikely to have been extremely low. Second, distal LAD pressures fell throughout the injection of pentobarbital as a result of distal vasodilation caused by the drug. Thus any potential pressure gradient between the LAD and circumflex vascular beds would have been further reduced. In the presence of immature collateral vessels, it is thus unlikely that significant collateral flow would have occurred. Finally, LAD-to-circumflex flow was assessed by selective injections of I-125-labeled microspheres into the LAD perfusion cannula in the presence of a circumflex artery stenosis. I-125 counts in the central circumflex zone were not greater than atrial, right ventricular, or renal counts, indicating that significant LAD-to-circumflex bed collateral flow was not occurring during conditions of circumflex stenosis. The few counts that were recorded in all tissues presumably represented arteriovenous shunting of minute quantities of microspheres. Assuming that intracoronary pentobarbital was distributed to circumflex myocardium in similar proportions as intracoronary I-125, only 0.09% of the 20 mg dose of pentobarbital, or 0.02 mg, would have reached circumflex myocardium. This is well below the threshold for a measurable negative inotropic effect (figure 4).

The relative importance of actual decreases in perfusion vs increases in oxygen consumption as the cause of “remote” myocardial ischemia and dysfunction might depend on metabolic and hemodynamic changes, alterations in ventricular geometry (thus, regional wall stress), amount of myocardium supplied by the occluded coronary artery, severity of stenosis in the nonoccluded vessel, and degree of collateral development. Caution must therefore be observed in extrapolating results from this anesthetized animal preparation to conscious animals or human beings. Nevertheless, the frequent demonstrating of wall motion abnormalities in areas of myocardium remote from the occluded artery2,7.24 indicates the potential clinical importance of these phenomena.

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References
6. Ideker RE, Behar VS, Wagner GS, Starr JW, Starmer CF, Lee KL,
HOMANS et al.

15. Joyce EE, Gregg D: Coronary artery occlusion in the intact unan-
23. Lew WYW, Chen Z, Guth B, Covell JW: Mechanisms in augment-
Mechanisms of remote myocardial dysfunction during coronary artery occlusion in the presence of multivessel disease.
D C Homans, E Sublett, K J Elsperger, J S Schwartz and R J Bache

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