The effect of inotropic stimulation on normal and ischemic myocardium after coronary occlusion

ANDREW J. BUDA, M.D., RAINER J. ZOTZ, M.D., AND KIM P. GALLAGHER, PH.D.

ABSTRACT During acute myocardial ischemia, there exists a zone of myocardial dysfunction that surrounds the central ischemic area that has been termed the functional border zone. We hypothesized that this nonischemic but dysfunctional myocardium may respond to an inotropic challenge. To address this issue, we studied 11 open-chest dogs during acute left circumflex (LCx) occlusion. Simultaneous two-dimensional echocardiograms and radioactive microsphere injections were used to create circumferential left ventricular flow-function maps at the papillary muscle level. Serial studies were performed at baseline, 15 min after LCx occlusion, and after the infusion of dobutamine during LCx occlusion. After occlusion, wall thickening decreased from 52 ± 8% (mean ± SEM) to −5 ± 5% (p < .01) in the central ischemic zone. The extent of left ventricular dysfunction measured 170 ± 11 degrees while the subendocardial hypoperfusion zone was 130 ± 9 degrees (p < .05), resulting in a functional border zone of 40 ± 11 degrees. During the infusion of dobutamine, wall thickening did not change in the central ischemic zone but increased adjacent to the functional border zone (p < .01) and in the normal zone (p < .05), reducing the extent of the functional border zone to 19 ± 16 degrees (p < .05). After dobutamine, the slope of transition of wall thickening from nonischemic to ischemic zones, measured directly from the left ventricular function map, increased on the free wall border (0.71 ± 0.11 to 0.95 ± 0.10, p < .02) to a greater extent than on the septal border (0.60 ± 0.08 to 0.73 ± 0.06, p = .07). We conclude that (1) nonischemic myocardium adjacent to ischemic tissue responds to inotropic challenge, (2) dobutamine produces a significant decrease in the size of the functional border zone, and (3) dynamic changes in wall thickening after inotropic intervention are greater in the functional border zone of the lateral free wall than at the septal border of the ischemic area.


IN THE CONTEXT of ventricular function, the term tethering has been used to describe the phenomenon of nonischemic dysfunction at the lateral margins of infarcted or ischemic myocardium occurring as a result of mechanical constraint or resistive loading of motion in normally perfused muscle. Several investigators have now described functional depression in myocardium adjacent to the ischemic zone. Recent studies using two-dimensional echocardiography have supported this concept in a number of experimental studies. Since this phenomenon results in a functional border zone and may lead to the overestimation of infarct size, it has clinical relevance.

Although it is now well accepted that ischemic myocardium may influence the function of normal adjacent tissue, the related concept that increased function in normal myocardium may likewise influence function in adjacent regions has not been investigated. In effect, this situation may contribute to a form of reverse tethering that could be defined as a pulling effect of one region on another. To test the hypothesis that normal, nonischemic myocardium may influence the function of adjacent regions, we performed simultaneous two-dimensional echocardiographic and radioactive microsphere studies during inotropic intervention after acute coronary occlusion and examined circumferential left ventricular flow-function relationships. Our results support the hypothesis that dynamic changes in the size of functional border zone occur and are produced by changes in adjacent nonischemic myocardium.
Methods

Mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg) and ventilated artificially with room air delivered by a Harvard respirator via an endotracheal tube. A thoracotomy was performed in the fifth intercostal space, the lungs were retracted, and the heart was supported in a pericardial cradle. Polyvinyl catheters were placed in the left internal jugular vein for administration of fluid and drug, in the left atrium for injection of radioactive microspheres for determination of regional myocardial blood flow, and in the left carotid artery and femoral artery for blood pressure recording and withdrawal of the microsphere reference sample. A segment of the left circumflex coronary artery was dissected free proximal to the first major obtuse marginal branch and a hydraulic occluder was placed around it to produce coronary occlusion.

Experimental protocol. Eleven animals underwent occlusion of the proximal circumflex artery with a hydraulic occluder. Heart rate and arterial pressures were recorded before occlusion and throughout the subsequent duration of the study. Tracer-labeled microspheres (141Ce, 51Cr, 103Ru, 95Nb, or 46Sc) (New England Nuclear, 15 μm diameter) were injected for determination of regional myocardial blood flow by the reference withdrawal method. The specific isotopes used were determined by availability at the time of the study. The microspheres, suspended in 10% Dextran with 0.01% Tween 80, were ultrasonicated and vortex agitated before injection. One to two million microspheres were injected into the left atrium over an 8 to 10 sec period. Starting 10 sec before and continuing for 90 sec after microsphere injection, reference arterial blood samples were withdrawn simultaneously from the carotid and femoral arteries at a constant rate of 7 ml/min with a Harvard withdrawal pump.

Two-dimensional echocardiography was performed with a Diasonics 3400R scanner and a 2.5 MHz transducer. Images were recorded on a videocassette recorder for later analysis. The two-dimensional echocardiographic transducer was placed on the closed right side of the chest, which served as a standoff to allow full visualization of the circumferential extent of the left ventricle in the short-axis projection. The left ventricle was scanned from aortic valve to the apex in the short-axis projection and the midposterior papillary muscle position was identified. Two-dimensional echocardiographic studies were subsequently obtained at the same time as microsphere injections. In view of the possible effects of premature contractions on regional contractile function and flow, care was taken to measure variables of left ventricular function and to inject microspheres during periods of sinus rhythm.

The initial two-dimensional echocardiogram and radioactive microsphere injections were performed approximately 10 min after coronary artery occlusion. After the initial studies, a dobutamine infusion was started at 10 μg/kg/min and continued for 15 min. At this point, repeat two-dimensional echocardiograms and radioactive microsphere injections were performed and the study was concluded.

Echocardiographic analysis. With the use of a minicomputer-based video digitizing system, end-diastolic and end-systolic frames were selected for analysis. In brief, a blinded observer who was unaware of the experimental protocol carefully traced endocardial and epicardial borders directly from the video display using a digitizing tablet for three consecutive beats. All two-dimensional echocardiographic measurements were then reported as the mean of three consecutive beats. Area ejection fraction was calculated as: left ventricular end-diastolic area – end-systolic area/end-diastolic area × 100%.

A wall thickening map was then constructed as previously reported. Percent wall thickening was calculated with a radial contraction model and a fixed diastolic center of mass at 22.5 degree intervals over the full 360 degree circumference. For correction of rotation and to serve as an internal landmark for regional flow measures, the midpoint of the posterior papillary muscle was fixed at 135 degrees. The mean ± SD percent wall thickening was calculated for three normal beats and 95% tolerance limits for baseline conditions were established in each individual animal. The functional map of the normal range for each individual animal was used for comparison with occlusion values. Systolic wall thickening during occlusion was defined as abnormally reduced if it was less than the lower tolerance established for thickening under control conditions. The circumferential extent of dysfunction was defined by the intercept of the occlusion functional map with the lower normal tolerance limit. The degree of dysfunction was measured as a planimetered area between the occlusion functional map and the lower normal tolerance limit. In addition, four regions consisting of two segments each were identified on the regional function map for statistical comparison of wall thickening and subendocardial blood flow under control conditions and after coronary occlusion. The central ischemic region was defined as two consecutive sectors contained within the ischemic area. The border zone region was defined as one to two sectors immediately adjacent to the ischemic area. The region adjacent to the border zone was the two sectors immediately adjacent to the border zone region. The normal region was defined as two consecutive sectors remote from the ischemic area.

Regional blood flow maps. At the conclusion of the experiments, the dogs were killed with intravenous KCl. The heart of each was removed and placed in formalin to allow easier sectioning. The left ventricle was sectioned from apex to base in short axis at 5 mm intervals. Two 5 mm slices of myocardium corresponding to the midposterior papillary muscle level were dissected into 16 22.5 degree full-thickness sectors corresponding to those in the two-dimensional echocardiographic study. Each sample was then cut into three pieces of approximately equal thickness from endocardium to epicardium. The location of each piece of tissue was recorded and the tissue samples were weighed and placed in counting vials for assay of radioactivity in a Tracor (Model 1185) gamma scintillation counter. After correcting the counts in each tissue sample for background and overlapping counts with simultaneous equations, blood flow was calculated with the equation: 

\[ Q_m = (C_m × Q_r)/Cr, \] 

where 

\[ Q_m = \text{myocardial blood flow (ml/min)}; \] 

\[ C_m = \text{counts/min in tissue samples}; \] 

\[ Q_r = \text{withdrawal rate of the reference arterial sample (ml/min)}; \] 

\[ Cr = \text{counts/min in the reference arterial sample}. \] 

Flow per gram of tissue was calculated by dividing flow by the weight of the appropriate sample. Background and overlap corrections and blood flow calculations were performed on an Apple II + microcomputer. Circumferential blood flow maps were generated with a computer-assisted program. Hypoperfusion was defined as a 50% decrease in subendocardial blood flow, and the circumferential extent of hypoperfusion was measured in degrees. In addition, four regions consisting of two segments each were identified, as previously described, for analysis of blood flows under control conditions and after occlusion.

Data analysis. The circumferential function (measured as wall thickening) and perfusion maps were superimposed to compare the extent of dysfunction with the extent of flow restriction (figure 1). In some animals, geometric distortion related to fixation produced spatial registration irregularities at the lateral borders of the flow-function maps. In these cases, the maps were superimposed by identifying the centers of the hypoperfusion and dysfunctional zones and generating the maps laterally from these centers. In all animals, the functional border zone was defined as the absolute difference (measured in degrees and millimeters) between the circumferential extent of
FIGURE 1. A. Circumferential regional flow-function map obtained during occlusion. One lateral functional border zone is illustrated. Note that the flow border is contained within the function border. B. Circumferential regional flow-function map in the same animal as in A after dobutamine. Note the marked increase in wall thickening in the normal myocardium between 225 and 360 degrees, and the marked increase in the free wall slope of dysfunction. Note also that after dobutamine, the function border is now contained within the flow border.
hypofunction and the circumferential extent of hypoperfusion. The slope of left ventricular dysfunction was calculated for each lateral functional border. The region in the area of 0 to 50 degrees corresponded to the septal border, whereas the region in the area of 150 to 200 degrees was the free wall border. Each slope was measured by performing regression analysis on the function points from the central ischemic zone to the normal myocardium on each lateral border, as illustrated in figure 2.

**Statistical analysis.** All values are expressed as mean ± SE. Analysis of variance was used to analyze differences within groups across conditions. When a significant effect was observed, paired t tests were used to discriminate which conditions differed from one another. Because multiple comparisons were performed, a Bonferroni correction of the acceptable p level was used. The probabilities were considered to be statistically significant when less than .05.

**Results**

**Hemodynamic and global left ventricular function.** The dogs weighed 21 ± 1 kg. Hemodynamic and global left ventricular changes after coronary occlusion are summarized in table 1. Heart rate was 137 ± 5 beats/min at baseline, and did not change after occlusion. Mean arterial blood pressure was 107 ± 3 mm Hg and decreased to 91 ± 7 mm Hg (p < .05) after coronary occlusion. The two-dimensional echocardiographic left ventricular end-diastolic area measured 10.1 ± 0.4 cm² at baseline and increased to 13.6 ± 0.4 cm² after coronary occlusion (p < .01). Similarly, the left ventricular end-systolic area increased from 4.0 ± 0.4 to 8.6 ± 0.4 cm² (p < .01) after coronary occlusion. As a result, the two-dimensional echocardiographic area ejection fraction fell from 61 ± 2% at baseline to 37 ± 2% (p < .01) after coronary occlusion.

After the infusion of dobutamine, heart rate did not change and blood pressure returned to baseline values. There was no change in left ventricular end-diastolic area, but left ventricular end-systolic area improved to 7.4 ± 0.4 cm² (p < .05), resulting in a slight but significant improvement in left ventricular area ejection fraction to 43 ± 2% (p < .05).

**Regional left ventricular function.** Within seconds after left circumflex coronary occlusion, a localized wall motion and wall thickening abnormality was visually apparent on the two-dimensional echocardiograms from each of the animals. The wall thickening values in the normal zone, the zone adjacent to the functional border zone, the functional border zone, and the central ischemic zones, are summarized in table 2 and figure 3. After coronary occlusion, there was a tendency for wall thickening to increase in the normal zone, with a significant decrease in the zones adjacent to the functional border zone, the functional border zone, and the central ischemic zone. Actual dyskinesis (-5.2 ± 1.5%) occurred in the central ischemic zone. The circumferential extent of thickening abnormality measured 170 ± 11 degrees and the degree of dysfunction measured from the function map was 29.3 ± 2.0 cm². The absolute slope of left ventricular dysfunc-

![FIGURE 2](http://circ.ahajournals.org/)

**FIGURE 2.** A wall thickening map illustrating the method we used to estimate the slope of left ventricular dysfunction at each lateral border. Each slope was measured by performing linear regression analysis on the function points at both lateral borders.
tion after coronary artery occlusion was greater for the left ventricular free wall (0.71 ± 0.11) than for the septal wall (0.60 ± 0.08, p < .05) (figure 4).

After administration of dobutamine, wall thickening increased in the normal zone to 93.8 ± 8.9% and in the zone adjacent to the functional border zone to 55.5 ± 4.5% (p < .01). However, wall thickening in the functional border zone did not change and there was a tendency for increased dyskinesis in the central ischemic zone. As a result of the changes in the normal zone and the zone adjacent to the functional border zone, the extent of functional abnormality decreased with dobutamine to 148.0 ± 8.5 degrees (p = .03). The degree of left ventricular dysfunction tended to increase with dobutamine to 32.3 ± 4.0 cm², but this did not reach statistical significance. The absolute slope of left ventricular dysfunction increased significantly (p < .01) in the free wall to 0.95 ± 0.10 and remained significantly greater (p < .05) than the slope of the septal wall, which measured 0.73 ± 0.07 (figure 4). The change in the slope of left ventricular dysfunction correlated with the change in percent wall thickening in the free wall (r = .57, p < .05), but not that in the septal wall (r = .05, p = NS).

Coronary blood flows. The coronary blood flows in the normal zone, the zone adjacent to the functional border zone, the functional border zone, and the central ischemic zone are summarized in table 3 and figure 5. At baseline, subendocardial blood flows were similar in all four regions. After coronary occlusion, there was a significant decrease in blood flow in the central ischemic region to 0.06 ± 0.02 ml/min/g (p < .01), but no change occurred in any of the other three regions. The circumferential extent of hypoperfusion after coronary artery occlusion measured 130 ± 9 degrees. After dobutamine, there was no change in blood flow in the central ischemic zone and a tendency for increased blood flow in the other three zones, but these changes did not reach statistical significance.

### Table 1

<table>
<thead>
<tr>
<th>Hemodynamics and left ventricular global variables</th>
<th>Baseline</th>
<th>Occlusion</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>137 ± 5</td>
<td>132 ± 4</td>
<td>138 ± 7</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>107 ± 3</td>
<td>91 ± 7²</td>
<td>103 ± 8</td>
</tr>
<tr>
<td>LVED area (cm²)</td>
<td>10.1 ± 0.4</td>
<td>13.6 ± 0.4²</td>
<td>13.1 ± 0.5²</td>
</tr>
<tr>
<td>LVES area (cm²)</td>
<td>4.0 ± 0.4</td>
<td>8.6 ± 0.4²</td>
<td>7.4 ± 0.4²</td>
</tr>
<tr>
<td>LV area EF (%)</td>
<td>61 ± 2</td>
<td>37 ± 2²</td>
<td>43 ± 2³</td>
</tr>
</tbody>
</table>

HR = heart rate; LVED = left ventricular end-diastolic; LVES = left ventricular end-systolic; MAP = mean arterial pressure.

*²p < .05 vs baseline; *³p < .01 vs baseline; *⁴p < .05 vs occlusion.

### Table 2

<table>
<thead>
<tr>
<th>Left ventricular wall thickening</th>
<th>Baseline</th>
<th>Occlusion</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal zone (%)</td>
<td>50.8 ± 4.4</td>
<td>64.7 ± 6.0</td>
<td>93.8 ± 8.9³</td>
</tr>
<tr>
<td>Adjacent to FBZ (%)</td>
<td>50.2 ± 3.8</td>
<td>38.6 ± 2.4²</td>
<td>55.5 ± 4.5²</td>
</tr>
<tr>
<td>FBZ (%)</td>
<td>47.8 ± 4.3</td>
<td>22.4 ± 2.9³</td>
<td>26.9 ± 2.9⁴</td>
</tr>
<tr>
<td>Central ischemic zone (%)</td>
<td>51.6 ± 8.3</td>
<td>-5.2 ± 1.5⁴</td>
<td>-14.6 ± 5.8⁴</td>
</tr>
</tbody>
</table>

FBZ = functional border zone.

*p < .05 vs baseline; *p < .01 vs baseline; *p < .05 vs occlusion; *p < .01 vs occlusion.

The circumferential extent of the hypoperfusion zone did not change after infusion of dobutamine.

**Circumferential flow-function relations.** After coronary artery occlusion, the circumferential extent of left ventricular dysfunction was significantly greater than the extent of the hypoperfusion zone (170 ± 11 vs 130 ± 9 degrees, p = .005). Thus, the functional border zone measured 40 ± 11 degrees (figure 5). After dobutamine, the functional border zone decreased to 19 ± 16 degrees (p < .05) related to the decrease in the circumferential extent of the left ventricular dysfunction (figure 6). Of particular interest, in four of the 11 animals studied, a positive functional border zone after coronary occlusion changed to an actual negative functional border zone after the infusion of dobutamine (figure 1).

**Discussion**

The hypothesis that ischemic myocardium mechanically tethers adjacent normal myocardium was initially proposed to explain results of several experiments that demonstrated functional abnormalities in normally perfused myocardium adjacent to ischemic tissue.⁴⁻¹¹ Subsequent studies⁴⁻¹¹ have provided additional support for the existence of the functional border zone, which may be defined as a discrete area exhibiting functional abnormalities despite normal perfusion immediately adjacent to an ischemic area. Although there is some controversy concerning the size of this functional border zone, previous studies in our laboratories⁶,¹⁰ and by other investigators¹¹ suggest that it extends laterally a total of approximately 40 to 50 degrees (or 8 to 9 mm on either lateral border), similar to our present findings. The existence of the functional border zone helps to explain the observation that functional variables overestimate the extent of myocardial ischemia or infarction in experimental and clinical investigations.², ¹⁶⁻¹⁹

The present study extends our previous work by...
demonstrating that the spatial dimensions of the functional border zone can be altered with inotropic intervention. Our results also indicate that a significant increase in wall thickening in the region immediately adjacent to the functional border zone occurs during inotropic stimulation after coronary occlusion, which leads to an increase in the slope of transition from dysfunctional to normally thickening myocardium, as shown in figure 1. Consequently, the size of the functional border zone decreases significantly.

It is notable that in four of the 11 animals we studied, this effect was so pronounced that there was a reversal of the flow and function relationships at the ischemic border. Normally during ischemia the functional border is outside the perfusion border, but in these four dogs, the transition between normal and abnormal wall thickening was actually within the ischemic area (i.e., inside the perfusion boundary), resulting in a negative value for the functional border zone. This observation in approximately a third of the dogs we studied suggests the intriguing possibility that a form of “reverse tethering” may occur during inotropic stimulation. Reverse tethering could be defined as an apparent improvement in ischemic zone function such that it may appear to be active due to contraction of nonischemic muscle. This is in contrast to the conventional notion of “tethering,” in which ischemic muscle influences motion in the nonischemic area. Although we are unable to state conclusively that this occurred, we suggest it represents a worthwhile area of additional investigation.

There are alternative explanations for our results. For example, it is possible that the functional border zone consists of an intermingling of peninsulas of normal and ischemic myocardium, supplied in turn by two capillary beds discrete and unconnected, one from the nonoccluded artery and one from the occluded artery. After inotropic stimulation, the capillaries supplied by the nonoccluded artery could result in hyperemic flow, whereas flow in the occluded artery would remain markedly decreased. This would create a normal mean flow in the region of the functional border zone, although function would be reduced due to the admixture of ischemic fibers. Thus, with an inotropic challenge, normal myocardial fibers would be stimulated and overall function would improve without an effect on mean flow.

Our data must also be considered in the context of our experimental conditions. The dobutamine infusion produced a pressor response that increased mean arte-

![Figure 3](image-url)
The effect, also known as the coronary distention hypothesis, states that increasing intravascular pressure distends the myocardial vessels, which in turn increases myocardial stretch with increased cardiac performance as a result of a Frank-Starling effect. It is also possible that a dose-response relationship to dobutamine may be present, but this was not investigated in the present study. Although time control experiments were not performed in this study, the fact that flow-function relations and the functional border zone are unchanged over time is supported by our preliminary data.22, 23

Another important observation was the asymmetry of the slope of transition of regional ventricular function from ischemic to nonischemic regions. The lateral wall had a significantly greater slope of transition compared with the septal wall. This suggests that the septum may exert an additional tethering or constraining effect on normal myocardium that does not occur in the regions of the lateral free wall. It is also interesting to note that during inotropic challenge, the lateral free wall slope of dysfunction increased significantly, whereas that of the lateral septal region did not. Alternatively, the difference in slope may be related to a flatter septum than free wall due to counterpressure from the right ventricle. This might tend to distribute the more ischemic subendocardium along a broader span of the functional border zone.

It is notable that despite the gradual transition of functional impairment from normal to ischemic zones after coronary occlusion, wall thickening in both the normal zone and the zone adjacent to the functional border zone improved by approximately 45% after dobutamine. This suggests that inotropic stimulation can recruit myocardial function in zones that appear mildly depressed after coronary occlusion. Since the left ventricular area ejection fraction improved significantly after dobutamine, regional recruitment of mildly depressed regional function appeared to enhance global left ventricular performance despite ongoing ischemic dysfunction.

The mechanism underlying the existence of the functional border zone is not well established and there are a number of possible explanations. The hypothesis that it represents a mechanical tethering effect is sup-

### TABLE 3
Coronary blood flows

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Occlusion</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subendocardial</td>
<td>1.22±0.13</td>
<td>1.22±0.18</td>
<td>1.43±0.20</td>
</tr>
<tr>
<td>Midmyocardial</td>
<td>1.25±0.14</td>
<td>1.19±0.15</td>
<td>1.80±0.18</td>
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<tr>
<td>Subepicardial</td>
<td>1.14±0.14</td>
<td>1.02±0.13</td>
<td>1.56±0.18</td>
</tr>
<tr>
<td>Adjacent to FBZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subendocardial</td>
<td>1.29±0.14</td>
<td>1.22±0.17</td>
<td>1.53±0.21</td>
</tr>
<tr>
<td>Midmyocardial</td>
<td>1.17±0.15</td>
<td>0.99±0.15</td>
<td>1.42±0.14</td>
</tr>
<tr>
<td>Subepicardial</td>
<td>1.26±0.16</td>
<td>1.15±0.17</td>
<td>1.59±0.19</td>
</tr>
<tr>
<td>FBZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subendocardial</td>
<td>1.21±0.10</td>
<td>0.90±0.16</td>
<td>1.16±0.24</td>
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<tr>
<td>Midmyocardial</td>
<td>1.13±0.14</td>
<td>0.73±0.10</td>
<td>0.92±0.19</td>
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<tr>
<td>Subepicardial</td>
<td>1.17±0.15</td>
<td>0.90±0.14</td>
<td>0.96±0.19</td>
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<tr>
<td>Central ischemic zone</td>
<td></td>
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<td></td>
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<tr>
<td>Subendocardial</td>
<td>1.21±0.14</td>
<td>0.06±0.02</td>
<td>0.06±0.03</td>
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<tr>
<td>Midmyocardial</td>
<td>1.18±0.15</td>
<td>0.11±0.03</td>
<td>0.14±0.06</td>
</tr>
<tr>
<td>Subepicardial</td>
<td>1.15±0.12</td>
<td>0.17±0.05</td>
<td>0.36±0.11</td>
</tr>
</tbody>
</table>

All values ml/min/g.
FBZ = functional border zone.
*p < .05 vs baseline; **p < .01 vs baseline; ***p < .01 vs occlusion.
ported by the studies in vitro of Tyberg et al.\textsuperscript{24} They demonstrated that a hypoxic muscle in series with a normal muscle causes asynergy of contraction and relaxation of both muscles. An alternative explanation for the existence of a functional border zone is that regional stress amplification occurs in myocardium adjacent to the ischemic zone. Bogen et al.\textsuperscript{25, 26} proposed that localized increases in left ventricular stress at the lateral borders of infarcted myocardium produce functional abnormalities despite normal perfusion. Although theoretically appealing, the model of Bogen et al.\textsuperscript{25} is difficult to verify experimentally given the problems in directly measuring regional myocardial stress. However, it is interesting to note that Bogen's prediction of the size of regional stress amplification using his conceptual model\textsuperscript{21} corresponds closely to our experimental results concerning the lateral extent of the functional border zone. A third explanation is that localized ischemia occurs because of local alterations in supply-demand ratio despite normal perfusion. Recent positron-emission tomographic studies have indicated that localized metabolic abnormalities occur surrounding a central ischemic zone,\textsuperscript{27} but whether these correspond to the functional border zone is unknown.

The interpretation of our data is influenced by the method of analysis.\textsuperscript{11} This is best illustrated by comparing our results regarding wall thickening in specific myocardial regions during coronary occlusion to those of Lima et al.\textsuperscript{8} It is striking that our wall thickening results are very similar despite differences in the specific methods used to identify these regions (table 2).
Unlike Lima et al., we generated full circumference flow-function maps to precisely measure the extent of the functional border zones during occlusion and after inotropic challenge. If we had only used the left ventricular wall thickening data as presented in table 2, we may have predicted a significantly larger functional border zone. By making our estimates of the size of the functional border zone directly from our circumferential flow-function maps, rather than from the categorical analysis (table 2) alone, we found that the extent of nonischemic dysfunction was relatively limited. Thus, the different form of analysis we used may help explain the discrepancy between the findings of our study and that of Lima et al. It is noteworthy that most studies tend to support the existence of a relatively confined, discrete functional border zone involving approximately 10% to 15% of the left ventricular circumference.

Although our definition of the hypoperfusion zone as that in which there was a 50% decrease in subendocardial blood flow was arbitrary and based on previously reported data, it is important to emphasize the existence of an abrupt decrease in blood flow at both lateral borders. Thus, a change in the threshold for blood flow abnormality is unlikely to significantly influence the width of our functional border zone or our conclusions.

Our study may have certain clinical implications. It should be recognized that functional abnormalities may be improved significantly during inotropic infusion and may decrease the functional overestimation of ischemia and infarction. Regional recruitment of mildly depressed function leads to improved overall left ventricular performance. Thus, after inotropic infusion during acute myocardial ischemia, residual functional abnormalities may better reflect the actual ischemic area. These clinical implications further underscore the importance of metabolic imaging studies that may enable assessment of the viability of myocardial tissue rather than its function. This is particularly important in determining whether myocardium has been salvaged by specific interventions or whether complex flow-function alterations are contributing to what is perceived as improvement. Finally, our results emphasize the difficulty with the use of functional variables to precisely distinguish between ischemic and nonischemic tissues, particularly when inotropic infusions are simultaneously being used during the ischemic period. We conclude that serial functional studies should be interpreted cautiously in the setting of myocardial ischemia when inotropic infusions are being used to support cardiac performance.

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References
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