The Distribution of Functional Impairment across the Lateral Border of Acutely Ischemic Myocardium


SUMMARY. To evaluate the degree and lateral extent of dysfunction in nonischemic myocardium adjacent to ischemic muscle, we measured systolic wall thickening with sonomicrometers during circumflex coronary occlusion in 12 anesthetized, open-chest dogs. The locations of the wall thickness measurements relative to the perfusion boundary were determined with myocardial blood flow (microspheres) maps constructed from multiple, small tissue samples. Five minutes after circumflex occlusion, systolic wall thickening in the central ischemic zone decreased from $3.00 \pm 0.61$ (mean $\pm$ SD) mm to $-0.61 \pm 0.36$ mm ($P < 0.01$). In nonischemic myocardium greater than 10 mm from the perfusion boundary, systolic wall thickening increased from $2.56 \pm 0.57$ to $3.24 \pm 0.72$ mm ($P < 0.01$). In nonischemic myocardium within 10 mm of the perfusion boundary, systolic wall thickening was slightly but significantly reduced compared with control ($2.72 \pm 0.80$ to $2.44 \pm 0.79$ mm, $P < 0.05$), supporting the concept of regional dysfunction in nonischemic myocardium at the lateral borders of an ischemic area. Sigmoid curves were fitted to the data to model changes in wall thickening as a continuous function of distance from the perfusion boundary. This allowed estimation of the extent of dysfunction into nonischemic myocardium which averaged less than 8 mm (approximately 30 degrees of endocardial circumference) at one border. The level of functional impairment in this zone was relatively modest, and systolic wall thickening in the immediate border area was reduced more than 50% from control only in tissue characterized by a blood supply of mixed ischemic and nonischemic origin. We conclude that a functional border zone exists lateral to an acutely ischemic area, but measurement of regional function produces relatively small exaggeration of the size of the acutely ischemic zone if severe reduction in mechanical performance is used to define the extent of the ischemic area. (Circ Res 58: 570-583, 1986)

CONSIDERABLE interest has focused recently on the extent to which nonischemic muscle, adjacent to ischemic or damaged myocardium, exhibits mechanical dysfunction. This constitutes an important issue for assessment of infarct size with imaging modalities such as two-dimensional echocardiography. The circumferential distribution of impaired wall thickening or wall motion has been reported to overestimate infarct size by most investigators, but the amount of overestimation varies considerably, (Wyatt et al., 1981; Neimenen et al., 1982; Pandian et al., 1983; Buda et al., 1985; Lima et al., 1985; Homans et al., 1985; Force et al., 1985; Gibbons et al., 1985; Sakai et al., 1985). For example, Lima et al. (1985) used two-dimensional echocardiography in open-chest dogs to demonstrate a reduction in wall thickening up to 2.5 cm from the perfusion boundary produced by acute circumflex coronary occlusion. Homans et al. (1985), using a similar preparation, reported that the degree of nonischemic dysfunction was relatively mild and that the extent of severe dysfunction provided a relatively accurate estimate of infarct size, in marked contrast to the results obtained by Lima et al. Consequently, the lateral extent and degree of nonischemic dysfunction remains uncertain.

In a related study, we examined the effect of acute coronary occlusion on subendocardial segment shortening on either side of the interface between ischemic and nonischemic myocardium (Gerren et al., 1984). The level of dysfunction in normally perfused myocardium adjacent to the ischemic area was modest, similar to the report by Homans et al. (1985), but in apparent contrast to the experimental reports of several other investigators (Kerber et al., 1975; Kerber et al., 1976; Wyatt et al., 1976; Cox and Vatner, 1982; Guth et al., 1984; Lima et al., 1985) who used regional measurements of myocardial function. Because the subendocardial segments in our previous study spanned up to 16 mm of myocardium, it is possible that a narrower zone of more severe dysfunction was not detected.

Therefore, the objective of the present study was to make more discrete measurements of regional function. To do so, we measured systolic wall thickening, rather than segment shortening, with sonomicrometers arrayed on either side of the perfusion boundary. Wall thickening is a useful method
for evaluating regional myocardial function (Sasayama et al., 1976) that integrates mechanical performance across all layers of the myocardium and is extremely sensitive to ischemia (Kerber et al., 1975; Gallagher et al., 1983; Guth et al., 1984; Gallagher et al., 1984). By constructing circumferential perfusion maps from microsphere determinations of myocardial blood flow, we could delineate the position of the perfusion boundary and accurately identify the location of the functional measurements relative to the perfusion boundary (Gerren et al., 1984). Plotting the changes in wall thickening as a continuous function of distance from the perfusion boundary enabled us to determine the distribution of functional impairment across the ischemic-nonischemic interface.

**Methods**

**Experimental Preparation**

The study was performed in open-chest dogs anesthetized with halothane (end-tidal concentration 0.5–0.7%) and artificially ventilated. Arterial blood gases and pH were checked periodically to ensure they were in the normal range and that the Po2 exceeded 100 mm Hg. Intravenous fluids were infused to sustain normal arterial pressures, and hematocrits were determined periodically to make certain hemodilution (hematocrit less than 30%) did not occur. The dogs were instrumented as shown in Figure 1. A Millar high-fidelity micromanometer was passed into the left ventricle via the carotid artery and aorta for measurement of left ventricular pressure. Tygon catheters were placed in the left ventricle (via the apex to verify calibration of the Millar micromanometer in mm Hg), left atrium (for injection of microspheres), and femoral and carotid arteries (for obtaining two simultaneous reference withdrawal samples of arterial blood for calculation of myocardial blood flow). A screw clamp occluder was positioned around the proximal circumflex coronary artery to produce total coronary occlusion.

Regional myocardial function was measured with sonomicrometers arrayed to measure transmural wall thickness (Bugge-Asperheim et al., 1969; Sasayama et al., 1976). The sonomicrometers were implanted in four locations, as schematically depicted in Figure 1. One pair was placed in the central ischemic area perfused by the left circumflex artery, and a second pair was placed in the central nonischemic (or control) area, perfused by the left anterior descending artery. The two remaining pairs were placed on either side of the estimated position of the perfusion boundary (inset, Fig. 1) produced by occluding the circumflex artery. As a guide to estimate the position of the perfusion boundary, we used the epicardial vascular anatomy. Previous experience indicated that the boundary was approximately midway between the epicardial branches of the circumflex and left anterior descending arteries. As shown in the inset of Figure 1, one crystal of each wall thickness pair was in the subendocardium and the other crystal was attached to the epicardium, over the position of the inner crystal. The inner crystal was inserted tangentially through the myocardium to the endocardium. The epicardial crystal, attached to a dacron patch, was sewn to the epicardium with shallow sutures after locating the position of least distance between the two crystals while monitoring the signals with an oscilloscope (Sasayama et al., 1976). The signals from the ultrasonic dimension gauges were processed with a Triton (model 120) sonomicrometer. Data were not used if crystals were improperly aligned or if inadequate sectioning of the myocardium resulted in poor delineation of the perfusion

![Figure 1](https://example.com/figure1.png)
boundary. Location of the inner crystals within the subendocardial third of the myocardial wall and correct alignment of the crystals across the wall (Gallagher et al., 1985) was confirmed at the time of necropsy during the careful sectioning required for tissue sample preparation to determine myocardial blood flows.

**Myocardial Blood Flow Measurements**

Regional myocardial blood flow was measured with tracer-labeled microspheres (15 μm in diameter, New England Nuclear) utilizing the reference withdrawal method (Heymann et al., 1977). Two injections were made in every experiment, using one of six available isotopes (111In, 113Sm, 51Cr, 198Ru, 154Nb, 46Sc) for each flow determination. The choice of isotopes was determined by which isotopes were available at the time, and the order of their injection was randomized. Approximately 1–2 million microspheres were injected into the left atrium for measuring blood flows. Reference arterial samples were obtained simultaneously from both the femoral and carotid arteries at a constant rate (7.0 ml/min) with a Harvard withdrawal pump; withdrawals were initiated prior to the injection of microspheres and completed 2 minutes later. If the counts in the two reference samples varied by greater than 15%, indicating poor mixing, the data were discarded. The reference sample counts were averaged for the calculation of myocardial flows. Each bottle of microspheres was placed in an ultrasonic bath with subsequent vortex agitation prior to injection, and droplets of the microsphere suspension were periodically examined under a microscope to ensure that adequate dispersal had been achieved.

At the end of the experiments, the dogs were killed with intravenous KCl. The heart was removed and placed in formalin to facilitate sectioning. Dimension gauges were placed in the heart to allow careful evaluation of their position in the wall, at the time of heart sectioning. Multiple full thickness sections were obtained around complete rings of the left ventricle. Each block of tissue was divided into three pieces of approximately equal thickness from the endocardial to epicardial surfaces. The location of each piece of tissue and the position of the ultrasonic crystals were recorded, then the tissue samples were weighed and placed in counting vials for assay of radioactivity in a Tracor (model 1185) γ 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 (Heymann et al., 1977): Qm = (Cm × Qt)/Cr where Qm = myocardial blood flow (ml/min), Cm = counts/min in tissue samples, Qt = withdrawal rate of the reference arterial sample (ml/min), and Cr = 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 plus microcomputer.

These procedures enabled construction of myocardial blood flow "maps" around the circumference of the left ventricle in which the position of the dimensional measurements could be located. Tissue samples in myocardium straddling the perfusion boundary were approximately 3 mm wide, similar to the preparation described recently by Murdock et al. (1983). The location of the "perfusion boundary" was determined by the position of the flow gradient in the circumferential blood flow map as shown in Figure 2. This figure shows flow maps from four of the experiments included in the present study.

Note that one sample during coronary occlusion (the first data point left of the perfusion boundary) usually had blood flow intermediate between the ischemic and nonischemic zones on either side of it. The location of wall thickening measurements are indicated in this figure, as well. Although we sometimes used dyes to separate the circumflex and left anterior descending supplied myocardium to aid in sectioning the tissue, we relied solely on the blood flow data to delineate the location of the perfusion boundary. We conservatively designated the perfusion boundary as the junction between the high flow and intermediate flow sample (Fig. 2) because we required that nonischemic border zone wall thickness measurements be located completely on the nonischemic side of the perfusion boundary.

**Experimental Protocol**

Systolic wall thickening and myocardial blood flow measurements were made in 12 dogs. After control recordings were completed and the first set of microspheres had been injected, the circumflex artery was abruptly occluded with the screw clamp. Between 5 and 7 minutes after occlusion, when hemodynamics and regional dimensions were stable, a second injection of microspheres was made while continuously recording these parameters.

Because the myocardial tissue samples used to locate the perfusion boundary were small (200–400 mg), the numbers of microspheres in these samples were quite low. To demonstrate that precise delineation of the perfusion boundary was achievable with economically feasible quantities of microspheres, we studied an additional three dogs. In these experiments, approximately 1.5 million microspheres were injected during control conditions. The same quantity of spheres was injected 10 minutes after coronary occlusion, similar to the amount of microspheres used in the experiments focusing on regional functional changes described above. A third injection of microspheres was made 5 minutes later, using 6–7 million spheres, in order to determine whether a larger number of microspheres altered localization of the perfusion boundary.

**Data Analysis**

Recordings were made during each experiment on an eight-channel Hewlett-Packard pressurized-ink recorder and on magnetic tape for subsequent analysis. Variables analyzed were wall thickness at end-diastole (identified as the point corresponding to the onset of the positive dP/dt signal) and end-systole (defined as the point 20 msec prior to peak negative dP/dt), extent of wall thickening, mean ejection phase velocity of thickening, left ventricular systolic and end-diastolic pressure, heart rate, and regional myocardial blood flows. The extent of wall thickening was calculated as the difference in millimeters between end-diastolic and end-systolic dimensions, and was also expressed as a percentage change from end-diastolic wall thickness. We used three parameters of systolic function: systolic wall thickening (mm), percent-age thickening, and mean ejection phase velocity of thickening. Dimensional and hemodynamic data were analyzed from recordings made at 100 mm/sec or were analyzed by digitizing the recorded data from analog tape with a DEC Micro PDP-11 computer system. Ten to 20 cardiac cycles were averaged at each condition, using the beats occurring during the microsphere injections. The blood flow values reported from the ischemic and nonischemic border zones represent blood flow from the tissue
samples spanned by the individual dimension measurements. Central ischemic and nonischemic blood flows are averages from several tissue samples remote from the perfusion boundary.

Hemodynamic, dimensional, and myocardial blood flow data were analyzed at two time periods (with paired t-tests), during control conditions and after total coronary occlusion in all 12 dogs. Unpaired t-tests were used to compare wall thickness variables and blood flow data in four locations: (1) the central ischemic area, (2) the ischemic border zone, (3) nonischemic border zone, and (4) central nonischemic or control area. Because multiple comparisons were performed, the acceptable alpha level was adjusted to 0.0083 (0.05 divided by six, the number of possible comparisons) with the Bonferroni inequality (Morrison, 1967). When P < 0.05 or P < 0.01 is indicated in the tables or text, it represents the corrected value.

In addition to the categorical analysis, we also evaluated the wall thickening data as a continuous function of distance from the perfusion boundary. To model mathematically the distribution of wall thickening change across the perfusion boundary we assumed that the nonischemic tissue had a wall thickening asymptote, N, and that the ischemic tissue had a wall thinning asymptote, I. One mathematical function that has these asymptotes and also changes monotonically between them is the following:

\[
y = 1 + \frac{N-I}{(2\pi\sigma^2)^{1/2}} \int_{-\infty}^x \exp\left[-(x-\mu)^2/2\sigma^2\right] \, dx \quad (1)
\]

This is a form of the Normal Distribution Function (Morrison, 1967). In Figure 3, we review the properties of this function. The value \(\mu\) corresponds to the position on the x-axis of the midpoint of the change between the asymptotes and \(\sigma\) is a value that describes how rapidly the change is made. Note that a change in \(x\) from \(\mu - 2\sigma\) to \(\mu + 2\sigma\) means that the function \(y\) changes over 95% of its range: N-I. Applied to the distribution of wall thickening change, the value of \(\sigma\) describes the extent of the transition from abnormal to normal regional function. A small value of \(\sigma\) indicates a relatively rapid transition; a large value of \(\sigma\) implies a broad transition area. The modeling function (Eq. 1) was fit to the data set from each dog and to the pooled data from all dogs by minimizing the variance and by using computerized nonlinear minimization techniques that we use routinely in spectroscopic studies (Dunham et al., 1977, 1980; Hagen et al., 1985).

Results

Localization of the Perfusion Boundary

Figure 4 shows data from three experiments performed to determine whether or not we had used sufficient numbers of microspheres to delineate accurately the position of the perfusion boundary. Although the quantities of microspheres in the tissue samples (250–400 mg) were very small, increasing the number of injected microspheres from approximately 1.5 million to 6–7 million had no effect on localization of the perfusion boundary. Blood flow values were similar for the two injections of microspheres after coronary occlusion, even in the ischemic samples which averaged 0.02 ± 0.01 ml/min per g and 0.04 ± 0.03 ml/min per g in the low and
high quantity injections, respectively. Although the error in flow estimates is quite high when the number of microspheres per (ischemic) sample is in the range we encountered (Heymann et al., 1977), the ischemic flows were so low that an error of ± 50% or more would minimally influence the absolute blood flow values. Our main objective was not to quantify ischemic levels of perfusion precisely, but rather, to distinguish ischemic from nonischemic tissue and to localize the interface between these areas. The data in Figure 4 indicate we could successfully achieve that goal with injections limited to approximately 1-2 million microspheres.

**Hemodynamics and Blood Flow**

Heart rate increased a small amount from 107 ± 15 (mean ± sd) beats/min during control conditions to 111 ± 18 (P < 0.03) after occlusion of the circumflex artery. Peak systolic left ventricular pressure decreased from 114 ± 10 mm Hg to 96 ± 11 mm Hg (P < 0.01). Left ventricular end-diastolic pressure increased from 8.2 ± 1.5 mm Hg to 13.3 ± 2.6 mm Hg (P < 0.01).

Myocardial blood flow data are summarized in Table 1. During control conditions, blood flow was similar in all four locations. After circumflex coronary occlusion, blood flow was reduced substantially in the ischemic area. There were no significant differences between blood flow in the central ischemic area and tissue samples containing ischemic border zone wall thickness gauges. Blood flow was reduced most dramatically in the subendocardium and midmyocardium. In the nonischemic area, small reductions in midmyocardial and subepicardial perfusion were evident in the tissue samples containing nonischemic border zone gauges. There were no significant differences, however, in blood flow to any layer between the nonischemic border zone samples and the central nonischemic area (Table 1). These measurements indicate we achieved our objective of locating nonischemic border zone wall thickness measurements in homogeneously perfused tissue adjacent to the perfusion boundary. The relative abruptness of the interface between ischemic and nonischemic areas is demonstrated in Figure 2, which graphically presents the location of the perfusion boundary in four of the experiments.

**Wall Thickness Data**

These data are summarized in Table 2. Examples of recorded tracings are shown in Figure 5, which is from one of the experiments (number 1) used to exemplify a circumferential blood flow "map" in Figure 2. Beat-averaged waveforms from the same experiment are presented in Figure 6 to demonstrate more clearly the changes in wall thickening following coronary occlusion. The locations of the dimension gauges from which the analog tracings were derived are shown in Figure 2. During control conditions, wall thickening, percentage thickening, and mean ejection phase velocity of thickening were comparable in all four locations (Table 2).

During circumflex coronary occlusion, end-diastolic wall thickness decreased in all four locations (Figs. 5 and 6). The average decreases were 13.1% in the central ischemic area, 15.8% in the ischemic border zone, 9.3% in the nonischemic border zone, and 11.0% in the nonischemic area (Table 2). The average distances from the perfusion boundary of the wall thickening measurements in these four categories were 13 ± 3 mm (central ischemic area), 5 ± 3 mm (ischemic border zone), 4 ± 2 mm (nonischemic border zone), and 15 ± 4 mm (nonischemic area). Thickening was replaced by systolic thinning in the central ischemic area after coronary occlusion. The average reduction from control in thickening was −127% (greater than 100% indicates net thinning during systole), in percentage thickening was −131%, and in mean ejection phase velocity of thickening was −99% (Table 2).

A marked disparity was evident between the two border zone wall thicknesses. For example, as demonstrated in Figures 5 and 6, thickening was eliminated in the ischemic border zone wall thickness, whereas thickening in the nonischemic border zone remained approximately the same as the control level. The border zone gauges were separated by less than 10 mm (see number 1, Fig. 2), in this
FIGURE 4. Examples of perfusion boundary delineation with small and large numbers of microspheres per sample. Average blood flow in the small tissue samples near the perfusion boundary (PB) are presented graphically in the lower right (panel D). Average blood flow (in ml/min per g) on the ischemic (IS) and nonischemic (NIS) sides of the PB are shown with bar graphs. Average numbers of microspheres per sample are superimposed on the bars. Data are presented from control conditions (C, open squares), after approximately 1.5 million spheres were injected 5 minutes after circumflex coronary occlusion (OCCL 1, solid circles) and after injection of approximately 6-7 million spheres (OCCL 2, open circles). Although substantially larger numbers of spheres were present in samples for the OCCL 2 injection, average blood flow values were quite similar (panel D) and perfusion boundary delineation was identical (panels A, B, and C). Example emphasizing the relative abruptness of the transition in wall thickening near the perfusion boundary. For all of the experiments, the average reductions from control in the extent of ischemic border zone wall thickening and percentage thickening were -111% and -113%, respectively. Mean ejection phase velocity of thickening decreased an average of -91% (Table 2). In the nonischemic area, at a greater distance from the perfusion boundary, wall thickening increased significantly by 27% over control values (Table 2).

Wall thickening data during coronary occlusion are plotted as a function of distance from the perfusion boundary in Figures 7 and 8. Regional function is plotted on the y-axis as a percentage of control condition wall thickening. Each data point corre-

TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Ischemic area</th>
<th>Ischemic border zone</th>
<th>Nonischemic border zone</th>
<th>Nonischemic area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 12)</td>
<td>(n = 12)</td>
<td>(n = 12)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Subendocardium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.98 ± 0.28</td>
<td>NS</td>
<td>1.00 ± 0.30</td>
<td>NS</td>
</tr>
<tr>
<td>TCO</td>
<td>0.02 ± 0.02†</td>
<td>NS</td>
<td>0.06 ± 0.06†</td>
<td>NS</td>
</tr>
<tr>
<td>Midmyocardium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.90 ± 0.30</td>
<td>NS</td>
<td>0.87 ± 0.32</td>
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<tr>
<td>TCO</td>
<td>0.05 ± 0.04†</td>
<td>NS</td>
<td>0.06 ± 0.06†</td>
<td>NS</td>
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<tr>
<td>Subepicardium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.92 ± 0.31</td>
<td>NS</td>
<td>0.91 ± 0.28</td>
<td>NS</td>
</tr>
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<td>TCO</td>
<td>0.11 ± 0.09†</td>
<td>NS</td>
<td>0.12 ± 0.10†</td>
<td>NS</td>
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<tr>
<td>Mean transmural</td>
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<tr>
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<td>NS</td>
<td>0.92 ± 0.28</td>
<td>NS</td>
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<tr>
<td>TCO</td>
<td>0.06 ± 0.05†</td>
<td>NS</td>
<td>0.08 ± 0.08†</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: C, control; TCO, total coronary occlusion; P, probability of difference between groups (corrected value for multiple comparisons).

* P < 0.05 and † P < 0.01 C vs. TCO values (paired t-test). NS, nonsignificant. Data are presented as mean ± so.
TABLE 2
Transmural Wall Thickness Data in Four Myocardial Zones during Control Conditions and after Coronary Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Ischemic area (n = 9)</th>
<th>Ischemic border zone (n = 10)</th>
<th>Nonischemic border zone (n = 12)</th>
<th>Nonischemic area (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDWT (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>10.51 ± 1.16</td>
<td>NS</td>
<td>11.46 ± 1.58</td>
<td>NS</td>
</tr>
<tr>
<td>TCO</td>
<td>9.18 ± 1.15†</td>
<td>NS</td>
<td>10.70 ± 1.53†</td>
<td>NS</td>
</tr>
<tr>
<td>ESWT (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>13.51 ± 1.27</td>
<td>NS</td>
<td>14.18 ± 1.97</td>
<td>NS</td>
</tr>
<tr>
<td>TCO</td>
<td>8.57 ± 1.29†</td>
<td>0.01</td>
<td>13.14 ± 1.85†</td>
<td>NS</td>
</tr>
<tr>
<td>dWT (mm)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>3.00 ± 0.61</td>
<td>NS</td>
<td>2.72 ± 0.80</td>
<td>NS</td>
</tr>
<tr>
<td>TCO</td>
<td>−0.61 ± 0.36†</td>
<td>0.01</td>
<td>2.44 ± 0.79*</td>
<td>0.05</td>
</tr>
<tr>
<td>%dWT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>29.1 ± 6.5</td>
<td>NS</td>
<td>23.8 ± 6.8</td>
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</tr>
<tr>
<td>TCO</td>
<td>−6.9 ± 4.1†</td>
<td>0.05</td>
<td>23.0 ± 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>MEP dW/dt (mm/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>14.5 ± 3.3</td>
<td>NS</td>
<td>12.5 ± 3.8</td>
<td>NS</td>
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<tr>
<td>TCO</td>
<td>0.4 ± 0.7†</td>
<td>0.01</td>
<td>10.2 ± 3.4*</td>
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</tr>
</tbody>
</table>

Abbreviations: EDWT, end-diastolic wall thickness; ESWT, end-systolic wall thickness; dWT, ESWT-EDWT; %dWT = (dWT/EDWT) x 100; MEP dW/dt, mean ejection phase velocity of thickening; C, control (preocclusion); TCO, total coronary occlusion; P, probability of difference between groups (corrected value for multiple comparisons); NS, nonsignificant.

* P < 0.05 and † P < 0.01 C vs. TCO (paired t-test); data presented as mean ± SD.

Evaluating Table 2, we observe that the wall thickness measurements in the ischemic area are generally increased after coronary occlusion compared to the control conditions, with significant differences indicated by the asterisks. For instance, the end-diastolic wall thickness (EDWT) increased from 10.51 ± 1.16 mm to 11.46 ± 1.58 mm in the ischemic area, and from 9.18 ± 1.15 mm to 10.70 ± 1.53 mm in the nonischemic area, with respective probability values of NS and NS.

Conversely, in the ischemic border zone, the wall thicknesses generally decreased after occlusion, with significant reductions observed in the end-systolic wall thickness (ESWT) and the mean ejection phase velocity of thickening (MEP dW/dt) parameters. For example, the ESWT decreased from 13.51 ± 2.41 mm to 8.57 ± 1.29 mm, and the MEP dW/dt decreased from 26.7 ± 6.3 mm/sec to 23.0 ± 7.5 mm/sec, with respective probability values of 0.01 and 0.01.

The nonischemic border zone and area showed more variable responses, with some parameters increasing and others decreasing after occlusion. However, no significant changes were observed in the nonischemic area, as indicated by the NS values.

These findings suggest that coronary occlusion significantly impacts the myocardial wall thickness and contractility in both ischemic and nonischemic regions, with more pronounced effects observed in the ischemic zones.

FIGURE 6. Examples of individual wall thickness waveforms and pressure-wall thickness loops before and after coronary occlusion. They are from the same experiment shown in Figure 2 (number 1, upper left) and Figure 5. Control (C) condition tracings are presented with solid lines; occlusion (O) tracings are presented with dashed lines. These waveforms represent beat-averaged data from 20 digitized consecutive cardiac cycles. The salient feature of the figure is the relatively small change in nonischemic border zone (NIS BZ) wall thickening post-occlusion. Abbreviations the same as in Figure 5.

The functional border zone as the distance from the perfusion boundary to 97.5% of the nonischemic asymptote (i.e., $\mu + 2\sigma$, Table 3) then the extent of nonischemic dysfunction was $8 \pm 4$ mm. Estimated from the composite data set, the extent of nonischemic dysfunction, defined in this manner (as any, even mild dysfunction), was $7$ mm. If a less conservative criterion (moderate dysfunction) is used to classify dysfunction, such as wall thickening at or below control condition values (100% line in Figs. 7 and 8), then the size of the functional border zone at one lateral margin is approximately $4$ mm (or 15 degrees) of endocardial circumference. The extent of severe dysfunction (wall thickening 50% or less of control condition values) corresponds closely to the edge of the ischemic area, there being an estimated functional border zone of only $1$ mm at one lateral margin by this criterion.

Table 4 contains a summary of data on the average circumference at the endocardium and epicardium of the left ventricles used in our study. The average...
extent of the ischemic area (defined by the positions of the perfusion boundaries determined from the blood flow maps) was 41.5 ± 5.7% (range 32.8–51.1%) in the cross-sectional rings of left ventricle-containing dimension gauges. No significant relationship was demonstrable between the extent of the ischemic area and the extent of the ischemic area (defined by the positions of the perfusion boundaries determined from the blood flow maps) was 41.5 ± 5.7% (range 32.8–51.1%) in the cross-sectional rings of left ventricle-containing dimension gauges. No significant relationship was demonstrable between the extent of the ischemic area and the extent of the ischemic area.

**TABLE 3**

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>I</th>
<th>N</th>
<th>$\mu$</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−12</td>
<td>117</td>
<td>3.10</td>
<td>1.62</td>
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<tr>
<td>2</td>
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<td>3.21</td>
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**Composite best fit parameters**

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<th>$\sigma$</th>
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<td>128</td>
<td>0.51</td>
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**FIGURE 8.** Composite graph of wall thickening data from all of the experiments plotted relative to the position of the perfusion boundary. The x- and y-axes are arranged in the same manner as Figure 7. Although the data are from 12 different experiments, the points are distributed with relatively little scatter around the composite sigmoid curve. It should be noted that 3 mm to the left (ischemic side) of the perfusion boundary corresponds to the sample with intermediate blood flow values, probably representing a mixed ischemic and nonischemic blood supply (Murdock et al., 1983).

Discussion

Our objective was to determine the distribution of functional change across the perfusion boundary produced by acute coronary occlusion. It is well established that the perfusion boundary is sharply demarcated (Hearse et al., 1977; Hirsol et al., 1977; Harken et al., 1978; Schaper, 1979; Yellon et al., 1981; Scheel et al., 1982; Cox and Vatner, 1982; Factor et al., 1982; Liedtke et al., 1982; Murdock et al., 1983). Several previous studies, however, have indicated that regional myocardial function adjacent to the ischemic area is impaired even though perfusion is normal in this area. Although there appears to be general agreement that an ischemic or infarcted area is surrounded by a zone of nonischemic dysfunction, reports of its magnitude vary substantially. The present results support the concept of a functional border zone in nonischemic myocardium, but its lateral extent was more limited than we had anticipated, and it was characterized by relatively mild dysfunction. The categorical analysis of wall thickening change after coronary occlusion (Table 2) demonstrated that nonischemic muscle within 1 cm of the perfusion boundary was characterized by wall thickening reduced by only 10% from control values. The subtlety of this degree of change is apparent in Figure 6, in which representative wall thickening waveforms before and after occlusion are presented. Compared with wall thickening more than 1 cm from the perfusion boundary, greater impairment in the nonischemic border zone was evident (approximately 25% less thickening than in the central nonischemic area) but even by this standard it can only be described as moderate dysfunction.

Plotting the changes in wall thickening as a continuous function of distance from the perfusion boundary (Fig. 7 and 8) enabled us to reconstruct the distribution of impairment across the junction between ischemic and nonischemic myocardium. A continuum of dysfunction extended across the per-
fusion boundary, but the transition between dyskinetic and normal wall thickening was achieved over a relatively short distance (approximately 10–15 mm of endocardial circumference). Although proximity to the perfusion boundary was associated with greater dysfunction, wall thickening was reduced more than 50% from control condition values only within the ischemic area or in the tissue with mixed ischemic and nonischemic blood supply.

Figure 9 is presented to illustrate what our data imply in terms of a full cross-section of the left ventricle. By assuming that the lateral extent of nonischemic dysfunction is the same at both perfusion boundaries, we used the composite sigmoid fit (Fig. 8) and average circumferential distance measurements from all of the dogs (Table 4) to construct the diagram. Regional function is plotted as a percentage of thickening during control conditions on the y-axis vs. position (x-axis) around the circumference of the left ventricular cross-section, measured in millimeters at the endocardium and epicardium or in degrees. The ischemic area and the distribution of wall thickening change are shown together to convey the relationship between size of ischemic area and the extent of myocardium displaying reduced wall thickening predicted by our results. Because nonischemic dysfunction is evident lateral to each perfusion boundary, the dysfunctional area is larger than the ischemic area, a finding consistent with most previous studies.

The amount of overestimation, however, depends on how dysfunction is defined (Table 4). Given the

![Diagram](image-url)

**Figure 9.** Proposed distribution of functional impairment in a full cross-section of the left ventricle, based on the findings of this study. The distribution is based on the assumption that changes in wall thickening across the perfusion boundaries are symmetrical. The extent of the ischemic area (corresponding to a 42% region at risk, the average value from all 12 experiments) and position of the perfusion boundaries (PB) are indicated. Superimposed on the simplified blood flow map (MBF, solid line) is the distribution of wall thickening expressed as a percentage of control condition thickening (dWT, dashed line). On the x-axis are indicated distances around the cross-section in degrees and in millimeters of endocardial or epicardial circumference. The total dysfunctional zone exceeds the size of the ischemic region by approximately 37%, if any, even mild dysfunction (wall thickening less than 97.5% of the nonischemic asymptote) is considered significant. Moderate dysfunction (wall thickening less than control condition value, i.e., 100% on y-axis) decreases the overestimation to 20%. The extent of severe dysfunction (defined as wall thickening less than 50% of control values), however, is not shown on the graph because it corresponds so closely to the size of the ischemic region. The stippled areas represent the functional border zone at each lateral margin of the ischemic area.
"noise level" of data derived from two-dimensional echocardiography and other clinically applicable modalities (Falsetti et al., 1981), it is unlikely that mild dysfunction as we defined it (Table 4) could be detected with clinical techniques. In our view, a more realistic criterion is wall thickening reduced from control condition values (moderate dysfunction). This translates to an overestimation of the ischemic area by 20% on the average and a functional border zone of 4–5 mm (20 degrees) at the endocardium of each lateral border. Severe nonischemic dysfunction was limited to a few mm (or 4–8 degrees) of endocardial circumference (Figs. 7 and 8; Table 4), which means that the extent of severe dysfunction corresponded closely to the size of the ischemic area. Because modest impairment of wall thickening characterized most of the functional border zone, we conclude that relatively small exaggeration of ischemic zone size is possible with measurement of regional function, given the constraint that severe reduction in mechanical performance is used to define the perimeters of the ischemic area.

It is only in recent studies that quantitative data on the lateral extent of nonischemic dysfunction has been reported. Earlier investigations related that dysfunction was evident outside an ischemic or infarcted area, but little information on the position of the perfusion boundary or location of the functional measurements was made available. Guth et al. (1984), for example, measured wall thickness with sonomicrometry and regional blood flow with microspheres in chronically instrumented pigs during 2-minute circumflex artery occlusion. In the ischemic zone, intense flow reduction and dyskinetic wall motion were produced, similar to the observations made in our study. In the adjacent nonischemic zone, wall thickening was reduced significantly by an average of 49% from control, although mean transmural blood flow was not altered in that area which was reported to be 1–2 cm from the left circumflex bed. Relatively large myocardial samples were obtained for analysis of blood flow, however, which meant that the position of the functional measurements relative to the ischemic-nonischemic perfusion interface could not be determined with precision. Kerber et al. (1975, 1976) measured wall thickening with M-mode echocardiography in open-chest, anesthetized dogs. They observed impairment of wall thickening in myocardium adjacent to an ischemic area that varied as a function of distance from the ischemic zone, but no quantitative data were reported to document the relationship between thickening and proximity to the perfusion boundary.

Previous experimental studies using two-dimensional echocardiography compared the extent of dysfunction with infarct size. Some studies of this type reported substantial overestimation of infarct size by echocardiograms obtained early after coronary occlusion (Wyatt et al., 1981; Niemenen et al., 1982), supporting the concept of a large functional border zone. In other studies, however, the correspondence between infarct size and extent of the dysfunctional zone was good (Pandian et al., 1983; Gibbons et al., 1985). The disparity among two-dimensional echocardiographic studies may be related to differing methods of echo analysis, the use of infarct size rather than region at risk to correlate with extent of dysfunction, and variable approaches to perfusion boundary delineation.

More recent investigations have included data on the relationship between the position of the perfusion boundary and location of functional measurements. In a previous study from our laboratory, in which subendocardial segment shortening was measured orthogonal to the perfusion boundary, we observed that segments extending 8–16 mm from the perfusion boundary into nonischemic myocardium were characterized by shortening that was not significantly different from control values (Gerren et al., 1984). Segment shortening in the control area, more remote from the perfusion boundary, increased significantly, suggesting that there was modest impairment in the adjacent zone because shortening there failed to increase. We concluded that the nonischemic border zone segment data represented an integrated measurement across muscle in which the transition from dyskinetic to augmented shortening was completed. This predicted that the zone of significant nonischemic dysfunction should be less than 16 mm wide, which was confirmed in the present study by utilizing more discrete measurements of regional function. Preliminary findings by Buda et al. (1985) provide additional corroboration. Two-dimensional echocardiography was used to measure systolic wall thickening around the full circumference of left ventricles before and after circumflex coronary occlusion. Wall thickening data were superimposed on circumferential myocardial blood flow maps to produce graphs similar to that presented in Figure 9. The functional border zone extended 8–9 mm (or 49 degrees) of endocardial circumference into nonischemic myocardium, and wall thickening was reduced an average of 56% within this zone, adjacent to the ischemic margin.

Two-dimensional echocardiography was used in the study by Homans et al. (1985) and their data also support the existence of a relatively small functional border zone. Regional function was measured as endocardial wall motion and was simultaneously evaluated with ultrasonic dimension gauges arrayed to measure subendocardial segment lengths in the vicinity of the perfusion boundary (Homans et al., 1985). Significant correlations were established between distance from the border of ischemia and echocardiographically defined changes in wall motion or change in segment shortening after coronary occlusion. This documented that proximity to the perfusion boundary correlated with more severe dysfunction. The mean distance of echocardiographic measurements in nonischemic myocar-
dium adjacent to the ischemic area was approximately 10 mm, yet they demonstrated an average reduction in wall motion of only 24%. Subendocardial segment shortening, measured less than 9 mm from the border of ischemia, decreased 19% after coronary occlusion. Homans et al. (1985) concluded that the degree of nonischemic dysfunction was relatively mild and that the extent of severe dysfunction was similar to the size of the ischemic zone. Our results agree closely with those of Homans et al. and extend them by focusing on wall thickening as a measure of regional myocardial function and by using nonlinear curve fitting to model the distribution of functional impairment across the perfusion boundary.

Sakai et al. (1985) used a different approach to measure regional function adjacent to an ischemic area. Epicardial segment shortening was measured parallel to the ischemic-nonischemic interface with sonomicrometers in anesthetized, open-chest pigs during occlusion of the left anterior descending artery. Systolic shortening 3 mm from the ischemic margin (delineated with patent blue violet dye) was reduced 45% from control and shortening 9 mm from the margin decreased 25%. Exponential regression analysis demonstrated that nonischemic dysfunction extended approximately 15 mm from the perfusion boundary at the epicardium early after coronary occlusion. Our measurements of circumferential extent of nonischemic dysfunction, made at or within a few millimeters of the perfusion boundary, were consistent with the substantial dysfunction we observed. The model of Bogen et al. (1980) predicts the transition zone from dyskinetic to normal wall thickening as a measure of regional myocardial function and by using nonlinear curve fitting to model the distribution of functional impairment across the perfusion boundary.

The study of Lima et al. (1985) was also performed in open-chest dogs, but differs quantitatively from our results and the others reviewed above. Wall thickening was measured with two-dimensional echocardiography, enabling circumferential assessment of regional function in a full cross-section of the left ventricle. During occlusion of the circumflex artery, dysfunction extended to regions relatively distant from the ischemic border. Although Lima et al. (1985) observed that the perfusion boundary is abrupt, similar to our findings and those of other investigators (Murdock et al., 1983), the functional border zone extended over 25 mm rather than 10 mm (or less) as we observed. The reason for this major discrepancy is not clear, but it may be related to different methodologies for measuring wall thickness and defining the position of the perfusion boundary. Although there is agreement among studies that a functional border zone exists, only Lima et al. (1985) report that nonischemic dysfunction extends more than 10–15 mm beyond the perfusion boundary.

The mechanism of nonischemic dysfunction during acute occlusion is not clearly established. It is not due to ischemia or even relative ischemia (Lima et al., 1985) and the likelihood of biochemical ab-
crometry is analogous to evaluation of regional function with clinical techniques such as two-dimensional echocardiography. Unlike segment length shortening measured with sonomicrometers, wall thickening avoids potential problems with gauge alignment relative to fiber orientation. In addition, the sonomicrometers measured regional function in relatively small sections of myocardium, minimizing the ‘averaging’ effect of measuring across a centimeter or more of muscle that may be possible with segment lengths. Proper alignment of wall thickness sonomicrometers across the wall is vital for obtaining valid information. Therefore, considerable care was taken to verify proper alignment at the time of necropsy following our usual criteria for acceptable placement (Gallagher et al., 1985).

Differences in the size of the ischemic zone may also play an important role in determining nonischemic wall thickening changes during occlusion, as well. We attempted to minimize this potential error by performing the experiments in the same part of the heart in each dog (basal portion of the heart with the ischemic area supplied by the circumflex artery). Fortunately, the circumferential extent of ischemia varied over a relatively narrow range (Table 4) in the slices of myocardium containing the dimension gauges, supporting the consistency of this experimental factor across experiments. Our study applies only to myocardium in the basal half of the left ventricle. Potential variability in patterns of nonischemic dysfunction may well exist in other locations or with different distributions of ischemia. Likewise, the effects of altered loading conditions, changes in contractility, and replacement of infarcted muscle with scar tissue remain to be determined.

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Address for reprints: Kim P. Gallagher, Ph.D, Thoracic Surgery Research Lab, R3484 Kerper I, Box 056, The University of Michigan, Ann Arbor, Michigan 48109.

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Gallagher et al. / The Functional Border Zone


INDEX TERMS: Coronary occlusion • Microspheres • Myocardial blood flow • Sonomicrometers • Systolic wall thickening • Functional border zone • Nonischemic myocardial dysfunction
The distribution of functional impairment across the lateral border of acutely ischemic myocardium.

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