Changes in Contractility Fail to Alter the Size of the Functional Border Zone in Anesthetized Dogs


The functional border zone is nonischemic myocardium that exhibits reduced function adjacent to an ischemic area. To determine if the functional border zone can be modified by pharmacologic interventions that alter contractility, we infused isoproterenol (0.04–0.10 μg/kg/min) or administered propranolol (2 mg/kg) during circumflex coronary occlusion in nine anesthetized, open-chest dogs. We measured systolic wall thickening on both sides of the perfusion boundary, which was delineated with myocardial blood flow (microsphere) maps constructed from small tissue samples. By fitting sigmoid curves to the composite systolic wall thickening data after coronary occlusion, we modeled the distribution of functional impairment across the perfusion boundary. Defined as the distance from the perfusion boundary to 97.5% of the nonischemic asymptote of the sigmoid fits, the functional border zone was 31° of circumference after coronary occlusion alone. Isoproterenol increased +dP/dt by 58% and augmented nonischemic systolic wall thickening without changing the lateral extent of the functional border zone (32°). Propranolol reduced +dP/dt by 24% and depressed nonischemic systolic wall thickening, but the size of the functional border zone remained limited to 28°. Within the functional border zone, wall thickening was significantly but only moderately reduced (−28%) compared with thickening in nonischemic myocardium more than 10 mm away from the perfusion boundary. The ratio of nonischemic border zone to central nonischemic area wall thickening remained the same with each intervention. We conclude that the dimensions of the functional border zone are fixed early after coronary occlusion and that inotropic interventions do not modify the extent or relative severity of nonischemic regional dysfunction. (*Circulation Research* 1987;61:166–180)

In recent studies from this laboratory and others, it has been demonstrated that the area rendered dysfunctional by acute coronary occlusion is larger than the size of the ischemic area. Identified as the functional border zone, nonischemic myocardium exhibiting reduced systolic wall thickening extends approximately 25–30° of circumference from the ischemic-nonischemic interface into normal muscle. Although the precise mechanism of nonischemic dysfunction remains uncertain, accurate characterization of the phenomenon may prove important for evaluation of infarct size with clinically applicable techniques (such as two-dimensional echocardiography or radionuclide ventriculography).

Because positive and negative inotropic agents are frequently used in the setting of myocardial infarction, whether such agents modify the size of the dysfunctional area constitutes a potentially important clinical issue. We hypothesized that increasing or decreasing contractility was unlikely to change the size of the region at risk. Altering contractility, however, could influence the characteristics of the functional border zone by changing the degree of interaction between ischemic and nonischemic myocardium. Therefore, the objective of the present study was to determine the effect of increased and decreased contractility on the lateral extent and relative severity of nonischemic dysfunction during acute coronary occlusion.

Regional myocardial function was measured with sonomicrometers arrayed to measure wall thickness on both sides of the perfusion boundary produced by occlusion of the circumflex coronary. The position of the perfusion boundary and locations of the wall thickness measurements were delineated by constructing circumferential perfusion maps from microsphere determinations of myocardial blood flow. The effect of changes in contractility on the distribution of functional impairment across the perfusion boundary was evaluated by fitting sigmoid curves to the wall thickening data during occlusion and occlusion with isoproterenol infusion or propranolol administration.
Materials and Methods

Experimental Preparation

The study was performed in 9 open-chest dogs anesthetized with halothane (end-tidal concentrations, 0.5–0.7%) and artificially ventilated using techniques described previously. Briefly, 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 carotid artery and aorta for measurement of left ventricular coronary artery to produce total coronary occlusion (control) area perfused by the left anterior descending artery. A second pair was placed in the central nonischemic (or control) area perfused by the left circumflex artery, and the other pair was on either side of the 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. Two remaining pairs were on either side of the estimated position of the perfusion boundary produced by occluding the circumflex artery. As a guide to estimate the position of the perfusion boundary, the epicardial vascular anatomy was used. Previous experimental experience indicated that the boundary was approximately midway between the epicardial branches of the circumflex and left anterior descending arteries.1

One crystal of each wall thickness pair of sonomicrometers 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. The signals from the ultrasonic dimension gauges were processed with a Triton Model 120 sonomicrometer (San Diego, Calif.). Data were not used if crystals were improperly aligned or if inadequate sectioning of the myocardium resulted in poor delineation of the perfusion boundary. Location of the inner crystals within the subendocardial third of the myocardial wall and correct alignment of the crystals across the wall were confirmed at the time of necropsy during the careful sectioning required for tissue sample preparation to determine myocardial blood flows.3

Regional Myocardial Blood Flow Measurements

Regional myocardial blood flow was measured with tracer-labelled microspheres (1.5 μm diameter, New England Nuclear, Boston, Mass.) using the reference withdrawal method. Up to 4 injections were made in every experiment, using 1 of 6 available isotopes (141Ce, 113Sn, 31Cr, 103Ru, 99Nb, and 48Sc) 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 (9.2 ml/min) with a Harvard withdrawal pump; withdrawals were initiated prior to the injection of microspheres and were completed 2 minutes later. The reference sample counts were averaged for the calculation of myocardial flows. If the counts in the two reference samples differed by greater than 10%, the data were not used. 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 injections of potassium chloride. The heart was removed and placed in formalin to facilitate sectioning. The sonomicrometers were left in the heart to allow careful evaluation of their position in the wall at the time of heart sectioning. Sixteen to twenty full-thickness sections were obtained around complete rings of the left ventricle that were 1.5–2.0 cm in height. Each transmural block of tissue was divided into three pieces of approximately equal thickness from the endocardial to epicardial surfaces. The 10–14 samples straddling the perfusion boundary were approximately 3 mm wide at the endocardium, similar to the preparation described by Murdock et al and Hearse et al. The remaining tissue samples were 8–20 mm wide at the endocardium. 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 gamma scintillation counter (Elk Grove, Ill.). After correcting the counts in each tissue sample for background and overlapping counts with simultaneous equations, blood flow was calculated with the equation: Qm = (Cm X Qr)/Cr, where Qm is myocardial blood flow (ml/min), Cm is counts/min in tissue samples, Qr is arterial reference sample flow (ml/min), and Cr is 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. The location of the perfusion boundary was determined by the position of the flow gradient in the circumferential blood flow map as exemplified in Figure 1. This figure demonstrates two flow maps from one of the experiments included in the present study. The upper graph presents subendocardial and subepicardial blood flow during total coronary occlusion alone in a portion of the circumferential perfusion map. The lower graph shows blood flow during total coronary occlusion plus iso-
propranolol infusion. The location of wall thickening measurements are indicated in this figure with hatched bars. Although dyes were occasionally used to aid in sectioning the tissue, we relied solely on the blood flow data to delineate the location of the perfusion boundary.

When samples with intermediate blood flow values were encountered (as in Figure 1), the perfusion boundary was designated as falling between the high flow and intermediate flow samples if the intermediate level of blood flow was 40% or less than the average flow in the nonischemic area. If the intermediate sample had blood flow between 40–60% of average flow in the nonischemic area, the position of the perfusion boundary was considered to pass through the center of the sample. If the intermediate sample had blood flow that was greater than 60% of the nonischemic area average, the perfusion boundary was designated as being the left margin of the intermediate sample. Figure 1 represents an experiment in which the intermediate sample had blood flow that was 66% of average flow in the nonischemic area during coronary occlusion alone and 69% of nonischemic flow during coronary occlusion plus isoproterenol. Therefore, the perfusion boundary was designated to be at the left margin of the intermediate sample. The perfusion boundary was used as a point of reference to locate the function measurements (made with sonomicrometers). Because the true boundary is irregular rather than a straight line, our estimate of its location represents an approximation with an uncertainty of 1–2 mm at the endocardium (or 4–6° of circumference).

Experimental Protocol

Systolic wall thickening and myocardial blood flow measurements were made in 9 dogs. Six dogs were used to characterize systolic wall thickening in 4 myocardial locations around the minor axis of the left ventricle during isoproterenol (0.04–0.10 μg/kg/min) infusion prior to coronary occlusion. In so doing, we sought to determine whether there was regional variability in the response to isoproterenol infusion, which has been demonstrated to exist along the major (or long) axis of the heart.69 Dimensional and hemodynamic data were obtained during control conditions and during isoproterenol infusion in these experiments. The isoproterenol infusion was then stopped, and 30 minutes were allowed for the animals to return to baseline conditions. Control preocclusion recordings were obtained in all 9 dogs, and the first set of microspheres was injected. Then the circumflex coronary artery was abruptly occluded with the screw clamp. Once hemodynamic parameters and regional dimensions were stable (approximately 10 minutes postocclusion), a second injection of microspheres was made. In all 9 dogs, isoproterenol was intravenously infused (0.04–0.10 μg/kg/min) to increase systolic wall thickening in the nonischemic area by approximately 25%. Mild aortic constriction was used as needed to maintain peak left ventricular systolic pressure at the same level observed during coronary occlusion alone. After stabilization, a third injection of microspheres was performed. Then the isoproterenol infusion was discontinued, and the aortic constriction released. A recovery period of at least 30 minutes was allowed to ensure absence of any residual isoproterenol effects. In 7 of the 9 dogs, propranolol was administered (2 mg/kg) as a continuous intravenous infusion over 10 minutes. Complete β-blockade was verified by demonstrating that a bolus of intravenous isoproterenol (10 μg) produced no hemodynamic or dimensional effects. After establishing steady conditions, the fourth and final microsphere injection was performed. The total time from circumflex coronary occlusion to the end of the experiments in which both isoproterenol and propranolol were infused varied from approximately 60 to 90 minutes.

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
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0.05 or p<0.01 is indicated in the tables or text, it
totes and also changes monotonically between them is
asymptote, I. The function used that has these asymp-
during the microsphere injections.
The modeling function was fit to the data set from each
of the midpoint of the change between the asymptotes,
periods differed from one another. To account for
parisons were performed, the acceptable a-level was
nonischemic or control area. Because multiple com-
zone, 3) nonischemic border zone, and 4) central
perfusion boundary to 97.5% of the nonischemic
represents the corrected value.

Hemodynamic, dimension, and myocardial blood
flow data were evaluated with analysis of variance
(during control conditions, total coronary occlusion,
and total coronary occlusion with isoproterenol or
propranolol). When overall significance was detected,
paired t tests were used to discriminate which time
periods differed from one another. To account for
multiple comparisons, the acceptable minimum a-
level was adjusted to 0.017 (0.05 divided by 3, the
number of comparisons made) with the Bonferroni
inequality.17 Unpaired t tests were used to compare wall
thickness variables and blood flow data in four loca-
tions: 1) central ischemic area, 2) ischemic border
zone, 3) nonischemic border zone, and 4) central
nonischemic or control area. Because multiple com-
parisons were performed, the acceptable a-level was
adjusted with the Bonferroni inequality.17 When p<
0.05 or p<0.01 is indicated in the tables or text, it
represents the corrected value.

In addition to categorical analysis, wall thickening
data were also evaluated as a continuous function of
distance from the perfusion boundary.7 To mathemat-
ically model the distribution of wall thickening
change across the perfusion boundary, nonischemic tissue
was assumed to have a wall thickening asymptote, N, and
ischemic tissue was assumed to have a wall thinning
asymptote, I. The function used that has these asympto-
tes and also changes monotonically between them is
the following:

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

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. Applied to the distribution of wall thickening
change, the value of \( \beta \) describes the extent of the
transition from abnormal to normal regional function.
The modeling function 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 as previously described.7 The
sigmoid curve fits were used to define the lateral extent
of the functional border zone as the distance from the
perfusion boundary to 97.5% of the nonischemic

Results

Isoproterenol Infusion During Baseline Conditions
To determine if systolic wall thickening changed
uniformly in all 4 sonomicrometer locations, isopro-
terenol (0.04-0.10 \( \mu g/kg/min \)) was infused into 6
animals after control measurements had been per-
formed but before circumflex coronary occlusion.
An example of beat-averaged waveforms from one of
the experiments is shown in Figure 2 to demonstrate the
substantial augmentation in wall thickening achieved
with isoproterenol infusion and to show that the
response was similar in all four locations. During the
isoproterenol infusion, heart rate increased from 100 ±
10 to 135 ± 7 bpm (\( p<0.01 \)). Left ventricular peak
systolic pressure did not change significantly (from 123
± 11 to 123 ± 7 mm Hg) but left ventricular end-
systolic pressure decreased from 6.4 ± 2.4 to 4.5 ±
2.6 mm Hg (\( p<0.01 \)). The isoproterenol infusion

Figure 2. Examples of beat-averaged waveforms of wall
thickness during control (C) conditions and isoproterenol (ISO,
0.10 \( \mu g/kg/min \)) infusion before coronary occlusion was
produced. Tracings represent average waveforms from ten digitized
cardiac cycles in four locations. Percentls represent wall
thickening expressed as percent of end-diastolic wall thickness.
Each panel is identified by category wall thickness measurement
represented after coronary occlusion. Ischemic wall thickness
(IS WT) was located in posterior wall; ischemic border zone (IS
BZ WT) and nonischemic border zone (NIS BZ WT) wall
thickneses were located in lateral wall near junction between
left anterior descending and circumflex supplied myocardium;
nonischemic wall thickness (NIS WT) was located in anterior
wall. Wall thickening increased markedly, and relative changes
were similar in all four locations, demonstrating that there was
no regional variability in response to isoproterenol infusion in
circumferential plane of left ventricle sampled by sonomic-
eters. ED, end-diastole; ES, end-systole.
increased +dP/dt from 2,328 ± 138 to 3,820 ± 508 mm Hg/sec (p < 0.01).

End-diastolic wall thickness tended to increase during isoproterenol infusion, but a significant difference was not demonstrated. A marked increase in end-systolic wall thickness was consistently observed and accounted for the approximately 30% (p < 0.01) increase in wall thickening that was observed on the average in the four locations: 2.95 ± 0.72 to 4.12 ± 0.88 mm in the ischemic area or posterior wall, 2.55 ± 0.72 to 3.39 ± 0.59 mm in the ischemic border zone or lateral wall, 2.30 ± 0.43 to 3.06 ± 0.52 mm in the nonischemic border zone or lateral wall, and 3.14 ± 0.79 to 4.04 ± 0.76 mm in the nonischemic area or anterior wall. There were no significant differences in systolic wall thickening when the individual zones around the minor axis of the left ventricle were compared with each other during control conditions or with the infusion of isoproterenol, in contrast to the significant regional differences documented to exist along the major (long) axis of the heart. Therefore, differences among the wall thickening location categories during coronary occlusion with isoproterenol infusion could not be attributed to regional variability.

Hemodynamics and Blood Flow During Coronary Occlusion

Heart rate did not change significantly during circumflex coronary occlusion alone (from 102 ± 15 to 110 ± 18 bpm), but it increased significantly to 147 ± 16 bpm (n = 9, p < 0.01) during isoproterenol infusion when compared with coronary occlusion alone and decreased from 115 ± 17 to 104 ± 16 bpm (n = 7, p < 0.05) after propranolol administration. Aortic constriction was used to minimize the potential consequences of change in afterload, therefore peak systolic left ventricular pressure after coronary occlusion was not significantly changed with the addition of isoproterenol infusion (from 108 ± 18 to 120 ± 10 mm Hg) or propranolol (from 112 ± 15 to 105 ± 13 mm Hg).

Peak +dP/dt increased from 1,898 ± 326 mm Hg/sec during coronary occlusion alone to 3,148 ± 610 mm Hg/sec with the infusion of isoproterenol (n = 9, p < 0.01), demonstrating that we had successfully augmented contractility. Coronary occlusion with propranolol decreased peak +dP/dt from 1,925 ± 310 to 1,469 ± 292 mm Hg/sec (n = 7, p < 0.05) when compared with coronary occlusion alone, documenting that contractility was reduced.

Myocardial blood flow data are summarized in Table 1. Myocardial Blood Flow (ml/min/g) in 4 Zones During Control Conditions, Circumflex Coronary Occlusion, and Occlusion With Isoproterenol Infusion (n = 9)

<table>
<thead>
<tr>
<th>Zone</th>
<th>Control</th>
<th>Isoproterenol Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.06 ± 0.28</td>
<td>0.96 ± 0.28 NS</td>
</tr>
<tr>
<td>TCO</td>
<td>0.03 ± 0.03</td>
<td>0.13 ± 0.13 NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TCO + ISO</td>
<td>0.03 ± 0.04</td>
<td>0.14 ± 0.19 NS</td>
</tr>
<tr>
<td>Nonischemic border zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.01 ± 0.27</td>
<td>0.87 ± 0.27 NS</td>
</tr>
<tr>
<td>TCO</td>
<td>0.05 ± 0.05</td>
<td>0.16 ± 0.14 NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TCO + ISO</td>
<td>0.07 ± 0.07</td>
<td>0.13 ± 0.20 NS</td>
</tr>
<tr>
<td>Nonischemic area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.00 ± 0.33</td>
<td>1.04 ± 0.34 NS</td>
</tr>
<tr>
<td>TCO</td>
<td>0.11 ± 0.11</td>
<td>0.25 ± 0.22 NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TCO + ISO</td>
<td>0.11 ± 0.10</td>
<td>0.27 ± 0.26 NS</td>
</tr>
</tbody>
</table>

ENDO, subendocardial; MID, midmyocardial; EPI, subepicardial; C, control; TCO, total coronary occlusion; TCO + ISO, total coronary occlusion with isoproterenol; p, probability of difference between groups; *p < 0.05.

Data reported as mean ± SD.
Tables 1 and 2. To more clearly present the results, data from the 9 experiments in which isoproterenol was infused are organized separately (Table 1) from the seven experiments in which we also administered propranolol (Table 2). During control conditions, blood flow was not significantly different in the four locations. After coronary occlusion, perfusion was markedly reduced in the central ischemic area. Blood flow in the ischemic border zone samples was not significantly different from that in the central ischemic area. Likewise, there were no significant differences between blood flow in the tissue samples containing nonischemic border zone wall thickness gauges and those containing central nonischemic (or control) gauges. An example of perfusion boundary delineation is shown in Figure 1, which demonstrates that the ischemic-nonischemic interface was relatively abrupt and that its position was not changed even when blood flow was greatly augmented with isoproterenol infusion. In the cross-sectional rings of the left ventricle containing the sonomicrometers, the size of the ischemic area averaged 151 ± 13° (range, 129°-174°) or 42 ± 4% of circumference.

With the addition of isoproterenol or propranolol to coronary occlusion, no significant changes in ischemic zone perfusion were observed (Tables 1 and 2). During isoproterenol infusion, blood flow was significantly augmented in the nonischemic border zone and central nonischemic area by an average of approximately 50% (Table 1). With the addition of propranolol, however, perfusion decreased in the nonischemic border zone and nonischemic area by approximately 20% (Table 2). The blood flow changes in the two nonischemic locations during coronary occlusion, coronary occlusion plus isoproterenol, and coronary occlusion plus propranolol were not significantly different from one another, demonstrating that the nonischemic border zone wall thickness gauges had been located successfully in normally perfused tissue adjacent to the perfusion boundary. The steepness of the perfusion gradient increased with isoproterenol and decreased with propranolol, but the location of the interface between ischemic and nonischemic tissue remained the same.

### Wall Thickness Data During Coronary Occlusion

These data are summarized in Tables 3 and 4. The dimensional data are organized (like the blood flow data) with separate tables for the 9 experiments with isoproterenol infusion (Table 3) and the 7 experiments in which propranolol was also given (Table 4). Examples of analog recordings from one of the experiments in which both isoproterenol and propranolol were administered are shown in Figure 3. Beat-averaged waveforms from the four sonomicrometer locations of a different experiment are shown in Figures 4 and 5 to

### Table 2. Myocardial Blood Flow (ml/min/g) in 4 Zones During Control Conditions, Circumflex Coronary Occlusion, and Occlusion With Propranolol (n = 7)

<table>
<thead>
<tr>
<th></th>
<th>Ischemic area</th>
<th>p</th>
<th>Ischemic border zone</th>
<th>p</th>
<th>Nonischemic border zone</th>
<th>p</th>
<th>Nonischemic area</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDO</td>
<td>C</td>
<td>1.13 ± 0.27</td>
<td>NS</td>
<td>1.03 ± 0.30</td>
<td>NS</td>
<td>1.11 ± 0.40</td>
<td>NS</td>
<td>0.98 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>TCO</td>
<td>0.04 ± 0.04†</td>
<td>&lt;0.01</td>
<td>0.15 ± 0.15†</td>
<td>&lt;0.01</td>
<td>1.10 ± 0.34</td>
<td>NS</td>
<td>1.09 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>TCO + PROP</td>
<td>0.03 ± 0.04†</td>
<td>&lt;0.01</td>
<td>0.12 ± 0.12†</td>
<td>&lt;0.01</td>
<td>0.84 ± 0.26</td>
<td>NS</td>
<td>0.84 ± 0.26</td>
</tr>
<tr>
<td>MID</td>
<td>C</td>
<td>1.05 ± 0.26</td>
<td>NS</td>
<td>0.91 ± 0.29</td>
<td>NS</td>
<td>0.90 ± 0.22</td>
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<td>0.89 ± 0.25</td>
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<tr>
<td></td>
<td>TCO</td>
<td>0.07 ± 0.06†</td>
<td>&lt;0.01</td>
<td>0.20 ± 0.20†</td>
<td>&lt;0.01</td>
<td>0.87 ± 0.29</td>
<td>NS</td>
<td>1.00 ± 0.35</td>
</tr>
<tr>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>TCO + PROP</td>
<td>0.06 ± 0.06†</td>
<td>&lt;0.01</td>
<td>0.17 ± 0.17†</td>
<td>&lt;0.01</td>
<td>0.73 ± 0.21</td>
<td>NS</td>
<td>0.82 ± 0.15</td>
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<tr>
<td>EPI</td>
<td>C</td>
<td>1.02 ± 0.34</td>
<td>NS</td>
<td>1.02 ± 0.32</td>
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<td>0.91 ± 0.24</td>
<td>NS</td>
<td>0.95 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>TCO</td>
<td>0.13 ± 0.12†</td>
<td>&lt;0.01</td>
<td>0.29 ± 0.23†</td>
<td>&lt;0.01</td>
<td>0.90 ± 0.21</td>
<td>NS</td>
<td>0.99 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>TCO + PROP</td>
<td>0.17 ± 0.16†</td>
<td>&lt;0.01</td>
<td>0.33 ± 0.20†</td>
<td>&lt;0.01</td>
<td>0.69 ± 0.16</td>
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<td>0.70 ± 0.17</td>
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<tr>
<td>MEAN</td>
<td>C</td>
<td>1.06 ± 0.28</td>
<td>NS</td>
<td>0.99 ± 0.27</td>
<td>NS</td>
<td>0.97 ± 0.27</td>
<td>NS</td>
<td>0.94 ± 0.22</td>
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<tr>
<td></td>
<td>TCO</td>
<td>0.08 ± 0.07†</td>
<td>&lt;0.01</td>
<td>0.21 ± 0.19†</td>
<td>&lt;0.01</td>
<td>0.96 ± 0.26</td>
<td>NS</td>
<td>1.02 ± 0.28</td>
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<td></td>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>TCO + PROP</td>
<td>0.09 ± 0.09†</td>
<td>&lt;0.01</td>
<td>0.21 ± 0.16†</td>
<td>&lt;0.01</td>
<td>0.76 ± 0.20</td>
<td>NS</td>
<td>0.79 ± 0.16</td>
</tr>
</tbody>
</table>

ENDO, subendocardial; MID, midmyocardial; EPI, subepicardial; C, control; TCO, total coronary occlusion; TCO + PROP, total coronary occlusion with propranolol; p, probability of difference between groups; †p < 0.01, compared with control values.

Data reported as mean ± SD.
demonstrate in greater detail the changes in wall thickening during control conditions, after coronary occlusion, occlusion with isoproterenol infusion, and occlusion with propranolol.

During control conditions, there were no significant differences in wall thickness measurements among the four locations (Tables 3 and 4). After circumflex coronary occlusion, end-diastolic wall thickness decreased in all four locations. The average distances from the perfusion boundary of the wall thickening measurements in the four location categories were 67 ± 20° or 20 ± 6 mm of endocardial circumference (central ischemic area), 18 ± 5° or 5 ± 1 mm (nonischemic border zone), and 58 ± 14° or 17 ± 4 mm (central nonischemic or control area). In the ischemic area and ischemic border zone, wall thickening was replaced by wall thinning or akinesia during systole, consistent with the intense ischemia produced in the circumflex-supplied myocardium. Adjacent to the perfusion boundary, nonischemic border zone wall thickening tended to decrease but was not significantly different on the average after coronary occlusion when compared with control conditions (Tables 3 and 4). Likewise, there were no significant changes in percent thickening or mean ejection phase velocity of thickening. At a greater distance from the perfusion boundary, however, systolic wall thickening in the central nonischemic area increased by approximately 20% during coronary occlusion (Tables 3 and 4).

The infusion of isoproterenol during coronary occlusion did not significantly change end-diastolic wall thickness when compared with coronary occlusion alone (Table 3). End-systolic wall thickness in the nonischemic myocardium increased significantly, accounting for the 33% increase in nonischemic border zone thickening and 31% increase in nonischemic area thickening. In the circumflex-supplied myocardium, no significant changes in wall thinning were observed with isoproterenol infusion. Figures 3 and 4 demonstrate in greater detail the changes in wall thickening during control conditions, after coronary occlusion, occlusion with isoproterenol infusion, and occlusion with propranolol.

### Table 3. Transmural Wall Thickness Data in 4 Myocardial Zones During Control Conditions, Circumflex Coronary Occlusion, and Occlusion With Isoproterenol Infusion

<table>
<thead>
<tr>
<th></th>
<th>Ischemic area (n = 9)</th>
<th>Ischemic border zone (n = 8)</th>
<th>Nonischemic border zone (n = 9)</th>
<th>Nonischemic area (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EDWT (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>11.12 ± 2.00</td>
<td>11.18 ± 1.37</td>
<td>11.13 ± 1.17</td>
<td>12.19 ± 2.56</td>
</tr>
<tr>
<td>TCO</td>
<td>9.98 ± 2.05†</td>
<td>10.04 ± 1.47†</td>
<td>10.45 ± 1.07†</td>
<td>11.43 ± 2.36†</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TCO + ISO</td>
<td>10.01 ± 2.15†</td>
<td>10.20 ± 1.63†</td>
<td>10.60 ± 1.18*</td>
<td>11.68 ± 2.46</td>
</tr>
<tr>
<td><strong>ESWT (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>13.93 ± 2.24</td>
<td>13.61 ± 1.74</td>
<td>13.44 ± 1.40</td>
<td>15.41 ± 3.21</td>
</tr>
<tr>
<td>TCO</td>
<td>9.36 ± 2.03†</td>
<td>9.81 ± 1.61†</td>
<td>12.37 ± 1.28†</td>
<td>15.09 ± 2.97</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TCO + ISO</td>
<td>9.43 ± 2.11†</td>
<td>10.18 ± 1.79†</td>
<td>13.09 ± 1.43</td>
<td>16.43 ± 3.24†</td>
</tr>
<tr>
<td><strong>dWT (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2.81 ± 0.81</td>
<td>2.42 ± 0.74</td>
<td>2.31 ± 0.51</td>
<td>3.23 ± 1.03</td>
</tr>
<tr>
<td>TCO</td>
<td>−0.61 ± 0.40†</td>
<td>−0.19 ± 0.44†</td>
<td>1.92 ± 0.64</td>
<td>3.66 ± 0.99†</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TCO + ISO</td>
<td>−0.58 ± 0.42†</td>
<td>−0.01 ± 0.61†</td>
<td>2.49 ± 0.81</td>
<td>4.75 ± 1.21†</td>
</tr>
<tr>
<td><strong>9dWT</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>25.8 ± 7.3</td>
<td>21.7 ± 6.1</td>
<td>20.8 ± 4.3</td>
<td>26.9 ± 8.1</td>
</tr>
<tr>
<td>TCO</td>
<td>−6.3 ± 4.2†</td>
<td>−2.4 ± 4.4†</td>
<td>18.5 ± 6.5</td>
<td>32.6 ± 8.7†</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TCO + ISO</td>
<td>−6.0 ± 4.4†</td>
<td>−0.2 ± 6.0†</td>
<td>23.8 ± 8.4</td>
<td>40.3 ± 12.5†</td>
</tr>
<tr>
<td><strong>MEP dW/dt</strong> (mm/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>14.2 ± 4.9</td>
<td>10.6 ± 2.8</td>
<td>9.5 ± 3.1</td>
<td>13.3 ± 4.9</td>
</tr>
<tr>
<td>TCO</td>
<td>−0.1 ± 0.9†</td>
<td>1.0 ± 1.8†</td>
<td>7.9 ± 2.5</td>
<td>13.9 ± 4.2</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TCO + ISO</td>
<td>0.8 ± 1.5†</td>
<td>3.4 ± 3.5†</td>
<td>13.5 ± 4.8†</td>
<td>23.0 ± 6.7†</td>
</tr>
</tbody>
</table>

C, control; TCO, total coronary occlusion; TCO + ISO, total coronary occlusion with isoproterenol infusion; EDWT, end-diastolic wall thickness; ESWT, end-systolic wall thickness; dWT, ESWT – EDWT; 9dWT, (dWT/EDWT) x 100; MEP dW/dt, mean ejection phase velocity of thickening; p, probability of difference between groups; *p<0.05, †p<0.01, compared with control values.

Data reported as mean ± SD.
strate replacement of systolic wall thickening by thinning in the central ischemic area after coronary occlusion. Similar effects are evident in the ischemic border zone in Figure 3. In the experiment shown in Figure 4, the ischemic border zone sonomicrometers were located at the perfusion boundary, and limited active wall thickening was observed with isoproterenol infusion. Both pairs of nonischemic crystals (right panels, Figure 4) demonstrate well-maintained thickening after coronary occlusion alone and dramatic increases of thickening during isoproterenol infusion. The relative increases in wall thickening were not significantly different between the nonischemic border zone and central nonischemic area as shown in Figure 6.

Propranolol did not significantly change end-dias-
stolic or end-systolic wall thickness when compared with coronary occlusion alone in the central ischemic area and ischemic border zone (Figures 3 and 5 and Table 4). As shown in Figure 5, wall thickening was conspicuously reduced in the nonischemic myocardium (right panels). On the average, wall thickening decreased significantly by 22% in the nonischemic border zone and by 20% in the central nonischemic area. The relative reductions in nonischemic systolic wall thickening produced by propranolol administration were not significantly different (Figure 6).

Wall thickening data during coronary occlusion from four of the experiments are plotted as a function of distance (in degrees) from the perfusion boundary in Figure 7. Regional function is plotted on the y axis as a decimal fraction of control condition wall thickening. Each data point corresponds to one wall thickness measurement, and its position relative to the x axis corresponds to the distance of the measurement (in degrees) from the perfusion boundary, which is designated as zero. Positive numbers (right of the perfusion boundary) indicate nonischemic myocardium, and negative numbers indicate ischemic myocardium. The sigmoid curves in Figure 7 show the distribution of

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Table 4. Transmural Wall Thickness Data in 4 Myocardial Zones During Control Conditions, Circumflex Coronary Occlusion, and Occlusion With Propranolol

<table>
<thead>
<tr>
<th></th>
<th>Ischemic area (n = 7)</th>
<th>Ischemic border zone (n = 6)</th>
<th>Nonischemic border zone (n = 7)</th>
<th>Nonischemic area (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>TCO</td>
<td>TCO + PROP</td>
<td></td>
</tr>
<tr>
<td>EDWT (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>11.70 ± 1.87</td>
<td>10.42 ± 2.13†</td>
<td>10.49 ± 2.34*</td>
<td></td>
</tr>
<tr>
<td>TCO</td>
<td>11.58 ± 1.01</td>
<td>10.41 ± 1.21†</td>
<td>10.53 ± 1.22†</td>
<td>NS</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TCO + PROP</td>
<td>10.55 ± 1.27†</td>
<td>NS</td>
<td>11.42 ± 1.27†</td>
<td>NS</td>
</tr>
<tr>
<td>ESWT (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>14.55 ± 2.17</td>
<td>9.79 ± 2.11†</td>
<td>10.21 ± 2.37†</td>
<td></td>
</tr>
<tr>
<td>TCO</td>
<td>13.92 ± 1.14</td>
<td>10.17 ± 1.41†</td>
<td>10.36 ± 1.33†</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TCO + PROP</td>
<td>10.36 ± 1.33†</td>
<td>NS</td>
<td>11.91 ± 1.48†</td>
<td>NS</td>
</tr>
<tr>
<td>dWT (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2.85 ± 0.92</td>
<td>-0.63 ± 0.45†</td>
<td>-0.28 ± 0.38†</td>
<td></td>
</tr>
<tr>
<td>TCO</td>
<td>2.34 ± 0.55</td>
<td>-0.24 ± 0.51†</td>
<td>-0.19 ± 0.39†</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>TCO + PROP</td>
<td>1.85 ± 0.72</td>
<td>1.49 ± 0.69*</td>
<td>2.82 ± 1.09</td>
<td></td>
</tr>
<tr>
<td>%dWT</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>C</td>
<td>24.6 ± 7.6</td>
<td>-6.2 ± 4.7†</td>
<td>-2.9 ± 4.0†</td>
<td></td>
</tr>
<tr>
<td>TCO</td>
<td>20.4 ± 5.1</td>
<td>-2.4 ± 5.1†</td>
<td>-1.8 ± 3.9†</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>TCO + PROP</td>
<td>19.7 ± 7.3</td>
<td>17.8 ± 7.3</td>
<td>14.5 ± 7.0</td>
<td>23.9 ± 5.4</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 ± 5.5</td>
<td>-0.2 ± 1.0†</td>
<td>0.1 ± 0.9†</td>
<td></td>
</tr>
<tr>
<td>TCO</td>
<td>10.0 ± 2.0</td>
<td>0.9 ± 2.1†</td>
<td>0.5 ± 2.0†</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>TCO + PROP</td>
<td>9.6 ± 3.5</td>
<td>8.2 ± 2.8</td>
<td>6.4 ± 2.8†</td>
<td>NS</td>
</tr>
</tbody>
</table>

C, control; TCO, total coronary occlusion; TCO + PROP, total coronary occlusion with propranolol; 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; p, probability of difference between groups; *p < 0.05, <0.01, compared with control values.

Data reported as mean ± SD.
functional impairment across the perfusion boundary during coronary occlusion alone, occlusion plus isoproterenol, and occlusion plus propranolol. The lateral extent of dysfunction was defined conservatively as the distance from the perfusion boundary to 97.5% of the nonischemic asymptote (i.e., μ + 2σ). During isoproterenol infusion, the nonischemic asymptotes increased in each experiment, but the lateral extents of dysfunction were minimally altered. Propranolol, on the other hand, reduced the nonischemic asymptotes but also did so without markedly affecting the lateral extent of the functional border zone.

Composite sigmoid curves and data from all of the experiments are presented in Figure 8. As shown in the lower right panel, the lateral extent of dysfunction (or functional border zone) in the composite fit was 31° (approximately 7–10 mm of endocardial circumference) during coronary occlusion alone. The average value derived from the individual sigmoid fits was 35 ± 22°. During isoproterenol infusion, the position of the ischemic asymptote was not changed, but the nonischemic asymptote increased from 1.12 to 1.43 in the composite fit (Figure 8), consistent with the significant increase in nonischemic area wall thickening shown in the categorical analysis (Table 3). Individual values increased from 1.22 ± 0.26 to 1.58 ± 0.35 (p<0.01). The lateral extent of nonischemic dysfunction, however, did not change during isoproterenol infusion. The composite fit value was 32°, and the mean value from individual experiments (38 ± 19°) did not differ from coronary occlusion alone.

Propranolol administration did not change the ischemic asymptote but reduced the nonischemic asymptote value from 1.12 to 0.86 in the composite fit (individual values, from 1.24 ± 0.28 to 0.92 ± 0.24, p<0.01). Similar to the effect of augmented contractility, decreased contractility due to propranolol administration produced no change in the size of the functional border zone. In the composite fit, the lateral extent of nonischemic dysfunction decreased slightly from 31 to 28°. Individual values decreased from 37 ± 25 to 25 ± 23°, but the change was not statistically significant. Thus, increases and decreases in contractility substantially modified wall thickening in the nonischemic myocardium, but there was little effect on the size of the functional border zone (Figure 8).

Discussion

Isoproterenol, propranolol, and other agents capable of changing contractility are used frequently in the setting of acute myocardial ischemia. Because the size of the dysfunctional zone exceeds the size of the ischemic dysfunction, however, did not change during isoproterenol infusion. The composite fit value was 32°, and the mean value from individual experiments (38 ± 19°) did not differ from coronary occlusion alone.

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Inotropic Agents and the Functional Border Zone

Figure 4. Beat-averaged waveforms of wall thickness (WT) during control (C) conditions, total coronary occlusion (TCO), and total coronary occlusion plus isoproterenol (TCO + ISO). Tracings represent average waveforms from ten digitized cardiac cycles in four location categories described in text. ○, end-diastole (ED); □, end-systole (ES). Salient features of figure are 1) drastic reductions in wall thickening produced in central ischemic (IS) area and ischemic border zone (IS BZ) by coronary occlusion; 2) small increases in wall thickening evident in nonischemic border zone (N/S BZ) and central nonischemic (NIS) area during coronary occlusion; and 3) substantial augmentation of thickening in nonischemic gauges (right panels), while dyskinesia was sustained in central ischemic area during isoproterenol infusion. IS BZ gauges were located at perfusion boundary in this example and exhibited increase in thickening during isoproterenol infusion, which we interpret to reflect influence of augmented contractility in nonischemic muscle adjacent to ischemic-nonischemic interface.

Another potential source of error is the use of sigmoid curves to model the distribution of wall thickening impairment because the type of curve fit that is used will influence the derived estimates of lateral nonischemic dysfunction. A sigmoid curve probably oversimplifies the relation between location and contractile performance during coronary occlusion, but the quality of the individual and composite fits (Figures 7 and 8) suggest that a sigmoid curve provides a reasonable approximation. In addition, the nonischemic asymptote of the sigmoid curve fits is dictated primarily by the wall thickening measurements located the farthest distance from the perfusion boundary (nonischemic area category). The assumption was made that they were representative of remote nonischemic function. Because we did not sample wall thickening throughout the entire nonischemic area, however, it is possible that what we described as an asymptote may have a significant slope. Consequently, we must acknowledge that our estimates of lateral nonischemic dysfunction may be limited by how well the nonischemic area measurements reflect wall thickening remote from the perfusion boundary.

Our first objective was to establish whether changes in contractility altered the lateral extent of nonischemic dysfunction. Accordingly, changes in wall thickening were plotted as a continuous function of distance from the perfusion boundary to determine the distribution of functional impairment across the junction between ischemic and nonischemic myocardium (Figures 7 and...
8) with and without inotropic interventions. By applying sigmoid curve fits to the wall thickening data, the disadvantage of using limited numbers of sonomicroimeters to sample regional function could be minimized. Defined as the distance from the perfusion boundary to 97.5% of the nonischemic asymptote of the sigmoid curve, the functional border zone extended 32° (composite fit, Figure 8) into nonischemic myocardium during coronary occlusion alone, similar to our earlier findings and those of other investigators. Iso-
proterenol and propranolol were administered during coronary occlusion to produce changes in contractility that were primarily evident in the nonischemic area.

Despite producing significant changes in nonischemic perfusion (Tables 1 and 2) and wall thickening (Tables 3 and 4), neither agent altered the size of the functional border zone. Therefore, we conclude that the lateral extent of nonischemic dysfunction is not affected by changes in contractility. Supporting this conclusion are preliminary results obtained in conscious dogs using similar methods for evaluating the functional border zone. Coronary occlusion in awake dogs is characterized by reflex increases in sympathetic tone, which should have affected the nonischemic area in a manner similar to the isoproterenol infusion (with supported aortic pressure) that we used in the present study. Nonischemic dysfunction rapidly recovered to control levels across 30° of circumference, in close agreement with the results summarized in Figure 8.

Isoproterenol and propranolol affected contractile performance in the ischemic areas minimally when compared with coronary occlusion alone, while wall thickening in the nonischemic areas was substantially altered (Tables 3 and 4). Although the absolute levels of thickening were less in the nonischemic border zone than in the central nonischemic area, the relative increases and decreases in thickening produced by isoproterenol and propranolol were comparable in both locations. Normalized as shown in Figure 6, nonischemic border zone wall thickening averaged the same percent of central nonischemic wall thickening as during coronary occlusion alone when isoproterenol was infused (72%) and nearly the same percent (74%) after propranolol administration. This finding indicates that the degree of wall thickening reduction adjacent to the perfusion boundary was the same with or without inotropic interventions. Consequently, we conclude that the relative severity of functional impairment, like the lateral extent of nonischemic dysfunction, cannot be modified by changing contractility. Similar results were obtained in anesthetized dogs in which aortic constriction during circumflex coronary occlusion was used to modify regional function in nonischemic myocardium. Elevated afterload substantially reduced wall thickening in the nonischemic area, but the ratio of nonischemic border zone to central nonischemic thickening changed minimally from 72 to 69%, and the lateral extent of the functional border zone was not changed significantly.

It is important to note, however, that nonischemic wall thickening (even in close proximity to the perfusion boundary) could be manipulated successfully with isoproterenol and propranolol. A recent preliminary report by Rapien et al supports this finding. They studied regional function in anesthetized pigs, instrumented with subepicardial sonomicrometers aligned to measure segment shortening parallel to the ischemic myocardium similar to the preparation described by Sakai et al. Three millimeters from the perfusion boundary, dL/dt increased from 5.6 ± 1.9 mm/sec during coronary occlusion alone to 11.8 ± 4.6 mm/sec with the addition of dobutamine infusion. In similar fashion, dL/dt 10 mm from the perfusion boundary increased from 5.9 ± 2.7 to 12.2 ± 2.0 mm/sec. Comparable results were obtained with isoproterenol infusion. In agreement with our findings, the authors concluded that inotropic agents can enhance myocardial contractility in normally perfused but functionally impaired myocardium adjacent to an area of acute ischemia.

A preliminary report by Buda et al also supports this conclusion. They demonstrated increased systolic wall thickening (measured with two-dimensional echo-
FIGURE 7. Individual examples of sigmoid curves fitted to wall-thickening data during total coronary occlusion (TCO), total coronary occlusion plus isoproterenol (TCO + ISO) infusion, and total coronary occlusion plus propranolol (TCO + PROP) administration from four experiments. Wall thickening (dWT) is expressed on y axis as decimal fraction of control condition values. Distance on x axis is in degrees with the position of perfusion boundary (PB) designated as zero. Positive numbers are on nonischemic side of PB; negative numbers are on ischemic side. Upper panels show data from experiments representative of average results. Lower panels demonstrate more extreme examples. Data and curves in Panel 1 are from same experiment shown in Figure 3. Data and curves in Panel 4 are from same experiment shown in Figures 4 and 5.

cardiography) during dobutamine infusion in the border zone and adjacent nonischemic myocardium. In contrast with our results, however, Buda et al interpreted their data to indicate that dobutamine infusion decreased the size of the functional border zone. The apparent discrepancy with our conclusion is probably related to differences in how the functional data were analyzed. They evaluated the functional border zone and zone adjacent to the functional border zone by comparing postocclusion data with systolic wall thickening during baseline conditions prior to coronary occlusion. When dobutamine was infused, however, myocardium close to the perfusion boundary was characterized by augmented thickening that equaled or exceeded preocclusion control values, although this zone did not contract as vigorously as myocardium in the central nonischemic area 2–3 cm from the perfusion boundary. Therefore, the size of the functional border zone, referenced to baseline condition values, appeared to decrease. Because we defined the extent of nonischemic dysfunction by referencing it to thickening values in the central nonischemic area during each intervention rather than baseline conditions, no change in the functional border zone was apparent.

Lima et al. also measured wall thickening with two-dimensional echocardiography in anesthetized dogs. In contrast with our results and those of Sakai et al. and Buda et al., dysfunction extended to regions relatively distant from the ischemic border during circumflex artery occlusion. Although Lima et al. observed an abrupt perfusion boundary, the functional border zone extended over 25 mm rather than 10 mm (or less). They also reported an increase in nonischemic border zone systolic wall thickening with propranolol, which markedly differs from our findings (Table 4 and Figure 8).

We observed no augmentation of thickening in the nonischemic border zone with propranolol administration but, rather, a decrease. Systolic wall thickening in this zone was proportional to thickening in nonische-
mic myocardium farther from the perfusion boundary during coronary occlusion and with both inotropic interventions (Figure 6). We are at a loss to explain the discrepancy, especially since the very low dose of propranolol (0.1 mg/kg) used by Lima et al\(^3\) may not have achieved complete \(\beta\)-blockade. Different methodologies for measuring wall thickening and defining the position of the perfusion boundary may account for the difference although it is notable that Buda et al\(^9,34\) and Force et al\(^6\) who also used two-dimensional echocardiography to examine the functional border zone, obtained results similar to ours.

Bogen et al\(^33\) proposed a mathematical model that may explain the mechanism of lateral nonischemic dysfunction. They calculated the degree of stress concentration at the interface between infarcted and noninfarcted myocardium based on modeling of the left ventricle as a sphere. Stress concentration was maximal immediately adjacent to the interface, which is consistent with the substantial dysfunction we observed at or within a few degrees of the perfusion boundary (Figures 7 and 8). From the interface between normal and infarcted tissue, Bogen et al\(^35\) predicted logarithmic recovery of normal function that is completed over approximately 45\(^\circ\) of circumference or less, which is in reasonable agreement with our findings. Bogen et al\(^36\) also explored the theoretic impact of inotropic changes on ventricular function during myocardial infarction and predicted that stress concentration should be augmented when contractility of noninfarcted myocardium is elevated. One issue that Bogen et al did not address, however, was the distance over which stress concentration returns to normal levels during positive or negative inotropic stimulation. Our data suggest that the lateral extent of nonischemic myocardium with elevated stress concentration (which may correspond to the functional border zone) remains relatively constant despite significant changes in inotropic state.

**Figure 8.** Composite data sets and composite sigmoid curve fits from all experiments. \(x\) and \(y\) axes are arranged in same manner as Figure 7. Individual data points and sigmoid curves are shown during total coronary occlusion (TCO) alone, total coronary occlusion plus isoproterenol (TCO + ISO) infusion, and total coronary occlusion plus propranolol (TCO + PROP) administration. Three composite sigmoid curves are shown together in lower right panel. Values (in degrees) represent lateral extent of functional border zone (defined as \(\mu + 2 \sigma\), or distance from perfusion boundary to 97.5\% of nonischemic asymptote). Although nonischemic asymptote was shifted substantially by isoproterenol or propranolol, distance nonischemic dysfunction extended from perfusion boundary was minimally affected.
Nonischemic dysfunction has also been explained in terms of tethering,\textsuperscript{2,3} which implies that motion in nonischemic muscle is mechanically restricted by dyskinetic muscle in the adjacent ischemic area. Because stress concentration may be the result of tethering, however, we speculate that the two terms simply describe different aspects of the same phenomenon. Unfortunately, our data and those of other investigators do not allow experimental distinction between stress concentration and tethering, given that tethering is essentially an intuitive rather than a mathematically rigorous concept. Both have appeal as potential mechanisms, but additional investigation will be required to determine if there really is a difference between the two concepts.

In conclusion, our data confirm the existence of a narrow functional border zone during acute ischemia produced by circumflex coronary occlusion. Although it was possible to manipulate levels of systolic wall thickening in the functional border zone with inotropic interventions, the lateral extent and relative severity of nonischemic dysfunction were not modified by positive or negative changes in contractility. To what degree the functional border zone and its responsiveness to inotropic agents is modified by a longer ischemic period or development of a chronic infarct remains to be determined.

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References
30. Liedke AJ, Nellis SH, Whitesell LF: Effects of regional ischemia on metabolic function in adjacent aerobic myocard-
31. Prinzen FW, Prinzen TT, Arts T, Reneman RS: Gradients in epicardial shortening and transmural blood flow from ischemic towards normal left ventricular myocardium (abstract). J Mol Cell Cardiol 1985;17:225

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Changes in contractility fail to alter the size of the functional border zone in anesthetized dogs.
D H Drake, T B McClanahan, X H Ning, R A Gerren, W R Dunham and K P Gallagher

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