Dobutamine Echocardiography for Determining the Extent of Myocardial Salvage After Reperfusion
An Experimental Evaluation

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Background Although dobutamine echocardiography is being increasingly used to determine the presence of viable myocardium in patients who have undergone successful reperfusion therapy, the physiological basis for such a use has not been clearly defined. Because postischemic myocardium has contractile reserve, we hypothesized that the absolute degree of wall thickening induced by dobutamine during reflow would be directly related to the amount of myocardium that has escaped necrosis.

Methods and Results Three groups of 12 dogs each were studied at baseline and during 2 to 6 hours of coronary artery occlusion and 15 minutes of reperfusion. In group 1 dogs, which did not receive dobutamine during any of these stages, percent wall thickening at these stages was 32±6%, -2±6%, and 5±6%, respectively, and there was no relation between infarct size and percent wall thickening during reflow (r=.20, P=.51). In group 2 dogs, which received 15 μg/kg per minute of dobutamine at all stages, wall thickening at these stages was 40±8%, 0±8%, and 19±10%, respectively, and a good inverse correlation was noted between infarct size and percent wall thickening during reflow (r=-.81, P=.001). In group 3 dogs, in which wall thickening during reflow was measured both before and during infusion of 15 μg/kg per minute of dobutamine, it was 5±8% and 18±14%, respectively, at these stages. Although the correlation between infarct size and percent wall thickening was poor in the absence of dobutamine (r=.36, P=.26), an excellent inverse correlation was noted between the two in the presence of dobutamine (r=-.93, P<.001). A fair inverse correlation was also noted between infarct size and the absolute change in wall thickening induced by dobutamine (r=-.72, P<.01). Maximal wall thickening was noted at a dobutamine dose of 15 μg/kg per minute, and lower doses did not elicit thickening in the presence of larger infarcts despite the presence of viable myocardium.

Conclusions When myocardial necrosis coexists with postischemic myocardial dysfunction and no residual coronary stenosis, the absolute degree of wall thickening during dobutamine can be used to determine the extent of myocardium that has escaped necrosis. The dose of dobutamine needed to elicit maximal thickening of the postischemic myocardium is related to the amount of myocardial necrosis. (Circulation. 1994;90:1502-1512.)

Key Words • echocardiography • myocardium • reperfusion

Assessment of regional left ventricular (LV) function provides important insights in patients with coronary artery disease. For example, LV wall thickening at rest is abolished after a myocardial infarction involving a substantial portion of the myocardial thickness.1 In contrast, if the myocardium escapes necrosis as a consequence of timely reperfusion, recovery in function of the postischemic myocardium occurs, which is related to the severity and duration of myocardial ischemia.2,3

Unlike pure postischemic myocardial dysfunction without associated myocardial necrosis described in animal models,2,3 in the clinical setting—where thrombolytic therapy or mechanical intervention is used—it is rare to see postischemic myocardium without some degree of associated myocardial necrosis. Moreover, since it may take days to weeks for functional recovery of the postischemic myocardium to occur,4-6 assessment of regional LV function immediately after reperfusion does not indicate the extent of myocardial salvage that has been achieved. Since the endocardial half of the left ventricle is the major contributor toward wall thickening,7-10 regional function may not improve if a substantial portion of the endocardium is necrosed despite salvage of the remaining myocardium.1

Because postischemic myocardium has contractile reserve,2,3 we hypothesized that infusion of an inotropic agent such as dobutamine would increase thickening of the salvaged viable myocardium and that the absolute degree of thickening induced by dobutamine would be directly related to the amount of myocardium that has escaped necrosis. Our hypothesis would imply that in the presence of endocardial necrosis, the epicardial half of the myocardium—which under baseline condition does not thicken much7,8—would exhibit increased thickening in the presence of dobutamine if it has escaped necrosis. We tested this hypothesis in an open-chest canine model of coronary occlusion and reperfus-
sion where postischemic myocardial dysfunction coexisted with varying amounts of myocardial necrosis.

Methods

Three groups of 12 dogs each were studied. Regional wall thickening was assessed at baseline, during coronary artery occlusion, and after 15 minutes of reperfusion with two-dimensional echocardiography. In group 1 dogs, in which these measurements were made in the absence of dobutamine, the duration of occlusion was 2.8 ± 0.65 hours (range, 2 to 4 hours), with half the dogs receiving <3 hours of occlusion and the other half receiving 3 to 4 hours of occlusion. In group 2 dogs, in which all measurements were made in the presence of 15 μg/kg per minute of dobutamine, the duration of occlusion was 5.3 ± 1.4 hours (range, 2 to 6 hours), with only 2 dogs subjected to <3 hours of occlusion. In group 3 dogs, which did not receive dobutamine except during reflow and in which wall thickening during reflow was measured both before and during 15 μg/kg per minute of dobutamine, the duration of occlusion was 3.5 ± 0.5 hours, with 6 dogs each undergoing 3 and 4 hours of occlusion, respectively. Three group 1 and 3 group 2 dogs were also given increasing doses of dobutamine (from 5 to 20 μg/kg per minute) to determine the optimal dose needed to maximize regional wall thickening in the presence of postischemic myocardial dysfunction coexisting with varying amounts of myocardial necrosis. The protocol conformed to the American Heart Association guidelines for Animal Research Use and was approved by the Animal Research Committee at the University of Virginia.

Animal Preparation

The dogs were anesthetized with 30 mg/kg sodium pentobarbital (Abbott Laboratories), intubated, and ventilated using a respirator pump (model 607, Harvard Apparatus). Additional anesthesia was administered during the experiment as needed. A 7F catheter was placed in the right femoral artery for recording of arterial pressure and was connected to a multichannel recorder (model 4568C, Hewlett-Packard) via a fluid-filled transducer (model 1280C, Hewlett-Packard). Another 7F catheter was placed in the left femoral vein for the administration of fluids and drugs as needed.

A left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. Either the left anterior descending (LAD) or the left circumflex (LCx) coronary artery was dissected free from the surrounding tissues, and a tie with a snare was placed loosely around it. A 7F catheter was placed in the left atrium to measure pressure and to inject sonicated albumin microbubbles in group 1 and 3 dogs and technetium-99m in group 2 dogs.

Assessment of Regional Myocardial Thickening

Regional LV wall thickening was measured using two-dimensional echocardiography, which was performed with a phased array system (RTS5000, General Electric Medical Systems) and a 5-MHz transducer. A saline bath served as an acoustic interface between the heart and the transducer. Imaging was performed at the midpapillary muscle short-axis level at a depth setting of 8 cm, and the data were recorded on 1.25-mm VHS videotape using a Panasonic model AG6200 video recorder (Matsushita Electrical Co.).

The method of quantifying regional LV wall thickening has been described by us in detail elsewhere. In brief, images from videotape were transferred to the video memory of an off-line image analysis system (Mipron, Kontron Electronics) in a 244×244×8-bit matrix. A representative contraction sequence from end diastole to end systole (defined as the largest and smallest LV chamber sizes in the cardiac cycle, respectively) was identified, and all frames in the sequence were analyzed for regional wall thickening. In each frame, the junction of the right ventricular free wall and LV posterior wall was defined as the reference point, and 8 to 12 points were placed on the epicardium and endocardium, respectively, where these regions could be clearly defined. These points were automatically connected using cubic spline interpolation to define the epicardial and endocardial outlines, respectively. The observer could change portions of the outlines if they did not agree with those drawn by the computer while viewing the two-dimensional echocardiographic images and their accompanying overlays in cine-loop.

Wall thickness was measured automatically in each frame as the shortest distance between the epicardium and endocardium along 100 chords placed equidistant along the circumference of the heart, starting at the reference point. The maximal thickening or thinning of the LV wall in the entire systolic contraction sequence was then defined automatically for each chord. These values were averaged for chords present within the central 75% of the risk area. A plastic overlay defining the risk area in an end-diastolic frame was used for this purpose (see below).

Assessment of Risk Area

The risk area was measured in the group 1 and 3 dogs using myocardial contrast two-dimensional echocardiography and in the group 2 dogs using technetium autoradiography. We have previously demonstrated a close linear relation for the assessment of risk area measured by the two techniques using left atrial injections of technetium and sonicated albumin microbubbles (r = 0.92 ± 1.1, r = 0.95, P < 0.001).

In the group 1 and 3 dogs, 4 mL of 4.3 ± 0.3 μL sonicated albumin microbubbles with a concentration of 0.5 billion/mL (Molecular Biosystems Inc) was injected into the left atrium during coronary occlusion just before reperfusion. The two-dimensional echocardiographic contrast-enhanced images were reviewed on the off-line system, and the end-diastolic image with the maximal contrast effect in the nonoccluded region was selected for estimation of the risk area. The endocardial and epicardial borders in this image were hand-drawn, and the myocardial area was calculated as the difference between the epicardial and endocardial areas. The region with no contrast effect was defined and expressed as a percent of the myocardial area. It was also defined on a clear plastic overlay that was used to determine the region of the myocardium where wall thickening analysis was performed in the group 1 and 3 dogs.

In the group 2 dogs, risk area was defined using technetium autoradiography. Twenty milliliters of technetium-99m (Cardiolite, DuPont) was injected into the left atrium toward the end of the occlusion period. At the conclusion of the experiment, a short-axis slice corresponding to the plane of the two-dimensional echocardiographic image cut was from the excised heart. The slice was placed on double-emulsion x-ray film (X-Omatic AR, Eastman Kodak), which was exposed for 14 to 18 hours and developed using an automatic developer (model M35A, X-Omatic, Eastman Kodak). A back-illuminated image of the autoradiograph was captured into the off-line computer using a video camera (66 series, Dage-MTI Corp). The risk area—defined as the transmural defect on the autoradiograph—was planimetered and expressed as a percent of the myocardium in the short-axis slice. It was also drawn on a plastic overlay for determining the region where wall thickening analysis was performed in the group 2 dogs.

Determination of Infarct Size

The heart slice corresponding to the two-dimensional echocardiographic image was immersed in a solution of 1.3% 2,3,5-triphenyl tetrazolium chloride and 0.2 mol/L Sorenson’s buffer (KH₂PO₄ and K₂HPO₄ in distilled water, pH 7.4) at 37°C for 20 minutes and then fixed in 10% formalin. This technique for assessing infarct size has been validated against histological and electron microscopic evidence of tissue necro-
sis not only for longer periods (>3 hours) of coronary occlusion and reperfusion\textsuperscript{17} but also for shorter periods (90 to 240 minutes of coronary occlusion and 5 minutes of reperfusion).\textsuperscript{18} An image of the stained slice was captured into the off-line computer using the video camera, and the infarct was measured and expressed as a percent of the myocardial slice.

**Experimental Protocol**

After hemodynamic and two-dimensional echocardiographic data at baseline were acquired (without dobutamine in group 1 and 3 dogs and in the presence of 15 µg/kg per minute of dobutamine in group 2 dogs), 100 mg of lidocaine hydrochloride (Abbott Laboratories) was given intravenously in group 1 and 2 dogs followed by a 2 mg/min constant infusion; group 3 dogs did not receive any lidocaine. The proximal portions or midportions of the LAD or LCX were occluded for 2 to 6 hours to cause infarcts of varying sizes. Normal saline, phenylephrine, and sodium bicarbonate were given as needed to maintain hemodynamic and metabolic status within the physiological range during coronary occlusion in the group 1 and 2 dogs; no drugs were used in group 3 dogs to avoid the influence of any drug on either wall thickening or infarct size.

Toward the end of the occlusion period, wall thickening was measured using two-dimensional echocardiography in all dogs; risk area was determined using myocardial contrast two-dimensional echocardiography in the group 1 and 3 dogs and using technetium autoradiography in the group 2 dogs. The occlusion was then released, and after 15 minutes of reperfusion, two-dimensional echocardiography was again performed to measure wall thickening in the absence of dobutamine in group 1 dogs, in the presence of dobutamine in group 2 dogs, and both before and after infusion of dobutamine in group 3 dogs. In addition, in 3 group 1 and 3 group 2 dogs, at the end of the experiment, dobutamine was given for 3 minutes each in doses of 5, 10, 15, and 20 µg/kg per minute to determine the optimal dose for eliciting maximal thickening in the postischemic myocardium with varying degrees of coexistent myocardial necrosis. The dogs were then killed by pentobarbital overdose, the heart was excised, and the slice corresponding to the two-dimensional echocardiographic image was processed to determine risk area by technetium autoradiography in the group 2 dogs and infarct size in all three groups of dogs.

**Statistical Analysis**

Data were analyzed using RS1 (Bolt, Beranek, and Newman) resident on a VAX4000 computer system (Digital Equipment Corp.) and were expressed as mean±SD. Comparisons between wall thickening and infarct size were made using linear regression analysis. Comparisons between stages were made using one-way ANOVA. Statistical significance was defined as $P<0.05$ (two-sided).

**Results**

Three group 1 and 2 group 2 dogs required phenylephrine to maintain a systolic blood pressure of >90 mm Hg during coronary occlusion. Two group 1 and 1 each of group 2 and group 3 dogs required defibrillation in the first 30 minutes of coronary occlusion.

**Hemodynamic Data**

Hemodynamic data of all three groups of dogs are depicted in Table 1. In the group 1 dogs, which did not receive dobutamine, there were no significant differences in the aortic pressures during baseline, coronary occlusion, and reperfusion (Table 1). Although the left atrial pressure increased during occlusion, it did not differ significantly from baseline and reperfusion. In group 2 dogs, all pressures were measured in the presence of 15 µg/kg per minute of dobutamine (Table 1). Like the group 1 dogs, this group also did not show any statistical differences in aortic and left atrial pressures during any of the stages. Likewise, in group 3 dogs, there were also no significant differences in the aortic and left atrial pressures during the different stages in the absence of dobutamine (Table 1). After 15 µg/kg per minute of dobutamine was infused during reflow, although aortic pressures tended to be higher, no significant differences were noted compared with other stages because of a large variability in the blood pressure response to dobutamine (Table 1). There were no differences between the hemodynamics of group 2 and 3 dogs during reflow in the presence of dobutamine.

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**TABLE 1. Hemodynamic Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Occlusion</th>
<th>Reperfusion</th>
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<tr>
<td><strong>Group 1 Dogs</strong></td>
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<tr>
<td>Pressure</td>
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<tr>
<td>ASP, mm Hg</td>
<td>131±29</td>
<td>122±31</td>
<td>112±25</td>
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<tr>
<td>LAP, mm Hg</td>
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<td>8±3</td>
<td>5±2</td>
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<tr>
<td><strong>Group 2 Dogs</strong></td>
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<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Baseline</td>
<td>Occlusion</td>
<td>Reperfusion</td>
</tr>
<tr>
<td>ASP, mm Hg</td>
<td>127±43</td>
<td>140±48</td>
<td>129±52</td>
</tr>
<tr>
<td>LAP, mm Hg</td>
<td>9±6</td>
<td>13±8</td>
<td>14±8</td>
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<tr>
<td><strong>Group 3 Dogs</strong></td>
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</tr>
<tr>
<td>Pressure</td>
<td>Baseline</td>
<td>Occlusion</td>
<td>No Dobutamine</td>
</tr>
<tr>
<td>ASP, mm Hg</td>
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<td>122±13</td>
<td>115±15</td>
</tr>
<tr>
<td>LAP, mm Hg</td>
<td>6±3</td>
<td>6±3</td>
<td>7±4</td>
</tr>
</tbody>
</table>

ASP indicates aortic systolic pressure; LAP, mean left atrial pressure. Dobutamine given at 15 µg/kg per minute.
Risk Area and Infarct Size

Risk areas and infarct sizes in the three groups of dogs are depicted in Table 2. In the group 1 dogs, there was no difference in the infarct size in dogs with <3 hours occlusion compared with the 6 group 1 with 3-to-4-hour occlusion (42±33% of risk area versus 43±33% of risk area, P=.93).

Table 2. Risk Area and Infarct Size in the Three Groups of Dogs

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk Area (% Short-Axis Slice)</th>
<th>Infarct Size (% Risk Area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>42±11% (range, 28% to 61%)</td>
<td>42±31% (range, 0% to 82%)</td>
</tr>
<tr>
<td>Group 2</td>
<td>27±11% (range, 16% to 50%)</td>
<td>36±28% (range, 0% to 80%)</td>
</tr>
<tr>
<td>Group 3</td>
<td>40±12% (range, 24% to 62%)</td>
<td>37±32% (range, 0% to 84%)</td>
</tr>
</tbody>
</table>

Wall Thickening

In the group 1 dogs, wall thickening in the occluded bed at baseline, after 2 to 6 hours of occlusion, and after 15 minutes of reflow was 32±6%, -2±6%, and 5±6%, respectively. These values were significantly different (P<.001) from each other.

Fig 1 illustrates end-diastolic and end-systolic frames from two-dimensional echocardiographic images from a group 1 dog with a small LAD infarct (4% of risk area); Fig 2 illustrates similar data from a group 1 dog with a large LAD infarct (64% of the risk area). The risk areas (as a percent of the short-axis slice) were similar in the two dogs (55% and 61%, respectively). Despite very dissimilar infarct sizes, wall thickening within the infarct zone (depicted by arrows) was the same (3%). That is, the LAD bed in the dog with the smaller infarct did not demonstrate more thickening than in the dog with the larger infarct. As depicted in Fig 3A, the relation between infarct size, expressed as a percent of risk area, and percent wall thickening in the infarct bed in the group 1 dogs during reperfusion in the absence of dobutamine was poor: y=0.04x+3.7 (r=.20, P=.51, SEE=5.9).

In the 12 group 2 dogs, wall thickening in the occluded bed at baseline, during occlusion, and during reflow in the presence of 15 μg/kg per minute of dobutamine was 40±8%, 0±8%, and 19±10%, respectively. All three values were significantly (P<.001) different from each other. Although wall thickening during coronary occlusion was similar in group 1 and 2 dogs, it was significantly greater in the group 2 dogs during baseline (P<.02) and reflow (P<.001), indicating that although wall thickening could be augmented in the infarct bed by dobutamine before occlusion and after reflow, it could not be augmented in the presence of a total coronary occlusion despite the presence of viable myocardium.

Fig 4 depicts end-diastolic and end-systolic frames from two-dimensional echocardiographic images from a group 2 dog with a small LAD infarct (23% of risk area). Fig 5 illustrates similar data from a group 2 dog with a large LAD infarct (57% of the risk area). The risk areas (as a percent of the short-axis slice) were similar in the two dogs (50% and 40%, respectively). Wall thickening within the infarct zone (depicted by arrows) was significantly greater in the dog with a small suben-
docardial infarction (31%) compared with the one with a large nearly transmural infarction (5%). That is, unlike the situation in the group 1 dogs, in group 2 dogs receiving dobutamine, wall thickening was greater when the infarct was smaller and the amount of viable myocardium was greater.

Unlike the group 1 dogs (Fig 3A), there was a close inverse relation between infarct size, expressed as a percent of risk area, and wall thickening in the group 2 dogs (Fig 3B) in the presence of 15 μg/kg per minute of dobutamine: \( y = -0.29x + 29.0 \) (\( r = -0.81, P = .001, \text{SEE} = 6.3 \)). In the presence of dobutamine, therefore, the smaller the infarct (and hence the greater the extent of viable myocardium), the greater was the absolute wall thickening.

In the 12 group 3 dogs, wall thickening in the occluded bed at baseline, during occlusion, and during reflow in the absence of dobutamine was 32±8%, −2±4%, and 5±8%, respectively. All three values are significantly different from each other. In the presence of 15 μg/kg per minute of dobutamine, wall thickening during reflow increased (\( P < .01 \)) to 18±14%, a value very similar to that during reflow in the group 2 dogs in the presence of the same dose of dobutamine. After reflow, the average change in wall thickening caused by 15 μg/kg per minute of dobutamine was 12±12%.

Similar to the situation in group 1 dogs, as illustrated by open circles in Fig 6A, there was poor correlation between infarct size, expressed as a percent of risk area, and percent wall thickening during reflow in the group 3 dogs before the infusion of dobutamine: \( y = -0.13x + 10.0 \) (\( r = -0.36, P = .26, \text{SEE} = 6.6 \)). However, after the infusion of 15 μg/kg per minute of dobutamine, like the group 2 dogs and depicted as filled circles in Fig 6A, a close inverse relation is noted between infarct size, expressed as a percent of risk area, and percent wall thickening: \( y = -0.38x + 32.0 \) (\( r = -0.93, P < .001, \text{SEE} = 4.6 \)). Therefore, based on the data in Figs 3B and 6A one could surmise that, in the presence of 15 μg/kg per minute of dobutamine, approximately 30% thickening would be noted in the postischemic myocardium in the absence of infarction, whereas a total transmural infarction would result in no thickening despite using moderate doses of dobutamine.

As depicted in Fig 6B, an inverse relation was also noted in the group 3 dogs between infarct size, expressed as a percent of risk area, and the change in wall thickening induced by 15 μg/kg per minute of dobutamine: \( y = -0.27x + 22.0 \) (\( r = -0.72, P <.01, \text{SEE} = 8.7 \)). Unlike absolute wall thickening, however, change in thickening had more scatter, particularly when the infarction was small, which was related to a large variability in postischemic wall thickening noted in the absence of any infarction (Fig 6A). Based on the data depicted in Fig 6B, one could surmise that, in the presence of 15 μg/kg per minute of dobutamine, a change in wall thickening by >10% would indicate that more than half of the myocardium is viable, whereas a change in thickening by <10% would indicate that less than half of the myocardium is viable. No change in thickening occurred in the presence of large (>75%) infarctions.

Optimal Dose of Dobutamine

Table 3 depicts infarct size as a percent of risk area and wall thickening at baseline, during coronary occlusion, and during reflow in the absence and presence of different doses of dobutamine given to 3 group 1 and 3 group 2 dogs. Several facts are evident. First, the percent wall thickening both during occlusion and at reflow has no correlation with infarct size in the absence
of dobutamine ($r=.47$ and $r=.50$, respectively, $P=NS$). Second, at 5 μg/kg per minute of dobutamine, it is generally not possible to separate small from large infarcts on the basis of wall thickening; the correlation between infarct size and wall thickening at this dose of dobutamine was also not significant ($r=-.59$, $P=.22$). Third, the smaller the infarct, the more likely is adequate thickening to occur at 10 μg/kg per minute of dobutamine. At this dose, a strong inverse correlation was noted between infarct size and wall thickening ($r=-.88$, $P=.02$). Fourth, the smaller the infarct, the greater is the thickening at 15 μg/kg per minute of dobutamine. At this dose, an excellent negative correlation was noted between infarct size and wall thickening ($r=-.94$, $P=.001$). Finally, although not shown in Table 3, a dose of 20 μg/kg per minute of dobutamine did not cause any further increase in thickening compared with the dose of 15 μg/kg per minute.

Discussion

This study indicates that when myocardial necrosis coexists with postischemic myocardial dysfunction and no flow-limiting coronary stenosis coexists, the response of the myocardium to 15 μg/kg per minute of dobutamine can be used to determine the extent of myocardium that has escaped necrosis. Whereas regional LV wall thickening at rest cannot be used to assess the amount of myocardial necrosis immediately after reperfusion, an inverse linear relation is noted between infarct size and absolute wall thickening when the myocardium is stimulated with a moderate dose of dobutamine. Although we did not measure thickening in different layers of the myocardial wall in this study, our results indirectly suggest that the outer layers of the myocardium, which normally do not contribute significantly to wall thickening, do so under the effect of dobutamine. Finally, we showed that the dose of dobutamine needed to elicit maximal thickening of the postischemic myocardium is directly related to the amount of myocardial necrosis in the absence of a flow-limiting lesion. We believe that these findings may form a framework for the use of dobutamine echocardiography for determining myocardial viability after reperfusion.

Response of Postischemic Myocardium to Inotropic Stimulation

The postischemic myocardium is characterized by impairment in myocardial thickening, the duration of which is related to the period of ischemia.2,3 This myocardium has, however, been shown to have contractile reserve and thickens in response to various pharmacologic agents, including dobutamine.20-24 Most experimental studies that have demonstrated this phenomenon have used a model of pure postischemic dysfunction without any coexistent myocardial necrosis.20-24 In the clinical setting, however, such a situation is rare; after successful reflow, varying degrees of necrosis are usually present within the reperfused myocardium.

Our study demonstrates that at a dose of 15 μg/kg per minute and in the absence of a flow-limiting coronary stenosis supplying the postischemic myocardium, the degree of thickening of this myocardium is inversely related to the extent of necrosis present. This finding indicates that stimulation of the myocardium after successful reperfusion could provide an indirect estimation not only of the presence but also the amount of viable myocardium. Unlike the absolute degree of myocardial thickening, the change in wall thickening in the presence of 15 μg/kg per minute of dobutamine was not as predictive of the extent of myocardial viability. This phenomenon is probably related to the large variability in wall thickening noted in the postischemic myocardium even in the absence of necrosis, which may be related to loading conditions, myocardial blood flow, and other undefined causes. This variability in thickening noted in the absence of dobutamine is no longer seen in the presence of 15 μg/kg per minute of dobutamine, where the contractile reserve is directly related to the extent of salvaged myocardium. These results indicate that measurement of absolute wall thickening
at a standard dose of dobutamine may provide more important information regarding the extent of myocardial viability than assessing change in wall thickening. Our results support the earlier observations of Mercier and colleagues, who showed that regional function in the postischemic myocardium could be markedly enhanced by inotropic stimulation as long as there was no evidence of significant myocardial necrosis. These authors, however, did not study the effect of inotropic stimulation in animals with different degrees of myocardial necrosis. Although the postischemic myocardium has contractile reserve, our results indicate that the

Fig 4. Examples of end-diastolic (A) and end-systolic (B) frames from one group 2 dog with a small left anterior descending artery infarction (23% of risk area) limited exclusively in the subendocardial region (arrows) on triphenyl tetrazolium chloride staining of the heart (C). Significant thickening (31%) is noted within the infarct bed (arrows) in the presence of dobutamine. See text for details.

Fig 5. Examples of end-diastolic (A) and end-systolic (B) frames from one group 2 dog with a large, almost transmural left anterior descending artery infarction (57% of risk area) (arrows) on triphenyl tetrazolium chloride staining of the heart (C). Minimal thickening (5%) is noted within the infarct bed (arrows) in the presence of dobutamine. See text for details.
The degree of thickening during inotropic stimulation, even in the absence of necrosis, may not reach the same magnitude as that in the normal myocardium. In our study, when necrosis was not present, the average thickening achieved with 15 μg/kg per minute of dobutamine was about 30%, whereas that in the normal myocardium was 40%. Similar results have been reported by Becker and coworkers using epinephrine and Bolli and colleagues using isoproterenol in models of pure postischemic dysfunction not associated with myocardial necrosis. 

**Contractile Function of Different Myocardial Layers**

It has been shown previously that in the normal heart, most of the thickening occurs within the endocardial half of the left ventricle and that when flow to this region is diminished, overall myocardial thickening is severely reduced. It has also been reported that if the inner one fifth of the myocardial thickness has undergone necrosis, wall thickening can be severely reduced, and beyond this threshold there is no relation between wall thickening and the transmural extent of infarction.

Under basal conditions, therefore, it may not be possible to gauge the transmural extent of necrosis based on the degree of regional myocardial dysfunction.

Although we did not measure thickening in different layers of the myocardium in our study, our results suggest that myocardial tissue that would normally not contribute significantly to wall thickening under basal conditions does so under catecholamine stimulation. The data in Figs 3 and 6 suggest that if the infarction is totally transmural, no thickening will be noted even in the presence of 15 μg/kg per minute of dobutamine, while as more and more of the transmural thickness of the myocardium is spared necrosis, more and more thickening of the myocardium will be seen at this dose of dobutamine. As depicted in Table 3, this relation, however, would not necessarily be expected at lower doses of dobutamine.

That the outer layers of the myocardium respond to inotropic stimulation has some interesting implications. Because of necrosis involving a critical extent of the myocardial thickness, regional wall motion may be abolished at rest despite the presence of a significant amount of viable myocardium. During exercise or other forms of stress, however, where catecholamines are released, the outer layers of the myocardium may increase their thickening, thus enhancing wall motion and contributing to better overall LV function. This kind of response may be important in preventing LV dissynergy and dilation during stress and hence may contribute to improved functional status and survival in patients receiving successful thrombolysis even if they do not demonstrate spontaneous recovery in resting regional function.

Traditionally, viability has been determined by the spontaneous improvement in resting regional function after an intervention. Thus, the postischemic myocardium has generally been considered viable only when recovery in regional function has ultimately occurred after successful reperfusion. Based on our results, we believe that the response of the postischemic myocardium to inotropic stimulation may provide a better assessment of viability, since it could even be seen in patients with viable myocardium in whom resting function does not recover so long as no flow-limiting coronary stenoses are present in vessels subserving such myocardium.

**Optimal Dose of Dobutamine**

Our results indicate that there is no ideal dose of dobutamine required to elicit contractile reserve in the postischemic myocardium but that the dose needed to determine the extent of viable myocardium depends on the transmural extent of infarction. We did not find any further potentiation of wall thickening induced by dobutamine in the postischemic myocardium at doses >15 μg/kg per minute. Since we completely reversed the coronary occlusion to allow reflow, we could not exam-
The influence of the degree of residual stenosis on the effect of dobutamine on the postischemic myocardium. McGillem and colleagues have shown that the increase in myocardial thickening with dobutamine is impaired in the presence of a coronary stenosis that is capable of significantly exhausting coronary flow reserve.

Critique of Our Methods

The reason we did not see significant changes in hemodynamics during coronary occlusion despite large risk areas in some dogs was because we used pharmacologic agents and fluid therapy to keep the dogs alive during the period of coronary occlusion. We stopped these drugs at least 10 minutes before examining wall thickening during coronary occlusion and did not restart them during reflow. None of the group 3 dogs received these drugs because of their potential effects on infarct size and wall thickening. Lack of change in hemodynamics between stages in our dogs suggests that the principal reason for change in wall thickening in our study was due to ischemia and myocardial effect of dobutamine rather than changes in the loading conditions of the heart.

We used a sophisticated method of regional function analysis with two-dimensional echocardiography. Previous investigators have demonstrated significant spatial and temporal heterogeneity in regional function, especially in ischemic and postischemic myocardium. Thus, wall thickening estimation only from end-diastolic and end-systolic frames can underestimate the degree of regional dysfunction. We therefore used a semi-automated method that utilizes the entire systolic contraction sequence to determine myocardial thickening.

When this approach is used, the maximal degree of dysfunction can be measured irrespective of when it occurs in the cardiac cycle. At a sampling rate of 30 Hz, we cannot discriminate between end systole and end ejection using two-dimensional echocardiography and, therefore, chose the smallest LV chamber size to represent end systole. Similarly, we selected the largest LV size to represent end diastole.

In the group 1 dogs not receiving dobutamine, the duration of coronary occlusion was significantly shorter than in the group 2 and 3 dogs, which may impact on the estimation of infarct size. It has been clearly established previously that triphenyl tetrazolium chloride discriminates between infarcted and noninfarcted tissue undergoing prolonged periods of occlusion and reperfusion. The same investigators also have recently reported that this technique is equally capable of separating necrotic and nonnecrotic tissue undergoing shorter periods of occlusion (as little as 90 minutes) and reperfusion (5 minutes). Moreover, even if we excluded the 6 group 1 dogs with <3 hours of occlusion from analysis, our results would not change significantly. Only 2 group 2 and no group 3 dogs underwent <3 hours of coronary occlusion.

We measured risk area using two separate methods: myocardial contrast two-dimensional echocardiography and technetium autoradiography. We have previously demonstrated a close linear relation between these two techniques. It is conceivable that treatment with dobutamine during coronary occlusion may have influenced the results in the group 2 dogs. This is unlikely, however, since the infusion of dobutamine was performed only for a brief period (no more than 5 minutes) at each stage. Furthermore, the group 3 dogs with paired observations (with and without dobutamine) in each dog provided similar results. Finally, we did not have intermediate-sized infarcts in our group 3 dogs. However, data from this group and from group 2 dogs, which received only dobutamine and had infarcts of intermediate sizes, suggest that there is an inverse linear relation between infarct size and wall thickening in the postischemic myocardium in the presence of 15 µg/kg per minute of dobutamine.

Clinical Implications of Our Study

Dobutamine two-dimensional echocardiography is being used increasingly in the clinical setting for determining the presence of viable myocardium. To our knowledge, there have been no controlled experimental studies defining the physiological basis of using dobutamine two-dimensional echocardiography for this purpose. The results from our study form a framework based on which previous and future clinical observations using this technique can be interpreted.

It may be important to know the coronary anatomy before interpreting results of dobutamine two-dimen-

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**TABLE 3. Relation Between Dobutamine Dose and Wall Thickening**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Infarct Size*</th>
<th>Baseline</th>
<th>Occlusion</th>
<th>Reflow</th>
<th>5t</th>
<th>10t</th>
<th>15t</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>40</td>
<td>-5</td>
<td>7</td>
<td>10</td>
<td>14</td>
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<tr>
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<td>53</td>
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<td>9</td>
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<td>11</td>
<td>28</td>
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<tr>
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<td>36</td>
<td>-2</td>
<td>-1</td>
<td>8</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>28</td>
<td>-2</td>
<td>-4</td>
<td>14</td>
<td>32</td>
<td>39</td>
</tr>
</tbody>
</table>

Mean: 24±24 32±6 -2±4 5±6 10±5 19±10 26±15

*Expressed as a percent of risk area.
†In µg/kg per minute.
sional echocardiography in patients who have received thrombolysis. For instance, wall thickening may not increase in the presence of dobutamine either because there is very little viable myocardium or else a critical residual stenosis is still present despite substantial amounts of viable myocardium. Obviously, the implications of these two situations are different.

The dose of dobutamine required to elicit the maximal contractile reserve may be higher than the low-dose dobutamine used currently in clinical practice.\textsuperscript{31,32} Low-dose dobutamine may significantly underestimate the extent of viable myocardium. That myocardial response to this dose has been shown to correlate with ultimate recovery in regional function in some patients\textsuperscript{31,32} may simply be because spontaneous recovery in regional function is more likely to occur in those with the least amount of necrosis, and these patients are likely to respond to even low doses of dobutamine. Others with more necrosis but with significant amounts of viable myocardium who are not likely to demonstrate spontaneous recovery in regional function could be missed using these doses; consequently, higher doses would be required to elicit viable myocardium in these patients. Greater knowledge of the coronary anatomy could also make it easier to use larger doses safely in patients with mild residual necrosis.

In patients with noncritical residual stenosis who do not demonstrate spontaneous recovery in regional function, the myocardial response to dobutamine could be used to predict the long-term benefits of reperfusion therapy. Although speculative at this juncture, this aspect of dobutamine two-dimensional echocardiography may provide insights that are not readily available using other means. For instance, Pierard and colleagues\textsuperscript{33} noted viability on positron emission tomography in 11 of 17 patients with anterior myocardial infarction who had undergone successful thrombolysis within 3 hours of the onset of symptoms. Although all 11 showed improvement in function with 10 μg/kg per minute of dobutamine, only 6 showed spontaneous recovery later. Thus, dobutamine two-dimensional echocardiography at a moderate dose identified more viable myocardium than would have been predicted on the basis of spontaneous recovery in regional function. It is also likely that the 5 patients with viable myocardium who did not demonstrate spontaneous recovery in regional function but who showed enhanced regional function with dobutamine had enough normal myocardium to buttress the infarct tissue, thus preventing infarct expansion and heart failure.\textsuperscript{4} To address these and other issues, further studies are required to establish the role of dobutamine two-dimensional echocardiography in patients with postischemic myocardial dysfunction.

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