Response to Incremental Doses of Dobutamine Early After Reperfusion Is Predictive of the Degree of Myocardial Salvage in Dogs With Experimental Acute Myocardial Infarction

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OBJECTIVES We sought to determine whether the inotropic response to dobutamine might be useful for estimating the extent of viable myocardium soon after reperfusion.

BACKGROUND Early identification of viable myocardium in the presence of severe left ventricular dysfunction after reperfusion is important for clinical decision making.

METHODS Nine open-chest dogs had left anterior descending coronary artery occlusion for 40 to 180 min, followed by gradual reperfusion. The systolic thickening response to incremental dobutamine doses was measured with ultrasonic crystals and regional flow by microspheres.

RESULTS Dogs were divided into two groups based on triphenyl tetraazolium chloride infarct size (group 1: 9.3 ± 3.0% risk area; group 2: 51.1 ± 4.8%). In group 2 dogs with larger infarcts, regional flow during peak dobutamine was lower than it was in group 1 in endocardial (1.15 ± 0.22 vs. 2.64 ± 0.33 mL/min/g) and midwall (1.47 ± 0.32 vs. 2.92 ± 0.36 mL/min/g) layers, and endocardial flow in group 2 failed to increase from baseline (0.96 ± 0.07 vs. 1.15 ± 0.22 mL/min/g). Group 1 dogs demonstrated a dose dependent increase in systolic thickening with dobutamine versus a blunted response in group 2. The inotropic response to only 10 μg/kg/min of dobutamine was predictive of the degree of myocardial salvage.

CONCLUSIONS In the early postischemic stunning phase of reperfusion, the inotropic response to dobutamine is predictive of the degree of myocardial salvage and ultimate infarct size. The ability to distinguish between stunned versus necrotic myocardium early after reperfusion was most likely due to the presence of subendocardial flow reserve during dobutamine in dogs with predominantly salvaged myocardium. (J Am Coll Cardiol 2000;35:1960–8) © 2000 by the American College of Cardiology

With recent advances in the treatment of acute myocardial infarction (MI), more patients with reduced left ventricular function survive the acute event. Thrombolytic therapy or primary angioplasty are aimed at salvaging ischemic myocardium. Whereas coronary reperfusion instituted early during acute MI may reduce the extent of myocardial necrosis, it is well known that myocardium salvaged by reperfusion does not immediately regain appreciable contractile function because of postsischemic stunning (1). Thus, it is difficult to utilize the status of resting systolic function in the infarct zone early after reperfusion for assessment of viability. Resting single photon emission computed tomography perfusion imaging is problematic for viability assessment early after reperfusion because of partial volume-related defects in the infarct zone of asynergy (2,3). The early determination of inotropic reserve in the infarct zone could be a sensitive indicator of infarct zone salvage and sustained viability.

There is often a mixture of necrosis and salvaged myocardium in a region of severe infarct-related asynergy after reperfusion therapy in patients with MI. A satisfactory outcome after reperfusion therapy would be a small area of necrosis with coexistence of stunned myocardium. Stunned myocardium manifests inotropic reserve that can be elicited by the administration of inotropic agents such as isoproterenol or dobutamine. The results of experimental studies of stunned myocardium (4,5) suggest that early assessment of myocardial viability might be possible by evaluating regional inotropic reserve with catecholamine infusion. Most experimental studies (4–7) that have demonstrated inotropic

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reserve during dobutamine infusion have used a model without any coexistent myocardial necrosis. However, in the clinical setting, such a situation is rare and varying degrees of necrosis are usually present within the reperfused myocardium after successful reperfusion therapy. Accordingly, we sought to determine whether the inotropic response to incremental doses of dobutamine might be useful for estimating the extent of viable myocardium in the presence of coexistent necrotic myocardium early after reperfusion. The hypothesis tested was that the greater the extent of necrosis after reperfusion, the less the inotropic response to incremental doses of intravenously administered dobutamine.

**METHODS**

**Surgical preparation.** Thirteen fasted, adult mongrel dogs (mean weight, 25.0 ± 0.8 kg; range, 22.7 to 31.8 kg) were anesthetized with sodium pentobarbital (30 mg·kg⁻¹), tracheally intubated and mechanically ventilated with room air on a respirator (model 613, Harvard Apparatus, Holliston, Massachusetts) with positive end-expiratory pressure of 5 cm H₂O. A left lateral thoracotomy was performed at the level of the fifth intercostal space, and the heart was suspended in a pericardial cradle. A proximal portion of the left anterior descending coronary artery (LAD) was dissected free of the epicardium and loosely encircled with two snare occluders. Animals were instrumented as previously described for measurement of hemodynamics, LAD and left circumflex coronary artery (LCx) coronary flows and regional systolic thickening using Doppler crystals (8). The femoral arteries were cannulated with 8F polyethylene catheters for arterial blood gas monitoring (model 170, CIBA-Corning, East Walpole, Massachusetts) and for arterial reference blood withdrawals for microsphere determination of regional blood flows (9). The left external jugular vein was cannulated with an 8F catheter for the infusion of dobutamine.

Throughout each experiment, heart rate, arterial and left atrial pressures, LAD and LCx flows, systolic wall thickening and left ventricular pressure and its first time derivative (dP/dt) were continuously monitored and recorded on a 16-channel thermal array chart recorder (K2-G, Astro-med, Inc.). All experiments were performed with the approval of the University of Virginia Animal Research Committee and were in compliance with the position of the American Heart Association on the use of research animals.

**Experimental protocol.** The experimental protocol is illustrated in Figure 1. After instrumentation of the animals, steady-state hemodynamic and wall thickening measurements were made for 15 min, and radiolabeled microspheres were injected to measure baseline myocardial blood flow. The technique used in our laboratory to quantify regional myocardial blood flow by the radioactive microsphere technique was described previously (8–10). The LAD was then partially occluded to produce a 50% reduction in baseline LAD flow. After 30 min of sustained low flow, the LAD was totally occluded for 40 to 180 min with the second snare occluder. At the end of the occlusion period, hemodynamic indexes and wall motion were measured, and microspheres were injected. The LAD stenosis was then fully released, permitting restoration of normal flow. Thickening and hemodynamic indexes were quantified at 45 min after stenosis release to assess recovery of function with flow restoration. Next, dobutamine was infused in 3 min dose increments of 5, 10, 20 and 30 μg·kg⁻¹·min⁻¹ intravenously (model 3400, SIMS Graseby Limited Watford, Hertfordshire, United Kingdom), and hemodynamic indexes and wall motion were measured at the end of every stage. At the peak dose of 30 μg·kg⁻¹·min⁻¹, microspheres were injected. Ten minutes after ending the dobutamine infusion, the LAD was totally reoccluded and 20 mL of monastral blue dye was rapidly injected into the left atrial catheter to delineate the anatomic risk area. The dogs were then killed with an overdose of sodium pentobarbital and potassium chloride. Of the thirteen dogs that underwent the surgical procedure, four died of ventricular fibrillation during the occlusion or early reperfusion stages of the experimental protocol yielding a total of nine dogs that comprise this study.

**Determinant of regional myocardial systolic thickening.** Regional systolic thickening was measured by the epicardial crystal pulsed-Doppler technique (11,12). This technique
Postmortem determination of risk area and infarct size. The endocardial and epicardial surfaces of each heart slice and the borders of the monastral blue dye-determined risk area were carefully traced onto acetate sheets. The heart slices were then incubated for 10 min at 37°C in a 2% solution of triphenyl tetrazolium chloride (TTC) to determine infarct area, and the infarct area was traced onto the previous acetate sheets. Risk and infarcted areas were determined with a digital planimeter program (DigiPlan, Scientific Computing Solutions, LLC, Charlottesville, Virginia) as previously described (13,14). Risk area was expressed as a percentage of the left ventricle, and infarct area as a percent of risk area (%RA) between the two groups. *p < 0.01 vs. group 1.

RESULTS

Risk area and infarct size. Dogs were arbitrarily divided into two groups according to infarct size. Five dogs had an infarct size comprising <15% of risk area and were designated as group 1. The remaining four dogs had an infarct size of ≥15% of risk area and were designated as group 2. Figure 2 displays mean risk area and infarct size in both groups. There was no significant difference in the LAD risk area by monastral blue dye between the two groups (24.1 ± 3.9% vs. 25.8 ± 2.9%, respectively). By TTC staining, group 2 dogs had significantly larger infarcts than group 1 (51.1 ± 4.8% vs. 9.3 ± 3.0% of risk area, respectively, p < 0.01).

Figure 2. Bar graph comparing mean risk area as a percent of left ventricle (%LV) and infarct size as a percent of risk area (%RA) between the two groups. *p < 0.01 vs. group 1.

Hemodynamic data. Mean hemodynamic data are summarized in Table 1. There were no significant differences in serial changes of all indexes between the two groups. Heart rate was stable during stenosis, occlusion and reperfusion periods in both groups. During dobutamine infusion, heart rate increased significantly in a graded fashion with increasing doses of dobutamine from 5 μg·kg⁻¹·min⁻¹ in group 2 dogs and from 10 μg·kg⁻¹·min⁻¹ in group 1 dogs. Mean arterial pressure in group 1 decreased during partial reperfusion and full reperfusion and increased significantly during 5, 10, 20 μg·kg⁻¹·min⁻¹ of dobutamine. However, at 30 μg·kg⁻¹·min⁻¹, mean arterial pressure was similar to that seen at full reperfusion. In group 2 dogs, mean arterial pressure decreased during early reperfusion through the stenosis and full reperfusion and did not significantly increase during dobutamine infusion. Left atrial pressure did not change throughout the experiments in both groups.

Left ventricular dP/dt was stable after the stenosis was
### Hemodynamic Parameters

<table>
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<tr>
<th>Group 1 (&lt;15% infarction)</th>
<th>HR (beats/min)</th>
<th>AP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>dP/dt (mm Hg-s(^{-1}))</th>
<th>LAD flow (mL/min(^{-1}))</th>
<th>LCx flow (mL/min(^{-1}))</th>
<th>Dobutamine ((\mu g\cdot kg^{-1}\cdot min^{-1}))</th>
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<tr>
<td>Base</td>
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<td>106 ± 10</td>
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<td>2,160 ± 222</td>
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<td>8 ± 1</td>
<td>2,007 ± 154</td>
<td>10 ± 2†</td>
<td>47 ± 4</td>
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<td>89 ± 5*</td>
<td>9 ± 1</td>
<td>1,700 ± 189</td>
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<td>87 ± 10*</td>
<td>7 ± 1</td>
<td>1,710 ± 267</td>
<td>20 ± 3</td>
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<th>AP (mm Hg)</th>
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<th>dP/dt (mm Hg-s(^{-1}))</th>
<th>LAD flow (mL/min(^{-1}))</th>
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<td>1,513 ± 110</td>
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<td>39 ± 11</td>
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Values are expressed as mean ± SEM. *p < 0.05 vs. baseline; †p < 0.01 vs. baseline; ‡p < 0.05 vs. full reperfusion; §p < 0.01 vs. full reperfusion.

There were no significant differences in all indexes between the two groups. Left atrial pressure did not change through the experiment.

AP = mean arterial pressure; base = baseline; dP/dt = peak positive first derivative of left ventricular pressure with respect to time; Full = full reperfusion; HR = heart rate; LAD = left anterior descending coronary artery; LAP = left atrial pressure; LCx = left circumflex coronary artery; mm Hg = millimeter mercury; Occ = occlusion; Part = partial reperfusion; Sten = stenosis.
Regional Myocardial Blood Flow

Table 2.

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<tr>
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<th>Baseline</th>
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<th>Midwall</th>
<th>Epicardium</th>
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<tr>
<td>Group 2 (≥15% infarct size)</td>
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<td>0.22 ± 0.03</td>
<td>0.95 ± 0.06</td>
<td>0.54 ± 0.06</td>
<td>0.99 ± 0.06</td>
<td>0.88 ± 0.10</td>
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</table>

Note: Flows are expressed in ml min/g. Results are expressed as mean ± SEM. Group 1 = partial reperfusion with residual stenosis. Group 2 = 15% infarct size.

Figure 3. Comparison of myocardial blood flow in the left anterior descending coronary artery zone at the 30 μg·kg⁻¹·min⁻¹ dobutamine infusion. Note that endocardial, midwall and transmural blood flows in dogs with larger infarct size (group 2) were significantly lower than values in dogs with a smaller infarct size (group 1). Endocardial flow in group 2 failed to increase from baseline at peak dobutamine infusion. *p < 0.05 vs. group 1; †p < 0.01 vs. group 1.

In contrast, group 2 dogs showed a significant attenuation of inotropic reserve in the infarct zone (Fig. 4B) with little enhancement of thickening in response to even the highest dose of dobutamine. Although no significant differences in inotropic response to dobutamine between the two groups was seen at the 5 μg·kg⁻¹·min⁻¹ dobutamine dose, thickening increase was significantly attenuated in group 2 at 10, 20 and 30 μg·kg⁻¹·min⁻¹ dobutamine infusion compared with group 1. Regional wall thickening of the normal LCx zone was similar between the two groups during the 5 μg·kg⁻¹·min⁻¹ dobutamine infusion. A biphasic response to dobutamine was not seen, because the LAD was fully patent at the time of dobutamine infusion.

The individual thickening responses to increasing doses of dobutamine for all nine dogs are shown in Figure 5. As shown, there was a strong inverse relationship between thickening and infarct size for the 10, 20 and 30 μg·kg⁻¹·min⁻¹ doses of dobutamine. No significant correlation was seen between infarct size and the systolic thickening response at the 5 μg·kg⁻¹·min⁻¹ dose of dobutamine. Thus, the 5 μg·kg⁻¹·min⁻¹ dose of dobutamine infusion did not discriminate between the small and large infarct sizes. However, as shown in Figure 4, the inotropic responses to 10 to 30 μg·kg⁻¹·min⁻¹ doses of dobutamine...
stenosis; *p<0.05 vs. LCx; †p<0.01 vs. LCx.

**DISCUSSION**

The major finding of this study was that, although severity of resting infarct zone asynergy after coronary reperfusion was the same in dogs with small (9% of the risk area) and large infarct (51% of the risk area) sizes, the inotropic response to incremental doses of dobutamine early after reflow well differentiated the two groups. Dogs with smaller infarcts (group 1) and asynergy due predominantly to postreperfusion myocardial stunning showed significant inotropic reserve soon after reflow, whereas the inotropic response to incremental doses of dobutamine was markedly attenuated in dogs with larger infarct sizes and less myocardial salvage after reflow (group 2).

**Effects of dobutamine on myocardial blood flow.** Dobutamine has generally been used as an inotropic agent to increase myocardial contractility in the failing heart. Dobutamine stimulates the beta_1_-adrenergic receptor and increases regional wall thickening with increases in heart rate and systolic blood pressure. It is likely that dobutamine may cause dilation of coronary resistance vessels by means of both myocardial metabolic factors and by stimulation of beta_2_-adrenergic receptors on the coronary vessels (15). Coronary flow increases either via a direct vasodilatory effect or via autoregulation due to increased oxygen demand resulting from increased work (15–17).

In this study, dobutamine enhanced myocardial blood flow in all layers of myocardium in group 1 dogs, which had an average infarct size of approximately 9% of the area at risk in the LAD zone. In contrast, although epicardial blood flow at peak dobutamine infusion increased similarly in group 1 and 2 dogs, midwall and endocardial blood flows at peak dobutamine infusion in group 2 dogs were significantly less than those observed in dogs with a smaller infarct size. Endocardial blood flow at peak dobutamine infusion in group 2 dogs did not significantly increase from baseline, suggesting that ischemic injury during occlusion and after reperfusion occurred principally in the endocardium as observed previously (18). This failure of full flow restoration after reperfusion is associated with extensive capillary damage, myocardial cell swelling and microvascular obstruction. In this study, coronary flow reserve during dobutamine infusion in dogs with small infarcts and severe postischemic stunning was comparable with myocardial flow responses in the normal LCx bed. Endocardial blood flow in group 2 dogs with larger areas of necrosis failed to increase from baseline at peak dobutamine infusion (0.96 ± 0.07 mL·min^{-1}·g^{-1} vs. 1.15 ± 0.22 mL·min^{-1}·g^{-1}) reflecting absence of flow reserve in response to inotropic stimulation. The absence of significant flow reserve in the endocardium corresponded to the location of the dominant infarcted area as assessed by TTC staining of postmortem samples. In contrast, midwall and epicardial blood flow in group 2 increased during the dobutamine infusion, providing evidence of some residual myocardial viability in the outer layers of the risk area.

**Effects of dobutamine on systolic function.** Traditionally, viability has been ascertained by demonstration of spontaneous improvement in resting regional function after an intervention such as reperfusion (19–21). This improvement may take from days to weeks to be evident. The response of postischemic and severely asynergic myocardium to inotropic stimulation should provide a better early assessment of viability than assessment of resting function alone (22). In this experimental study, wall thickening was absent in all dogs, regardless of infarct size, before dobut-
amine infusion. Although wall thickening in the LAD region was actually dyskinetic in both groups after full reperfusion of the LAD, the responses to the incremental doses of dobutamine were quite different in the two groups of animals. In group 1 dogs, thickening increased in a dose dependent manner during 5, 10 and 20 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) dobutamine infusion and plateaued after 20 \( \mu g \cdot kg^{-1} \cdot min^{-1} \). In group 2 dogs, the response to dobutamine infusion was blunted and did not significantly increase from baseline even at the peak dobutamine dose. These results indicate that the magnitude of contractile reserve to inotropic stimulation is not related to basal systolic contraction. A previous study from our laboratory reported a marked dependence of transmural myocardial thickening on subendocardial blood flow (23). Subepicardial and midwall thickening fraction were highly dependent upon subendocardial flow rather than upon actual flows in these myocardial layers. In this study, the ability to increase endocardial blood flow in response to dobutamine was most likely the major mechanism permitting enhanced wall thickening during high-dose dobutamine infusion in dogs with smaller infarcts and concomitant stunning. In group 2 dogs, flow reserve was still present in midwall and epicardial layers, but transmural thickening did not increase because of lack of endocardial flow increase in response to inotropic stimulation despite a totally patent vessel. Lack of endocardial flow reserve in this model is consistent with irreversible subendocardial injury.

Because this study was designed to evaluate the influence of flow reserve and inotropic response in wall thickening after full reperfusion, the dogs did not have residual infarct-vessel stenoses at the time of dobutamine administration. The presence of a severe residual stenosis, even without significant subendocardial necrosis, could prevent an increase in endocardial blood flow in response to inotropic stimulation and increased myocardial oxygen demand. This may result in the absence of thickening at any dose of dobutamine or thickening at low doses of dobutamine with subsequent deterioration at high doses (biphasic response). McGillem et al. (24) described that dopamine or dobutamine failed to increase systolic thickening in dogs with severe coronary stenoses where reactive hyperemia was reduced to <20% of baseline. If a stenosis limits the required increase in blood flow and oxygen delivery, ischemia occurs and wall thickening diminishes (or fails to increase) despite the presence of viable myocardium. Therefore, if a severe residual stenosis is present after reperfusion, systolic thickening may not increase with dobutamine, even in the instance of a small infarct size (25,26) or may show a biphasic response.

The dose of dobutamine required to elicit maximal contractile reserve may be higher than the low-dose dobutamine used currently in clinical practice (22). Low-dose dobutamine may significantly underestimate the extent of viable myocardium. The fact that the myocardial response to low-dose dobutamine (5 to 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \)) has been shown to correlate with ultimate recovery in regional function in some patients 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. Our results show that, with a dobutamine infusion of only 10 μg·kg⁻¹·min⁻¹, dogs with small versus large infarct sizes could be separated, and this separation became even greater at higher doses of the drug. Thus, after reperfusion after varying duration of coronary occlusion, residual systolic dysfunction may be due to necrosis, stunning or a combination of both.

Implications for clinical dobutamine echocardiography. Multiple studies have evaluated the use of dobutamine stress echocardiography for the identification of viable myocardium after reperfusion therapy for acute MI (4,22,25–33). In acute animal models of reversible posts ischemic dysfunction and MI, improved wall thickening during inotropic stimulation accurately differentiated reversible from fixed dysfunction (4,22,31,32). Increase in wall thickening during dobutamine infusion only occurred in segments with minimal infarction (22,32). In clinical studies, Piéraud et al. (27) studied 17 patients treated with thrombolysis within 3 h of an acute MI. During dobutamine infusion, patients found to have normal perfusion and glucose uptake by positron emission tomography showed an improvement in function in the asynergic regions, correlating with improvement in function at follow-up. This study suggested that dobutamine echocardiography can identify viable myocardium very early after reperfusion. In a study by Smart et al. (25), contractile reserve by low-dose (4 μg·kg⁻¹·min⁻¹) dobutamine stress echocardiography was an independent predictor of functional recovery after thrombolysis for MI, which was superior to the other clinical criteria. The findings of the study in group 1 dogs with smaller infarct size and myocardial stunning are in agreement with observations of previous studies in dogs (22,25,32,33).

Studies using myocardial contrast echocardiography lend support to the concept that microvascular integrity may be a marker for viable myocardium. Ragosta et al. (34) showed a strong correlation between evidence of an intact microcirculation and subsequent improvement in regional wall motion in patients with documented patency of the infarct-related artery after recent MI. Ito et al. (35) demonstrated that patients with evidence of reflow by myocardial contrast echocardiography in the myocardial area at risk after reperfusion therapy had greater improvement in global and regional left ventricular function on follow-up than patients with no reflow. Our data further show that the thickening response to inotropic stimulation is an indirect marker of preserved subendocardial flow reserve. If viability is to be assessed by imaging microvascular integrity, evaluation of blood flow must be undertaken in the subendocardial region.

Study limitations. Since this study was performed in an acute open-chested canine model, we were unable to assess late spontaneous recovery of resting systolic function to correlate with dobutamine responses early after reflow. Our study design employed incremental doses of dobutamine in the early phase of reperfusion to assess contractile reserve as a predictor of late recovery of function. Although stunned myocardium will normally recover systolic function over time, it can take days or even weeks before systolic function significantly improves.

Another limitation of this study is that we did not evaluate the effect of a residual coronary stenosis on the inotropic response to dobutamine. As previously mentioned, dobutamine infusion in the presence of a residual stenosis and preserved subendocardial viability may result in the absence of thickening or a biphasic thickening response. If thickening is absent with incremental doses of dobutamine in this setting, then the extent of viability after reperfusion would be underestimated. The pattern of poor inotropic reserve would appear similar to the pattern seen with total reperfusion and a large infarct size. Further experimental work in dogs with small infarcts and a residual infarct vessel stenosis appears warranted to test this hypothesis.

Conclusions. In summary, the experimental data from this study indicate that myocardial stunning associated with a small infarct size is characterized by enhanced systolic thickening during dobutamine infusion given soon after reflow, whereas a failure to demonstrate increased thickening with dobutamine is suggestive of more irreversible injury. Despite the severe depression of wall motion during the early phase of reperfusion, the inotropic response to just 10 μg·kg⁻¹·min⁻¹ of dobutamine is predictive of the degree of myocardial salvage and ultimate infarct size. To date, clinical studies using dobutamine echocardiography or dobutamine magnetic resonance imaging are most often performed late during the course of hospitalization to assess viability and residual ischemia in postinfarct patients. The results of this experimental study suggest that viability and extent of salvage might be accurately assessed within 60 to 90 min after reperfusion, particularly when infarct-vessel patency is achieved. Data derived from low-dose dobutamine echocardiography early after reperfusion, particularly if coupled with contrast echocardiography, could be clinically useful. The combined determination of microvascular integrity and flow and inotropic reserve with dobutamine stress should provide an accurate early assessment of myocardial viability after reperfusion therapy in acute MI.

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