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Myocardial Contrast Echocardiography Versus Dobutamine Echocardiography for Predicting Functional Recovery After Acute Myocardial Infarction Treated With Primary Coronary Angioplasty

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Objectives. **We sought to compare myocardial contrast echocardiography with low dose dobutamine echocardiography for predicting 1-month recovery of ventricular function in acute myocardial infarction treated with primary coronary angioplasty.**

Background. **The relation between myocardial perfusion and contractile reserve in patients with acute myocardial infarction, in whom anterograde flow is fully restored without significant residual stenosis, is still unclear.**

Methods. **Thirty patients with acute myocardial infarction treated successfully with primary coronary angioplasty underwent intracoronary contrast echocardiography before and after angioplasty and dobutamine echocardiography 3 days after the index infarction. One month later, two-dimensional echocardiography and coronary angiography were repeated in all patients and contrast echocardiography in 18 patients.**

Results. **After coronary recanalization, 26 patients showed myocardial reperfusion within the risk area, although 4 did not. At 1-month follow-up, all patients had a patent infarct-related artery without significant restenosis. Both left ventricular ejection fraction and wall motion score index within the risk area significantly improved in the patients with reperfusion ([mean ± SD] 38 ± 8% vs. 48 ± 12%, $p < 0.005$; and 2.35 ± 0.5 vs. 2 ± 0.6, $p < 0.001$, respectively), but not in those with no reflow. Of the 72 nonperfused segments before angioplasty, 27 showed functional improvement at follow-up. Myocardial contrast echocardiography had a sensitivity and a negative predictive value similar to dobutamine echocardiography in predicting late functional recovery (96% vs. 89% and 89% vs. 93%, respectively), but a lower specificity (18% vs. 91%, $p < 0.001$), positive predictive value (41% vs. 86%, $p < 0.001$) and overall accuracy (47% vs. 90%, $p < 0.001$).**

Conclusions. **Microvascular integrity is a prerequisite for myocardial viability after acute myocardial infarction. However, contrast enhancement shortly after recanalization does not necessarily imply a late functional improvement. Thus, contractile reserve elicited by low dose dobutamine is a more accurate predictor of regional functional recovery after reperfused acute myocardial infarction than microvascular integrity.**

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It is well known that early restoration of anterograde flow in patients with acute myocardial infarction can limit the progression of myocardial necrosis and should enhance the functional recovery of postischemic dysfunctioning myocardium (1–3). Clinical methods to predict left ventricular functional recovery after reperfusion have focused on contractile reserve, myocardial perfusion or metabolic activity (4). Recently both contractile reserve during dobutamine infusion and myocardial perfusion by myocardial contrast echocardiography have been used to predict recovery of regional myocardial function in patients with acute myocardial infarction. In the postinfarction reperfused myocardium, the degree of contractile reserve elicited by dobutamine echocardiography provides a reliable assessment of the extent of viable myocardium (5–8), especially in the absence of residual stenosis limiting hyperemic flow (9). In contrast, myocardial contrast echocardiography is a validated technique for assessing the spatial distribution of microvascular perfusion, and recent studies have demonstrated that microvascular integrity is closely associated with myocardial cellular viability after acute myocardial infarction in humans (10–13). However, the relation between microvascular integrity and inotropic reserve of reperfused postischemic dysfunctioning myocardial segments is still unclear. These two aspects of viability may in fact provide different information regarding functional recovery after reperfusion, and it is not known which of them is more accurate in this setting. Thus, the aim of this study was to compare dobutamine echocardiography and myocardial contrast echocardiography in predicting 1-month functional recovery of regional ventricular function in patients

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Abbreviations and Acronyms

ANOVA = analysis of variance
df = degrees of freedom
ECG = electrocardiogram, electrocardiographic
TIMI = Thrombolysis in Myocardial Infarction

with acute myocardial infarction treated with successful primary percutaneous transluminal coronary angioplasty.

Methods

Patients and study protocol. We prospectively compared dobutamine echocardiography with myocardial contrast echocardiography in 37 patients with acute myocardial infarction selected among 121 patients referred to the catheterization laboratory of the Division of Cardiology of Careggi Hospital for emergency primary coronary angioplasty between January 1995 and December 1995. The study inclusion criteria were: 1) symptoms of acute myocardial infarction that persisted for longer than 30 min associated with an elevation >0.1 mV in the ST segment in two or more contiguous electrocardiographic (ECG) leads; 2) presentation within 6 h after the onset of symptoms or between 6 and 24 h if there was evidence of continuing ischemia; 3) total occlusion of the infarct-related artery; and 4) successful primary coronary angioplasty (defined as Thrombolysis in Myocardial Infarction [TIMI] flow grade 3 and residual stenosis <30%). Exclusion criteria included the presence of either cardiogenic shock or evident clinical instability. No upper age limit was used. Seven (18%) of 37 patients were excluded from the analysis because of either inadequate image quality on the echocardiogram recorded in the catheterization laboratory (four patients) or insufficient contrast effect (three patients). Thus, 30 patients (23 men, 7 women, mean age 60 ± 11 [range 36 to 83]) were enrolled in the study. The research protocol was approved by the local ethics committee, and informed consent was obtained from each patient by one of the investigators (L.B.).

Myocardial contrast echocardiography was performed during acute coronary occlusion, on completion of diagnostic coronary angiography and contrast left ventriculography, and was repeated shortly after coronary angioplasty. Low dose dobutamine echocardiography was performed at a mean of 3 days (range 2 to 5) after admission. Two-dimensional echocardiography and coronary angiography were obtained in all patients, and myocardial contrast echocardiography was repeated in 18 patients 1 month after primary coronary angioplasty.

Myocardial contrast echocardiography. Patients were studied in the supine position. Myocardial contrast echocardiography was performed by injecting 3 ml of iopamidol (Iopamiro, Bracco SpA, Italy), hand-agitated during its passage through a three-way stopcock (14,15), followed by a 3-ml saline flush into the left main and right coronary artery ostia through standard angiographic coronary catheters. In six patients with an occluded left anterior descending coronary artery, contrast injection was performed only in the left main ostium. Echocardiographic images were generated by commercially available imaging systems (Aloka model SSD-830 2.5- and 3.5-MHz transducers and Hewlett-Packard Sonos 2500 2.5-MHz transducer). In each patient the standard echocardiographic view delineating the most asynergic walls was chosen; specifically, the apical four-chamber view was selected in 5 patients, the five-chamber view in 21, the two-chamber view in 2 and the parasternal short-axis view in 2. The gain setting controls were adjusted at the beginning of each study and kept unchanged throughout the study. Echocardiographic images were recorded from before the injection up to 3 min later by a 0.5-in. VHS videotape recorder (Panasonic NV 410). After coronary angioplasty, ultrasound contrast material was injected into the recanalized infarct-related artery using the same echocardiographic view. A 12-lead ECG was continuously monitored during the procedure.

Dobutamine echocardiography. Patients underwent dobutamine echocardiography at a mean of 3 days (range 2 to 5) after the onset of myocardial infarction, while taking all prescribed medications. Echocardiograms were obtained by a commercially available electrical sector scanner (Aloka model SSD 870) equipped with 2.5- and 3.5-MHz transducers. Although all standard views were acquired and recorded, the initial myocardial contrast echocardiographic images were reviewed before each echocardiographic study to depict the same echocardiographic view as best as possible. Images were displayed in real time and were recorded on a videotape by a 0.5-in. VHS cassette recorder (Sony SVO-140PA).

During continuous ECG and two-dimensional echocardiographic monitoring, an intravenous infusion of dobutamine (5 μg/kg body weight per min) was started with an infusion pump and continued for 5 min and then increased to 10 μg/kg per min for another 5 min. The criteria for stopping dobutamine infusion included hypotension, angina and significant ventricular arrhythmias.

Data analysis. *Two-dimensional contrast echocardiographic images* were analyzed by three readers (D.R., P.B., L.B.) who had no knowledge of the clinical and angiographic data. The left ventricle was divided according to a 16-segment model (16). In each segment myocardial contrast echocardiographic effect was scored as 0 (no visible contrast effect), 0.5 (patchy myocardial contrast enhancement or opacification of the epicardial layer only) or 1 (homogeneous contrast effect) (12). When there was a disagreement about the results, the majority judgment was binding. The echocardiographic view delineating the most asynergic walls was chosen for contrast echocardiographic analysis. In this view the risk area was defined as an area not showing contrast enhancement (score 0) and was determined in the postinjection cycles showing the best delineation between contrast-enhanced and nonenhanced myocardium. A score of 0.5 or 1 within the area at risk after

angioplasty was interpreted as reperfusion. A patient was considered to have adequate reperfusion if ≥50% of segments within the area at risk were opacified on myocardial contrast echocardiography.

Dobutamine echocardiograms were analyzed by two readers (G.C., C.M.) blinded to clinical, angiographic and myocardial contrast echocardiographic data. Discrepancies were resolved by consensus. Regional wall motion was assessed according to the same 16-segment model used for contrast echocardiography. For each segment wall motion was scored as 1 (normal), 2 (hypokinetic), 3 (akinetic) or 4 (dyskinetic). In evaluating regional wall motion abnormalities, attention was also paid to the systolic thickening in the central portion of each segment. In each patient both a global and an area at risk wall motion score index were derived. The latter was obtained by averaging the scores from each segment within the area at risk. A single myocardial segment within the area at risk was considered responsive to dobutamine echocardiography if the wall motion score decreased by at least one grade during any stage of the dobutamine infusion compared with the baseline study. A patient was considered improved on dobutamine echocardiography if wall motion improved in two or more contiguous segments.

When performing follow-up echocardiography, again, particular attention was paid to obtain the same echocardiographic view selected during contrast and dobutamine echocardiography. Late reversible dysfunction was defined as improved wall motion (a reduction in segmental score of at least one grade) at late follow-up compared with the baseline study. The left ventricular ejection fraction was calculated according to the area-length method.

All angiograms were analyzed by two experienced observers (D.A., L.B.) blinded to myocardial contrast and dobutamine echocardiographic results. Discrepancies were resolved by consensus. The infarct-related artery was analyzed using a quantitative, computer-assisted, edge-detection system (Siemens Hicor II), which compared the stenotic segment defined by the observer with a "normal" segment defined in the same vessel, and expressed the result as percent stenosis. In all patients the infarct-related artery was analyzed both before and after primary coronary angioplasty to assess residual stenosis. Contrast flow through the epicardial vessel was graded using the standard TIMI trial flow scale of 0 to 3 (17). The same views of coronary arteries were used at follow-up to assess arterial patency, restenosis rate and global left ventricular functions.

Statistical analysis. Continuous data are expressed as mean value ± SD. The statistical significance of the changes in ejection fraction, heart rate, systolic blood pressure and wall motion score index was tested using two-way, repeated measures analysis of variance (ANOVA) with the Tukey post hoc test. Sensitivity, specificity, predictive values and accuracy were evaluated according to standard definitions. Comparisons of proportions were performed using the chi-square test. A value of $p < 0.05$ was considered statistically significant.

Results

Clinical and angiographic patient characteristics. The ECG location of acute myocardial infarction was anterior in 24 patients and inferior in 6. The infarct-related artery was the left anterior descending coronary artery in 24 patients, the right coronary artery in 3 and the circumflex artery in 3. Coronary lesions involved a single vessel in 17 patients, two vessels in 10 and three vessels in 3. The echocardiographic left ventricular ejection fraction on admission was 38 ± 8%. All patients achieved successful coronary reperfusion with <30% residual stenosis and TIMI flow grade 3. After 1 month all patients had a patent infarct-related artery and none exhibited significant restenosis (>50% lumen diameter narrowing).

Safety. No patient showed hemodynamic derangement, complex ventricular or supraventricular arrhythmias or augmentation of chest pain during or immediately after myocardial contrast echocardiography. Furthermore, intracoronary injection of the contrast medium did not produce further changes in the ST-T segment on a 12-lead ECG continuously monitored during and after contrast echocardiography. Similarly, no complication occurred during dobutamine infusion. Heart rate increased from 83 ± 13 beats/min at rest to 99 ± 15 beats/min at peak dobutamine infusion ($p < 0.05$), and systolic blood pressure increased from 119 ± 11 mm Hg at rest to 132 ± 14 mm Hg at peak dobutamine infusion ($p < 0.05$).

Myocardial perfusion in the acute stage. Myocardial perfusion by contrast echocardiography was evaluated in a total of 180 segments. During coronary occlusion myocardial perfusion defects were observed in all patients and involved 72 segments (40% of explored segments). Shortly after infarct-related artery recanalization, the majority of patients (26 of 30) showed myocardial reperfusion of previously ischemic segments. Of 72 segments within the area at risk, 63 were reperfused; of these, 41 (65%) showed homogeneous contrast effect (score 1) and 22 (35%) a partial enhancement pattern (score 0.5). Despite successful angioplasty, myocardial perfusion defects were still present in four patients (no-reflow phenomenon) and involved nine segments (12% of the segments within the area at risk).

Effects of myocardial reperfusion on left ventricular function. According to ANOVA there was a significant effect of the grouping factor (reflow vs. no-reflow: $F = 8.34$, degrees of freedom [df] = 28, $p < 0.01$). No significant effect was observed for the repeated measures factor (baseline vs. follow-up: $F = 1.99$, $p = 0.16$), nor for the interaction ($F = 1.58$, $p = 0.21$). In the 26 patients with myocardial reperfusion after coronary angioplasty, left ventricular ejection fraction by two-dimensional echocardiography significantly improved from the baseline to the follow-up study (39 ± 8% vs. 48 ± 12%, $p < 0.006$), although no improvement was noted in the four patients with the no-reflow phenomenon (30 ± 7% vs. 31 ± 15%, $p = 0.99$). With regard to wall motion score index in the area at risk, two-way ANOVA showed a significant reflow effect ($F = 4.75$, $p < 0.004$) and an even more significant repeated measures effect ($F = 5.63$, $p = 0.024$). However, there was no significant interaction between the two factors

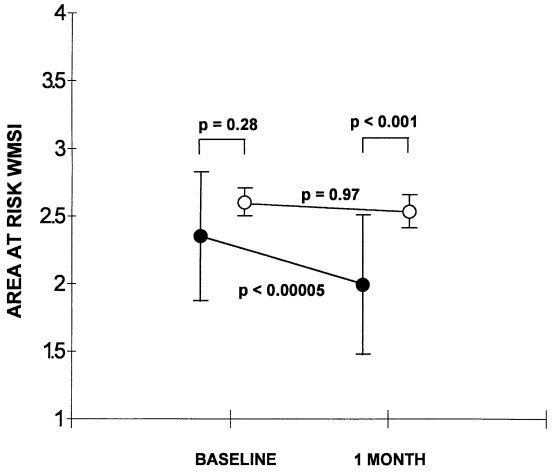


Figure 1. Plots of wall motion score index (WMSI) in the area at risk in the acute and chronic stages of myocardial infarction in patients with (**open circles**) and without residual contrast defects (**solid circles**).

(F = 2.48, p = 0.12). The reperfused patients showed a significant reduction in the wall motion score index in the area at risk from the baseline (before angioplasty) to the follow-up studies (2.35 ± 0.5 vs. 2 ± 0.6, p < 0.0005), although no significant difference was noted among the patients with the no-reflow phenomenon (2.63 ± 0.1 vs. 2.55 ± 0.2, p = 0.97) (Fig. 1).

Prediction of regional functional recovery by myocardial contrast echocardiography and dobutamine echocardiography. Functional recovery at follow-up was observed in 14 (54%) of the 26 patients with myocardial reperfusion and in none of the 4 patients with the no-reflow phenomenon. All of the 14 dobutamine responders and only 1 of the 16 nonresponders showed a late improvement in left ventricular regional function. Thus, the sensitivity of myocardial contrast echocardiography and dobutamine echocardiography for predicting late functional improvement in individual patients was 100% and 93%, and specificity 25% and 100%, respectively.

Of the 63 reperfused segments (score 1 or 0.5), shortly after coronary angioplasty, 26 (41%) showed an improvement in wall motion score after 1 month, whereas 37 did not. In contrast, only 1 of the 9 nonreperfused segments showed a late functional recovery. Of the 41 segments with normal perfusion (score 1), 18 improved at 1 month, whereas 23 did not. Finally, functional recovery occurred only in 9 of 31 segments with partial (score 0.5) or no reflow (score 0).

Abnormal wall motion was observed before dobutamine echocardiography in all 72 segments within the area at risk, of which 28 improved during dobutamine infusion. At 1 month, functional recovery occurred in 24 (86%) of 28 segments with contractile reserve, and in 3 (7%) of 44 segments without contractile reserve. According to ANOVA there was a significant grouping factor effect (dobutamine responders vs. nonresponders: F = 13.7, df = 28, p < 0.001) and a very high within-group repeated measures effect (baseline vs. follow-up: F = 58.5, p = 0.000001). Also, the relation between the two effects was highly significant (F = 32.1, p < 0.00005). Total wall motion score index significantly decreased from baseline to follow-up studies in dobutamine responders (2.34 ± 0.4 vs. 1.7 ± 0.4, p < 0.002), although remained unchanged in dobutamine nonresponders (2.48 ± 0.2 vs. 2.4 ± 0.2, p = 0.48) (Fig. 2).

Table 1 gives the sensitivities, specificities, predictive values and accuracy of myocardial contrast echocardiography and dobutamine echocardiography for predicting late functional recovery of individual segments. The two methods had similar sensitivities and negative predictive values in predicting functional recovery; however, contractile reserve by dobutamine echocardiography had a significantly better specificity (91% vs. 18%, p < 0.001), positive predictive value (86% vs. 41%, p < 0.001) and overall accuracy (90% vs. 47%, p < 0.001) than perfusion by myocardial contrast echocardiography. When data were adjusted to take into consideration only the homogeneous pattern of contrast enhancement as the threshold value, specificity increased to 49%, but sensitivity decreased to 67%. When all the dysfunctional segments in each selected echocardiographic view at the time of coronary occlusion—independently of myocardial perfusion—were included in the

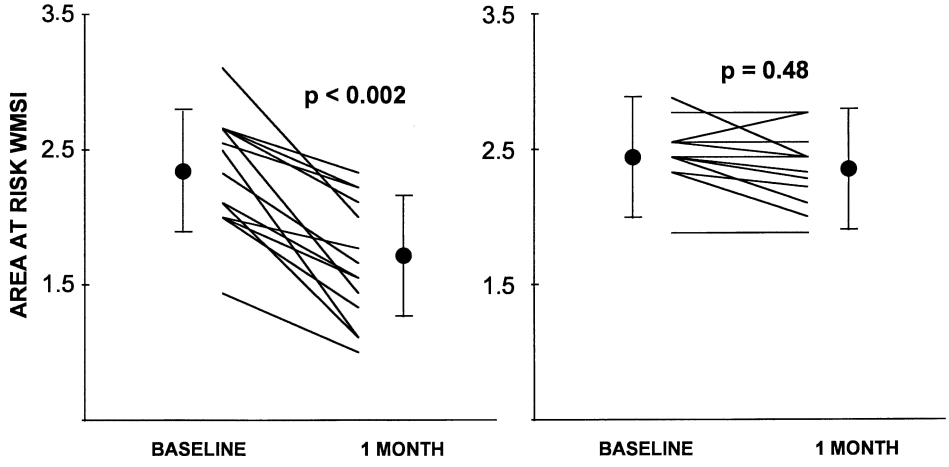


Figure 2. Plots of area at risk wall motion score index (WMSI) at baseline and at 1-month follow-up in dobutamine responders (**left**) and nonresponders (**right**).

Table 1. Comparative Sensitivity, Specificity, Predictive Values and Accuracy of Perfusion by Myocardial Contrast Echocardiography and Contractile Reserve by Dobutamine Echocardiography in Predicting Late Functional Recovery

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
MCE (score 0.5–1)	25/27 (96%)	8/45 (18%)	25/63 (41%)	8/9 (89%)	34/72 (47%)
MCE (score 1)	18/27 (67%)	22/45 (49%)	18/41 (44%)	22/31 (71%)	40/72 (56%)
DE	24/27 (89%)	41/45 (91%)*	24/28 (86%)*	41/44 (93%)	65/72 (90%)*

*$p < 0.001$. Data presented are number (%) of segments. DE = dobutamine echocardiography; MCE = myocardial contrast echocardiography.

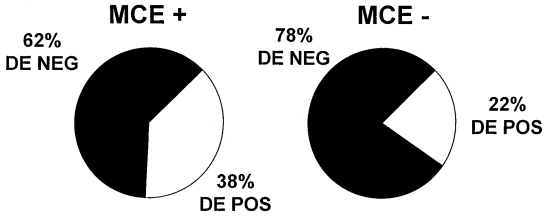
analysis, sensitivity and specificity for myocardial contrast echocardiography and dobutamine echocardiography were, respectively, 97% and 13% and 82% and 88%.

Correlation between contractile reserve and myocardial perfusion. Of the 72 dysfunctional segments in the area at risk, 12 were hypokinetic, 56 were akinetic and 4 were dyskinetic. Dysfunctional segments were more likely to exhibit perfusion than contractile reserve (88% vs. 39%, $p < 0.001$). The two techniques were concordant in 31 segments (43%), so perfusion and contractile reserve were either present or both absent. Concordance was higher in hypokinetic segments (75%) than in akinetic or dyskinetic segments (35%). The disagreement between the two techniques was related primarily to the finding of segments considered viable by contrast echocardiography that did not show contractile reserve by dobutamine echocardiography (39 segments, or 54% of the total number of segments with rest wall motion abnormalities) (Fig. 3).

Myocardial perfusion in the chronic stage. Data on myocardial perfusion by contrast echocardiography at 1 month after the index infarction were available in 18 patients. All these patients had normal (score 1) myocardial perfusion after angioplasty. Nevertheless, in three patients a contrast defect reappeared at the follow-up study, involving a total of 7 segments. All these segments were unresponsive to dobutamine infusion and none showed an improvement in wall motion at follow-up.

Reproducibility. On when myocardial contrast echocardiography results were interpreted, there was complete agreement between the three observers in 168 of 180 segments (93%), and in the remaining 12 segments, a consensus was reached. Similarly, intraobserver agreement was good (96%).

Figure 3. Pie charts showing concordance between myocardial perfusion by contrast echocardiography (MCE) and contractile reserve by dobutamine echocardiography (DE). DE POS (DE NEG) = presence (absence) of contractile reserve during low-dose dobutamine infusion; MCE+ (MCE−) = patients with (without) reflow after infarct-related artery recanalization.



Intraobserver and interobserver variabilities were also assessed for dobutamine echocardiography. The two observers concordantly scored 92% (66 of 72) of the dissynergic segments within the area at risk as having dobutamine-responsive or dobutamine-unresponsive wall motion. Intraobserver variability was assessed by one reader (G.C.). Segments were concordantly scored as dobutamine responsive or unresponsive in 94% (68 of 72).

Discussion

Myocardial contrast echocardiography is gaining interest as a promising method of assessing myocardial viability after acute myocardial infarction. Normal microvascular perfusion is present in regions of viable myocardium, whereas regions of necrosis do not demonstrate microvascular perfusion or show poor perfusion. The assessment of viability by use of this technique has been previously demonstrated in postinfarction patients by several investigators (10–12). However, a direct comparison of myocardial contrast echocardiography with other validated methods such as dobutamine echocardiography for assessing myocardial viability in patients with acute myocardial infarction, in whom anterograde flow is fully restored without significant residual stenosis, is still missing. In this setting, when myocardial necrosis coexists with postischemic myocardial dysfunction and no flow-limiting residual stenosis, dobutamine echocardiography has the potential to accurately assess the extent of viable myocardium (9). Similar to the results reported by Ito et al. in 1992 (10) and more recently by others investigators (18), we found that myocardial segments can show residual perfusion defects despite restoration of anterograde flow, indicating that angiographically successful coronary recanalization, even with a TIMI flow grade 3, does not necessarily imply adequate myocardial perfusion. In addition, patients with early no-reflow exhibit a poor functional recovery at follow-up. However, acutely reperfused segments at myocardial contrast echocardiography often did not demonstrate contractile reserve at 3 days; such segments generally did not show late functional improvement. Thus, the major new findings of the present study are that contrast enhancement shortly after reflow does not necessarily imply regional functional recovery in the chronic stage and that contractile reserve elicited by dobutamine echocardiography 3 days after acute myocardial infarction is more accurate than early perfusion, as assessed by myocardial contrast echocardi-

ography, for predicting functional recovery in patients in whom reperfusion is achieved by means of primary coronary angioplasty.

Microvascular integrity, contractile reserve and myocardial viability. Cardiac imaging techniques that evaluate myocardial viability on the basis of myocardial perfusion, cell membrane integrity, contractile reserve and metabolic activity are being used increasingly in the clinical arena (4). Each of these techniques explores one aspect of viability, and fundamental differences may exist between viability expressed by one method with respect to others (19). Thus, the finding of the present study, that only half of the segments with homogeneous contrast enhancement had preserved contractile reserve and demonstrated improvement at late follow-up, should not be surprising. There are several possible explanations: 1) The infarct area may be a mixing of islands of viable and necrotic myocites (20). In this scenario it is possible that perfusion, although to a lesser extent than normal regions, may be detected despite functional integrity that is precluded by an insufficient number of viable myocites. This hypothesis might be suggested by the patchy pattern of contrast enhancement, which appeared to be a less specific marker of myocardial viability than the homogeneous pattern. 2) Because of hyperemia during the early hours of reperfusion (21–23), myocardial contrast echocardiography may underestimate infarct size and overestimate myocardial salvage (24). This may be particularly true when the residual stenosis within the infarct-related artery is not severe enough to attenuate hyperemic flow, as in our series. The use of an exogenously administered coronary vasodilator, such as dipyridamole, to unmask the reduced microvascular reserve of the infarcted tissue has been recently proposed (25); however, this approach may be unpractical or even unsafe during coronary angioplasty performed for the treatment of an evolving acute myocardial infarction. Third, a temporal dissociation between microvascular and cellular damage may exist (26,27), and recent studies have suggested that late evaluation of myocardial perfusion by contrast echocardiography correlates with late functional recovery more closely than myocardial perfusion evaluated shortly after reperfusion (28,29). The dynamic nature of myocardial perfusion is further confirmed by the present study, where perfusion defects reappeared 1 month after coronary reflow, despite the absence of coronary restenosis.

One may speculate that reperfusion injury and the time delay from the cell death to the destruction of capillary network may be a possible explanation for the absence of contractile reserve evaluated in a relatively late phase after reperfusion and the lack of recovery of regional function at follow-up. Finally, we chose the recovery of contractility as the primary end point because of its prognostic relevance; however, we cannot exclude that microvascular integrity also plays a role in the clinical outcome by a different mechanism, such as prevention of ventricular remodeling.

Study limitations. Several potential limitations of the present study should be acknowledged. The number of patients was relatively small, and dobutamine and contrast echocardiography were not performed simultaneously. Moreover, we did not compare myocardial contrast echocardiography with other accepted methods of assessing myocardial viability. However, dobutamine echocardiography has been shown to compare favorably with both thallium-201 scintigraphy and positron emission tomography both in acute and chronic ischemic heart disease (5,30,31). The assessment of the risk area during coronary occlusion requires injections into both the coronary ostia, which were not performed in six patients. In these patients collateral flow distal to the occluded infarct-related artery was not demonstrated during myocardial contrast echocardiography, and hence the functional risk area was likely overestimated (32).

The analysis of contrast echocardiographic images was performed only in one cross-sectional view; thus, the analysis of functional recovery was based on a small number of segments relative to a total number of dysfunctional segments. This may explain the substantial improvement in left ventricular function despite the small number of segments within the area at risk showing functional improvement at follow-up. The performance of dobutamine echocardiography was tested in a setting where no patient had significant residual stenosis. Therefore, the results of the present study may not be directly applicable to clinical situations where residual stenosis is present. An additional potential limitation of this study is that follow-up echocardiography was performed 1 month after coronary angioplasty, whereas recent studies show that left ventricular function can improve in a substantial number of segments several months after an acute infarction (33). Finally, the analysis of regional function was semiquantitative. However, this qualitative approach has been largely adopted for clinical studies with stress echocardiography in ischemic heart disease (34). Similarly, our method of assessing myocardial contrast effect was subjective and only one section was explored; a quantitative approach was not possible in all patients given the quality of the studies, which were obtained during cardiac catheterization with the patients in the supine position, and the current limitations of the technique. These factors, along with the complexity of the protocol, may have affected the feasibility of the study.

Conclusions. Our data indicate that preserved myocardial perfusion is a prerequisite for myocardial viability after a reperfused myocardial infarction. In fact, functional recovery of the postinfarction reperfused myocardium is observed only when adequate tissue flow is restored, which is highly improbable in patients with the no-reflow phenomenon. However, contrast enhancement shortly after reperfusion does not necessarily imply a late functional improvement. In the setting of acute myocardial infarction successfully treated with primary coronary angioplasty without residual stenosis limiting hyperemic flow, contractile reserve by dobutamine echocardiography appears to be more accurate than myocardial perfusion by contrast echocardiography for predicting reversible regional myocardial dysfunction.

References

1. Verani MS, Roberts R. Preservation of cardiac function by coronary thrombolysis during acute myocardial infarction: fact or myth? J Am Coll Cardiol 1987;10:470–6.
2. White HD, Norris RM, Brown MA, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. N Engl J Med 1987;317:850–5.
3. The GUSTO angiographic investigators. The effect of tissue plasminogen activator, streptokinase, or both, on coronary artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–22.
4. Dilsizian V, Bonow RO. Current diagnostic techniques on assessing myocardial viability in patients with hibernating and stunned myocardium. Circulation 1993;87:1–20.
5. Pierard LA, De Lansheere CM, Berthe C, Rigo P, Kulbertus HA. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. J Am Coll Cardiol 1990;15: 1021–31.
6. Barilla F, Gheorghiade M, Alam M, Khaja F, Goldstein S. Low-dose dobutamine in patients with acute myocardial infarction identifies viable but not contractile myocardium and predicts the magnitude of improvement in wall motion abnormalities in response to coronary revascularization. Am Heart J 1991;122:1522–31.
7. Smart SC, Sawada S, Ryan T, et al. Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction. Circulation 1993;88:405–15.
8. Watada H, Ito H, Oh H, et al. Dobutamine stress echocardiography predicts reversible dysfunction and quantitates the extent of irreversibly damaged myocardium after reperfusion of anterior myocardial infarction. J Am Coll Cardiol 1994;24:624–30.
9. Sklenar J, Ismail S, Villanueva FS, Goodman C, Glasheen WP, Kaul S. Dobutamine echocardiography for determining the extent of myocardial salvage after reperfusion—an experimental evaluation. Circulation 1994;90: 1502–12.
10. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis: a predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992;85:1699–1705.
11. Agati L, Voci P, Bilotta F, et al. Influence of residual perfusion within the infarct zone on the natural history of left ventricular dysfunction after acute myocardial infarction: a myocardial contrast echocardiographic study. J Am Coll Cardiol 1994;24:336–42.
12. Ragosta M, Camarano G, Kaul S, Powers ER, Sarembock IJ, Gimple LW. Microvascular integrity indicates myocellular viability in patients with recent myocardial infarction. New insights using myocardial contrast echocardiography. Circulation 1994;89:2562–9.
13. Camarano G, Ragosta M, Gimple LW, Powers ER, Kaul S. Identification of viable myocardium with contrast echocardiography in patients with poor left ventricular systolic function caused by recent or remote myocardial infarction. Am J Cardiol 1995;75:215–9.
14. Ito H, Tomooka T, Sakai N, et al. Time course of functional improvement in stunned myocardium in risk area in patients with reperfused anterior infarction. Circulation 1993;87:355–62.
15. Nanto S, Masuyama T, Lim Y, Hori M, Kodama K, Kamada T. Demonstration of functional border zone with myocardial contrast echocardiography in human hearts. Simultaneous analysis of myocardial perfusion and wall motion abnormalities. Circulation 1993;88:447–53.
16. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358–67.
17. The TIMI study group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. N Engl J Med 1985;312:932–6.
18. Kenner MD, Zajac EJ, Kondos GT, et al. Ability of the no-reflow phenomenon during an acute myocardial infarction to predict left ventricular dysfunction at one-month follow-up. Am J Cardiol 1995;76:861–8.
19. Kaul S. There may be more to myocardial viability than meets the eye! [editorial comment]. Circulation 1995;92:2790–3.
20. Bodenheimer MM, Banka VS, Hermann GA, Trout RG, Pasdar H, Helfant R. Reversible asinergy: hystopathologic and electrocardiographic correlations in patients with coronary artery disease. Circulation 1976;53:792–6.
21. White FC, Sanders M, Bloor CM. Regional redistribution of myocardial blood flow after coronary occlusion and reperfusion in the conscious dog. Am J Cardiol 1978;42:234–43.
22. Heyndrickx GR, Amano J, Patrick TA, et al. Effects of coronary artery reperfusion of regional myocardial blood flow and function in conscious baboons. Circulation 1985;71:1029–37.
23. Cobb FR, Bache RJ, Rivas F, Greenfield JC. Local effects of acute cellular injury on regional myocardial blood flow. J Clin Invest 1976;57:1359–68.
24. Kaul S, Pandian NG, Guererro JL, Gillam LD, Okada RD, Weyman AE. The effects of selectively altering the collateral driving pressure on regional perfusion and function in the occluded coronary bed in the dog. Circ Res 1987;61:77–85.
25. Villanueva FS, Glasheen WP, Sklenar J, Kaul S. Characterization of spatial patterns of flow within the reperfused myocardium by myocardial contrast echocardiography. Implications in determining the extent of myocardial salvage. Circulation 1993;88:2596–606.
26. Olafsson B, Forman MB, Puett DW, et al. Reduction of reperfusion injury in the canine preparation by intracoronary adenosine: importance of the endothelium and the no-reflow phenomenon. Circulation 1987;76:1135–45.
27. Kloner RA, Rude RE, Carlson N, Maroko PR, DeBoer LWV, Braumwald E. Ultrastructural evidence of microvascular damage and myocardial cell injury after coronary artery occlusion: which comes first? Circulation 1980; 62:945–52.
28. Ito H, Iwakura K, Oh H, et al. Temporal changes in myocardial perfusion patterns in patients with reperfused anterior wall myocardial infarction. Their relation to myocardial viability. Circulation 1995;91:656–62.
29. Lim YJ, Nanto S, Masuyama T, Kohama A, Hori M, Kamada T. Myocardial salvage: its assessment and prediction by the analysis of serial myocardial contrast echocardiograms in patients with acute myocardial infarction. Am Heart J 1994;128:649–56.
30. Baer FM, Voth E, Deutsch HJ, Schneider CA, Schicha H, Sechtem U. Assessment of viable myocardium by dobutamine transesophageal echocardiography and comparison with fluorine-18 fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol 1994;24:343–53.
31. Panza JA, Dilsizian V, Laurienzo JM, Curiel RV, Katsiyiannis PT. Relation between thallium uptake and contractile response to dobutamine. Implications regarding myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction. Circulation 1995;91:990–8.
32. Sabia PJ, Powers ER, Jayaweera AR, Ragosta M, Kaul S. Functional significance of collateral blood flow in patients with recent acute myocardial infarction: a study using myocardial contrast echocardiography. Circulation 1992;85:2080–9.
33. Galli M, Marcassa C, Bolli R, et al. Spontaneous delayed recovery of perfusion and contraction after the first 5 weeks after anterior infarction. Evidence for the presence of hibernating myocardium in the infarcted area. Circulation 1994;90:1386–97.
34. Picano E, Lattanzi F, Orlandini A, Marini C, L'Abbate A. Stress echocardiography and the human factor: the importance of being expert. J Am Coll Cardiol 1991;17:666–9.