Detection of Myocardial Viability by Contrast Echocardiography in Acute Infarction Predicts Recovery of Resting Function and Contractile Reserve

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OBJECTIVES

We sought to determine whether myocardial contrast echocardiography (MCE) performed before and early after primary coronary stenting (PCS) in patients with acute myocardial infarction (AMI) could predict recovery of resting left ventricular systolic function and contractile reserve.

BACKGROUND

Myocardial contrast echocardiography can be used to assess perfusion within the risk area before PCS and the extent of necrosis soon after PCS.

METHODS

In 30 patients with AMI, MCE and two-dimensional echocardiography were performed before PCS and 3 to 5 days and 4 weeks after PCS. Contractile reserve was assessed by dobutamine echocardiography at four weeks in patients with persistent severe wall-motion abnormalities.

RESULTS

Of segments without perfusion at 3 to 5 days, 95% had severe hypokinesis to akinesis at 4 weeks. Of segments with normal perfusion at 3 to 5 days, 90% had normal wall motion or mild hypokinesis at 4 weeks, whereas those with partial perfusion at 3 to 5 days were evenly divided between normal wall motion, hypokinesis, and akinesia. In segments with persistent severe wall-motion abnormalities at four weeks, contractile reserve was found in >80% of segments with perfusion, compared with only 10% of segments without detectable perfusion (p < 0.01). The presence of myocardial perfusion by MCE before PCS was associated with maintained or improved perfusion at 3 to 5 days and eventual recovery of resting wall motion.

CONCLUSIONS

Myocardial contrast echocardiography performed early after PCS provides information on the extent of infarction, and hence the likelihood for recovery of resting systolic function or contractile reserve. The presence of perfusion before PCS, from either collateral or antegrade flow, predicts the maintenance of perfusion and recovery of systolic function. (J Am Coll Cardiol 2003;41:827–33) © 2003 by the American College of Cardiology Foundation

In patients with acute myocardial infarction (AMI), the primary treatment goal is re-establishment of epicardial artery patency and restoration of microvascular perfusion. Prompt and complete microvascular reflow results in salvage of most of the myocardium at risk and eventual recovery of resting systolic function. When myocardial salvage is partial, resting function in the risk area may not recover because systolic contractile function at rest is dependent largely on thickening of the endocardial region (1,2). Even when resting function does not recover, partial viability may still be beneficial for contractile reserve, exercise tolerance, prevention of remodeling, and survival (3–6).

The spatial extent of necrosis can be evaluated early after AMI by myocardial contrast echocardiography (MCE), which assesses the region of microvascular damage. In this study, we hypothesized that the extent of viability by MCE performed early after primary coronary stenting (PCS) in patients with AMI predicts the degree of recovery of systolic function; and that in segments with persistent severe wall-motion abnormalities, the presence of at least partial viability by MCE identifies segments with contractile reserve. We also performed MCE before revascularization to determine whether the presence of perfusion in the risk area before PCS, from either collateral flow or antegrade flow in the infarct-related artery (IRA), predicts restoration of normal perfusion after PCS and eventual recovery of resting function.

METHODS

Study design. The study protocol was approved by the Human Investigation Committee at the University of Virginia, and all patients gave informed consent. In 30 patients with ST-segment elevation AMI referred for PCS, MCE was performed to assess microvascular perfusion, and two-dimensional (2-D) echocardiography was performed to assess wall motion immediately before PCS, and 3 to 5 days and 4 weeks after PCS. In selected patients with persistent severe wall-motion abnormalities, contractile reserve was assessed by low-dose dobutamine echocardiography at four weeks.
Patient population. Consecutive patients with ST-elevation AMI presenting within 8 h of symptom onset referred for primary PCS were enrolled. The diagnosis of AMI was made on the basis of symptoms consistent with myocardial ischemia for $\geq 30$ min and $\geq 2$ mm ST-segment elevation in two or more contiguous electrocardiogram leads. Patients with a history of prior AMI, wall-motion abnormalities in more than one vascular territory on the initial echocardiogram, cardiomyopathy, hemodynamic instability, or allergy to blood products were excluded.

Coronary angiography and stenting. All patients received oral aspirin (324 mg) and intravenous heparin. Angiography was performed using standard views. Coronary angioplasty and stenting (3.0 to 4.5 mm diameter) of the IRA was performed and deemed successful in all patients. Clopidogrel (300 mg) was given orally before PCS and continued (75 mg per day) for the duration of the study. Intravenous glycoprotein IIb/IIIa antagonist was administered at the discretion of the operating physician. The Thrombolysis In Myocardial Infarction (TIMI) flow grade (7) before and following PCS was assessed by a reader blind to the clinical and echocardiographic data.

MCE. Intermittent ultraharmonic imaging was performed using a Sonos 5500 ultrasound system (Philips Ultrasound, Andover, Massachusetts) with transmission and receive frequencies of 1.3 and 3.6 MHz, respectively. Images were acquired in the apical two-, three-, and four-chamber views. The maximal mechanical index was used and the acoustic focus was placed at the level of the mitral valve and adjusted to the apex when needed to exclude near-field artifacts. A dynamic range of 60 dB was used and compression was set at 80. For each patient, settings were kept constant for all stages.

After acquisition of baseline images, Optison (Mallinckrodt Medical, St. Louis, Missouri) was administered intravenously as a continuous infusion (0.5 ml·min$^{-1}$) and adjusted to produce optimal opacification without far-field attenuation. After several beats of continuous imaging, end-systolic images were acquired at pulsing intervals (PI) of every 1 to 10 cardiac cycles to allow incremental replenishment of microbubbles into the tissue in the ultrasound imaging sector following each high-power pulse (8).

2-D and dobutamine echocardiography. Wall motion was assessed by 2-D echocardiography with and without contrast enhancement of the left ventricular cavity in the apical two-, three-, and four-chamber imaging planes. Wall motion was assessed using tissue harmonic imaging before contrast infusion. At the end of each microbubble infusion performed for assessment of perfusion, settings were optimized for left ventricular cavity opacification by decreasing the mechanical index to 0.4 to 0.5, placing the acoustic focus at the apex, and adjusting the gain settings as needed. For assessment of contractile reserve at four weeks, wall motion was assessed during infusion of incremental doses of dobutamine from 5 to 20 $\mu$g·kg$^{-1}$·min$^{-1}$ during continuous electrocardiogram and blood pressure monitoring. Cine loops were acquired at frame rates $\geq 30$ Hz.

Data analysis. Analysis of echocardiographic data was performed by an experienced reader blind to the clinical and angiographic data. Myocardial contrast echocardiography and wall motion data were assessed separately. For each view, the left ventricle was divided into six equal segments. Resting wall motion in each segment was scored as 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, or 5 = dyskinesis based on review of the noncontrast and contrast-enhanced video clips. Segments that were severely hypokinetic to dyskinetic on the initial study before PCS constituted the risk area. For each study, a wall motion score index in the risk area (WMSI-RA) was derived by summing all wall motion scores in the risk area and dividing by the total number of segments. In selected patients with persistent severe wall motion abnormalities (WMSI-RA $\geq 2.5$ and at least two segments with scores $\geq 3$) at four weeks, the presence of contractile reserve was defined by an improvement of $\geq 1$ grade during dobutamine infusion, except for dyskinetic segments, which were considered viable only if a score of $\leq 3$ was achieved.

Myocardial perfusion was assessed from MCE images obtained during intermittent ultraharmonic imaging. Each segment was assigned a single perfusion score based on both the change in myocardial signal intensity with prolongation of the PI and the degree of opacification at the longest PI. Scores were graded as 2 = normal (homogenous opacification approximating that of the normal region at the longest PI and normal rate of increase in signal with PI prolongation), 1 = reduced (partial or reduced opacification compared with the normal region at the longest PI and/or reduced rate of increase in signal intensity with PI prolongation), or 0 = absent (no opacification despite prolongation of the PI). A perfusion score index in the risk area (PSI-RA) was derived by dividing the summed perfusion scores in the risk area by the number of segments. Segments in which perfusion could not be assessed because of attenuation or other imaging artifacts were excluded from analysis for both WMSI-RA and PSI-RA. One-third of all studies were randomly chosen to assess interobserver variability with a second expert reader.

Statistical methods. Data are expressed as the mean $\pm$ SD. Comparisons were made using the Student $t$ test (paired) or by chi-square analysis. The relationship between

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<td>IRA</td>
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<td>2-D</td>
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WMSI-RA and PSI-RA data was analyzed by regression analysis and data were curve-fitted using a least-squares fit. The R value was derived from R^2 or the regression sum of squares divided by the total sum of squares. Differences were considered significant at p < 0.05.

RESULTS

Patient characteristics and clinical variables. The clinical variables for the patient cohort are presented in Table 1. Antegrade flow in the IRA was found in 40% of patients by arteriography before PCS. Stenting was successful in re-establishing epicardial artery patency in all patients and 87% had angiographic TIMI-3 flow after the procedure. There were no deaths or clinical evidence for recurrent ischemic events (rehospitalization for angina or acute coronary syndrome, or repeat coronary angiography) in the four-week interval after PCS.

Temporal course of myocardial perfusion. In the studies randomly chosen to assess interobserver variability, concordance between the two readers was good for both segmental wall motion scores (92% concordance, kappa = 0.91) and perfusion scores (82% concordance, kappa = 0.60). Discordance was attributable mostly to wall motion scores assigned as 3 versus 4, and for perfusion scores assigned 1 versus 2.

The perfusion scores on MCE for segments within the risk area assessed 3 to 5 days after PCS according to their perfusion scores before PCS are shown in Figure 1. In the 68 segments with no perfusion (score = 0) before PCS, 51 (75%) had restoration of perfusion (score = 1 or 2) at 3 to 5 days. Myocardial contrast echocardiography images demonstrating almost complete restoration of myocardial perfusion in the risk area after PCS are illustrated in Figure 2. In the 156 risk area segments with partial or normal perfusion (score = 1 or 2) before PCS, 147 (94%) had improved or maintained perfusion at 3 to 5 days, the majority of which was categorized as normal (Fig. 1), whereas only 9 (6%) demonstrated absence of perfusion. Of segments with perfusion before PCS, 45% were in patients who had spontaneous reflow of their IRA on angiography before PCS, whereas the remainder were in patients with occluded arteries. Segmental perfusion scores at 4 weeks were almost identical to those at 3 to 5 days, with differences found in only 14 of 227 segments (6%) within the risk area. Myocardial perfusion and recovery of resting systolic function. Wall-motion scores within the risk area 4 weeks after PCS according to MCE-derived myocardial perfusion 3 to 5 days after PCS are depicted in Figure 3A. Almost all segments without perfusion (score = 0) at 3 to 5 days had severe wall motion abnormalities at 4 weeks, approximately 75% of which were akinetic or dyskinetic. Almost all segments with normal perfusion (score = 2) at 3 to 5 days had normal wall motion or were only mildly hypokinetic at 4 weeks. The majority of these segments (62%) had completely normal wall motion. In segments with partial perfusion (score = 1) at 3 to 5 days, wall motion at 4 weeks was evenly divided between normal wall motion, mild hypokinesis, severe hypokinesis, and akinesis.

Table 1. Clinical and Angiographic Data

<table>
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<th>Variable</th>
<th>n (%)</th>
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<tr>
<td>Age (median, yrs)</td>
<td>58</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>20/10</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>Time from symptom onset (h)</td>
<td>4.9 ± 1.9</td>
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<tr>
<td>Totally occluded IRA, n (%)</td>
<td>18 (60%)</td>
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<tr>
<td>Infarct artery, n (%)</td>
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<tr>
<td>LAD</td>
<td>12 (40%)</td>
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<tr>
<td>RCA</td>
<td>16 (53%)</td>
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<tr>
<td>LCx</td>
<td>2 (7%)</td>
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<tr>
<td>Postprocedural TIMI-3 flow, n (%)</td>
<td>26 (87%)</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor, n (%)</td>
<td>24 (80%)</td>
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GP = glycoprotein; IRA = infarct-related artery; LAD = left anterior descending coronary artery; LCx = left circumflex; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

Figure 1. Perfusion scores for segments within the risk area assessed by myocardial contrast echocardiography 3 to 5 days after primary coronary stenting (PCS) according to their perfusion scores assigned immediately before PCS. p < 0.01 for differences between the groups by chi-square analysis. Perfusion score at 3 to 5 days: white bar = 0; striped bar = 1; black bar = 2.

Figure 2. Examples of myocardial contrast echocardiography images in the apical four-chamber plane illustrating near complete myocardial reperfusion in a patient undergoing successful primary coronary stenting (PCS) of a totally occluded left anterior descending coronary artery (LAD). Images were obtained at a pulsing interval of 10 cardiac cycles and demonstrate little perfusion in the LAD territory before PCS (left image) and restoration of perfusion except for a small portion of the distal septum at 3 to 5 days (right image).
Because the likelihood of maintaining normal microvascular perfusion after PCS was much greater when perfusion was present before PCS (Fig. 1), we investigated whether perfusion before PCS predicted eventual recovery of wall motion. The relation between myocardial perfusion in segments within the risk area before PCS and wall motion at four weeks is depicted in Figure 3B. Almost all segments with normal perfusion and the majority of segments with partial perfusion had normal wall motion or were mildly hypokinetic at four weeks.

The relation between the PSI-RA 3 to 5 days after PCS and the WMSI-RA at 4 weeks is depicted in Figure 4. Those patients with excellent perfusion in the risk area (high PSI-RA) after PCS had near complete recovery of wall motion (low WMSI-RA), whereas patients with very poor perfusion did not recover function. The relation for all patients was, however, nonlinear owing to lack of recovery of wall motion (high WMSI-RA) in those with an intermediate degree of perfusion in the risk area after PCS. Illustrated in Figure 5 are end-systolic MCE images obtained from a patient with an intermediate PSI-RA and persistent akinesis in much of the risk area. These images suggest that subendocardial or patchy infarction was responsible for lack of recovery of resting wall motion in patients with intermediate perfusion scores.

**Myocardial perfusion and contractile reserve.** To determine whether the presence of viability detected by MCE confers contractile reserve in patients whose resting function did not recover, wall motion response to dobutamine was assessed. A subset of 9 patients with a PSI-RA of 0 to 1.5 at 3 to 5 days and a WMSI-RA $\geq$ 2.5 at 4 weeks (patients represented by the initial plateau in Fig. 4) were selected for dobutamine echocardiography. Augmentation in systolic thickening occurred in almost all risk area segments where perfusion was present, and occurred in few segments where perfusion was absent (Fig. 6). For the few segments where contractile reserve was observed despite no perfusion, the risk area was very small, and bordering segments always had normal perfusion.

**DISCUSSION**

In this study we have demonstrated that in patients with AMI the extent of microvascular integrity assessed by MCE early after primary percutaneous intervention provides information on myocardial viability. The new information provided by this study includes: 1) that the extent of recovery of resting systolic function correlates with the extent of perfusion by MCE; 2) that in regions with persistent severe wall motion abnormalities, the presence of patchy or epicardial viability identifies regions with contractile reserve; and 3) that the presence of perfusion within the risk area before PCS, from either collateral flow or spontaneous reperfusion of the IRA, is associated with small regions of infarction indicated by eventual recovery of resting systolic function.

Myocardial contrast echocardiography is well suited for assessing the integrity of the microcirculation and, hence, for determining the extent of myocardial necrosis early after AMI (9). Before the development of intravenous ultrasound
contrast agents, microbubbles were injected directly into the coronary artery during angiography to assess the distal capillary bed. In the current study, intravenous microbubble administration and intermittent high-power imaging algorithms were used to evaluate regional perfusion, and viability was determined by analyzing both the peak intensity at a long PI and the change in acoustic intensity with prolongation of the PI (10). Assessment of viability with MCE was delayed for several days after PCS because microvascular perfusion in the risk area immediately after epicardial artery reflow is dynamic because of hyperemia (11), and because microvascular reflow can substantially improve or worsen in the first few hours or days after epicardial artery reflow (12). We found that perfusion assessed 3 to 5 days after PCS was almost identical to that measured later in the chronic phase.

In patients with acute or recent AMI, the absence of microvascular perfusion determined by MCE with intracoronary injection of microbubbles predicts lack of recovery of resting left ventricular systolic function, irrespective of whether IRA patency is achieved (13–15). More recent studies using intravenous contrast administration and intermittent high-MI imaging techniques have shown similar results (16–20). In accord with prior studies, we found that resting wall motion invariably did not recover when myocardial perfusion was absent after PCS. In prior studies, however, the presence of perfusion by MCE early after AMI has not been completely reliable for predicting recovery of resting function (17,18,21). These findings do not necessarily imply a weakness in the imaging technique, but instead reflect the expected long-term outcomes when there is subendocardial or patchy infarction. Wall motion at rest is largely dependent upon endocardial thickening so that the transmural extent of viability in some of these studies may not have been sufficient to allow recovery of systolic function (1,2). In the current study, we determined on a segmental basis that the presence of completely normal perfusion at 3 to 5 days after PCS predicted the presence of normal or near-normal function at 4 weeks. When perfusion was present but reduced, reflecting partial infarction, resting wall motion at four weeks was variable. Many of these segments where resting function remained severely hypokinetic to akinetic were characterized by an epicardial rim of viable tissue.

Even when resting systolic function does not recover, the presence of partial viability after AMI is likely to be beneficial. Although mid- and epicardial portions of the left ventricle contribute little to resting function, they become important for augmentation of systolic performance during exertion. In patients with chronic ischemic dysfunction, revascularization of viable territories leads to improvement in inotropic reserve even when resting akinesia persists (5). Accordingly, we sought to determine whether the presence of viability in segments with persistent severe wall-motion abnormalities after primary revascularization identifies the ability to augment thickening with stress. Contractile reserve was measured by low-dose dobutamine echocardiography in the relatively small number of patients with poor wall-motion scores at four weeks. Almost all segments with perfusion had a positive inotropic response, whereas very few segments without perfusion improved. Our results are in accord with a recent report demonstrating that the degree of opacification on MCE (for the entire risk area rather than a segmental basis) correlated with the presence of contractile reserve in patients with recent AMI (21).
The presence of viability in the epicardial portions of the left ventricle overlaying the infarct bed is also beneficial for maintaining normal left ventricular shape and preventing adverse left ventricular remodeling (22). Left ventricular dilation after AMI has been shown to occur primarily in patients who have little or no contractile response to dobutamine (6), or who have complete absence of microvascular reflow by MCE with intracoronary injection of microbubbles (23). Hence, it is likely that patients in our study with persistent severe wall motion abnormalities but partial viability after PCS would be protected from adverse remodeling. We believe that more patients and longer follow-up would be required to adequately test this hypothesis.

In patients undergoing primary angioplasty, the presence of TIMI-3 epicardial artery flow before the procedure portends better prognosis in terms of mortality and development of congestive heart failure (24). This benefit is presumably due to preserved microvascular perfusion and enhanced myocardial salvage. In the current study, we demonstrated that microvascular perfusion in the risk area before PCS predicted postprocedural viability and recovery of resting function. Many of these segments were found in patients in whom anastomosis flow was detected in the IRA before PCS. The ability of MCE to predict TIMI 2 or 3 flow in the IRA before PCI has been demonstrated previously (20). However, MCE can also be used to assess collateral-derived myocardial blood flow, manifest by contrast enhancement that occurs at long PIs (25,26). It is, therefore, not surprising that perfusion in the risk area before PCS was also detected in a group of patients with completely closed infarct-related arteries. The presence of perfusion within the risk area, even when reduced compared to normal regions, portended a better prognosis in terms of perfusion status after intervention and recovery of resting systolic function. Loss of perfusion after PCS in segments that had normal perfusion before the procedure, presumably a result of distal microvascular embolization, was uncommon.

Methods for quantifying myocardial perfusion by contrast echocardiography are currently available that rely on the assessment of myocardial microvascular blood volume and blood velocity (8). Although quantification may have yielded more objective and reproducible data, it would have limited the clinical relevance of the study for several reasons. First, the means for quantifying perfusion by analyzing PI versus acoustic intensity data are currently not widely applied in the clinical setting. Second, quantification protocols in their current form are time consuming and are unlikely to be used when integrating information on perfusion acquired in the acute setting before PCS.

In summary, results of this study indicate that the extent of myocardial salvage can be determined by MCE early after PCS at a time when viability cannot be accurately assessed by contractile function because of posts ischemic stunning. Recovery of resting left ventricular function can no longer be considered the gold standard for assessing viability because this parameter does not detect salvage of epicardial portions of the myocardium, which may be important for maintaining left ventricular geometry, providing contractile reserve, and preventing heart failure symptoms. Myocardial contrast echocardiography is capable of detecting partial viability even in territories that remain akinetic, thereby providing information on prognosis and need for further protection from ischemic injury. Because MCE perfusion imaging can be performed rapidly at the patient bedside, it also provides the opportunity to evaluate myocardial blood flow in patients with AMI before intervention. With the evolving paradigms of transferring patients to regional AMI treatment centers for percutaneous intervention, it is possible that this information will prove valuable for determining optimal treatment strategies for individual patients.

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