Microvascular Integrity Indicates Myocardial Viability in Patients With Recent Myocardial Infarction

New Insights Using Myocardial Contrast Echocardiography

Michael Ragosta, MD; Gustavo Camarano, MD; Sanjiv Kaul, MD; Eric R. Powers, MD; Ian J. Sarembock, MB, ChB, MD; Lawrence W. Gimple, MD

Background Patency of the infarct-related artery (IRA) after acute myocardial infarction (AMI) may not reflect the magnitude of tissue perfusion. In animal models of AMI, myocardial cellular necrosis has been associated with extensive capillary damage. Because myocardial contrast echocardiography (MCE) can define the spatial distribution of microvascular perfusion, we hypothesized that it could be used in patients after recent AMI to distinguish myocardial regions that have an intact microvasculature and thus are viable from those without an intact microvasculature and thus are not viable.

Methods and Results One hundred five patients with a recent AMI (range, 1 day to 4 weeks; median, 8 days) who were undergoing cardiac catheterization were included in the study. Two-dimensional echocardiography was performed at baseline and repeated 1 month later to assess regional function within the infarct zone (scores of 1 to 5 indicating normal to dyskinetic segments, respectively). MCE was performed in the cardiac catheterization laboratory to assess microvascular perfusion within the infarct bed. A contrast score index was derived by assigning scores to individual segments within the infarct zone (0, 0.5, and 1 denoting no, intermediate, and homogeneous contrast effect, respectively) and deriving the average score within the infarct bed. Revascularization was performed as clinically indicated. Although the baseline wall motion score and the contrast score index were similar in the 90 patients with a patent IRA and the 15 patients with an occluded IRA (median±1 interquartile range, 3±1 versus 3.5±1; \(P=.41\)), wall motion score 1 month later was significantly better in those with open IRAs compared with those with closed IRAs (2±2 versus 3±2; \(P=.05\)). In the 90 patients with an open IRA, a strong correlation was noted between wall motion score 1 month later and the contrast score index \((\rho=-.64, P<.001)\). On multivariate analysis, the best correlate of the 1-month wall motion score was the contrast score index.

Conclusions In patients studied in the cardiac catheterization laboratory between 1 day and 4 weeks after AMI, an intact microvasculature as identified by MCE indicates myocardial regions that improve function 1 month later. This study demonstrates that microvascular patency is closely associated with myocardial cellular viability after AMI in humans.

Key Words • infarction • echocardiography • angiography

Patency of the infarct-related artery (IRA) after acute myocardial infarction (AMI) may not be associated with microvascular integrity and tissue perfusion. In animal models of AMI, myocardial necrosis has been associated with the loss of microvascular integrity. Zones of microvascular injury are located exclusively within the borders of irreversibly injured myocardium and occur in proportion to the extent and severity of cellular necrosis. This microvascular injury, in the absence of postischemic hyperemia, may be an important contributor to either no flow (the "no-reflow" phenomenon) or very low flow ("low-reflow" phenomenon), which develops within zones of necrosis early after reperfusion is established through the IRA.

Myocardial contrast echocardiography (MCE) uses air-filled microbubbles with a mean size ranging from 4 to 6 \(\mu m\) that act as scatterers of ultrasound. When injected directly into coronary arteries, these bubbles traverse the myocardial microvasculature and produce opacification on simultaneously performed two-dimensional echocardiography. During their transit through the myocardium, these bubbles remain entirely within the intravascular space. Regions with either no flow or very low flow (<15% of normal resting flow) do not show opacification during MCE.

Because MCE can be used to define the spatial distribution of microvascular perfusion, we hypothesized that it could be used in patients during the subacute phase of AMI to distinguish viable myocardial regions (those with intact microvasculature) from nonviable regions (those with disrupted microvascular architecture). The gold standard for myocardial viability used in this study was 1-month recovery in regional function in myocardium supplied by non-flow-limiting IRA.

Methods

Inclusion Criteria One hundred five patients with a recent AMI (1 day to 4 weeks) and associated regional wall motion abnormalities who...
were undergoing cardiac catheterization were included in the study. AMI was diagnosed if patients had diagnostic ECG changes and a creatine kinase level of >500 IU with MB isoforms. Patients with prior coronary bypass surgery, significant valvular heart disease, nonischemic cardiomyopathy, or clinical instability (hypotension requiring pressors or intra-aortic balloon pump or severe pulmonary congestion) were excluded. The decision to perform cardiac catheterization in these patients had been made by the patients' primary physician.

Protocol

The protocol was approved by the Human Investigation Committee at the University of Virginia, and patients gave informed consent. Immediately after diagnostic catheterization, baseline two-dimensional echocardiography was performed to assess regional function and MCE was performed to assess microvascular perfusion. Revascularization of the IRA was performed at the discretion of the referring physician. MCE was repeated only in patients who underwent successful angioplasty of a totally occluded IRA. Two-dimensional echocardiography was repeated at 1 month to assess changes in regional function.

Quantitative Coronary Angiography

The IRA was identified based on the ECG changes, angiographic appearance of the artery, and associated regional wall motion abnormalities. The IRA was analyzed using a quantitative computer-assisted approach that compares the stenotic segment defined by the observer with a "normal" segment defined in the same vessel and expresses the result as a percent stenosis. Significant coronary artery disease in other than the IRA was defined as >50% luminal diameter narrowing of the proximal or midportion of a major epicardial vessel or its major branches. In patients undergoing coronary angioplasty, percent stenosis of the IRA was measured both before and after the procedure. In patients undergoing coronary artery bypass surgery, the IRA after surgery was classified as having no residual stenosis.

MCE

We have previously described the method and its safety in humans. In brief, sonicated Renografin-76 (Squibb), which contains 500 000±200 000 microbubbles of air with a mean diameter of 6 μm, was injected into the left main (1.5 mL) and right coronary (1.0 mL) arteries during simultaneously performed transthoracic two-dimensional echocardiography in multiple views (midpapillary muscle short-axis and apical four- and two-chamber views). A 12-segment model of the left ventricle was used to assign the following contrast scores as depicted in Fig 1: 0, no opacification; 0.5, a patchy pattern in the entire segment; or 1, homogeneous opacification. A score of 0.5 was also assigned to segments with opacification noted only in the epicardium (Fig 2). The contrast score index for the infarct zone was calculated by dividing the sum of the contrast scores for individual segments within the infarct bed by the number of infarct segments with abnormal wall motion.

In patients with a totally occluded IRA, contrast patterns within the infarct bed were analyzed during injection of the nonoccluded arteries. The observed patterns result from collateral flow as described by us previously. The contrast patterns were also analyzed in these patients after successful angioplasty of total coronary occlusions during injection of contrast directly into the IRA.

Two-dimensional Echocardiography

Two-dimensional echocardiography was performed at baseline and 1 month later. The left ventricle was examined using standard views, and wall motion was scored for each of the 12 myocardial segments. Wall motion was graded for each segment as follows: 1, normal; 2, mild hypokinesia; 3, severe hypokinesia; 4, akinesia; and, 5, dyskinesia. The wall motion score within the infarct bed was derived by averaging the scores from each segment within the infarct territory. This analysis was performed by two experienced observers who were blinded to all other information. Our interobserver and intraobserver reproducibility using this method is good.
Statistical Analysis

All data were analyzed using R5/1 (Bolt, Beranek, and Newman). Normally distributed data were expressed as mean±1 SD, whereas ordinal data were expressed as median and interquartile range. Data within the same patients were compared using either paired Student's t or Mann-Whitney test, whereas comparisons between groups were performed using either the unpaired Student's t or Mann-Whitney test. Differences for single comparisons were considered significant at P<.05 (two-sided). Bonferroni's correction was implemented for multiple comparisons. Correlations between ordinal data were performed using Spearman's rank statistic. Multiple regression analysis was performed to predict 1-month wall motion score and improvement in wall motion score.

Results

Clinical Data

Of the 105 patients (median age, 58 years; age range, 33 to 78 years) studied after a median of 8 days from infarction, 83 (79%) were men. The mean peak serum creatine kinase levels of the entire patient cohort was 2034±1769 IU, and the mean left ventricular ejection fraction was 0.48±0.12. Fifty patients (48%) received thrombolytic therapy, and 20 (19%) had experienced a prior infarction. Only 15 patients (14%) had definitive evidence of post-AMI ischemia as documented by chest pain with associated ECG changes.

Quantitative Coronary Angiographic Data

The IRA was the left anterior descending in 46 (44%), the right coronary in 45 (43%), and the left circumflex in 14 (13%) patients. Forty-seven patients (45%) had multivessel coronary artery disease. Fig 3 is a flow chart of the initial and final percent stenoses in the 105 patients. Fifty-seven (55%) had total occlusion of the IRA, and 48 (45%) had a patent IRA at baseline. Revascularization was performed in 71 of 105 patients (68%), 64 by angioplasty and 7 with coronary bypass surgery. Forty-two of 57 patients (74%) with an initially occluded IRA underwent successful revascularization with a final percent stenosis of 15±11% (P=.0001 compared with baseline). Twenty-nine of 48 patients (57%) with an initially patent IRA underwent revascularization. In these 29 patients, the mean percent stenosis was reduced from 67±12% to 15±16% (P=.0001).

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In the 19 patients with an initially patent IRA who were treated medically, the mean percent stenosis was 47±24%. Thus, in the 90 patients with patent coronary arteries at discharge, the residual stenosis was 21±20%, and no patient had a final coronary stenosis of ≥80%.

**Contrast Scores Before and After Angioplasty of Totally Occluded Infarct Arteries**

MCE was performed before and after angioplasty in 35 patients with totally occluded IRAs who underwent angioplasty. In 32 of these patients (91%), the myocardial perfusion pattern was identical before and after angioplasty. These results indicate that in the majority of patients with a total coronary occlusion, contrast patterns resulting from collateral flow at the time of coronary occlusion (and depicted by injection of contrast in the nonoccluded arteries) are identical to the contrast patterns resulting from anterograde flow after the IRA has been opened (and contrast is injected directly into it). In 2 patients, small perfusion defects disappeared after angioplasty (probably due to postprocedural hyperemia\(^\text{21}\)), and in 1 patient, the perfusion defect shifted clockwise by one segment.

**Influence of Coronary Artery Patency on the Contrast Score Index and Functional Improvement**

The contrast score index within the infarct zone was not related to baseline IRA patency in our patients. The majority of patients (38 of 57; 67%) with a totally occluded IRA had a contrast score index of >0.50, as did patients (28 of 48; 58%) with a patent IRA (\(P=\text{NS}\)). A significant number of patients (20 of 48, 42%), therefore, had a contrast score index of ≤0.50 despite a patent IRA at baseline angiography. In the 50 patients treated at presentation with thrombolytic therapy, the contrast score index was similar in those with patent IRAs compared with those with occluded IRAs.

Late improvement in function was related to the final IRA patency status. The baseline wall motion score (median±interquartile range, 3±1 versus 3.5±1, \(P=.41\)) and the contrast score index (median±interquartile range, 0.8±0.5 versus 1±1; \(P=.34\)) were similar in the 90 patients with a patent IRA and the 15 patients with an occluded IRA. The wall motion score 1 month later, however, was significantly better in those with open IRAs than in those with occluded IRAs (2±2 versus 3±2, \(P=.05\)). The relations between IRA patency, contrast score index, and wall motion for patients with and without revascularization are depicted in Table 1. It is evident that all subgroups showed improvement in function 1 month later except for those with occluded IRAs who did not undergo revascularization.

**Influence of Contrast Score Index on Functional Improvement**

Because only the 90 patients with patent IRAs had improved regional function at 1 month, the relation between contrast score index and regional function was assessed only in this group. There was a poor (\(r=−.27\)) although statistically significant (\(P=.01\)) correlation between baseline wall motion score and contrast score index within the infarct bed. In contradistinction, a strong correlation was noted between wall motion score at 1 month and the contrast score index (\(r=−.64, P<.001\)). Improvement in wall motion score (change from baseline to 1 month) was also correlated with the contrast score index (\(r=.48, P<.01\)). This correlation was even stronger (\(r=.61, P<.001\)) in the 72 patients with severe hypokinesia, akinetia, or dyskinesia, in whom large improvements in wall motion would be possible. The results were also similar when the 20 patients with prior infarction were excluded from analysis (\(r=−.63, P<.01\)). Because some improvement in function could have already occurred spontaneously in the postschemic myocardium in patients studied more than 2 weeks after AMI, analysis was repeated after 13 such patients were excluded. The relation between contrast score index and 1-month wall motion score remained unchanged (\(r=−.65, P<.001\)).

The relation between contrast score index and improvement in wall motion score was further examined by dividing patients into four subgroups based on their baseline contrast score index: >0.75 (\(n=47\)), >0.50 to 0.75 (\(n=9\)), >0.25 to 0.50 (\(n=16\)), and ≤0.25 (\(n=18\)). Fig 4 depicts the relation between the baseline and 1-month wall motion score versus contrast score index in the four groups. Baseline wall motion score was similar in the four groups. Function at 1 month was better and improvement in function was greater (\(P<.01\)) in the groups with higher contrast score indexes (>0.50).

### Table 1. Relations Between Wall Motion Scores and Contrast Score Index Within the Infarct Bed Based on Epicardial Coronary Patency

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Initial Vessel Status</th>
<th>Contrast Score Index</th>
<th>Baseline</th>
<th>1 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who were revascularized (n=71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Open</td>
<td>0.75±0.50</td>
<td>3.0±1.0</td>
<td>2.0±1.0*</td>
</tr>
<tr>
<td>42</td>
<td>Closed</td>
<td>1.0±0.50</td>
<td>3.0±2.0</td>
<td>2.0±1.0*</td>
</tr>
<tr>
<td>Patients who were not revascularized (n=34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Open</td>
<td>0.5±0.7</td>
<td>3.4±1.0</td>
<td>2.3±1.3*</td>
</tr>
<tr>
<td>15</td>
<td>Closed</td>
<td>1.0±1.0</td>
<td>3.5±1.0</td>
<td>3.0±2.0</td>
</tr>
</tbody>
</table>

*\(P<.01\) compared with baseline wall motion score. Note that lower wall motion scores indicate better regional function. Data are depicted as median±1 interquartile range.
Table 2 lists the clinical, angiographic, and echocardiographic variables that were examined as correlates of 1-month wall motion score using multiple regression analysis. The contrast score index was the best correlate of the 1-month wall motion score ($\rho = -.64, P < .001$). After this variable was included in the model, the only other variable found to correlate with 1-month wall motion score was the baseline wall motion score ($\rho = -.49, P < .001$). When patients with only mild hypokinesia were excluded from analysis, baseline wall motion score was no longer an independent predictor of 1-month function.

**Discussion**

**Microvascular Patency and Myocellular Viability**

In animal models of AMI, myocellular necrosis has been associated with loss of the microvasculature.\(^1\)\(^-\)\(^6\) Zones of microvascular injury are located exclusively within the borders of irreversibly injured myocardium and occur in proportion to the extent and severity of myocellular necrosis. Immediately after AMI, either no flow (the no-reflow phenomenon\(^2\)) or very low flow (low-reflow phenomenon\(^2\)) is noted within zones of necrosis after reperfusion is established through the IRA. Our study demonstrates that MCE can be used in humans to assess the perfusion status of the microvasculature during the subacute phase of AMI and that microvascular perfusion patterns at that juncture identify myocardial viability.

Ito and colleagues\(^22\) performed MCE 15 minutes after reperfusion was established in patients with AMI presenting within 6 hours of onset of chest pain. They noted that in the 25% of their patient cohort with no myocardial opacification despite a patent IRA, regional and global functions were worse 1 month later compared with those showing opacification of the infarct bed. After reperfusion is established, however, coronary hyperemia persists for several hours.\(^23\)\(^-\)\(^24\) A marker of flow, such as microbubbles, therefore is likely to underestimate the amount of necrosis and overestimate the amount of salvaged myocardium.\(^25\) In a canine model of coronary occlusion and reperfusion, we demonstrated such to be the case during the first 3 hours of reperfusion.\(^26\) Kemper and colleagues\(^27\) also found an underestimation of infarct size in a similar model using MCE in the early hours after reperfusion.

Because the infarcted tissue has reduced microvascular reserve despite manifesting hyperemia,\(^28\)\(^-\)\(^29\) an exogenously administered coronary vasodilator can unmask this lack of reserve.\(^23\) Using this approach, we were able to accurately define infarct size with MCE only during vasodilation with intravenous dipyridamole. In the absence of dipyridamole, however, MCE underestimated infarct size during the first 3 hours of reflow.\(^26\) In the present study, all patients were examined at least 1 day after infarction, which was well after hyperemia resulting from reperfusion had abated. Baseline contrast score index was also measured before angioplasty because the procedure itself can result in hyperemia.\(^21\)

**Contrast Patterns Before and After Revascularization in Patients With Totally Occluded Infarct Arteries**

In patients with a totally occluded IRA, the perfusion pattern within the infarct bed was defined by injecting contrast into the nonoccluded vessel as previously described.\(^30\) After the IRA had undergone angioplasty, contrast was injected directly into it. We found that the perfusion pattern based on antegrade flow after revascularization was identical, in the majority of patients, to that based on collateral flow during coronary occlusion. This finding has two important implications. First,
regions supplied by collateral flow during coronary occlusion indicate zones where the microvasculature has remained intact. We have previously demonstrated that establishing antegrade flow to such myocardial regions even days to weeks after AMI results in improved function but that in the absence of antegrade flow, function does not improve despite good collateral flow.\textsuperscript{19} The results of the present study also support these observations.

Second, the very same region that demonstrates microvascular perfusion during coronary occlusion continues to show an intact microvasculature after antegrade flow is reestablished. Conversely, regions showing absence of microvascular patency during total coronary occlusion continue to have the same pattern after revascularization. These results indicate that in patients with or without a patent IRA, perfusion patterns that predict viability can be identified before any revascularization procedure is performed and could therefore guide the use of these procedures.

**Importance of Coronary Artery Patency for Functional Improvement**

The majority of our patients had severe stenosis or occlusion of the IRA at initial angiography and underwent revascularization based on the referring physicians' preference. The effect of coronary artery patency on the 1-month wall motion score therefore could not be determined in a randomized fashion. In 15 of our patients, however, angioplasty of the occluded IRA either was not performed or was not successful. In these patients, regional function did not improve despite a high mean contrast score index. Our study cohort did not include patients with severe residual stenosis of the IRA. We therefore could not determine the extent of improvement in viable tissue subtended by such vessels. Others, however, have suggested that a severe, flow-limiting residual stenosis in a patent IRA could inhibit functional improvement after AMI.\textsuperscript{31}

**Study Limitations**

The quantitative angiographic method used in the study measures percent coronary stenosis rather than absolute luminal area. The latter could have provided a more physiological assessment of flow limitation and may have helped determine the role of residual stenosis on functional recovery.\textsuperscript{32} However, at hospital discharge, our patients had either widely patent IRAs (with none having >80% stenosis) or IRAs that were totally occluded. The importance of a residual flow-limiting stenosis in a patent IRA on functional improvement in myocardial regions with a high contrast score index therefore could not be assessed in our study.

The variable interval between AMI and cardiac catheterization could have affected our results, because some patients with postischemic dysfunction may already have improved function by the time the initial echocardiogram was performed.\textsuperscript{18} Exclusion of patients studied after more than 2 weeks from their AMI did not, however, alter the results; removal of patients with prior infarction from analysis also did not affect the results.

Direct coronary injection of contrast agents can cause "streaming," resulting in fewer microbubbles reaching a myocardial bed and causing an artifactual reduction in myocardial intensity compared with another bed. Repeated injections and use of multiple imaging views minimized the potential errors that could have been caused by streaming.

The degree of contrast effect (videointensity) within the myocardium is related to the concentration of microbubbles within the myocardial microvasculature as long as it relates linearly to videointensity.\textsuperscript{33} Thus, myocardial videointensity is a direct measure of myocardial blood volume (volume of blood within the myocardial arterioles, capillaries, and venules). Because there is heterogeneity in myocardial perfusion even under normal conditions,\textsuperscript{24,35} caution has to be used for defining a region to have abnormal versus normal videointensity. With greater clinical experience, the discrimination between normal and abnormal microvasculature should become clearer.

**Clinical Implications**

The recognition that prompt reperfusion of the IRA reduces mortality after AMI\textsuperscript{10} has led to increasing interest in optimizing therapeutic regimens to accelerate the establishment of IRA patency and to prevent reocclusion. While the major end point of many angiographic trials has been IRA patency, recent results suggest that this may not correlate with actual tissue perfusion or myocardial salvage. For example, the Team-II investigators have demonstrated that patent IRAs with TIMI (Thrombolysis in Myocardial Infarction) grade 2 flow are associated with the same poor prognosis as totally occluded IRAs.\textsuperscript{37} TIMI grade 2 flow probably reflects loss of microvascular integrity, inadequate epicardial coronary patency, or both. In a study reported by Harrison and colleagues,\textsuperscript{38} although patients with occluded IRAs were less likely to have improved function compared with those with patent IRAs, the correlations between time to reperfusion, other clinical variables, and improvement in function were not strong. The present and similar studies\textsuperscript{39} have examined only apparent perfusion as assessed by patency of the IRA rather than tissue perfusion. Because neither the patency status nor the severity of stenosis of the IRA indicates the extent of microvascular integrity, assessment of microvascular perfusion may be essential in gaining further understanding of patient outcomes and of the relation between interventions and outcomes.

In patients after AMI, several mechanisms may be responsible for reduction in regional function: stunning,\textsuperscript{40} hibernation,\textsuperscript{41} and ischemia.\textsuperscript{42} In all instances, however, recovery in function will only occur if myocardial viability is present. Our results suggest that, in practical terms, it is immaterial what the mechanism or mechanisms of regional dysfunction are; as long as there is evidence for microvascular integrity, there is evidence for myocardial integrity. Although the presence of viability alone is not an indication for revascularization, the demonstration of flow-limiting lesions causing resting (hibernation\textsuperscript{40}) or stress-induced ischemia\textsuperscript{43} of viable tissue is a conventional indication for revascularization.

Several techniques have been used for the assessment of myocardial viability, although the basis for their use differs. Positron emission tomography demonstrates metabolic activity in dysfunctional myocardial cells.\textsuperscript{44}
whereas single-photon imaging identifies either intact cell membranes (20T130.45) or mitochondrial function (sestamibi46). The contractile reserve of dysfunctional but viable cells forms the basis of dobutamine echocardiography. In comparison, because MCE detects viability by defining microvascular perfusion, it has potential advantages over other techniques. For example, myocardial metabolic activity may be diminished as a result rather than as a cause of myocardial dysfunction, and measurement of metabolic activity by positron emission tomography may underestimate the magnitude of ultimate functional improvement. Partial volume effects resulting from the lack of regional motion may result in lower counts in viable but akinetic segments using single-photon tracers. Similarly, contractile reserve on dobutamine echocardiography may be masked in the presence of a critical stenosis. The spatial extent of microvascular integrity should, however, not be affected by these mechanisms.

Many patients with AMI have clinical indications for invasive evaluation. Because ECG and left ventriculography offer unreliable assessments of myocardial viability, alternate methods are needed. Our results indicate that patients who have improved myocardial function after AMI can be identified in the cardiac catheterization laboratory at the time of diagnostic angiography by the use of MCE. This prompt assessment of both coronary anatomy and the quality of microvascular perfusion (and thus myocardial viability) may aid in decision making for these patients. More studies are required to further define the role of MCE during emergency and nonemergency cardiac catheterization of patients with recent or evolving AMI.

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