Early Changes in Myocardial Perfusion Patterns After Myocardial Infarction: Relation With Contractile Reserve and Functional Recovery

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Objectives. The purpose of this study was to assess early temporal changes in myocardial perfusion pattern by myocardial contrast echocardiography (MCE) and their relation to myocardial viability in patients with reperfused acute myocardial infarction (AMI).

Background. Myocardial contrast echocardiography no-reflow is associated with poor contractile recovery after AMI. However, little is known regarding early reversibility of microvascular dysfunction and its relation to myocardial viability.

Methods. Intracoronary MCE was performed immediately after reflow and 9 days later in 28 patients with a first AMI and successful coronary recanalization (Thrombolysis in Myocardial Infarction trial grade 3 flow). Semiquantitative contrast score and wall motion score (WMS) were assessed in each initially asynergic segment at initial and repeat MCE study. Low dose dobutamine echocardiography (DE) was performed at day 10, and follow-up (FU) rest echocardiography was performed 6 weeks later.

Results. Among 200 initially asynergic segments, 49% exhibited no or heterogeneous contrast enhancement at initial MCE versus 24% at restudy (p < 0.001). Three groups of segments were defined according to early changes in contrast pattern: group A, “sustained no-reflow” (n = 17); group B, improved contrast score (n = 68), and group C, “sustained reflow” (n = 112). Group A segments showed no improvement in WMS at FU. In contrast, group B segments showed significant improvement in WMS at FU (p < 0.0001), and exhibited more frequently contractile reserve at DE (36% vs. 6%, p = 0.02) and contractile recovery at FU (34% vs. 7%, p = 0.03) than group A segments. Group C segments exhibited contractile reserve and contractile recovery in 47% and 51% of segments respectively.

Conclusions. Improvement in MCE perfusion pattern may occur after initial no-reflow in the days following reperfused AMI and is associated with preservation of contractile reserve and gradual regional functional recovery.

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In acute myocardial infarction, successful coronary recanalization is not always associated with adequate restoration of myocardial perfusion (1). Even in patients without residual vessel obstruction, flow to the infarct myocardium may be markedly reduced, suggesting microvascular dysfunction (“no-reflow” or “low-reflow” phenomenon) (2–4). Recently, myocardial contrast echocardiography (MCE) studies have shown that the myocardial contrast pattern in the risk area immediately after recanalization of the infarct-related artery (IRA) reflects the extent of microvascular damage and is related to contractile recovery (4–6). Although not always associated with late functional improvement, microvascular integrity has been shown to be a prerequisite for myocardial viability (5,7,8). In contrast, no-reflow has been consistently associated with poor recovery of contractile function (4,5).

Although this relationship between the MCE pattern in the acute phase of AMI and myocardial viability is established, recent studies have shown that impairment of tissue perfusion may be observed early after reperfusion in viable postischemic heart muscle as well as in irreversibly damaged myocardium (9,10) and that impairment of tissue perfusion may be partially reversible in the first hours or days after coronary reflow (10–13). Late recovery of ischemic microvascular damage has also been demonstrated in patients in the convalescent stage of AMI (14). However, little is known about the early changes of segmental myocardial perfusion patterns in the days following reperfusion in humans and the relation between early improvement in microvascular perfusion and myocardial viability.

Thus, the aims of the study were to assess the temporal changes in myocardial perfusion patterns by myocardial contrast echocardiography in the early period following reperfused AMI and their relation to myocardial viability defined as late functional recovery and/or contractile reserve elicited by low dose dobutamine echocardiography.

Methods

Study population. The study population comprised 28 patients (26 men, 2 women; mean age: 50 ± 11 years) with a first...
patients gave their informed consent to the study. The protocol was approved by the institution Ethical Committee on human research, and all treatments (nitrates, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors) were prescribed as needed; specifically all patients with anterior wall myocardial infarction or objective signs of left ventricular dysfunction received angiotensin-converting enzyme inhibitors.

**Echocardiographic studies.** All echocardiographic data were recorded using a commercially available phased-array system (Sonos 1500, Hewlett-Packard, 2.5-MHz transducer). Echocardiographic images were recorded on S-VHS videotapes for off-line analysis. In each patient, the same four standard parasternal and apical views were obtained for all echocardiographic studies.

Baseline two-dimensional echocardiography and MCE were performed in the catheterization laboratory with patient lying supine, a foam wedge under his right shoulder to obtain a lateral rotation of the thorax of approximately 30°.

Myocardial contrast echocardiography was performed 10 min after stable TIMI grade 3 flow in the IRA was obtained, by injecting 3 ml of sonicated Ioxaglate (Hexabrix 320, Guerbet, France) into the left main and right coronary arteries. One separate contrast injection was used for each of the four standard views to examine all myocardial segments. Echocardiographic images were recorded from 10 s before the injection until disappearance of myocardial contrast enhancement, with constant gain settings.

Low dose dobutamine echocardiography was performed 10 days after admission. After baseline echocardiography, dobutamine was infused in increments of 5, 10 and 15 μg·kg⁻¹·min⁻¹ IV at 5-min intervals. Echocardiographic standard-view images were recorded at baseline and during the last 2 min of each dobutamine infusion level. Echocardiographic images were continuously recorded on videotapes and digitized on-line in a quad-screen cineloop format (Freeland-Tomtec software). A 12-lead electrocardiogram and arterial blood pressure were recorded at baseline and at the end of each stage.

Echocardiographic analysis. According to the recommendations of the American Society of Echocardiography, a 16-segment left ventricular model was used for analysis of all echocardiographic data (baseline, LDDE, MCE and FU studies) (15). For the purpose of this study, myocardial risk area was defined as the area of abnormal wall motion (hypokinetic, akinetic or dyskinetic segments) in multiple tomographic planes in the acute phase of myocardial infarction.

**Myocardial contrast echocardiography.** Myocardial contrast echocardiography images were analyzed off-line from the videotape recording by consensus reading of two observers, blinded to wall motion scores and unaware of clinical and angiographic data. The contrast effect was graded in each initially hypo- or akinetic segment using a previously described semiquantitative contrast score (5): 0, no opacification; 0.5, heterogeneous pattern in the entire segment or opacification noted only in epicardium; 1, homogeneous opacification. In each patient, the contrast score index (CSI) for the dysynergic area was calculated by dividing the sum of the contrast scores for individual segments within this area by the number of dysynergic segments (5).

Myocardial segments were classified in three groups on the

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**Abbreviations and Acronyms**
- **CK**: creatine kinase
- **CSI**: contrast score index
- **ECG**: electrocardiographic
- **FU**: follow-up
- **IRA**: infarct-related artery
- **LDDE**: low dose dobutamine echocardiography
- **MCE**: myocardial contrast echocardiography
- **TIMI**: Thrombolysis in Myocardial Infarction trial
- **WMS**: wall motion score
- **WMSI**: wall motion score index
basis of contrast pattern changes between day 0 and day 9; those with “sustained no-reflow” (grade 0 at day 0 and day 9) (Group A), those with improvement in contrast pattern (improvement between day 0 and day 9 of at least one grade of contrast score) (Group B) (Fig. 1) and those with “sustained reflow” (grade 0.5 or 1 at day 0 without modification at day 9) (group C).

**Wall motion analysis.** Two-dimensional echocardiograms performed at day 0, day 9 and at FU were analyzed off-line by consensus reading of two experienced observers blinded to the clinical, angiographic and MCE data. Wall motion analysis was performed for each segment using a semiquantitative scoring system (1 = normal, 2 = hypokinesia, 3 = akinesia or dyskinesia). A mean segmental wall motion score (WMS) was calculated in each group of segments (groups A, B and C) by dividing the sum of the individual scores by the number of the segments in each group. Functional recovery of a single myocardial segment at day 9 or at FU was defined as a decrease of at least one grade of wall motion score compared with the baseline study. In each patient, a wall motion score index (WMSI) was computed by averaging the scores from each segment within the initially dyssynergic area.

**Low dose dobutamine echocardiography.** Low dose dobutamine echocardiography was analyzed by simultaneous comparison of digitally acquired cineloop images at baseline and at the three steps of stimulation. For each segment, contractile reserve was defined as a decrease of at least one grade of wall motion score at any stage of dobutamine infusion compared with the baseline study. A patient was considered a responder to dobutamine if wall motion improved in two or more contiguous segments.

**Reproducibility of myocardial contrast echocardiography.** To assess the reproducibility of ME analysis, 10 MCE studies were read in random order by the same pair of observers 2 months after initial scoring. Among 72 dyssynergic segments, segmental score agreement was 86% (kappa value, 0.72) and in all but one segment, the difference between the two scores was ≤1 grade.

**Statistical analysis.** As recently verified by Sawada et al. (16) in a study that compared the patterns of perfusion and metabolism in dobutamine responsive myocardium, a segment by segment analysis of the data should be appropriate in the absence of any consistent intrapatient correlation of the segment data. Therefore, we examined for each patient all possible correlations between the temporal changes in perfusion pattern in segments pairs within the risk area. In the 19 patients in whom reduced perfusion was present at least in two segments immediately after recanalization, the proportion of segments pairs that had no statistically significant correlation for contrast score evolution (p ≥ 0.05) was 84%. Because there were no consistent correlations, the segment was used as the unit of analysis.

Categorical data are presented as percentages, and quantitative data as mean ± SD. Parameters were compared with the use of commercially available statistical software (STATVIEW II, Abacus Concepts, Berkeley, CA). The statistical significance of differences between groups or repeated measures was determined by one-way analysis of variance and Scheffé’s test or chi-square analysis as appropriate. A p value <0.05 was considered significant.

**Results**

**Clinical and angiographic characteristics.** All 28 patients underwent initial and repeated MCE study. None of the patients exhibited any hemodynamic disorder, ECG changes or increased chest pain during contrast injections.

The IRA was the left anterior descending artery in 19 patients, the left circumflex in 1 patient and the right coronary artery in 8 patients. Reperfusion was achieved by coronary angioplasty in 21 patients (19 primary and 2 rescue angioplasty) and with intravenous thrombolysis in 6 patients (tissue plasminogen activator). In one patient, TIMI grade 3 flow was obtained after intracoronary nitroglycerin, and coronary angioplasty was not performed. The average time between the onset of pain and angiographically proven reperfusion (TIMI grade 3 flow) was 224 ± 68 min (range, 100 to 420 min). The mean peak serum CK level was 3,292 ± 1,834 IU (n < 195). All but one patient later developed Q waves on the ECG. No patient experienced reinfarction between the initial and FU studies.

All patients had a patent IRA (TIMI grade 3 flow) at repeat angiography performed 9 days after admission. All patients treated with thrombolytic therapy had ≥50% residual stenosis and underwent elective angioplasty of the culprit lesion. In these patients, MCE was performed 10 to 15 min after angioplasty. No patient had a final coronary stenosis of ≥30%.

Low dose dobutamine echocardiography was performed after repeat angiography in 24 patients. In four patients, LDDE was not performed because of left ventricular apical thrombus (n = 3) or complete recovery of wall motion (n = 1). Follow-up echocardiography was obtained in 24 patients.
Early myocardial contrast pattern evolution. At initial echocardiography, 204 myocardial segments were hypo- or akinetic (average: 7.2 ± 2.9 per patient). Four segments were excluded because of poor quality. Of the remaining 200 segments, 102 (51%) showed homogeneous opacification (grade 1), 50 segments (25%) showed heterogeneous opacification (grade 0.5) and 48 segments (24%) showed no contrast effect (grade 0). At restudy, 152 segments (76%) had homogeneous opacification, 31 segments (15%) had heterogeneous opacification and 17 segments (9%) showed no contrast enhancement (Fig. 2). The proportion of segments showing no or heterogeneous opacification in the area at risk was 49% at initial study and 24% at restudy (p < 0.001).

According to the evolution of their contrast score between day 0 and day 9, 17 myocardial segments (9%) were classified as “sustained no-reflow” (group A), 68 segments (34%) were classified as “improved contrast score” (group B) and 112 segments (57%) were classified as “sustained reflow” (group C). Worsening of perfusion score was observed in three segments, which were excluded from further analysis.

Temporal changes of contrast pattern and myocardial viability. Segmental analysis. The relation between the dynamic changes in contrast pattern from day 0 to day 9 and contractile recovery at day 9 and at FU is summarized in Figure 3. No functional improvement was observed between day 0 and FU in group A segments (“sustained” no-reflow). Group B segments (“improved contrast score”) showed a decrease in mean WMS from 2.95 ± 0.26 to 2.73 ± 0.56 at day 9 (p = 0.01) and to 2.52 ± 0.65 at FU (p < 0.0001 vs. day 0, p = 0.05 vs. day 9). Group C segments (“sustained reflow”) showed the most marked improvement with a decrease of mean segmental WMS from 2.79 ± 0.41 at day 0 to 2.36 ± 0.78 at day 9 (p < 0.0001) and to 2.19 ± 0.81 at FU (p < 0.0001 vs. day 0, p = NS vs. day 9). Improvement at FU tended to be greater in group B than in group A segments (p = 0.08) but remained lower than in group C segments (p = 0.009 group B vs. group C).

The percentage of segments exhibiting functional recovery at FU was significantly different in the three groups (p = 0.004). Functional recovery was observed more frequently among group C (43 of 85, 51%) than among group A segments (1 of 14, 7%) (p = 0.002), and was also observed more frequently among group B (20 of 59, 34%) than among group A segments (p = 0.03) (Fig. 4). Within group B segments, functional recovery was observed more frequently in segments with initial heterogeneous contrast pattern (score 0.5) than in segments with initial 0 score (40% vs. 16%; p = 0.01).

The relation between the dynamic changes in contrast pattern from day 0 to day 9 and contractile reserve elicited by LDDE was assessed in 145 segments presenting persistent wall motion abnormalities. The frequency of contractile reserve was significantly different in the three groups defined on the basis of changes in contrast pattern at MCE (p = 0.009). Contractile reserve was observed more frequently among group C (36 of 77, 47%), but also among group B (19 of 52, 36%), than among group A segments (1 of 16, 6%) (p = 0.003 and p = 0.02 respectively) (Fig. 4). Assuming that myocardial segments with either functional recovery between day 0 and day 9 or contrac-
tile reserve are viable, myocardial viability was observed in 2 group A (12%), in 23 group B (41%) and in 50 group C segments (58%) respectively (p < 0.0008).

Per patient analysis. Figure 5 illustrates the temporal changes between day 0 and day 9 in the individual values of regional CSI and WMSI in patients. Mean CSI increased from 0.69 ± 0.24 to 0.86 ± 0.19 (p < 0.001), and mean WMSI decreased from 2.84 ± 0.24 to 2.39 ± 0.40 (p < 0.001). There was no significant difference in the distribution of contrast scores and dynamic changes in contrast pattern between thrombolytic-treated patients and angioplasty-treated patients. Moreover, the same relationship between MCE pattern evolution and functional recovery was observed in the 21 angioplasty-treated patients as in the whole study population.

In dobutamine-responders (n = 16), WMSI significantly decreased from baseline to follow-up (2.86 ± 0.15 to 2.2 ± 0.34; p = 0.003). In contrast it remained unchanged in patients nonresponsive to dobutamine (n = 8) (2.94 ± 0.18 to 2.78 ± 0.23; p = 0.11).

Comparison of MCE and LDDE. Of 137 myocardial segments adequate for analysis both at DE and at follow-up, 60 exhibited improvement in function at follow-up. Functional recovery occurred in 48 (68%) of 70 segments responsive to dobutamine, and in 12 (18%) of 67 segments nonresponsive to dobutamine (p < 0.0001).

Table 1 lists performance of early MCE, late MCE, serial MCE and LDDE for predicting late functional recovery of individual segments. Although sustained reflow or improved opacification at serial MCE had a very high sensitivity in predicting recovery, positive predictive value was low. Dobutamine echocardiography had a significantly better specificity (71% vs. 15%; p < 0.001) and positive predictive value (69% vs. 44%; p < 0.001) than serial MCE in predicting recovery.

Discussion

The main finding of this study is that early improvement of myocardial contrast perfusion pattern in segments with initially impaired reflow is associated with contractile reserve and with a moderate but significant improvement in regional myocardial function at follow-up. In contrast, segments with sustained no-reflow exhibited no significant contractile reserve or functional recovery. These results suggest that early recovery of microvascular damage is associated with myocardial viability.

Early changes in myocardial perfusion patterns. The no-reflow phenomenon is frequently observed immediately after coronary recanalization (17). Although no-reflow is usually associated with myocardial necrosis and extensive microvascular injury, recent studies have shown the complexity and heterogeneity of microvascular alterations early after coronary reflow (10,18). First, reperfusion abnormalities can be demonstrated both in viable tissue and in irreversibly damaged myocardium (2,10), indicating that early MCE defects do not always reflect necrosis (9). Second, temporal changes in flow patterns have been documented after reperfusion (11,18,19), even in the area of MCE no-reflow (12,14), suggesting that postischemic microvascular dysfunction may be partially reversible. Several mechanisms may underlie the improvement of contrast pattern in viable postischemic myocardium, such as

Table 1. Comparative Sensitivity, Specificity and Predictive Values of Early Myocardial Contrast Echocardiography (MCE), Late MCE, Dobutamine Echocardiography (DE) and Serial MCE in Predicting Functional Recovery in Individual Segments

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCE day 0 (n = 161 segments)</td>
<td>66 (55 to 77)</td>
<td>60 (51 to 69)</td>
<td>53 (43 to 63)</td>
<td>73 (64 to 82)</td>
</tr>
<tr>
<td>MCE day 9 (n = 161 segments)</td>
<td>88 (80 to 96)</td>
<td>32 (23 to 41)</td>
<td>47 (38 to 56)</td>
<td>79 (67 to 91)</td>
</tr>
<tr>
<td>DE (n = 137 segments)</td>
<td>80 (70 to 90)</td>
<td>71 (61 to 81)</td>
<td>69 (58 to 80)</td>
<td>82 (73 to 91)</td>
</tr>
<tr>
<td>Serial MCE (n = 158 segments)</td>
<td>98 (95 to 100)</td>
<td>15 (8 to 22)</td>
<td>44 (36 to 52)</td>
<td>93 (80 to 100)</td>
</tr>
</tbody>
</table>

*p < 0.001 (serial MCE vs. DE). CI = confidence interval.
transient impairment of coronary reserve (3,13,19–21), spasm or residual thrombosis (19).

Our data showed early improvement in perfusion pattern in 34% of initially dyssynergic segments. In contrast, only 9% of segments exhibited sustained no-reflow. These findings confirm that at least a part of the initial perfusion abnormalities are reversible when early and complete coronary recanalization is obtained.

Relationship between microvascular improvement and myocardial viability. Although MCE no-reflow is generally associated with no or poor functional recovery (4,6,22), the relation between early improvement in myocardial perfusion and functional outcome has not been studied in man. The present study shows that segments with sustained no-reflow exhibit poor functional recovery. Conversely, segments with improved perfusion after initial no- or low-reflow exhibited some degree of functional improvement at follow-up. Contractile recovery, however, remained less marked and more progressive than in the “sustained reflow” group, confirming that improvement in myocardial perfusion may be partly dissociated from functional recovery (14). Furthermore, among segments that improve contrast pattern, contractile recovery occurred more frequently in segments with an initial heterogeneous pattern than in segments with initial no-reflow, suggesting a different degree of ischemic or reperfusion injury in these two groups of segments.

Recent studies have shown that contractile reserve under dobutamine infusion may provide a better assessment of the extent of viable myocardium than wall motion recovery, especially in the absence of residual coronary stenosis (23). In our study, segments with sustained no-reflow did not exhibit significant contractile reserve. In contrast, contractile reserve was observed in 36% of segments that improved contrast pattern.

The response to dobutamine in myocardial segments showing no contrast enhancement varies among studies (8,24,25). These differences may be partly related to differences in the timing of MCE and dobutamine echocardiography (9,26). Specifically, contractile reserve was present in 22% of segments without contrast when MCE was performed very early after myocardial infarction (8), whereas contractile reserve was never observed in such segments when MCE was performed before discharge (24,25). Both these data and our results strongly suggest that immediate and delayed “no-reflow” have different physiologic implications. Whereas acute no-reflow may be observed both in necrotic and in viable myocardium, late or “sustained no-reflow” suggests irreversible microvascular damage.

Comparison of MCE and dobutamine echocardiography for the prediction of late functional recovery. In keeping with recent studies, our data show that myocardial contrast echocardiography and LDDE have different diagnostic value in predicting late functional recovery after myocardial infarction (8,24–27). Although the sensitivity of the two techniques is quite similar, dobutamine echocardiography is more specific and accurate in predicting functional recovery than early or late MCE (8,24). In our study, only 51% of segments with sustained reflow and 39% of segments with improved opacification showed functional recovery at follow-up. Moreover, serial MCE, in spite of very high sensitivity, had the lowest positive predictive value in predicting functional recovery. These data further confirm that contrast enhancement, shortly or late after reperfusion, does not necessarily imply a late functional improvement (7,8,22,25,28).

Study limitations. Several limitations of the present study must be emphasized.

1. Although previous studies have shown good overall agreement between the extent of abnormal wall motion and that of the risk area determined with MCE (29), direct imaging of the risk area using myocardial contrast echocardiography before recanalization of the IRA would have been preferable (30), since wall motion may be influenced by factors other than ischemia, and wall motion abnormalities may also be observed in areas of normal perfusion. However, accurate assessment of the risk area via MCE requires multiple views, which may delay recanalization of the infarct artery.

2. The specific MCE protocol used in this study is time-consuming and not applicable in routine clinical practice. However, since the present study aimed at serial and semiquantitative assessment of segmental wall motion and perfusion, exhaustive measurements of contrast enhancement in all views and with repeated contrast injections ensured accuracy and detailed examination of all myocardial segments. Simplified protocols and, in the future, intravenous contrast injections may allow routine imaging of the area at risk and assessment of perfusion at the bedside.

3. The accuracy of perfusion assessment immediately after recanalization of the IRA in the acute phase may be questioned, in the light of experimental findings suggesting the need to use maximal vasodilatation prior to assessment of no-reflow (18,19). However, the absence of worsening of perfusion from day 0 to day 9 in our study suggests that no-reflow was not substantially underestimated.

4. Since our population included a limited number of highly selected patients with early and complete recanalization of the IRA (TIMI grade 3 flow), it is uncertain whether its conclusions apply to a more general population, including TIMI 2 grade patients in whom initial no-reflow is common, and patients with persistence of the IRA occlusion (TIMI 0 or 1) (31). However, focusing on patients with complete IRA patency ensured that perfusion abnormalities could not be ascribed to disturbances in epicardial coronary flow.

5. The optimal timing for assessing perfusion and wall motion dynamic changes remains to be determined. This issue will likely be clarified by future studies using intravenous contrast, thereby allowing serial noninvasive assessment.

Conclusions. Spontaneous improvement in MCE pattern is observed in the days following successful complete reperfusion of myocardial infarction, suggesting recovery of microvas-
cular dysfunction. Improvement in MCE pattern is associated with evidence of myocardial salvage, as assessed by contractile response to dobutamine and gradual segmental functional recovery.

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