ORIGINAL RESEARCH

Clinical outcome and left ventricular remodeling in AMI patients with insufficient myocardial reperfusion after recanalization

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Abstract

Aim: Myocardial contrast echocardiography (MCE) is effective in predicting myocardial viability and functional recovery on a segmental level in patients with acute myocardial infarction (AMI). In this study, we investigated whether insufficient myocardial reperfusion plays an important role in left ventricular (LV) remodeling and functional recovery in patients with thrombolysis in myocardial infarction (TIMI) flow grade 3 and corrected TIMI frame count (CTFC)<40 after recanalization of the infarct-related artery.

Method: Patients underwent intracoronary injection of microbubbles for echocardiographic assessment of myocardial microvascular perfusion, wall motion score, LV volume and ejection function (EF) at baseline, 30 minutes, one month and six months after recanalization. The patients with MCESI<1 were considered to have insufficient myocardial reperfusion (group A, n=11), while the patients with MCESI≥1 were considered to have sufficient myocardial reperfusion (group B, n=47) after AMI recanalization.

Results: The wall motion score index (WMSI) and the left ventricular ejection fraction (LVEF) showed significant improvement at 1 month and 6 months in group B, but only at six months in group A. Left ventricular end-systolic and

end-diastolic volumes (LVESV and LVEDV) were also significantly decreased at one and six months in group B. WMSI, LVESV, LVEDV and LVEF were significantly improved in group B in comparison with group A at one month and six months ($P<0.01$). By six months, significant correlations were seen in all patients between MCESI and changes in LVESV, LVEDV and LVEF at 6 months. Similar correlations were observed between the myocardial regional blood flow (Q) and changes in LVESV, LVEDV and LVEF.

Conclusion: Insufficient myocardial reperfusion was a strong independent predictor of LV remodeling and functional recovery in AMI patients with TIMI flow grade 3 and CTFC<40 after recanalization. MCE has important additional value for prognosis and risk assessment in patients with acute myocardial infarction following recanalization.

During acute myocardial infarction (AMI), myocyte loss is accompanied by loss of the myocardial microvasculature.¹ Early restoration of antegrade flow can limit the progression of myocardial necrosis and should enhance functional recovery of post-ischemic dysfunction of the myocardium.² The extent

of myocardial salvage is critically dependent upon blood flow to the area that is at-risk.³ Thus, the primary objective of reperfusion therapies should be not only to achieve rapid and sustained epicardial arterial patency, but also to restore microvascular flow and myocardial tissue reperfusion.

Myocardial contrast echocardiography (MCE) is an investigational technique that has been used to describe myocardial reperfusion in patients with restored patency of the infarct-related artery (IRA). Furthermore, this method has the ability to assess microvascular reperfusion and, by virtue of its temporal resolution, can also measure infarct-related changes in myocardial blood flow (MBF).⁴⁻⁷ The link between microvascular dysfunction and unfavorable clinical outcome in real time and for short- and intermediate-term prognoses has been addressed by several studies.⁸⁻¹⁰ The long-term prognosis after AMI, which is strongly related to progressive left ventricular (LV) remodeling, remains unexplored in patients with thrombolysis in myocardial infarction (TIMI) flow grade 3 and perfect angiographic results after recanalization. Thus, the present study was performed to (1) evaluate qualitative and quantitative MCE parameters in relation to functional recovery and LV remodeling and (2) assess the long-term prognostic impact of insufficient myocardial reperfusion after successful primary percutaneous coronary intervention (PCI) in the ST-segment elevation AMI-surviving patients with TIMI flow grade 3 and perfect angiographic results - corrected TIMI frame count (CTFC) <40.

Methods

Patients and study protocol

The study population consisted of 71 patients having a first ST-segment elevation AMI who were referred to our catheterization laboratory for emergent primary PCI. They were prospectively enrolled in this study if they met the following inclusion criteria: (1) confirmed first ST-segment elevation AMI and (2) suc-

cessful primary coronary angioplasty (defined as TIMI flow grade 3 residual stenosis <30% and CTFC<40) within 6-12 hours of the onset of symptoms.¹¹ Exclusion criteria were the following: (1) chronic total occlusion or inability to identify the IRA, (2) clinical signs of congestive heart failure or cardiogenic shock before revascularization, (3) post-infarction angina, (4) significant other cardiac disease, and (5) life-limiting non-cardiac disease. No upper age limit was applied. The research protocol was approved by the hospital ethics committee, and informed consent was obtained from each patient by one of the investigators.

Myocardial contrast echocardiography and two-dimensional echocardiography

Intracoronary MCE was performed at 30 minutes after successful coronary angioplasty by injection of 3 ml of SonoVue (Bracco, Byk-Gulden, Konstanz, Germany), which was hand agitated during its passage through a 3-way stopcock, followed by a 5 ml saline flush into the left main and right coronary artery ostia through standard angiographic coronary catheters.¹² Images were analyzed visually and quantitatively offline with a commercially available software tool (HDI Laboratory, Advanced Technology Laboratories, Bothell, Washington).

Two-dimensional contrast echocardiographic images were analyzed by two readers who had no knowledge of the clinical or angiographic data. The LV was divided according to a 16-segment model.¹³ In each segment, the MCE effect was scored as 0 (no visible contrast effect), 1 (patchy myocardial contrast enhancement or opacification on the epicardial layer), or 2 (homogeneous contrast effect). The echocardiographic view that delineated the most asynergic walls was chosen for contrast echocardiographic analysis. In this view, the risk area was defined as the area that did not show contrast enhancement (score 0) and was determined in the post-injection cycles to show the best delineation between contrast-enhanced and non-

enhanced myocardium. A score of 1 or 2 within a segment of the at-risk area after angioplasty was interpreted as reperfusion. In each patient, an area-at-risk MCE score index (MCESI) was derived by averaging the scores from each segment within the at-risk area.¹²

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 each patient, an infarct-zone wall motion score index (IZWMSI) was derived by averaging the scores from each segment within the at-risk area. LV volumes and ejection fractions were measured with the modified Simpson rule algorithm.^{13,14} A serial assessment of LV volumes was performed, at 30 minutes after successful recanalization by PCI and at 1 and six months in all eligible patients. The mean value of three measurements of the technically best cardiac cycles was calculated for each examination. Color Doppler of mitral regurgitation was graded with a scale of 0 to 4 (0=none, 1=mild, 2=moderate, 3=moderate to severe, and 4=severe).

Quantitative analysis

Plots of contrast intensity versus time were constructed and fitted to an exponential function, $y=A*(1-e^{-\beta t})$, as previously described.^{7,15} Curves were analyzed by an investigator blinded to the clinical and echocardiographic data. The plateau of signal intensity (A , representing capillary blood volume) and the slope of maximal intensity increase (β , representing mean myocardial red blood cell velocity) were measured, and the product of $A*\beta$ was calculated to estimate myocardial perfusion. Inter- and intraobserver variabilities for the estimation of the myocardial blood flow ($A*\beta$) were obtained by double-blinded observers by repeating the analysis of 20 representative myocardial contrast echocardiograms.

Coronary angiography

Selective coronary angiography was performed <12 hours after onset. Angiograms were analyzed and quantified by an independent cardiologist. The degree of stenosis was expressed as a percent decrease in the internal luminal diameter in relation to the normal reference. Coronary stenosis was defined as $\geq 75\%$ narrowing compared to the reference lumen diameter. TIMI flow grade, CTFC was assessed visually after PCI.^{16,17}

Outcome measures

LV volume and EF were based on repeated measurements in individual patients and on the upper 95% confidence limit of the intraobserver variability.¹⁸ Successful recanalization was defined as the restoration of TIMI flow grade 3 and residual stenosis of <30% at the end of the procedure. After hospital discharge, patients were required to take regular medication but no attempt was made to standardize therapy. All patients were asked to return for a clinical evaluation by one of the investigators at one and six months after discharge.

Results

Patient baseline characteristics

MCE was evaluated in a total of 346 segments. Before angioplasty, myocardial perfusion defects (at-risk areas) were observed in all patients and involved 172 segments. After IRA recanalization, 154 of the 172 segments within the at-risk area were reperfused. Of these reperfused areas, 81 showed a homogeneous contrast effect (score 2), and 73 displayed a partial enhancement pattern (score 1).

Of the 71 patients initially selected for the study, 5 (7%) were excluded for inadequate echocardiographic image quality, and 8 patients (11%) did not adhere to the follow-up protocol. Thus, 58 patients (46 men; mean age 64.2 ± 12 years, range 44 to 87 years) comprised the final study group.

TABLE 1. Clinical Characteristics of Study Patients (mean $\pm$ SD or %)

Item	All (n=58)	Group A (n=11)	Group B (n=47)
Age	64.2 $\pm$ 12	64 $\pm$ 10	63.8 $\pm$ 11
Males	46 (79)	8 (73)	38 (80)
Diabetes	6 (10)	1 (9)	5 (11)
Hypertension	20 (34)	4 (36)	16 (34)
Dyslipidemia	31 (53)	5 (45)	26 (55)
Smokers	17 (29)	3 (27)	14 (30)
Mitral regurgitation grade	0.48 $\pm$ 0.76	0.47 $\pm$ 0.73	0.51 $\pm$ 0.67
Collaterals (grade $\geq$ 2)	4 (7)	0(0)	4 (6)
CTFC (frames)	26.8 $\pm$ 4.8	29.3 $\pm$ 5.9	26.2 $\pm$ 4.4
Multivessel coronary artery disease	25 (43)	5 (45)	20 (43)
Area at risk	192 (48)	52 (61)	140 (53)
Symptom-to-balloon time	7.27 $\pm$ 2.65	8.02 $\pm$ 2.54	7.0 $\pm$ 2.67

All patients were divided into two groups: group A with MCESI $<$ 1 (n=11) and group B with MCESI $\geq$ 1 (n=47). MCESI $\geq$ 1 considered sufficient myocardial reperfusion and MCESI $<$ 1 considered insufficient myocardial reperfusion. There was no significant differences in pre-operative clinical characteristics between the two groups.

Based on the contrast reperfusion patterns, the patients were divided into two groups: the patients with a MCESI $<$ 1 were considered to have insufficient myocardial reperfusion (group A, n=11), while the patients with a MCESI $\geq$ 1 were considered to have sufficient myocardial reperfusion (group B, n=47) after AMI recanalization. There was no significant difference in the clinical characteristics between the two groups (Table 1).

Safety data

All 58 patients underwent successful mechanical reperfusion, including stent placement, and all achieved TIMI flow grade 3 with $<$ 30% residual stenosis. No effects of the SonoVue were noted on either rhythm or blood pressure, and no allergic reactions were observed during or 30 minutes after contrast agent administration.

Time course of changes in wall motion and LV function recovery

Wall motion analysis was feasible in the two groups and for a total of 928 segments. The wall motion score

index improved significantly at six months (2.40 $\pm$ 1.69) in group A patients. Greater improvement was seen in WMSI for patients in group B in comparison with those in group A at one month (1.79 $\pm$ 0.43 vs. 2.48 $\pm$ 1.79) or six months (1.69 $\pm$ 0.39 vs. 2.40 $\pm$ 1.69) (Figure 1).

Left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) increased progressively in patients in group A throughout the six months; however, significant improvement in LVESV (105.1 $\pm$ 11.5 vs. 93.4 $\pm$ 17.1) and LVEDV (143.8 $\pm$ 13.5 vs. 127.2 $\pm$ 8.5) was seen only at 6 months. Both LVESV and LVEDV decreased significantly from baseline to one month (from 85.1 $\pm$ 15.1 to 67.8 $\pm$ 16.4 and from 121.2 $\pm$ 11.6 to 112.3 $\pm$ 12.3) and six months (from 85.1 $\pm$ 15.1 to 62.5 $\pm$ 13.3, and from 121.2 $\pm$ 11.6 to 108.6 $\pm$ 11.7) in patients in group B. LV volumes were significantly larger in group A patients than in group B patients at one month and six months. Significant improvement was seen in the left ventricular ejection fraction (LVEF) at one month (44.4 $\pm$ 6.22 vs. 36.5 $\pm$ 6.3) and six months (46.0 $\pm$ 5.8 vs. 36.5 $\pm$ 6.3) in group B patients, but only at six months (38.6 $\pm$ 5.1 vs. 33.4 $\pm$ 7.1) in group A patients (Figure 2).

FIGURE 1. Change in the wall motion score index (WMSI) at one and six months post-angioplasty.

The wall motion score index improved at one month (1.79 ± 0.43) after angioplasty and showed further improvement at six months (1.69 ± 0.39) in group B patients. A significant change was observed only at six months (2.40 ± 1.69) in group A patients ($*P < 0.01$). This improvement was more pronounced in group B in comparison with group A at both one month (1.79 ± 0.43 vs. 2.48 ± 1.79) and six months (1.69 ± 0.39 vs. 2.40 ± 1.69) ($\#P < 0.01$).

FIGURE 2. Change in LVEF, LVESV and LVEDV one and six months post-angioplasty.

In group A, a significant increase in LVESV (105.1 ± 11.5 vs. 93.4 ± 17.1) and LVEDV (143.8 ± 13.5 vs. 127.2 ± 8.5) was seen by 6 months. In group B, a significant decrease in LVESV and LVEDV was seen at one month (67.8 ± 16.4 vs. 85.1 ± 15.1 , 112.3 ± 12.3 vs. 121.2 ± 11.6) and six months (62.5 ± 13.3 vs. 85.1 ± 15.1 , 108.6 ± 11.7 vs. 121.2 ± 11.6) ($*P < 0.01$). LV volumes were significantly larger in group A than in group B at one month and six months ($\#P < 0.01$). A significant improvement was seen in LVEF at one month (44.4 ± 6.22 vs. 36.5 ± 6.3) and six months (46.0 ± 5.8 vs. 36.5 ± 6.3) in group B but only at six months (38.6 ± 5.1 vs. 33.4 ± 7.1) in group A ($*P < 0.01$). LVEF showed significant improvement in group B in comparison with group A at one month (44.4 ± 6.22 vs. 36.09 ± 5.58) and six months (46.0 ± 5.8 vs. 38.6 ± 5.1) ($\#P < 0.01$).

Correlation between myocardial microvascular reperfusion and LV remodeling

MCESI at 30 minutes after successful PCI closely correlated with changes in LVESV ($r^2 = -0.69$), LVEDV ($r^2 = -0.70$) and LVEF ($r^2 = 0.62$) at six months in all patients. (Figure 3)

MCE quantification assessment ($Q = A \cdot \beta$) of perfusion was feasible in all of the 58 patients (35.9 ± 21.0) included in groups A (15.1 ± 8.6) and B (40.7 ± 20.1) at 30 minutes after successful PCI. Similarly, myocardial blood flow ($A \cdot \beta$) closely correlated with changes in LVESV ($r^2 = -0.69$), LVEDV ($r^2 = -0.64$) and LVEF ($r^2 = 0.65$) at six months in all patients. (Figure 4)

Discussion

It is well known that MCE is effective in predicting myocardial viability in patients after acute myocardial infarction. Previous studies that investigated myocardial reperfusion after myocardial infarction focused on

FIGURE 3. Correlation between the myocardial contrast echocardiography score index (MCESI) and LV remodeling. MCESI at 30 minutes after successful PCI correlated with changes in LVESV ($r^2=-0.69$), LVEDV ($r^2=-0.70$) and LVEF ($r^2=0.62$) at six months.

FIGURE 4. Correlation between myocardial blood flow ($A*\beta$) and LV remodeling. Myocardial blood flow ($A*\beta$) closely correlated with changes in LVESV ($r^2=-0.69$), LVEDV ($r^2=-0.64$) and LVEF ($r^2=0.65$) at six months in all patients.

the prediction of functional recovery on a segmental level.^{8,19-21} Because residual left ventricular function after infarction is a primary determinant of long-term survival, the prediction of global improvement is more important for patient risk stratification. Several studies have demonstrated the benefits of myocardial reperfusion, which leads to a reduction of infarct size and associated improvement in later regional and global ventricular function.²²⁻²⁵ On the other hand, LV remodeling after AMI is a precursor to the development of overt heart failure and is an important predictor of mortality. Multiple factors may contribute to LV remodeling at different stages, from the time of coronary occlusion until the development of ventricular dilation and dysfunction. Infarct size, anterior infarct location, transmural extent of necrosis, reperfusion status of the IRA, heart failure on admission, and a restrictive pattern of LV filling have been identified as major predictors of LV dilatation after myocardial infarction in various patient populations.²⁶ Successful coronary recanalization with satisfactory TIMI flow grade 3 and CTFC<40 does not always mean complete and sustained restoration of myocardial reperfusion and functional recovery.

This study provides information on the prognostic role of insufficient myocardial reperfusion by MCE in patients with AMI successfully treated by primary PCI. The strict inclusion criteria used in the study, which led to the exclusion of most high-risk patients who might have suffered severe LV dysfunction, produced a relatively low-risk series.

In this study, using intracoronary contrast for the assessment of myocardial microvascular reperfusion, LV remodeling and the prediction of recovery of function demonstrates that the wall motion score index improved at one month but not at 30 minutes after angioplasty. The wall motion score index showed further improvement at six months in patients with sufficient myocardial reperfusion. There were significant changes between the patients with insufficient myocardial reperfusion and those with sufficient reperfusion at one and six months. Both the LV end-systolic

and end-diastolic volumes progressively decreased in patients with sufficient myocardial reperfusion throughout the six months of the study. LV volumes were significantly larger in the insufficient myocardial reperfusion patients than in the sufficient myocardial reperfusion patients at one and six months. The LV ejection fraction showed significant improvement at one and six months in patients with sufficient myocardial reperfusion, but not in patients with insufficient reperfusion. The results of the present study clearly demonstrate the long-term prognostic value of myocardial reperfusion by MCE after successful PCI of the IRA in patients with AMI.

Furthermore, a direct and highly significant relationship was observed between the MCE quantification assessment, myocardial blood flow ($A \cdot \beta$) at 30 minutes after PCI and changes of LVEF, LVEDV and LVESV after six months. Similar results were observed in the qualitative assessment of MCE. These observations strongly suggest a link between myocardial reperfusion after successful PCI and LV remodeling.

Thus, insufficient myocardial reperfusion after successful PCI with TIMI flow grade 3 and CTFC<40 might be the pathophysiological link between reperfusion, LV remodeling, and long-term clinical outcome in AMI as it alters the mechanical properties of the infarcted myocardium. Embolization of plaque contents, platelet thrombus or platelet aggregation in the microcirculation may compromise the recovery of perfusion at the tissue level.²⁷ It is possible that microvascular embolization after successful angioplasty, which occurs in the later stages of reperfusion, is one of the reasons for the compromised recovery of tissue perfusion.

Limitations

This study excluded patients with chronic total occlusion and clinical signs of congestive heart failure or cardiogenic shock before revascularization. Therefore, we cannot generalize our results to patients with more

severe CAD. In addition, only a few diabetic patients (6) were included in our study. Severe microcirculatory disease, which is likely to occur in patients with diabetes, might have a significant influence on perfusion as well as myocardial function. This may need to be addressed separately. It is, however, felt that the stringent criteria used for patient selection compensated for the identified limitations of this study.

Conclusion

Insufficient myocardial reperfusion was a strong independent predictor of LV remodeling at follow-up. MCE has important additional value for prognosis and risk stratification for long-term outcome in patients with acute myocardial infarction after primary PCI.

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