Impact of Microvascular Dysfunction on Left Ventricular Remodeling and Long-Term Clinical Outcome After Primary Coronary Angioplasty for Acute Myocardial Infarction

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Background—We hypothesized that preserved microvascular integrity in the area at risk would favorably influence left ventricular (LV) remodeling and long-term outcome after acute myocardial infarction.

Methods and Results—Before and after successful primary angioplasty (percutaneous transluminal coronary angioplasty [PTCA]), 124 patients with acute myocardial infarction underwent intracoronary myocardial contrast echocardiography (MCE). An MCE score index (MCESI) was derived by averaging the single-segment score (0=not visible, 1=patchy, 2=homo-
genous contrast effect) within the area at risk. An MCESI ≥1 was considered adequate reperfusion. Mean follow-up was 46±32 months. After PTCA, 100 patients showed adequate reperfusion (no microvascular dysfunction, NoMD), whereas 24 did not (MD). MD patients had a higher mean creatine kinase (4153±2422 versus 2743±1774 U/L; P=0.002) and baseline wall-motion score index (2.61±0.31 versus 2.25±0.42; P<0.001) and a lower baseline ejection fraction (33±8% versus 40±7%; P<0.001). From day 1 on, LV volumes progressively increased in the MD patients (n=19) and were larger than those of NoMD patients (n=85) at 6 months (end-diastolic volume 170±55 versus 115±29 mL; P<0.001). MCESI was the most important independent predictor of LV dilation (OR 0.61, 95% CI 0.52 to 0.71, P<0.000001). By Cox analysis, MD represented the only predictor of cardiac death (OR 0.26, 95% CI 0.09 to 0.72, P=0.010) and combined events (cardiac death, reinfarction, and heart failure; OR 0.44, 95% CI 0.23 to 0.85, P=0.014). MD patients showed worse survival in terms of cardiac death (P<0.0001) and combined events (P<0.0001).

Conclusions—In reperfused acute myocardial infarction, MD within the risk area is an important predictor of both LV remodeling and unfavorable long-term outcome. (Circulation. 2004;109:1121-1126.)

Key Words: myocardial infarction ■ angioplasty ■ remodeling ■ survival ■ microcirculation

In acute myocardial infarction (AMI), early restoration of anterograde flow can limit the progression of myocardial necrosis and should enhance the functional recovery of postischemic dysfunctioning myocardium.1 The extent of myocardial salvage is critically dependent on blood flow to the risk area.2 Thus, the primary objective of reperfusion therapies should be not only to achieve rapid and sustained epicardial patency but also to restore microvascular flow and myocardial tissue perfusion. Embolization of plaque contents of platelet thrombus or platelet aggregation in the microcirculation with loss of endothelial integrity may compromise the recovery of perfusion at tissue level.3 Until recently, we have had limited access to diagnosing microvascular dysfunction in patients with AMI. With the availability of imaging technology, microvascular dysfunction, even after optimal recanalization of the epicardial vessel, has been documented in a far greater proportion of patients than was previously thought possible.4 Echocardiographic assessment of myocardial perfusion after intracoronary injection of microbubbles is an investigational technique that has been used to describe myocardial reperfusion in patients with restored patency of the infarct-related artery (IRA). The link between microvascular dysfunction, as assessed by intracoronary myocardial contrast echocardiography (MCE), and unfavorable clinical outcome has been suggested by several studies.5,6 However, the long-term prognosis after AMI, which is strongly related to progressive left ventricular (LV) dilation, remains unexplored in patients with microvascular dysfunction. Thus, we investigated the long-term prognostic impact of MCE microvascular dysfunction after successful primary percutaneous transluminal coronary angioplasty (PTCA) for AMI in terms of cardiac death and nonfatal events and LV function and remodeling in the surviving patients.
Methods

Patients and Study Protocol

The study population consisted of 143 patients with first AMI referred to our catheterization laboratory for emergency primary PTCA. They were prospectively enrolled in this study if they met the following inclusion criteria: (1) confirmed first AMI and (2) successful primary coronary angioplasty (defined as Thrombolysis in Myocardial Infarction trial [TIMI] flow grade 3 and residual stenosis <30%) within 6 hours of the onset of symptoms or between 6 and 24 hours if there was evidence of continuing ischemia. Exclusion criteria were (1) IRA diameter stenosis <70% with TIMI grade 3 flow, or inability to identify IRA, (2) clinical signs of congestive heart failure or cardiogenic shock in the first week after infarction, (3) postinfarction angina, (4) significant other cardiac disease, and (5) life-limiting noncardiac disease. No upper age limit was used. Of the 143 patients initially selected for the study, 9 (7%) were excluded for inadequate echocardiographic image quality, and 10 patients (8%) did not adhere to follow-up protocol. Thus, 124 patients (104 men; mean age 62±10 years, range 36 to 83 years) represent the final study group. The research protocol was approved by the hospital ethics committee, and informed consent was obtained from each patient by one of the investigators.

Intracoronary MCE was performed during acute coronary occlusion, on completion of diagnostic coronary angiography, and was repeated shortly after coronary angioplasty. MCE was performed by injection of 3 mL of iopamidol (Iopamiro, Bracco SpA), hand-agitated during its passage through a 3-way stopcock, followed by a 3-mL saline flush into the left main and right coronary artery ostia, agitated during its passage through a 3-way stopcock, followed by a 3-mL saline flush into the left main and right coronary artery ostia, through standard angiographic coronary catheters. A serial assessment of LV volumes within 24 hours of admission and at 1 and 6 months after the index infarction was obtained in 104 patients. In a subset of 60 patients, we compared peak creatine kinase value with 99mTc sestamibi myocardial scintigraphy for infarct size evaluation and achieved a good relation (r=0.625; P<0.0001). Thus, we used peak creatine kinase value as an indirect measure of infarct size in the entire study population. A repeat coronary angiography was obtained at 1 and 6 months after primary coronary angioplasty in all but 12 patients (112/120; 93% of eligible patients).

Data Analysis

Two-dimensional contrast echocardiographic images were analyzed by 2 readers who had no knowledge of the clinical and angiographic data. The LV was divided according to a 16-segment model. 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 effect), or 2 (homogeneous contrast effect). Discrepancies were resolved by consensus. The echocardiographic view that delineated the most asynergic walls was chosen for contrast echocardiographic analysis. In this view, the risk area was defined as an area that did not show contrast enhancement (score 0) and was determined in the postinjection cycles that showed the best delineation between contrast-enhanced and nonenhanced myocardium. A score of 1 or 2 within a segment of the area at risk 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 area at risk. Intrareader and interobserver variability values in the evaluation of segmental myocardial perfusion by MCE were 4% and 7%, respectively, which indicates the good reproducibility of the measurements.

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 (akineti), or 4 (dyskineti). In each patient, an infarct-zone motion score index (IZWMSI) was derived by averaging the scores from each segment within the area at risk. LV volumes and ejection fraction were measured with the modified Simpson rule algorithm. The mean value of 3 measurements of the technically best cardiac cycles was taken from each examination. Intrareader and interobserver variability values in the evaluation of end-diastolic volumes were <5%, which indicates the good reproducibility of the measurements. Color Doppler of mitral regurgitation was graded with a 0 to 4 scale (0 none, 1 mild, 2 moderate, 3=severe, and 4+=severe).

Definitions and Outcome Measures

LV dilatation was defined as an increase in end-diastolic volume ≥20%, based on repeated measurements in individual patients and on the upper 95% confidence limit of the intraobserver variability. According to the presence or absence of LV dilatation at 6 months after infarction, patients were divided into an LV remodeling group or a no LV remodeling group, respectively.

Successful PTCA was defined as the restoration of TIMI 3 grade flow and residual stenosis <30% at the end of the procedure. Restenosis was defined as ≥50% diameter stenosis of the culprit lesion on follow-up angiograms. A patient was considered to have adequate reperfusion if the MCE score index was ≥1.

Major cardiac events were defined as cardiac death, nonfatal reinfarction, and hospitalization for congestive heart failure and combined events (all of the aforementioned). All deaths were considered to be of cardiac origin unless a noncardiac origin was established clinically or at autopsy. For purposes of survival analyses, only 1 event (the first that occurred) was tabulated for each patient. After hospital discharge, patients were referred to their private physician, who regulated therapy. No attempt was made to standardize therapy. All patients were asked to return to our outpatient clinic for evaluation by one of the investigators 6 months after discharge and annually thereafter. For those patients who did not return to the clinic at the designated time, follow-up information was collected by telephone interview.

Statistical Analysis

Continuous data are expressed as mean±SD. Baseline data were compared by means of the χ2 test for categorical variables and unpaired t test for continuous variables. ANOVA with the Tukey post hoc test was used to analyze repeated measures of IZWMSI, ejection fraction, and LV volumes. Univariate and multivariate regression analyses were performed to identify variables that were independent correlates of LV remodeling at 6 months. Clinical, angiographic, and echocardiographic variables that were significant in univariate analyses, as well as those known to affect LV remodeling, which included symptom-to-balloon time and door-to-balloon time, were entered in the multivariate models. Event-free survival curves for all major cardiac events and combined events were constructed by the Kaplan-Meier method, and statistical differences between curves were assessed by log-rank test. Multivariate Cox proportional hazards regression model was used to identify independent predictors of major cardiac and combined events. Clinical, angiographic, and echocardiographic variables that were significantly different between survivors and nonsurvivors in the univariate model, as well as those known to have prognostic value, were included in the Cox models. A value of P<0.05 was considered statistically significant. Statistical analysis was performed with Statistica 4.5 for Windows and SPSS 8.0 for Windows.

Results

Myocardial Perfusion and Baseline Patient Characteristics

MCE was evaluated in a total of 742 segments. Before angioplasty, myocardial perfusion defects (area at risk) were observed in all patients and involved 367 segments (49.5% of explored segments). Shortly after IRA recanalization, 299 of 367 segments within the area at risk were reperfused; of these, 153 (51.2%) showed homogeneous contrast effect (score 2), and 146 (48.8%) displayed a partial enhancement pattern (score 1). From contrast reperfusion patterns, patients were divided into 2 subsets: group 1 with MCESI <1 (microvascular dysfunction, 24 patients) and group 2 with MCESI ≥1 (no microvascular...
dysfunction, 100 patients). Table 1 summarizes clinical, echocardiographic, and angiographic characteristics of these 2 subsets. There was no difference in age, gender, frequency of coronary risk factors, or multivessel disease between the 2 groups. However, patients with microvascular dysfunction had larger enzymatic infarct size and area at risk, had a significantly longer time from symptom onset to hospital admission, and more often had anterior infarcts. In addition, they had larger baseline LV volumes, higher IZWMSI, and lower ejection fraction.

**Angiographic Results**

All patients included in the study had successful PTCA. There was no significant difference in the percentage of stenting between patients with and without MCE microvascular dysfunction (71% versus 75%, respectively; \( P=0.67 \)). Restenosis and reocclusion rates during the 6 months after the index infarction were not significantly different in patients with or without MCE no reflow (25% versus 15%, \( P=0.118 \), and 15% versus 4%, \( P=0.074 \), respectively). Glycoprotein IIb/IIIa receptor inhibitors were used in 59 patients during the procedure (54% in group 1 and 46% in group 2, \( P=0.47 \)).

**Time Course of Changes in Regional and Global Ventricular Function and LV Volumes**

Serial echocardiographic examinations from baseline to 6 months were available in 104 patients. At baseline, both global and regional contractile function were significantly better in group 2 than in group 1 (ejection fraction 40±7% versus 33±8%, \( P=0.0005 \); IZWMSI 2.24±0.42 versus 2.61±0.30, \( P=0.00003 \), respectively). According to ANOVA, a significant improvement in LV ejection fraction was observed in group 2 from baseline to 1-month follow-up (from 40±7% to 48.5±10%) and from baseline to 6-month follow-up (from 40±7% to 51±11%), whereas only a slight and not significant improvement was found in group 1 (Figure 1A). Comparison between groups by ANOVA revealed that patients without microvascular dysfunction (group 2) had a significantly greater improvement in global ventricular function at 6 months than patients with microvascular dysfunction (group 1; Figure 1A). Similarly, IZWMSI showed a greater improvement in group 2 patients than in group 1 patients (Figure 1B).

LV end-systolic and end-diastolic volumes were higher in group 1 patients than in group 2 patients at baseline (92.3±45
versus 69.5 ± 20, *P* = 0.00002, and 142 ± 55.5 versus 117 ± 25.4, *P* = 0.00002, respectively). LV volumes progressively increased in group 1 patients from the early to late stage and were significantly larger than those of group 2 patients at each time point in the study (Figures 1C and 1D). In group 2 patients, both LV end-systolic and end-diastolic volumes decreased from baseline to 6 months, but only end-systolic volumes changed significantly (Figures 1C and 1D).

**Relation of Microvascular Dysfunction to LV End-Diastolic Volumes at 6 Months**

In Figure 2, LV end-diastolic volume at 6 months was plotted against the microvascular dysfunction assessed by MCE. A significant inverse correlation was found between the 2 variables (*r* = -0.519, *P* < 0.000001). Similarly, there was a direct relation between 6-month LV end-diastolic volumes and peak creatine kinase (*r* = 0.47, *P* < 0.000001) and baseline ejection fraction (*r* = -0.421, *P* = 0.000009). The prevalence of LV remodeling was significantly greater among patients with microvascular dysfunction that among those without (63% versus 11%, *P* < 0.0001, respectively).

To evaluate the independent contribution of microvascular dysfunction to LV dilation, stepwise multiple regression analysis was performed. Variables used for analysis were as follows: age, history of diabetes and hypertension, infarct location, peak creatine kinase value, extent of coronary artery disease, presence of significant collateral circulation, chronic occlusion, symptom-to-balloon time and door-to-balloon time, baseline IZWMSI, ejection fraction, LV end-diastolic volume, and mitral regurgitation grade. For multiple regression analysis, factors that yielded a probability value *P* < 0.1 in univariate analysis were selected. The most important predictor of 6-month LV remodeling was MCESI (*P* < 0.000001), followed by baseline LV end-diastolic volume (*P* < 0.0001), peak creatine kinase (*P* = 0.0002), collateral circulation (*P* = 0.010), and symptom-to-balloon time (*P* = 0.059; Table 2).

**Microvascular Dysfunction and Long-Term Clinical Outcome**

Clinical follow-up data were collected for all patients enrolled in the study. The mean length of clinical follow-up was 46 ± 32 days.

| TABLE 2. Predictors of LV Remodeling at Multivariate Analysis |
|---------------------------------|-----------------|--------|
|                                | OR (95% CI)     | *P*    |
| MCESI                          | 0.61 (0.52–0.71)| <0.000001 |
| EDV at baseline                | 0.73 (0.63–0.86)| <0.0001  |
| Peak CK, U/L                   | 1.33 (1.13–1.55)| 0.0002 |
| Collaterals (grade ≥ 2)        | 1.22 (1.05–1.42)| 0.010   |
| Symptom-to-balloon time, min   | 1.16 (1.00–1.36)| 0.059   |

*EDV* indicates end-diastolic volume; CK, serum creatine kinase.
months (range 1 to 101 months). During this period, 8 patients (6%) had nonfatal reinfarction, 6 (5%) were hospitalized for overt heart failure, and 9 (7%) had cardiac death. Overall, there were 23 major cardiac events (19%; cardiac death, nonfatal reinfarction, or hospitalization for heart failure). Additional revascularization procedures were performed in 28 patients (23%; Table 3).

Overall, cardiac death and hospitalization for congestive heart failure were significantly more common in patients with microvascular dysfunction than in those without it (Table 3). According to the Kaplan-Meier method, patients with microvascular dysfunction had a higher 5-year cardiac mortality rate (log-rank test \( P < 0.001 \)) and cumulative 5-year combined event rate (log-rank test \( P < 0.001 \)) than those without microvascular dysfunction (Figure 3). By multivariate Cox analysis, only microvascular dysfunction by MCE was identified as an independent predictor of cardiac death (OR 0.26, 95% CI 0.09 to 0.72, \( P = 0.010 \)) and combined events (OR 0.44, 95% CI 0.23 to 0.85, \( P = 0.014 \)).

**Discussion**

The results of the present study clearly demonstrate the long-term prognostic value of microvascular dysfunction by MCE after successful reopening of the IRA in patients with AMI. Patients with microvascular dysfunction more commonly experienced overt heart failure and cardiac death than did those without. They also showed advanced LV remodeling, as shown by serial echocardiographic examinations. Microvascular dysfunction by MCE strongly predicts cardiac events independent of other well-known early predictors of long-term outcome after AMI, such as age, enzymatic infarct size, and LV ejection fraction.

**Microvascular Dysfunction and LV Remodeling**

LV remodeling after AMI is a precursor of the development of overt heart failure and is an important predictor of mortality.\(^{11}\)\(^{12}\) 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,\(^{13}\) anterior infarct location,\(^{14}\) transmural extent of necrosis,\(^{9}\) perfusional status of the IRA,\(^{15}\) heart failure on admission,\(^{16}\) and restrictive pattern of LV filling\(^{17}\)\(^{18}\) have been identified as major predictors of LV dilatation after myocardial infarction in various patient populations. The importance of microvascular dysfunction by MCE complicating mechanical reperfusion after AMI as an additional major predictor of early LV remodeling has been suggested by recent studies.\(^{5}\)\(^{6}\) The present study confirms and expands these preliminary observations in that microvascular dysfunction by MCE was shown to be an important and independent contributor to subsequent changes in LV geometry and performance. LV volumes were larger among patients with microvascular dysfunction than among patients without it beginning with the baseline (24-hour) echocardiographic examination and continued to increase throughout the study period. Furthermore, a direct and highly significant relationship was found between the extent of microvascular dysfunction by MCE and LV end-diastolic volume at 6 months. In the present series, the extent of asynergy and enzymatic infarct size were significantly higher in patients with microvascular dysfunction. Obviously, this may account at least in part for the differences in LV volumes. However, the correlations between the change in LV end-diastolic volume index and peak creatine, IZWMSI, and LV ejection fraction were weaker than the correlation between end-diastolic volume index and the extent of microvascular dysfunction, and after controlling for enzymatic infarct size and LV function, microvascular dysfunction by MCE was the most powerful independent predictor of LV dilation. These observations strongly suggest a link between microvascular dysfunction and LV remodeling. A recent experimental study in a canine model of infarction and reperfusion has shown that increased stiffness of infarcted regions in the first days after reperfusion of AMI correlates significantly with the extent of microvascular obstruction in infarcted tissue and has an adverse effect on LV

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**Table 3. Clinical Events During Follow-Up in Patients With and Without Microvascular Dysfunction**

<table>
<thead>
<tr>
<th></th>
<th>Group 1, MD (n=24)</th>
<th>Group 2, NoMD (n=100)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>6 (25)</td>
<td>3 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal reinfarction</td>
<td>2 (8)</td>
<td>6 (6)</td>
<td>0.676</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>4 (17)</td>
<td>2 (2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Angina</td>
<td>4 (17)</td>
<td>19 (19)</td>
<td>0.792</td>
</tr>
<tr>
<td>Revascularization</td>
<td>3 (13)</td>
<td>25 (25)</td>
<td>0.188</td>
</tr>
</tbody>
</table>

MD indicates microvascular dysfunction. See text for details.

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**Figure 3.** Kaplan-Meier survival curves for cardiac death (a) and combined events (b) in patients with and without microvascular dysfunction after reperfused AMI.
remodeling independent of infarct size itself.19 Thus, microvascular obstruction after restoration of epicardial flow, by altering the mechanical properties of the infarcted myocardium, might be the pathophysiological missing link between reperfusion, LV remodeling, and clinical outcome in AMI.

Microvascular Dysfunction and Long-Term Clinical Outcome

Few reports are available concerning the relationship between microvascular integrity after successful epicardial recanalization and subsequent clinical outcomes.5,6,20,21 Most of them studied very small AMI populations treated with different reperfusion strategies at different times and were focused mainly on in-hospital or intermediate prognosis. Our prospective study provides information on the prognostic role of microvascular dysfunction by MCE in a quite homogeneous and unselected study population with AMI successfully treated by means of primary PTCA. 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, generated a relatively low-risk series. Nevertheless, 42% of patients with microvascular dysfunction experienced major cardiac events such as rehospitalization for overt heart failure and cardiac death. Moreover, microvascular dysfunction proved to be the only independent predictor of 5-year cardiac death and combined events. This, along with the ability to predict LV dilation after AMI, highlights the pathophysiological link between microvascular dysfunction, progressive LV dilation, development of congestive heart failure, and cardiac death.

Study Limitations

The results of this study should be considered in light of some limitations. First, the study population is relatively small and at low risk, with a low event rate, which may limit the statistical power to detect correctly all predictors of long-term clinical outcome. However, 42% percent of patients with microvascular dysfunction had overt heart failure or died, an impressive figure independent of the statistical power of the study. Second, the relatively low prevalence of microvascular dysfunction in our study population (19%), although very close to that observed in other similar studies, would have required a larger study population to definitively assess its prognostic role. Finally, the study assessed microvascular dysfunction after successful mechanical reperfusion in the era before the widespread use of glycoprotein IIb/IIIa receptor inhibitors during emergency PTCA for AMI.

Conclusions

Data from the present study show that in unselected patients with AMI successful treated with mechanical reperfusion, microvascular dysfunction assessed by MCE is a powerful independent predictor of 6-month LV dilation and long-term clinical outcome. Thus, microvascular integrity and adequate tissue reperfusion, even after optimal epicardial recanalization, represent the true standard for success of reperfusion. New strategies that limit myocardial damage after mechanical reperfusion in patients with AMI are needed.

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References

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