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The Extent of Microvascular Damage During Myocardial Contrast Echocardiography Is Superior to Other Known Indexes of Post-Infarct Reperfusion in Predicting Left Ventricular Remodeling

Results of the Multicenter AMICI Study

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Objectives We sought to evaluate the value of the extent of microvascular damage as assessed with myocardial contrast echocardiography (MCE) in the prediction of left ventricular (LV) remodeling after ST-segment elevation myocardial infarction (STEMI) as compared with established clinical and angiographic parameters of reperfusion.

Background Early identification of post-percutaneous coronary intervention microvascular dysfunction may help in tailoring appropriate pharmacological interventions in high-risk patients. The ideal method to establish effective microvascular reperfusion after percutaneous coronary intervention remains to be determined.

Methods A total of 110 patients with first successfully reperfused STEMI were enrolled in the AMICI (Acute Myocardial Infarction Contrast Imaging) multicenter study. After reperfusion, peak creatine kinase, ST-segment reduction, and Thrombolysis In Myocardial Infarction (TIMI) and myocardial blush grade were calculated. We evaluated perfusion defects with MCE by using continuous infusion of Sonovue (Bracco, Milan, Italy) in real-time imaging. The endocardial length of contrast defect (CD) on day 1 after reperfusion was calculated. Wall motion score index, the extent of wall motion abnormalities, LV end-diastolic volume, and ejection fraction after reperfusion and at follow-up also were calculated.

Results Of 110 patients, 25% evolved in LV remodeling and 75% did not. Although peak creatine kinase, ST-segment reduction >70%, and myocardial blush grade were not different between groups, in patients exhibiting LV remodeling, TIMI flow grade 3 was less frequent ($p < 0.001$), wall motion score index was greater ($p < 0.001$), and CD was greater ($p < 0.001$). At multivariate analysis, only TIMI flow grade <3 and CD with a cutoff of >25% were independently associated with LV remodeling. Among patients with TIMI flow grade 3, CD was the only independent variable associated with LV remodeling.

Conclusions Among patients with TIMI flow grade 3, the extent of microvascular damage, detected and quantitated by MCE, is the most powerful independent predictor of LV remodeling after STEMI as compared with persistent ST-segment elevation and myocardial blush grade. (J Am Coll Cardiol 2008;51:552–9) © 2008 by the American College of Cardiology Foundation

Early and sustained patency of the infarct-related artery (IRA) by either primary or rescue percutaneous coronary intervention (PCI) is the main goal in the care of patients with acute ST-segment elevation myocardial infarction (STEMI) (1,2). However, despite successful IRA recanalization, a substantial group of patients remain at risk of left ventricular (LV) remodeling and adverse clinical events, likely as a result of extensive post-ischemic microvascular damage (MD) (3). Early identification of such post-PCI

See page 566

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MD may help in tailoring aggressive pharmacological interventions in high-risk patients and in indicating early discharge in low-risk patients, thus allowing a more cost-effective use of restricted medical resources.

Post-PCI ST-segment resolution has been proposed as an easy method to assess reperfusion at the microvascular level. It has been found correlated to enzymatic infarct size, ejection fraction, and patient mortality (4) and, therefore, largely used in clinical trials (5,6). However, although the correlation between normalization of ST-segment elevation and myocardial reperfusion has been assessed in the experimental setting (7), in humans the interpretation of ST-segment resolution as an index of IRA patency after thrombolysis is still a matter of debate (8), and the correlation with microvascular reflow after PCI has been only inferred and never demonstrated.

Myocardial blush grade (MBG) is an alternative index of microvascular reflow after PCI (9). The accuracy of this index, however, is hampered by the limitations related to a visual analysis and to a semiquantitative score of a contrast blush in myocardial regions perfused by IRA. On the other hand, myocardial contrast echocardiography (MCE) is able to safely quantify the extent of MD at a patient's bedside (10).

Thus, we designed a multicenter prospective cohort study (AMICI [Acute Myocardial Infarction Contrast Imaging]) to assess the relative role of MD during MCE as compared with widely used indexes of post-infarct reperfusion (i.e., ST-segment resolution, MBG, and Thrombolysis In Myocardial Infarction [TIMI] flow grade) in predicting post-infarct LV remodeling.

Materials and Methods

Study population. Consecutive patients referred to the catheterization laboratories of the 3 centers involved in the study between January and November 2005 who underwent successful primary or rescue PCI within 6 h of onset of STEMI entered the AMICI trial. Diagnosis of STEMI was based on the following: 1) typical chest pain lasting more than 30 min and unresolved by nitroglycerin and 2) ST-segment elevation >0.1 mV in at least 2 contiguous leads in the initial electrocardiogram (ECG). Exclusion criteria were: 1) cardiogenic shock or clinical instability; 2) previous STEMI; 3) inadequate echocardiographic image quality; 4) malignant life-threatening diseases; and 5) inability to give informed consent. The ethical committees of the institutions involved approved the study, and all patients gave informed consensus to participate in the study.

PCI and medications. In all patients, catheterization was performed by the percutaneous femoral approach. After diagnostic coronary angiography, intracoronary nitroglycerin 0.1 mg was administered to reverse any possible epicardial spasm. Then, in all patients, primary PCI with stenting of the IRA was performed according to the clinical protocol used at our institution. All patients were treated with heparin (initial weight-adjusted intravenous bolus then further boluses administered) with the aim of obtaining an activated clotting time of 250 to 300 s in patients treated with abciximab and >300 s in the remaining subjects and with aspirin. Unless contraindicated, abciximab (0.25 mg/kg bolus plus infusion of 0.125 μg/kg/min for 12 h) was intravenously administered in all patients undergoing primary PCI, whereas in those with failed thrombolysis, abciximab use was left to the operator's discretion.

Coronary angiograms were stored on compact disk for off-line analysis. Flow in the IRA was graded by means of the TIMI flow classification. Successful PCI was defined as the restoration of TIMI flow grade 3 or 2 with residual stenosis of the culprit artery post-PCI <20% in all patients. We scored TIMI flow grade and MBG semiquantitatively as previously described (9).

Abbreviations and Acronyms

- **CD** = contrast defect
- **CSI** = contrast score index
- **ECG** = electrocardiogram
- **EDV** = end-diastolic volume
- **EF** = ejection fraction
- **ESV** = end-systolic volume
- **IRA** = infarct-related artery
- **LV** = left ventricular
- **MBG** = myocardial blush grade
- **MCE** = myocardial contrast echocardiography
- **MD** = microvascular damage
- **PCI** = percutaneous coronary intervention
- **ROC** = receiver-operating characteristic
- **TIMI** = Thrombolysis In Myocardial Infarction
- **WM** = wall motion
- **WMSI** = wall motion score index

ECG. A 12-lead ECG was recorded in all patients on admission to the hospital (first ECG) and in coronary care unit 90 min after PCI (second ECG). Patients with left bundle-branch block were excluded from the analysis, whereas patients with right bundle-branch block were included in the analysis, because a clear ST-segment elevation could be recognized in all of them. The first and second ECG of each patient were analyzed as pairs and graded for ST-segment resolution by an investigator who was unaware of the clinical data, angiographic findings, and outcome data. The sum of ST-segment elevation was measured 20 ms after the end of the QRS complex in leads I, aVL, and V_1 to V_6 for anterior, and leads II, III, aVF, and V_5 to V_6 for nonanterior myocardial infarction (4). We calculated ST-segment reduction as the percentage reduction in the second ECG compared with the first. The reproducibility of the classification of ECG was obtained by reanalysis of 50 ECGs by a second independent reader, and agreement between the 2 readers was found in 90% of cases with a correlation coefficient of 0.90 (95% confidence interval 0.83 to 0.94). Findings at coronary angiograms were used to confirm the infarct location being anterior when the IRA was the left anterior descending coronary artery or one of its side branches and nonanterior when the IRA was the right or the circumflex coronary artery.

MCE. In all patients, conventional transthoracic echocardiogram and MCE were performed within 24 h of coronary

JACC Vol. 51, No. 5, 2008
February 5, 2008:552–9

recanalization and a transthoracic echocardiogram was repeated at 6-month follow-up. The MCE studies were performed in real-time harmonic power Doppler using a Sonos 7500 (Philips, Andover, Massachusetts) ultrasound system. Acoustic power and compression were maximized, and gain settings were optimized at the onset of each study and held constant throughout. The focus was initially set at two-thirds of the depth of the image and then moved at the level of myocardial segment to be examined. Mechanical index was set at 1.6 for flash images and 0.1 for real-time images. The definitive setting of the ultrasound images was optimized after initial contrast infusion, kept constant throughout the study, and matched at follow-up MCE study. Ten consecutive heart beats after the flash were acquired in digital format for subsequent off-line analysis.

The intravenous contrast used in this study was Sonovue (Bracco, Milan, Italy), a second-generation ultrasound contrast agent that consists of microbubbles containing sulfur hexafluoride surrounded by a phospholipid shell. The mean size and concentration of microbubbles is 2.5 μm and 1 to $5 \cdot 10^8 \cdot ml^{-1}$, respectively. It is reconstituted by the addition of normal saline to the final solution of 5 ml. Sonovue was administered intravenously at the rate of 1 ml/min.

Contrast images were acquired in apical 4-chamber (Fig. 1), 2-chamber, and long-axis views; as soon as myocardial video intensity had reached a plateau, a flash of ultrasound with a very high mechanical index was given to destroy microbubbles in the sector and then the replenishment of bubbles was observed and digitally acquired and stored onto a magneto optical disk.

Echocardiographic data analysis. Two experienced observers who had no knowledge of the patient identity performed visual interpretation of echocardiograms; disagreement was resolved by consensus. Images were randomized across time points and patients. Regional wall motion (WM) was semiquantitatively scored according to the recommendations of the American Society of Echocardiography (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia) and a wall motion score index (WMSI) was calculated by the sum of the score of all segments divided by the total number of segments. Left ventricular end-diastolic volumes (EDVs) and end-systolic volumes (ESVs) were calculated from 4- and 2-chamber views using the modified Simpson biplane method. Ejection fraction (EF) was calculated from the formula: ([EDV − ESV]/EDV)%. Left ventricular remodeling was considered as a 20% increase in EDV at 6-month follow-up compared with 24-h echocardiogram.

None of the patients were excluded from the study because of inadequate echocardiographic window. Adequate MCE visualization was achieved in 95% of overall LV segments analyzed. All artifacts were excluded from analysis. More than one-half of the artifacts preventing assessment of MCE occurred in the basal inferoposterior (16%), lateral (11%), and anterior (28%) walls. Myocardial opacification at MCE, the echocardiographic parameter of MD, was visually assessed in each myocardial segment and semiquantitatively scored. Single perfusion score was assigned based on both the change in myocardial signal intensity throughout the replenishment curve and the degree of opacification at the peak contrast effect (11). Scores were graded as 1 = normal (homogeneous opacification approximating that of the normal region at peak and normal rate of increase in signal); 2 = reduced (partial or reduced opacification compared with the normal region at peak or reduced rate of increase in signal intensity); and 3 = absent (no opacification throughout replenishment time). A rate of increase was considered reduced if myocardial opacification occurred after the first 3 heartbeats after the flash. A contrast score index (CSI) was calculated by the sum of MCE score in each segment divided by the total number of segments. Endocardial length of transmural contrast defect (CD) (score = 3) and of WM abnormality was calculated in each apical view, averaged and expressed as percentage of LV endocardial length, as previously described (10,11).

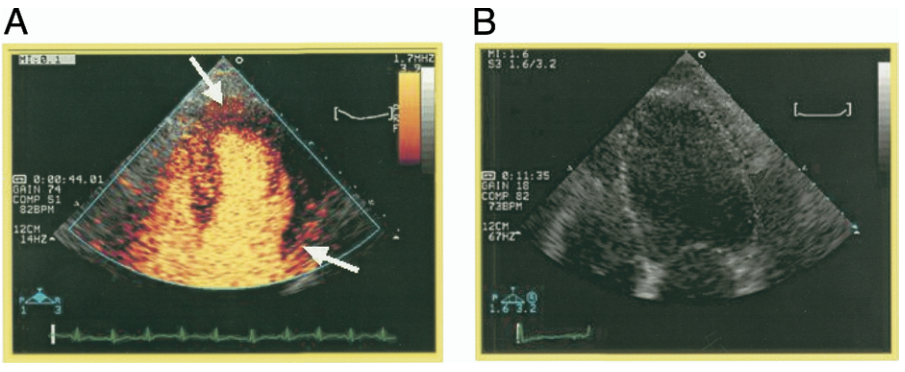

Figure 1 Example of Myocardial Contrast Echocardiography

(A) Myocardial contrast echocardiography in 4-chamber view on day 1 shows a large contrast defect on the lateral wall **(between arrows)** with normal end-diastolic volume. **(B)** Two-dimensional echocardiogram of the same patient at 6-month follow-up shows an enlarged left ventricle.

Two experienced observers who had no knowledge of the patient identity or conventional echocardiographic data performed the MCE data analysis. To assess intraobserver variability of MCE analysis, 16 MCE studies obtained in the first 8 patients were independently reviewed by the same observer (L.G.), 40 ± 10 days after initial scoring. We assessed interobserver variability by comparing the reading of 2 observers (L.G., L.A.). As previously reported, intraobserver and interobserver variability of CSI and CD analysis were 3.2 ± 2% and 4.2 ± 2% (absolute difference), respectively (10). For LV volume analysis, intraobserver and interobserver variability were 3.4 ± 1% and 5.1 ± 2%, respectively (10).

Statistical analysis. Statistical analysis was performed with the use of the SPSS software package for Windows 12.0 (SPSS Inc., Chicago Illinois). The study sample size was powered to demonstrate a different value of MD in predicting LV remodeling. We calculated that 100 patients had to be enrolled to have an alpha error of 0.05, a power of 0.80, a pooled variance of 320, and a mean difference of 5 in a prospective cohort study.

Mean and standard deviations were calculated for quantitative variables and percentages for qualitative variables. All variables were not-normally distributed and therefore differences between groups were tested with the Mann-Whitney *U* test for quantitative variables and by chi-square for percentages of qualitative variables. Differences were considered significant at $p \leq 0.05$.

We calculated the Spearman correlation coefficients considering the following variables: CD, WMSI − follow-up, ST-segment recovery %, EF − follow-up. For quantitative variables that showed a statistical significant difference between the median values of the 2 groups, remodeling and not remodeling, receiver-operating characteristic (ROC) curves were obtained to calculate cutoff values optimized to reach the best compromise in the prediction of LV remodeling, giving priority to sensitivity. Finally, a multivariate logistic regression analysis was conducted considering as dependent variable the occurrence of remodeling at follow-up. All the variables presenting a significance value <0.25 at univariate analysis were included in the model. The stepwise method with backward elimination was used, and odds ratios with 95% confidence intervals were calculated. The model was evaluated with Hosmer and Lemeshow test. A multiple linear regression was conducted using as dependent variable the EDV change at follow-up compared with 24 h, and r^2 was calculated.

Results

A total of 110 patients made the study population, with a mean age of 59 ± 11 years, 81 males. Of these, 27 patients (25%) evolved in LV remodeling at follow-up. Clinical characteristics of the 2 study groups are presented in Table 1. With the exception of a greater incidence of dyslipidemia in the remodeling group ($p = 0.019$) and of the number of diseased vessels ($p = 0.04$), all other variables were similar between groups.

Prediction of LV remodeling. All clinical, angiographic, and echocardiographic parameters included in the univariate analysis to predict LV remodeling are presented in Table 2. Using ROC curve analysis, we identified optimal cutoff values of echocardiographic parameters in the prediction of LV remodeling. The sensitivity and specificity of ST-segment resolution (cutoff <73%) were 95% and 34% (area under the curve = 0.60), respectively, whereas sensitivity and specificity of CD (cutoff >25%)

Table 1 Clinical and Angiographic Characteristics of the Study Population

	Remodeling (n = 27)	Nonremodeling (n = 83)	p Value
Age, yrs (mean ± SD)	63 ± 12	58 ± 10	0.065
Male gender, %	84	85	0.836
Smokers, %	52	66	0.178
Dyslipidemia, %	59	34	**0.019**
Hypertension, %	59	67	0.436
Diabetes mellitus, %	26	12	0.083
Positive family history of CAD, %	18	29	0.287
Killip class III or IV	0	1.2	1
Peak CK	2,687 ± 2,083	2,197 ± 1,191	0.316
Multivessel disease	42%	58%	0.274
Infarct-related artery, n (%)			0.325
LAD	23 (85.1)	59 (71.1)	
RCA	3 (11.1)	17 (20.5)	
LCX	1 (3.7)	7 (8.4)	
No. of diseased vessels			**0.04**
One	18 (66.7)	67 (80.8)	
Two	4 (14.8)	9 (10.8)	
Three	5 (18.5)	7 (8.4)	

Bold values indicate statistical significance.
CAD = coronary artery disease; CK = creatine kinase; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

JACC Vol. 51, No. 5, 2008
February 5, 2008:552–9

Table 2 Univariate and Multivariate Analysis of the Day 1 Predictors of Left Ventricular Remodeling at Follow-Up

Variable	Odds Ratio* (95% CI)	p Value	Odds Ratio† (95% CI)	p Value
Age >65 yrs	2.44 (0.97–6.19)	0.059		
Male gender	1.18 (0.35–3.96)	0.784		
Hypertension	0.58 (0.23–1.41)	0.231		
Diabetes	2.06 (0.66–6.32)	0.208		
Dyslipidemia	**2.8 (1.14–6.85)**	**0.024**		
Smoker	0.58 (0.23–1.35)	0.195		
Positive family history of CAD	0.55 (0.19–1.62)	0.277		
Time to treat	0.94 (0.84–1.04)	0.245		
ST-segment reduction cutoff <70%	1.15 (0.40–3.25)	0.79		
CK peak	0.99 (0.37–2.71)	0.996		
Initial TIMI score = 0	1.06 (0.74–1.52)	0.743		
Initial MBG = 0	0.55 (0.25–1.21)	0.138		
Final TIMI score <3	**5.84 (2.04–16)**	**0.001**	5.6 (1.40–22)	0.015
Final MBG <3	1.14 (0.36–3.67)	0.819		
Multivessel disease	**1.75 (1.02–2.99)**	**0.042**		
WMA cutoff >44%	**5.78 (2.09–15.8)**	**0.001**		
WMSI cutoff >1.9	**5.82 (2.19–15.4)**	**<0.0001**		
CD cutoff >25%	**6.48 (2.48–16)**	**<0.0001**	7 (1.86–27)	0.04
CSI cutoff >1.8	**8.85 (3.26–24)**	**<0.0001**		
EF cutoff <44.5%	**4.29 (1.71–10)**	**0.002**		
ESV cutoff <54.4 ml	1.08 (0.45–2.58)	0.864		
EDV cutoff <101 ml	1.95 (0.81–4.70)	0.136		
Hosmer-Lemeshow test			Chi-square = 0.39	0.820

*Univariate analysis; †multivariate analysis. **Bold** values indicate statistical significance.

CAD = coronary artery disease; CD = contrast defect; CI = confidence interval; CK = creatine kinase; CSI = contrast score index; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; MBG = myocardial blush grade; TIMI = Thrombolysis In Myocardial Infarction; WMA = wall motion abnormalities; WMSI = wall motion score index.

were 70% and 74% (area under the curve = 0.78), respectively. Residual extent of CD, accurately reflecting microvascular perfusion status, provides the best prediction of LV remodeling (Fig. 2). The cutoff of CD able to predict LV remodeling was also calculated separately according to the location of the IRA. In the left anterior descending territory, a CD of 25.5% predicted LV remodeling with 69% of sensitivity and 67% of specificity, whereas when the IRA was the right coronary artery, a CD of 31.6% predicted LV remodeling with 66% of sensitivity and 72% of specificity. Data on left circumflex as IRA were not sufficient to generate ROC curves.

All the variables presenting a significant value <0.25 were included in the multivariable analysis and, among those, only final TIMI flow grade <3 and CD with a cutoff of >25% were independently associated with LV remodeling (Table 2). Among patients with TIMI flow grade 3, CD was the only independent variable associated with LV remodeling (odds ratio 12.7; 95% confidence interval 2.65 to 61.2) (Table 3).

At multiple linear regression analysis, variables independently and directly correlated with EDV changes were diabetes ($p < 0.01$), CD ($p < 0.0001$), and CSI ($p < 0.003$), whereas TIMI grade 3 flow and WMSI were independently and inversely correlated ($p = 0.01$; $r^2 = 0.485$) (Table 4). The extent of CD was also linearly correlated with temporal changes in LV end-systolic volumes ($r = 0.5$; $p = 0.0005$), with changes in EDV ($r = 0.5$; $p = 0.0003$), and with changes in EF ($r = 0.4$; $p = 0.002$). Compared with ST-segment recovery, the extent of CD

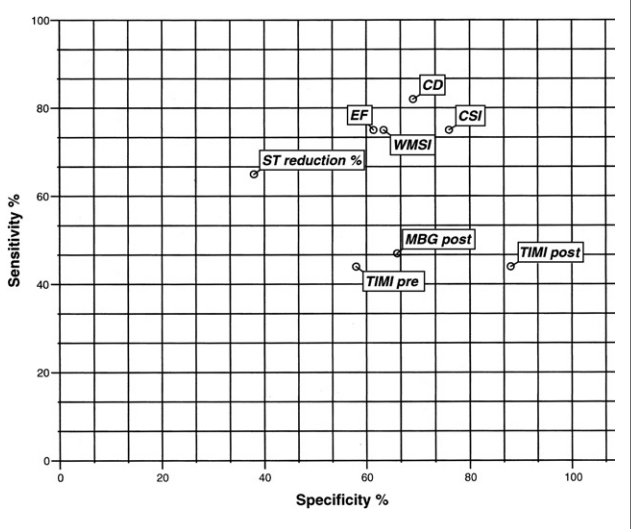

Figure 2 Prediction of Left Ventricular Remodeling

Sensitivity and specificity of different parameters studied in the prediction of left ventricular remodeling. CD = contrast defect; CSI = contrast score index; EF = ejection fraction; MBG = myocardial blush grade; TIMI = Thrombolysis In Myocardial Infarction; WMSI = wall motion score index.

Table 3 Univariate and Multivariate Analysis of the Day 1 Predictors of Left Ventricular Remodeling at Follow-Up in Patients With Grade 3 TIMI Flow

Variable	Odds Ratio* (95% CI)	p Value	Odds Ratio† (95% CI)	p Value
Age >65 yrs	1.23 (0.55–4.12)	0.121		
Male gender	1.18 (0.35–3.96)	0.784		
Hypertension	**0.25 (0.74–0.821)**	**0.024**		
Diabetes	2.62 (0.67–10.16)	0.163		
Dyslipidemia	**4.32 (1.28–14.50)**	**0.018**		
Smoker	0.59 (0.184–1.93)	0.388		
Positive family history of CAD	0.40 (0.08–1.95)	0.257		
Time to treat	0.98 (0.86–1.10)	0.757		
ST-segment reduction cutoff <70%	1.00 (0.98–1.02)	0.648		
CK peak	1 (1–1)	0.821		
Initial TIMI score 0	1.26 (0.81–1.26)	0.303		
Initial MBG 0	0.97 (0.41–2.30)	0.955		
Final MBG <3	1.16 (0.46–2.82)	0.738		
Multivessel disease	**2.46 (1.16–5.21)**	**0.019**		
WMA cutoff >44%	**1.03 (1.00–1.07)**	**0.029**		
WMSI cutoff >1.9	**7.4 (1.32–41)**	**0.02**		
CD cutoff >25%	**8.75 (3.22–46)**	**0.0001**	12.7 (2.65–61.2)	
CSI cutoff >1.8	**1.05 (1.01–1.09)**	**0.005**		
EF cutoff <44.5%	**0.90 (0.83–0.97)**	**0.013**		
ESV cutoff <54.4 ml	0.98 (0.95–1.01)	0.40		
EDV cutoff <101 ml	0.96 (0.93–0.99)	0.015		
Hosmer-Lemeshow test			Chi-square = 0.37	0.840

*Univariate analysis; †multivariate analysis. **Bold** values indicate statistical significance.
Abbreviations as in Tables 1 and 2.

demonstrated a much better linear correlation with WMSI and EF at follow-up (Fig. 3).

Discussion

The results of the AMICI multicenter study demonstrate that the extent of microvascular damage after PCI is the best predictor of LV remodeling in STEMI patients. Its predictive value is much greater than largely used clinical and angiographic parameters such as ST-segment resolution, TIMI flow grade, and MBG. Furthermore, for the first time, we provide cutoff values of MCE quantitative parameters of microvascular damage able to provide the best diagnostic accuracy in the prediction of LV remodeling.

Clinical value of ST-segment resolution. The ECG analysis of ST-segment resolution after primary PCI is a parameter easily available in the clinical arena. Patients with complete ST-segment elevation resolution have >90% likelihood of successful IRA recanalization. However, despite patent IRA, several patients may still show absent or partial ST-segment resolution. Thus, it has been suggested that persistent ST-segment elevation in patients with patent IRA might reflect the presence of microvascular obstruction (4–8,12,13). As a consequence, this ECG parameter has been largely used as a marker of microvascular damage and it has been shown to correlate with patient survival (12,13). However, its clinical value has recently been a matter of debate (14–17). In fact, in anterior STEMI patients, Bax et al. (14) showed no correlation between ST-segment recovery and EF or functional recovery at follow-up. Similarly, Poli et al. (15) showed no additional predictive value of ST-segment resolution when summed to MBG with respect to 6-month functional recovery. Finally, Sciagrà et al. (17) found, in the setting of patients who were treated with primary stenting and abciximab, a relatively low correlation between ST-segment resolution and infarct size and EF, suggesting the use of ECG findings only to categorize outcome as favorable or unfavorable but not to assess infarct size or LV function. In this multicenter study, we confirm and highlight the weak correlation between ST-segment resolution and EF and WMSI at 6-month follow-up, and we demonstrate that this ECG parameter is not able to predict post-infarct LV remodeling.

Table 4 Multiple Linear Regression

	β	SD	t	p Value
Constant	23.952	17.297	1.385	0.170
Diabetes	19.691	7.886	2.497	0.015
TIMI grade 3	−21.063	8.650	−2.435	0.017
WMSI	−23.733	9.490	−2.501	0.015
CSI	9.335	3.096	3.016	0.003
CD	0.938	0.239	3.921	0.000

$r^2 = 0.485$.
Abbreviations as in Table 2.

JACC Vol. 51, No. 5, 2008
February 5, 2008:552–9

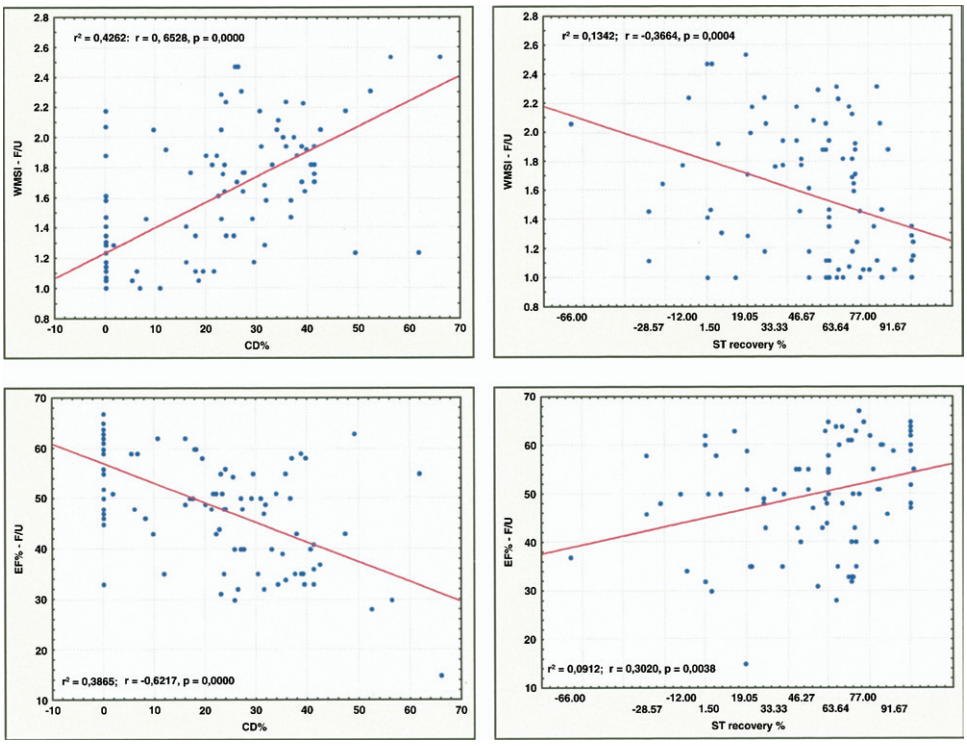

Figure 3 Correlations Between Perfusion and Function

(Left) Correlation between contrast defect (CD) length on day 1 after reperfusion and WMSI at 6-month follow-up (WMSI − F/U) **(top panel)** and ejection fraction (EF% − F/U) **(bottom panel)**. **(Right)** Correlation between ST-segment recovery after reperfusion and WMSI at 6-month follow-up (WMSI − F/U) **(top panel)** and ejection fraction (EF% − F/U) **(bottom panel)** as parameters of left ventricular function. Abbreviations as in Figure 2.

TIMI flow and MBG analysis. After PCI, TIMI flow grade is a widely used and clinically valuable angiographic parameter able to provide a semiquantitative measure of restored epicardial flow. Indirectly, TIMI flow grade is an expression of microvascular damage, because no-reflow occurs in 100% of patients with TIMI flow grade 2 but in only 30% of TIMI flow grade 3 patients (18–21). The data from this study confirm the importance to achieve a TIMI flow grade of 3 after PCI, because this parameter has an independent predictive value in the prediction of LV remodeling. However, among patients with TIMI grade 3 flow, only the extent of microvascular damage is able to provide a reliable prediction of LV remodeling. Thus, TIMI flow grade 3 is a good indicator of successful tissue reperfusion, but MCE evaluation is necessary to estimate effective microvascular damage and to accurately predict LV volume evolution and, consequently, patient prognosis. Similarly, MBG may provide an initial estimate of microvascular damage after PCI (9); however, as shown in this study, its accuracy in the prediction of LV remodeling is definitively low compared to the extent of MD at MCE.

Prediction of LV remodeling. In single-center studies, it has been shown that the extent of MD at MCE is a valuable parameter in the prediction of LV remodeling (3,22–24) and, using a validated methodology, Galiuto et al. (24) have provided an initial cutoff value of the extent of CD. However, this is the first multicenter study showing that, as compared with different widely used clinical parameters, the extent of MD at MCE is the only independent predictor and has the best diagnostic accuracy in the identification of LV remodeling. Furthermore, for the first time in a multicenter study, cutoff values not only of CD but also of all echocardiographic parameters able to predict LV remodeling have been identified by ROC analysis.

Clinical implications. Despite the clear evidence of the superior role of MCE in the diagnostic assessment of microvascular damage and in the prediction of LV remodeling, currently available contrast agents are not yet approved for myocardial perfusion, only for LV opacification. Thus, their use is limited to clinical studies and consequently restricted in the clinical arena. However, given the positive and important results of this and other studies, a future approval for their use in the assessment of myocardial perfusion might allow the collection of even more data and a widespread use of MCE in the clinical arena.

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REFERENCES

1. Grines CL, Browne KF, Marco J, et al., for the Primary Angioplasty on Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673–9.
2. de Boer MJ, Suryapranata H, Hoorntje JCA, et al. Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction. Circulation 1994;90:753–61.
3. Bolognese L, Carrabba N, Parodi G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation 2004;109:1121–6.
4. van't Hof A, Liem A, de Boer M, Zijlstra F. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615–9.
5. Matetzky S, Novikov M, Gruberg L, et al. The significance of persistence st elevation versus early resolution of ST segment elevation after primary PTCA. J Am Coll Cardiol 1999;34:1932–8.
6. Claeys MJ, Bosmans J, Veenstra L, et al. Determinants and prognostic implications of persistent ST-segment elevation after primary angioplasty for acute myocardial infarction. Importance of microvascular reperfusion injury on clinical outcome. Circulation 1999;99:1972–7.
7. Maroko PR, Libby P, Ginks WR, et al. Coronary artery reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. J Clin Invest 1972;51:2710–6.
8. de Lemos JA, Antman EM, McCabe CH, et al. ST-segment resolution and infarct related artery patency and flow after thrombolytic therapy. Am J Cardiol 2000;85:299–304.
9. van't Hof A, Liem A, Suryapranata H, et al. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction. myocardial blush grade. Circulation 1998;97:2302–6.
10. Galiuto L, Garramone B, Burzotta F, et al. Thrombus aspiration reduces microvascular obstruction after primary coronary intervention: a myocardial contrast echocardiography substudy of the REMEDIA Trial. J Am Coll Cardiol. 2006;48:1355–60.
11. Agati L, Tonti G, Pedrizzetti G, et al. Clinical application of quantitative analysis in real-time MCE. Eur J Echocardiogr 2004;45 Suppl 2:S9–15.
12. Krucoff MW, Johanson P, Baeza R, et al. Clinical utility of serial and continuous ST-segment recovery assessment in patients with acute ST-elevation myocardial infarction. Circulation 2004;110:533–9.
13. deLemos JA, Braunwald E. ST-segment resolution as a tool for assessing the efficacy of reperfusion therapy. J Am Coll Cardiol 2001;38:1283–94.
14. Bax M, de Winter RJ, Schotborgh CE, et al. Short and long-term recovery of left ventricular function predicted at the time of primary percutaneous coronary intervention in anterior myocardial infarction. J Am Coll Cardiol 2004;43:534–41.
15. Poli A, Fetiveau R, Vandoni P, et al. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty: real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. Circulation 2002;106:313–8.
16. Sorajja P, Gersh B, Costantini C, et al. Combined prognostic utility of ST-segment recovery and myocardial blush after percutaneous coronary intervention in acute myocardial infarction. Eur Heart J 2005;26: 667–74.
17. Sciagrà R, Parodi G, Migliorini A, et al. ST-segment analysis to predict infarct size and functional outcome in acute myocardial infarction treated with primary coronary intervention and adjunctive abciximab therapy. Am J Cardiol 2006;97:48–54.
18. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992;85:1699–705.
19. Agati L, Voci P, Hickle P, et al. Tissue-type plasminogen activator therapy versus primary coronary angioplasty: impact on myocardial tissue perfusion and regional function 1 month after uncomplicated myocardial infarction. J Am Coll Cardiol 1998;31:338–43.
20. Galiuto L, Lombardo A, Maseri A, et al. Temporal evolution and functional outcome of no-reflow: sustained and spontaneously reversible patterns following successful coronary recanalization. Heart 2003; 89:731–7.
21. Costantini CO, Stone GW, Mehran R, et al. Frequency, correlates and clinical implications of myocardial perfusion after primary angioplasty and stenting, with and without glycoprotein IIb/IIIa, in acute myocardial infarction. J Am Coll Cardiol 2004;44:305–12.
22. Greaves K, Dixon SR, Fejka M, O'Neill WW, Redwood SR, Marber MS, Senior R. Myocardial contrast echocardiography is superior to other known modalities for assessing myocardial reperfusion after acute myocardial infarction. Heart 2003;89:139–44.
23. Jeetley P, Swinburn J, Hickman M, Bellenger NG, Pennel DJ, Senior R. Myocardial contrast echocardiography predicts left ventricular remodeling following acute myocardial infarction. J Am Soc Echocardiogr 2004;17:1030–6.
24. Galiuto L, Gabrielli FA, Lombardo A, et al. Reversible microvascular dysfunction coupled with persistent myocardial dysfunction: implications for post-infarct left ventricular remodeling. Heart 2006;93: 565–71.