Original articles

Post-infarction microvascular integrity predicts myocardial viability and left ventricular remodeling after primary coronary angioplasty. A study performed with intravenous myocardial contrast echocardiography

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Key words:
Contrast media; Echocardiography; Microcirculation; Myocardial infarction; Stunned myocardium; Ventricular remodeling.

Background. **After acute myocardial infarction the preservation of the microvasculature is a prerequisite for myocardial viability, limited ventricular remodeling and a better prognosis. Intracoronary myocardial contrast echocardiography after acute myocardial infarction can detect the extent of microvascular damage. We hypothesized that intravenous myocardial contrast echocardiography after acute myocardial infarction treated with primary coronary angioplasty can predict the contractile reserve at low-dose dobutamine echocardiography, myocardial functional recovery and left ventricular remodeling.**

Methods. **We studied 37 patients with a first acute myocardial infarction and submitted to primary coronary angioplasty. All patients underwent echocardiography on the day they had the acute myocardial infarction, intravenous myocardial contrast echocardiography with power Doppler imaging 2.9 ± 0.5 days later and dobutamine echocardiography 3.7 ± 1.2 days after the acute myocardial infarction. In all cases, an echocardiography was performed at 3 months of follow-up.**

Results. **At intravenous myocardial contrast echocardiography, 25 patients showed contrast enhancement (reflow) and 12 a sizeable contrast defect (no-reflow). Reflow patients were found to have a regional wall motion score index similar to that of the no-reflow patients on the first day echocardiogram (2.6 ± 0.4 vs 2.8 ± 0.2, p = NS), but this parameter was smaller than that of the no-reflow patients at dobutamine echocardiography (1.5 ± 0.4 vs 2.6 ± 0.2, p < 0.0001) and at follow-up echocardiography (1.5 ± 0.5 vs 2.6 ± 0.2, p < 0.0001). The sensitivity and specificity of intravenous myocardial contrast echocardiography in identifying myocardial functional recovery at follow-up were 80 and 64%, while the sensitivity and specificity of dobutamine echocardiography were 85 and 76%. In no-reflow patients the left ventricular volumes increased from the acute to the chronic phase (end-diastolic volume from 71.9 ± 14.1 to 100.9 ± 40.6 ml/m^2, p < 0.0001, +28%; end-systolic volume from 43.1 ± 10.1 to 61.1 ± 30.1 ml/m^2, p < 0.0001, +29%), while they remained constant in reflow patients (end-diastolic volume from 71.8 ± 20.1 to 71.1 ± 15.4 ml/m^2, p = NS, -1%; and end-systolic volume from 39.9 ± 11.9 to 36.3 ± 12.8 ml/m^2, p = NS, -8%).**

Conclusions. **Intravenous myocardial contrast echocardiography is capable of identifying patients with a post-infarction contractile reserve and myocardial functional recovery; it also allows the early identification of patients prone to late left ventricular dilation, thus permitting a more aggressive diagnostic and therapeutic strategy.**

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Introduction

In patients with acute myocardial infarction (AMI) a preserved microcirculation within the risk area, in the presence of residual blood flow through the infarct-related vessel or collateral circulation, is a prerequisite for myocardial viability[1-3], for the regional and global left ventricular functional recovery[2,4-6], for limited left ventricular remodeling[7-9] and for a better prognosis[8,9].

Intracoronary myocardial contrast echocardiography (MCE) reliably assesses the microvascular integrity after AMI[2,5]; however, because of its invasiveness, it is not easily performable and repeatable.

Recent advances in ultrasound technology and the development of new echocontrast agents have made MCE feasible in

spite of the intravenous administration of contrast agents[10-12]. Intravenous MCE[11] in conjunction with advanced new ultrasound imaging modalities, such as harmonic power Doppler imaging[12], may permit the physician to investigate the status of the microcirculation. However, the potential of this technique in predicting the contractile reserve at low-dose dobutamine echocardiography (DE) and the myocardial functional recovery and left ventricular remodeling after AMI treated with primary coronary angioplasty is still poorly known.

Thus, we studied a series of patients with AMI and submitted to primary coronary angioplasty by intravenous MCE, DE and serial echocardiography in order to investigate the potential of intravenous MCE in evaluating the microvascular integrity and myocardial viability (as assessed by the contractile reserve and functional recovery at follow-up) as well as the relationship between microvascular integrity and ventricular remodeling.

Methods

Patient population and study protocol. Forty-three consecutive patients hospitalized in our Intensive Care Unit for a first AMI entered the study. The inclusion criteria were: 1) typical anginal pain lasting > 30 min, 2) an ST-segment elevation > 0.5 mV in ≥ 2 contiguous ECG leads, and 3) suitability for primary coronary angioplasty in the infarct-related artery. Patients were not eligible if they had a previous myocardial infarction, a coronary artery bypass graft or other cardiac surgery. Six patients were excluded: 3 due to suboptimal transthoracic image quality and 3 due to complex ventricular arrhythmias contraindicating the DE study; all patients gave written informed consent. Thus, the final study population consisted of 37 patients. Twenty-four patients had an anterior infarction, 11 inferior and 2 lateral; 31 had a Q-wave and 6 a non-Q-wave infarction. All 37 patients underwent primary coronary angioplasty within 12 hours of the onset of chest pain (at a mean of 4.2 ± 3.5 hours); among them, 31 (84%) were submitted to intravascular stenting. In all patients the TIMI flow grade was evaluated[13] and a successful coronary angioplasty was defined as < 30% residual stenosis.

The baseline left ventricular regional wall motion and volumes were assessed at two-dimensional echocardiography using the biplane Simpson's method, within the first day of hospital admission. Intravenous MCE was performed 2.9 ± 0.5 days and low-dose DE 3.7 ± 1.2 days after the AMI. A follow-up echocardiography was performed 12.2 ± 1.3 weeks later to assess the contractile recovery and ventricular volumes.

Echocardiographic studies. Echocardiographic images were recorded using commercially available systems equipped with second harmonic imaging and power Doppler (Agilent Sonos 5500, Andover, MA, USA, and Acuson Sequoia 512, Mountain View, CA, USA) and digitally stored on magneto-optical disks and on S-VHS videotapes for off-line analysis.

The contrast agent used in this study was Levovist® (Schering AG, Berlin, Germany), a 400 mg/ml suspension of galactose microparticles in sterile water injected into a cubital vein at a dose of 10 ml and using a specific infusion pump (Medrad Pulsar, Indianola, PA, USA). The contrast medium suspension was first administered as a small bolus (2 ml injected at approximately 0.5 ml/s into a vein of the right arm) and then as an infusion (approximately 8 ml, at a velocity of 3 ml/min). Echocardiographic studies were obtained using power Doppler technology and interrupted transmission imaging[11,12].

Apical views were systematically explored during MCE in order to assess myocardial perfusion. Interrupted transmission was performed by triggering every ≥ 3 cardiac cycles. Imaging was performed, when necessary, during held breathing (to avoid intense wall motion artifacts), and the end-systolic "triggering point" was set at a moment of the cardiac cycle when heart translation and contraction were minimal (e.g. during isovolumic relaxation). Due to the low acoustic power in the lateral zones of the ultrasound field, when necessary apical 4- and 2-chamber and long-axis views were obtained by shifting the lateral wall and the anterior wall to the center of the sector during contrast infusion. A high "mechanical index" was used with triggered imaging to maximize bubble destruction and, thus, the high intensity signal deriving from it[12]. Since focus placement has been shown to have a major impact on the display of contrast, it was placed at the level of the mitral valve. However, in cases of a suspected artifact, scanning was repeated after having moved the focus to the near field. Low-dose DE was started at 5 μg/kg/min for 5 min and then continued for a further 5 min at 10 μg/kg/min.

Echocardiographic analysis. The left ventricle was divided into 16 segments as visualized at the apical 4- and 2-chamber and long-axis views. A global and a regional wall motion score index in the risk area was calculated. A myocardial segment was considered to have spontaneous functional myocardial recovery if the wall motion score at follow-up echocardiography was lower than that calculated at the time of the first echocardiogram.

For the purpose of this study, the myocardial risk area was defined as the area of dysfunction (hypokinetic, akinetic or dyskinetic segments) within the predicted risk area in the acute phase of myocardial infarction[2,6,9].

Myocardial contrast echocardiography. Evaluation of MCE studies was performed off-line by two experienced cardiologists in a blinded manner. In particular, they were unaware of the clinical and angiographic data of the patients and of the presence, if any, and location of wall motion abnormalities.

A segment was considered as opacified at MCE if it showed enhancement after contrast injection. A contrast defect was considered as a relative decrease in contrast enhancement in one region compared with others in the same view. The contrast effect was graded using a previously described semiquantitative contrast score[3,6]: 0 = no opacification; 0.5 = reduced or patchy myocardial contrast enhancement in the entire segment; 1 = homogeneous opacification. Myocardial segments with an incomplete contrast effect because of shadowing, inadequate transthoracic ultrasound penetration, wrong triggering mode or MCE artifacts (blooming from the cavity, flashing artifacts), were considered as not assessable. A myocardial segment with a score of 0 or 0.5 was considered as not adequately perfused. A patient was considered as having an adequate post-AMI reflow if ≥ 50% of segments within the risk area had score 1 at MCE. In each patient the percentage extent of enhanced myocardium after MCE within the risk area was calculated as follows: number of segments within the risk area with score 1 at MCE/number of segments within the risk area × 100.

Low-dose dobutamine echocardiography. The evaluation of DE was performed by two experienced observers who were unaware of the MCE and angiographic results. In agreement with previous studies[1,2,6], each segment was scored and the wall motion score index calculated at baseline and at the second stage (10 μg/kg/min) of DE; a single myocardial segment within the risk area was defined as showing a contractile reserve if it was dyskinetic or akinetic at baseline and became at least hypokinetic or if it was akinetic or hypokinetic at baseline and became normokinetic during the dobutamine test.

Statistical analysis. Categorical data are presented as percentages, and quantitative data as mean ± SD. Analysis of variance for repeated measures was used for comparisons within each group and between different protocol time steps. The statistical significance of the differences between groups was determined by the one-way ANOVA (multiple comparisons with Student-Newman-Keuls test) or the McNemar test, as appropriate. A p value < 0.05 was considered statistically significant. Linear regression analysis was performed between the microvascular integrity at MCE (as the percent extent of the initial risk area) and the regional or global wall motion score index in the three different echocardiograms (at rest, at DE and at follow-up).

Inter and intraobserver variability. To assess the inter and intraobserver variability, in 10 randomly selected MCE studies a second experienced observer and the same first observer 2 months after initial scoring, evaluated the myocardial perfusion grade according to the semiquantitative contrast score previously described in the "Echocardiographic analysis" section.

The interobserver segmental score agreement for the MCE perfusion grade was 88% and in all but two segments the difference between the two scores was ≤ 1 grade. The intraobserver segmental score agreement was 93% and in all segments the difference between the two scores was ≤ 1 grade.

Results

At MCE opacification of ≥ 50% and of < 50% of myocardial segments in the risk area was present in 25 and 12 patients respectively (reflow and no-reflow patients); except for the mean age and percentage of TIMI 3 flow, there were no statistically significant differences between these two groups in clinical and angiographic characteristics (Table I).

Microvascular integrity, contractile reserve and functional recovery at follow-up. In the 37 patients, 220 out of the 236 myocardial segments in the risk area (93%) were analyzable at MCE. At the first day

Table I. Clinical characteristics.

	Reflow (n=25)	No-reflow (n=12)	p
Age (years)	55.4 ± 10.6	64.9 ± 10.9	0.016
Male	22 (88%)	9 (75%)	0.598
Peak CK (U/l)	1630 ± 1208	2450 ± 2130	0.143
Infarct location (% anterior)	15 (60%)	9 (75%)	0.598
Chest pain onset to admission time (hours)	3.7 ± 4.3	4.3 ± 4.2	0.691
TIMI 3 flow	18 (72%)	3 (25%)	0.019
No. diseased vessels	1.6 ± 0.5	1.9 ± 0.7	0.143
Risk factors			
Diabetes	3 (12%)	3 (25%)	0.598
Hypertension	11 (44%)	7 (58%)	0.655
Smoking	19 (76%)	7 (58%)	0.461
Hypercholesterolemia	10 (40%)	4 (33%)	0.961

echocardiogram the acute regional and global score indexes were similar in the 25 patients with reflow and in the 12 patients with no-reflow. At DE and at follow-up echocardiography both the regional and global score indexes were significantly smaller in the reflow group compared to the no-reflow one (Table II). No significant correlation was found between the percentage extent of myocardium with microvascular integrity within the risk area at MCE and the resting regional wall motion score index (r = -0.17, p = NS), while a significant negative correlation was found with the regional score index during DE (r = -0.55, p = 0.005) and at follow-up (r = -0.60, p = 0.001).

Similar results were obtained for the correlation of the percentage of myocardium with microvascular integrity versus the global score index at rest (r = -0.18, p = NS), during DE (r = -0.66, p < 0.0001) and at follow-up (r = -0.58, p = 0.001).

Microvascular integrity and TIMI grade. Patients were divided into three groups on the basis of the TIMI grading in the infarct-related artery and of the presence or absence of reflow within the risk area: 1) patients with TIMI 0, 1, 2 flow (n = 8); 2) patients with no-reflow despite restoration of TIMI 3 flow (TIMI 3/no-reflow group, n = 9), 3) patients with reflow after restoration of TIMI 3 flow (TIMI 3/reflow group, n = 20). Despite the fact that they were similar at the first day echocardiogram, the regional and global score indexes during DE and at follow-up were significantly smaller in TIMI 3/reflow patients, than in patients with either TIMI 0, 1, 2 flow and TIMI 3/no-reflow (Table III). TIMI 0, 1, 2 flow and TIMI 3/no-reflow patients did not show any differences in the regional and global wall motion score indexes during DE and at follow-up. In figure 1 two different examples of MCE reflow and no-reflow in two different patients with antero-apical infarctions after TIMI 3 flow had been successfully restored in the infarct-related artery following primary coronary angioplasty are shown.

Prediction of regional functional recovery at myocardial contrast echocardiography and dobutamine echocardiography. At follow-up functional recovery was observed in 112 of 137 myocardial segments considered viable and in only 19 of the 80 non-viable myocardial segments at DE (Table IV). Among the 131 segments showing normal perfusion at MCE (score 1), 95 were found to have an improved wall motion score at 3 months of follow-up, whereas 36 did not.

Table II. Functional outcome.

	Reflow (n=25)	No-reflow (n=12)	p
No-reflow ratio to risk area (%)	15.8 ± 19.2	82.5 ± 10.1	0.001
RWMSI			
On the first day	2.6 ± 0.4	2.8 ± 0.2	0.112
During DE	1.5 ± 0.4*	2.6 ± 0.2	0.000
After 3 months	1.5 ± 0.5*	2.6 ± 0.2	0.000
GWMSI			
On the first day	1.8 ± 0.3	1.9 ± 0.2	0.303
During DE	1.2 ± 0.2*	1.9 ± 0.4	0.005
After 3 months	1.2 ± 0.3*	1.9 ± 0.4	0.005

All data are expressed as mean ± SD. DE = dobutamine echocardiography; GWMSI = global wall motion score index; RWMSI = regional wall motion score index in the risk area. * = p < 0.001 vs wall motion score index during the first day.

Table III. Functional outcome for patients with coronary artery recanalization with different TIMI grades.

	TIMI 0, 1, 2 (n=8)	TIMI 3 reflow (n=20)	TIMI 3 no-reflow (n=9)
No-reflow ratio to risk area (%)	59.1 ± 21.4	16.2 ± 15.4*	60.1 ± 11.1
RWMSI			
On the first day	2.7 ± 0.4	2.5 ± 0.4	2.6 ± 0.3
During DE	2.3 ± 0.5§	1.5 ± 0.6*§	2.2 ± 0.5§
After 3 months	2.1 ± 0.5§	1.5 ± 0.5*§	2.2 ± 0.4§
GWMSI			
On the first day	1.7 ± 0.2	1.7 ± 0.3	1.7 ± 0.2
During DE	1.6 ± 0.3	1.3 ± 0.3**§	1.6 ± 0.3
After 3 months	1.6 ± 0.3	1.3 ± 0.3**§	1.6 ± 0.2

All data are expressed as mean ± SD. Abbreviations as in table II. * = p < 0.001 and ** p < 0.05 vs TIMI 0, 1, 2 and TIMI 3 no-reflow patients; § = p < 0.001 vs same group on the first day.

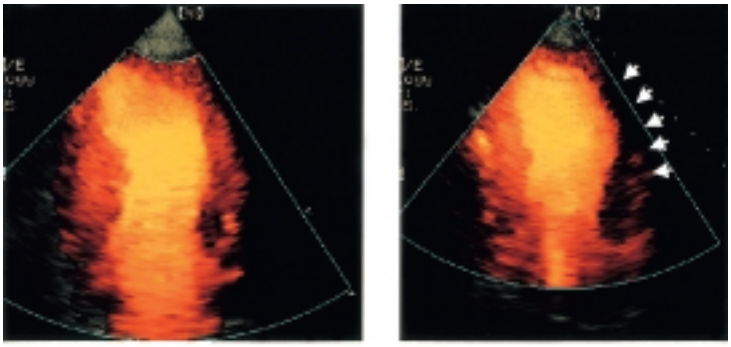

Figure 1. *Images from two different patients with apical-anteroseptal myocardial infarction following recanalization of the left anterior descending artery. The patient* on the right *had a persistent perfusion defect (no-reflow,* arrowheads*), whereas the patient* on the left *demonstrated reflow in the same region. PTCA = coronary angioplasty.*

Table IV. Potential of dobutamine echocardiography (DE) and myocardial contrast echocardiography (MCE) in identifying dysfunctioning viable myocardial segments after acute myocardial infarction.

Overall	No. segments	Recovery at follow-up		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		Present	Absent				
Viability at DE	137	112	25				
No viability at DE	99	19	80				
				85	76	82	81
MCE reflow (1)	131	95	36				
MCE no-reflow (0 and 0.5)	89	24	65				
				80	64	73	73
MCE reflow (0.5 and 1)	165	108	57				
MCE no-reflow (0)	55	11	44				
				91	44	65	80

NPV = negative predictive value; PPV = positive predictive value. 1 = homogeneous opacification; 0.5 = reduced or patchy enhancement; 0 = no opacification.

Of the 89 segments showing absent or partial perfusion at MCE (score 0 or 0.5), 24 were found to have an improved wall motion score at follow-up, whereas 65 did not. The sensitivity, specificity and predictive values of DE and of the different MCE scores in predicting the functional recovery of individual myocardial segments are shown in table IV.

Within the risk area, 144 (65%) myocardial segments were akinetic and 76 (35%) hypokinetic. When considering only the myocardial segments which were akinetic at the first day echocardiogram, functional recovery occurred more frequently in the 73 myocardial segments showing complete opacification at MCE (74% during DE and 73% at follow-up) than in the 71 segments with absent or partial opacification at MCE (28% at DE and 30% at follow-up; $p < 0.0001$ vs complete opacification; Fig. 2).

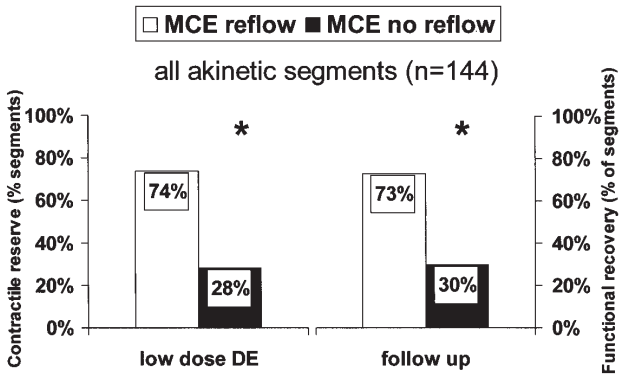

Figure 2. *Bar graph showing the wall motion recovery as percent of myocardial segments akinetic at first day with contractile reserve* (left panel) *at dobutamine echocardiography (DE) and functional recovery* (right panel) *at follow-up echocardiogram. MCE = myocardial contrast echocardiography. * = p < 0.0001.*

Microvascular integrity and left ventricular remodeling. At the first day echocardiogram, there were no differences in the ventricular end-diastolic and systolic volumes between reflow and no-reflow patients. In patients with no-reflow, the ventricular volumes increased significantly from baseline to the 3-month follow-up

(end-diastolic volume from 71.9 ± 14.1 to 100.9 ± 40.6 ml/m^2, p < 0.0001, +28%; end-systolic volume from 43.1 ± 10.1 to 61.1 ± 30.1 ml/m^2, p < 0.0001, +29%). On the contrary, in patients with MCE reflow there was a non-significant trend towards a reduction in ventricular volumes (end-diastolic volume from 71.8 ± 20.1 to 71.1 ± 15.4 ml/m^2, p = NS, -1%; end-systolic volume from 39.9 ± 11.9 to 36.3 ± 12.8 ml/m^2, p = NS, -8%). Thus, at the 3-month follow-up, the end-diastolic and end-systolic volumes, as well as the volume percentage changes, were significantly greater in patients with MCE no-reflow than in those with MCE reflow (Fig. 3).

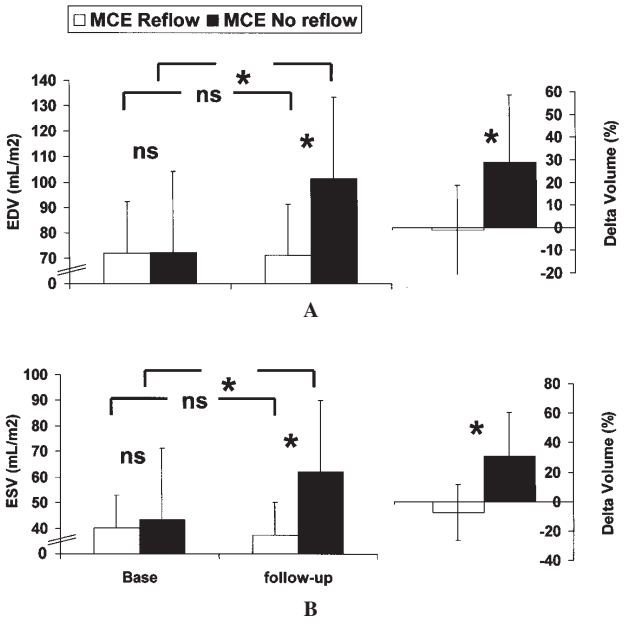

Figure 3. *Bar graph showing end-diastolic volume (EDV)* (upper panel) *and end-systolic volume (ESV)* (lower panel)*, at first day and at follow-up echocardiography and their percentage of changes (delta volume). MCE = myocardial contrast echocardiography. * = p < 0.0001.*

Discussion

In the early phases of AMI, recanalization of the infarct-related artery does not necessarily imply adequate myocardial reperfusion. The "no-reflow" phenomenon (absence of reperfusion in the presence of adequate recanalization) is the expression of microvascular damage[2], constitutes a negative determinant for myocardial viability[1-3,5,6] and is an important factor for ventricular remodeling and major cardiac events[4,7,8]. No-reflow can be reliably detected at intracoronary MCE[2,9].

Recently, a myocardial echocontrast effect has been obtained both in animals and in humans after intravenous echocontrast injection, thanks to new echocontrast agents and advanced ultrasound technologies[11,14,15]. Triggered imaging avoids ultrasound microbubble destruction[10], mostly in association with power Doppler[11,12] which detects strong signals deriving from microbubble explosion and conceals the low Doppler signal from myocardial tissue.

The present study demonstrates that in patients with a recent AMI submitted to primary coronary angioplasty, the microvascular integrity within the risk area, as assessed at intravenous MCE, predicts the contractile reserve at DE and the functional recovery at follow-up and identifies those patients who are less prone to late ventricular dilation. In fact, in our patients with post-AMI microvascular reflow both the regional and overall ventricular functions improved more (as expressed by lower values of regional and global score indexes) than in patients without reflow, both at DE and at follow-up.

Although previous intracoronary studies analyzed the MCE perfusion in hypo and akinetic segments[1,2,6], we also separately evaluated the akinetic segments which are less prone to spontaneous recovery. Even in this subgroup of segments a great potential of MCE in defining myocardial segments with reflow was observed, with a greater chance of a spontaneous or dobutamine-induced contractile recovery. We also analyzed the diagnostic potential of MCE reflow in relation to the TIMI flow in the infarct-related coronary artery. As previously observed[1,5,15], the results of MCE were independent of the TIMI flow. In our subgroup of patients with AMI and optimal angiographic recanalization (TIMI 3), the myocardial functional recovery was still strongly related to the MCE patterns (Table III). Similarly, we also found that at DE the contractile reserve was greater in patients with TIMI 3 and myocardial reflow than in patients with TIMI 3 and no-reflow; in fact, patients with TIMI 3 and no-reflow showed a myocardial contraction behavior similar to that observed in patients with incomplete coronary recanalization (TIMI < 3). Therefore, the presence of a salvaged microvascular network is a necessary prerequisite for the preservation of myocardial viability after AMI even in the presence of an optimal TIMI grade. This finding is in agreement with the fact that even an optimal post-angioplasty angiographic recanalization (TIMI 3 flow) of the infarct-related coronary artery can indicate just an "illusionary reperfusion"[16] and not be sufficient to preserve the real functional microvasculature[5,17]. Conversely, the microvascular reflow demonstrated at intracoronary MCE is the strongest predictor of myocardial functional recovery, independently of the presence or absence of an angiographic collateral circulation[17] or of the status of the infarct-related artery[5].

Sensitivity and specificity of intravenous myocardial contrast echocardiography. In our series of patients, the sensitivity for the detection of myocardial contractile recovery was lower and the specificity higher than those reported for intracoronary MCE[1]. Methodological and technical problems can account for this: the lower percentage of false positive studies could be explained by the fact that we performed MCE 3 days after AMI, and not immediately after coronary

angioplasty (as is common practice during intracoronary MCE) when post-ischemic hyperemia can overestimate the real perfusion conditions. In fact, according to a recent study the microvascular integrity estimate for the prediction of myocardial viability should be performed neither too shortly after recanalization (immediately after primary coronary angioplasty) nor during the stage of convalescence[18]. On the other hand, the higher percentage of false negative MCE studies is likely to be due to either destruction of microbubbles or to a low Doppler signal intensity caused by slow myocardial blood flow within the risk area. When myocardial segments with partial opacification at MCE (score 0.5) were considered together with those with full opacification (score 1), the sensitivity increased and the specificity decreased, approximating the ones described in previous intracoronary MCE studies[1,2] (Table IV).

As in previous intracoronary studies[1,2,6], our series of patients was affected by a certain percentage of false positive reflow at MCE (apparent discrepancy between the microvascular integrity and the absence of functional recovery), with a consequent specificity reduction. This finding can be at least partially explained by several factors: 1) the preservation of the subepicardial microvasculature, because the ischemic injury during AMI may not be sufficient to irreversibly damage the transmural microvasculature, thus leading to the creation of islands of viable and necrotic myocytes (mostly in the subendocardium); 2) the presence of temporal dissociation between microvascular and cellular damage; in fact, MCE performed a few days after AMI correlates with the functional recovery more closely than that performed shortly after reperfusion[6,14,18]; 3) early post-ischemic hyperemia can cause, within the risk area, a temporary reflow increase not followed by functional recovery at follow-up[19]. This last possibility has been underlined by a study demonstrating that 25% of patients with primary coronary angioplasty and good reflow at early MCE (20 min after recanalization), showed intramural hemorrhage at nuclear magnetic resonance and no wall motion functional recovery[19].

We did not find a correlation between the extent of no-reflow and the regional wall motion score index at the first day echocardiogram, probably because of the presence of a variable amount of stunned myocardium so early after AMI. Conversely, the extent of no-reflow was significantly correlated with the regional score index at DE or at follow-up echocardiography. This finding is in agreement with experimental data showing that myocardial contractility during DE, but not in baseline conditions, is directly related to the histological extent of myocardial salvage after reperfusion[20]. Therefore, despite the fact that the correlation coefficients are not strict (the two techniques evaluate different pathophysiological aspects), intravenous MCE seems to have an important role in the early prediction of the extent of myocardial salvage and consequently of necrosis.

The preservation of the microvascular network was probably the basis for the preservation of the myocyte viability, unraveled at DE and evident at the follow-up echocardiogram.

Ventricular remodeling and microvascular obstruction. The different prognostic weight of the characteristics of myocardial infarction is important for the understanding of the pathophysiology of post-infarction ventricular remodeling. It has been demonstrated that the presence of myocardial viability is the cornerstone for the preservation of ventricular remodeling[21]. In the present study patients with no-reflow at intravenous MCE showed progressive dilation and larger ventricular volumes at follow-up than those with reflow. These results are in agreement with similar previous experimental data showing that microvascular obstruction, as detected at magnetic resonance 10 days after AMI, predicted more fibrous scar formation and left ventricular remodeling; moreover, at multivariate analysis, this microvascular obstruction was related to ventricular dilation independently of the infarct size[7].

The microvascular salvage has been demonstrated to be correlated with post-infarct ventricular remodeling, independently of the patient's age and sex, of the time interval between pain onset and coronary angioplasty, of the pre-angioplasty patency of the infarct-related artery, and of the post-angioplasty residual stenosis. In fact, using intracoronary MCE, Ito et al.[8] demonstrated that the extent of no-reflow after AMI is the most powerful predictor of left ventricular remodeling and is also a determinant of survival after AMI.

Study limitations. The best method to determine the risk area is the direct imaging of the perfusion defect at MCE before recanalization of the coronary artery. In our study, in order to avoid any delay in the invasive recanalization procedure, we determined the risk area by evaluating the early extent of abnormal wall motion in the predicted risk area, since it was shown that it closely correlates with direct imaging of the perfusion defect[9].

The time course of the dimensions of MCE defects in patients with an AMI and normal perfusion at early MCE is still poorly known[10,18]. We did not perform serial MCE in our patients; we performed MCE on the third day following AMI. This is early enough to provide information with a potential diagnostic and therapeutic impact[7] but at the same time allowed us to avoid the phase of reactive hyperemia[6,14].

Clinical implications. Major strengths of this study are represented by 1) the first data available on the sensitivity and specificity of intravenous MCE in evaluating the contractile reserve and functional myocardial recovery after AMI treated with primary coronary angioplasty, 2) the highly selective enrollment of patients submitted to primary coronary angioplasty, and 3) the analysis of intravenous MCE after AMI to predict ventricular remodeling.

Despite the fact that DE more accurately detects viable myocardium than MCE, the information obtained with intravenous MCE is very sensitive. Besides, the technique may be performed in the very early phases of myocardial infarction to evaluate the microvascular status of the myocardial area at risk. Moreover, MCE and DE investigate different areas of the myocardial segment at risk: DE stimulates myocytes to contract; conversely MCE investigates the preservation of the microvasculature, which can be a prerequisite for myocardial recovery. Further studies are necessary to determine which information is more precious for prognostic evaluation in the very early phases of AMI.

The possibility of evaluating the microvascular reflow non-invasively, at the bedside after primary coronary angioplasty, and to repeat this measurement when clinically indicated, gives intravenous MCE a unique advantage over intracoronary MCE. This potential can be particularly useful for the early assessment of the extent of myocardial salvage, and hence of myocardial viability, as well as for the early identification of patients with extensive no-reflow and a higher risk of late ventricular remodeling. It could also be useful for the serial evaluation of the extent of microvasculature integrity, for the evaluation of microvessel salvage by pre-infarction angina[22], for the assessment of the time course of no-reflow, and lastly for the assessment of the therapeutic intervention aimed at limiting post-AMI no-reflow.

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