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JACC Vol. 31, No. 2
February 1998:338–43

Tissue-Type Plasminogen Activator Therapy Versus Primary Coronary Angioplasty: Impact on Myocardial Tissue Perfusion and Regional Function 1 Month After Uncomplicated Myocardial Infarction

LUCIANO AGATI, MD, PAOLO VOCI, MD, PHD, PATRICK HICKLE, MD,* DARIO C. VIZZA, MD, CAMILLO AUTORE, MD, FRANCESCO FEDELE, MD, STEVEN B. FEINSTEIN, MD,* ARMANDO DAGIANTI, MD

Rome, Italy and Chicago, Illinois

Objectives. **This study sought to compare the impact of primary coronary angioplasty and thrombolytic therapy for acute myocardial infarction (AMI) on 1-month infarct size and microvascular perfusion.**

Background. **The effect of the reperfusion strategies of primary coronary angioplasty and thrombolytic therapy on microvascular integrity still remains to be determined.**

Methods. **Sixty-two consecutive patients with a first AMI, undergoing intravenous tissue-type plasminogen activator (t-PA) therapy (32 patients, Group I) or primary angioplasty (30 patients, Group II), were studied. Only patients with 1-month Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 were selected for the study. Patients in whom primary angioplasty was unsuccessful or those with clinical evidence of failed reperfusion were excluded. Microvascular perfusion was assessed at 1 month by intracoronary injection of sonicated microbubbles. Contrast score index (CSI) and wall motion score index (WMSI) were derived using qualitative methods.**

Results. **At baseline there were no significant differences between groups for age, risk factors, time to hospital presentation, Killip class on admission, prevalence of multivessel disease or anterior infarct site, infarct area extension before reperfusion, peak creatine kinase levels and postinfarction treatment. Conversely, significant differences between groups were found at follow-up for percent residual infarct related-artery (IRA) stenosis (70 ± 12 vs 36 ± 14 [mean ± SD], $p = 0.0001$), CSI (1.02 ± 0.4 vs. 1.49 ± 0.5, $p = 0.0003$) and WMSI (1.67 ± 0.3 vs. 1.45 ± 0.3, $p = 0.015$). In particular, in the subset of patients with TIMI grade 3 flow, a perfusion defect occurred in one or more segments subtended by the IRA in 72% of Group I versus 31% of Group II patients ($p < 0.00001$) and in 27% of Group I versus 8% of Group II segments ($p < 0.00001$).**

Conclusions. **The present study shows, in a highly selected cohort with successful IRA recanalization, that primary angioplasty is more effective than thrombolysis in preserving microvascular flow and preventing extension of myocardial damage at 1-month after AMI.**

(J Am Coll Cardiol 1998;31:338–43)
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Several large clinical trials (1,2) have definitively shown that the primary goal of treatment for patients with evolving myocardial infarction is the rapid and sustained restoration of anterograde coronary blood flow throughout the infarct-related artery (IRA).

In the past decade, important progress has been achieved in both pharmacologic and mechanical techniques to obtain the prompt restoration of full anterograde flow in the IRA. Recent studies have confirmed that either primary percutaneous transluminal coronary angioplasty (PTCA) or intravenous thrombolysis may improve in-hospital survival and patient prognosis. Comparative studies between these two reperfusion strategies (3,4) have shown that immediate PTCA is more effective than thrombolysis in restoring patency and preventing IRA reocclusion.

However, recent myocardial contrast echocardiographic (MCE) data have suggested (5) that microvascular perfusion may remain impaired despite restoration of flow in the previously occluded epicardial coronary artery ("no-reflow" phenomenon). Therefore, coronary artery patency should not be considered synonymous with microcirculatory reflow (6). The reestablishment of tissue-level perfusion within the jeopardized myocardium may be the ultimate goal of treatment for patients with an evolving myocardial infarction. The MCE assessment of microvascular integrity after reperfusion and 1 month later is a good predictor of the definitive infarct size and also provides useful estimates on residual myocardial viability (7–9).

From the Department of Cardiology and Cardiac Surgery, "La Sapienza" University of Rome, Italy; and *Department of Cardiology, University of Illinois at Chicago, Chicago, Illinois. This study was presented in part at the 69th Annual Scientific Sessions of the American Heart Association, New Orleans, Louisiana, November 1996.

Manuscript received June 19, 1997; revised manuscript received October 1, 1997, accepted October 13, 1998.

Address for correspondence: Dr. Luciano Agati, Department of Cardiovascular and Respiratory Sciences, "La Sapienza" University of Rome, Viale del Policlinico 155, 00161 Rome, Italy. E-mail: agati@axrma.uniroma1.it.

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0735-1097/98/$19.00
PII S0735-1097(97)00487-7

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AMI = acute myocardial infarction
CK = creatine kinase
CSI = contrast score index
IRA = infarct-related artery
MCE = myocardial contrast echocardiography (echocardiographic)
PTCA = percutaneous transluminal coronary angioplasty
TIMI = Thrombolysis in Myocardial Infarction
t-PA = tissue-type plasminogen activator
WMSI = wall motion score index

To our knowledge, no study to date has evaluated the impact on microvascular integrity of different reperfusion modalities for acute myocardial infarction (AMI). The purpose of the present study was therefore to assess the extent of myocardial perfusion defect and infarct size 1 month after IRA recanalization by either intravenous thrombolysis or primary PTCA.

Methods

Patients. The research protocol was approved by the Institutional Review Board of the University of Illinois at Chicago Hospital and by the ethical committee of "La Sapienza" University of Rome School of Medicine. The enrollment of patients began on January 2, 1993 and ended on March 8, 1994. The study included 62 consecutive patients (14 women, 48 men, mean [±SD] age 56 ± 8 years) who were admitted to the coronary care unit within 6 h after the onset of AMI (ST segment elevation ≥2 mm in two or more contiguous leads, followed by significant enzyme release). Thirty-two patients received intravenous tissue-type plasminogen activator (t-PA) (Group I), and 30 patients underwent primary PTCA (Group II). Blood samples were collected every 4 h for cardiac enzyme determination. Patients were selected for this investigation if they met the following inclusion criteria: 1) technically adequate echocardiographic studies allowing the detection of the entire left ventricular endocardial contour during cardiac catheterization; 2) age <75 years; 3) no contraindication to thrombolytic therapy; 4) no previous AMI or coronary artery bypass graft surgery; 5) stable clinical condition during the hospital period, with no major clinical events; and 6) IRA patency with Thrombolysis in Myocardial Infarction (TIMI) (10) flow grade 2 or 3 at 1-month follow-up coronary angiography. Patients in whom primary angioplasty was unsuccessful or with clinical evidence of failed reperfusion after thrombolysis (i.e., persistent chest pain or <50% reduction of ST segment elevation in association with peak creatine kinase (CK) release occurring 12 h after the onset of therapy) (11) were excluded. The choice between treatments was independent of clinical characteristics of patients and coronary artery disease severity and was dependent only on the availability of the catheterization laboratory staff to perform emergency PTCA. All selected patients subsequently developed Q waves on the 12-lead surface electrocardiogram.

Treatment protocol. Each patient received intravenous nitroglycerin in a dosage aimed at reducing systolic blood pressure to 110 mm Hg. Additional therapy was given on indication only. Patients assigned to accelerated t-PA received an intravenous bolus of 15 mg and then an infusion of 0.75 mg/kg body weight (up to 50 mg) over 30 min and 0.5 mg/kg (up to 35 mg) over the next 60 min, accompanied by an intravenous heparin bolus of 5,000 IU and then 1000 IU/h, with dose adjustment to maintain an activated partial thromboplastin time between two or three times the normal value for at least 2 days (1,12). Patients assigned to PTCA were immediately transported to the catheterization laboratory and underwent coronary angiography. Once the culprit vessel was identified, balloon PTCA was performed to establish patency.

Coronary artery cineangiography. Coronary angiography and angioplasty were performed by standard procedure and equipment. Left and right coronary arteries were imaged in multiple views, including craniocaudal angulations. Follow-up angiograms were obtained at 1 month. IRA identification was based on electrocardiographic changes, angiographic appearance of the artery and associated regional wall motion abnormalities. Significant coronary artery disease other than that in the IRA was defined as ≥50% reduction in lumen diameter of a major epicardial coronary artery or one of its major branches in each of the two orthogonal projections. The anterograde radiocontrast flow through the IRA was determined on coronary angiography performed at 1 month using the TIMI criteria (10). Collateral flow was scored according to the classification of Rentrop et al. (13). The presence of grade 2 or 3 collateral flow was considered significant. Coronary angiography and angioplasty data were collected and analyzed by three experienced observers. Consensus on procedural success, TIMI grade and extent of coronary artery disease and collateral flow was reached in all cases.

Echocardiographic analysis. Two-dimensional echocardiographic images were obtained before reperfusion and at 1-month follow-up by commercially available echocardiographic instruments. Baseline images were used to assess the initial extent of left ventricular dysfunction. Follow-up images were paired with the corresponding baseline images and directly compared to assess changes in regional function. The left ventricle was examined using standard echocardiographic views, and wall motion was scored for each segment using a 16-segment left ventricular model. A previously described semiquantitative scoring system (14) (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia) was used to analyze each study. The wall motion score index (WMSI) within the infarct bed was derived by averaging the scores from each segment within the infarct territory.

All echocardiograms were analyzed independently by two experienced observers (P.V., P.H.) who had no knowledge of patient data or each other's results. In the rare case of disagreement, a third observer (L.A.) reviewed the study and his judgment was binding. Our interobserver and intraobserver

variability for semiquantitative analysis of wall motion abnormalities in patients with AMI is good (7,9,15–17).

Myocardial contrast echocardiography. Microvascular perfusion was assessed at 1 month using MCE by intracoronary injection of sonicated microbubbles. Contrast echocardiography was performed using a previously described method (7,9,18,19). In brief, 0.5 to 2 ml of sonicated contrast agent was separately injected into the left main and right coronary arteries after diagnostic coronary angiography during simultaneously performed transthoracic two-dimensional echocardiography in multiple views. A commercially available sonicating system was used (Heat Systems Ultrasonics). Gain settings were optimized at the beginning of each study and kept constant throughout the study. Microvascular perfusion was assessed in the end-diastolic frame of the postinjection cycle showing the best delineation between contrast-enhanced and nonenhanced myocardium. The aforementioned 16-segment model of the left ventricle was used to assign the following contrast scores (7,9): 0 = no enhancement; 0.5 = patchy enhancement; 1 = homogeneous enhancement. The contrast score index (CSI) for the infarct zone was calculated by dividing the sum of the contrast scores for each segment within the infarct bed by the number of infarct segments analyzed. In case of disagreement over scoring, a consensus was reached after open discussion.

Statistical analysis. Continuous baseline and outcome variables are given as mean value ± SD, whereas discrete variables are given as absolute values and percentages. Comparison between continuous variables was performed using two-tailed Student *t* test. Categoric variables were compared using a conventional chi-square test. Fisher exact test was applied if there was an expected cell value <5. Differences for single comparisons were considered significant at $p < 0.05$.

Results

Baseline clinical, angiographic and echocardiographic data. Of 73 patients admitted to our coronary care unit during the enrollment period with a first reperfused AMI and with an adequate acoustic window, seven (five in Group I, and two in Group II) were excluded because of unstable clinical conditions during the hospital period and four (three in Group I, one in Group II) because of IRA occlusion at 1-month coronary angiography. The remaining 62 patients were enrolled in the study.

The culprit lesion was in the left anterior descending coronary artery in 41 (66%) of 62 patients, the left circumflex coronary artery in 6 (10%) and the right coronary artery in the remaining 15 (24%). Multivessel coronary artery disease was present in 24 patients (38%). Table 1 shows the baseline characteristics of patients undergoing t-PA (Group I) or primary PTCA (Group II). There was no significant difference in terms of age, gender, risk factors, time to presentation, Killip class on admission, prevalence of multivessel coronary artery disease or anterior infarct site, WMSI at day 1, peak CK and postinfarction treatment.

Table 1. Baseline and 1-Month Characteristics of Patients With Acute Myocardial Infarction Undergoing Intravenous Thrombolysis or Primary Coronary Angioplasty

	t-PA (n = 32)	PTCA (n = 30)	p Value
Age (yr)	56 ± 8	57 ± 4	NS
Hypertension	8 (25%)	7 (23%)	NS
Diabetes	5 (15%)	5 (16%)	NS
Tobacco use	20 (62%)	18 (60%)	NS
Time to presentation (h)*	4.1 ± 1.1	4.0 ± 1.3	NS
Killip class (day 1)	1.2 ± 0.4	1.3 ± 0.3	NS
Multivessel disease	12 (37%)	12 (40%)	NS
Anterior MI	23 (72%)	20 (67%)	NS
Peak CK (mg/dl)	4,320 ± 2,210	4,146 ± 2,460	NS
WMSI			
Day 1	1.75 ± 0.3	1.73 ± 0.3	NS
Day 30	1.67 ± 0.3	1.45 ± 0.3	0.015
Contrast score index	1.02 ± 0.4	1.49 ± 0.5	0.0003
Residual IRA stenosis (%)	70 ± 12	36 ± 14	0.0001
TIMI grade 3 flow	18 (56%)	22 (73%)	NS
Collateral channels after treatment for MI	0	5 (16%)	NS
Beta-blockers	9 (28%)	8 (26%)	NS
Ca channel blockers	19 (59%)	20 (66%)	NS
ACE inhibitors	8 (25%)	7 (23%)	NS

*Time from onset of symptoms of myocardial infarction (MI) to presentation in coronary care unit. Data presented are mean value ± SD or number (%) of patients. ACE = angiotensin-converting enzyme; Ca = calcium; CK = creatine kinase; IRA = infarct-related artery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TIMI = Thrombolysis in Myocardial Infarction; t-PA = tissue-type plasminogen activator; WMSI = wall motion score index.

Influence of reperfusion modality on 1-month regional function, myocardial perfusion and angiographic data. A slight, nonsignificant reduction in infarct size from day 1 to day 30 was observed in the t-PA–treated group, whereas a significant reduction in infarct area extension was observed in the PTCA-treated group ($p = 0.009$). Accordingly, contrast score at 1 month was significantly lower in the t-PA group than in the PTCA group ($p = 0.0003$) (Table 1). In particular, a perfusion defect was found in one or more segments supplied by the IRA in 26 (81%) of 32 Group I patients versus 10 (33%) of 30 Group II patients ($p < 0.00001$); analysis by segment showed a perfusion defect in 82 (37%) of 221 Group I segments versus 24 (15%) of 153 Group II segments ($p < 0.00001$).

At 1-month after coronary angiography, conservatively treated patients showed a higher grade of residual IRA stenosis ($p = 0.0001$) and a lower prevalence of TIMI grade 3 reflow (Table 1).

Relation between coronary reflow and myocardial reflow at 1-month follow-up. Normal coronary angiography radiocontrast runoff through the IRA (TIMI grade 3 reflow) was found in 40 (65%) of 62 patients. CSI was significantly higher in this subset of patients than in the remaining 22 patients with TIMI grade 2 reflow (1.48 ± 0.39 vs. 0.67 ± 0.25, $p < 0.0001$, respectively).

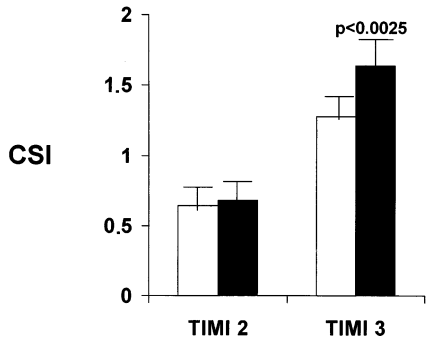


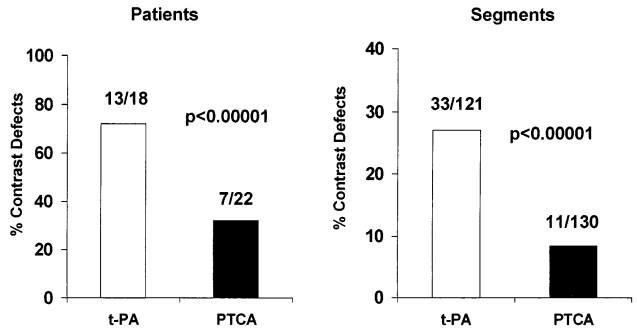
Figure 1. Bar graphs showing relation between myocardial contrast score index and quality of coronary reflow in patients treated with t-PA therapy (**open bars**) versus PTCA (**solid bars**). Independent of reperfusion strategies, patients with TIMI grade 2 reflow had a higher grade of microvascular dysfunction at 1-month. Conversely, when TIMI grade 3 flow was achieved, patients treated more aggressively also exhibited more preserved myocardial perfusion at follow-up.

Figure 1 shows the relation between myocardial perfusion and coronary reflow in the t-PA–treated patients compared with the angioplasty group. In the subset of patients with TIMI grade 2 reflow, myocardial perfusion was similarly reduced in both groups. In contrast, in the subset of patients with TIMI grade 3 reflow, contrast score was significantly higher in the angioplasty group ($p < 0.0025$). In particular, among patients with TIMI grade 3 reflow, MCE showed no myocardial perfusion in one or more segments subtended by the IRA in 72% Group I versus 31% Group II patients ($p < 0.00001$) and in 27% Group I versus 8% Group II segments ($p < 0.00001$) (Fig. 2). Thus, microvascular perfusion seems more preserved at 1-month follow-up in angioplasty-treated patients only if TIMI grade 3 reflow is achieved.

Discussion

Previous randomized trials (3,4) have shown that treatment by primary PTCA rather than intravenous t-PA is an independent predictor of survival in patients with high risk anterior wall infarction and results in a lower rate of stroke and recurrent myocardial ischemia. In particular, de Boer et al. (20) recently demonstrated that primary PTCA results in a smaller infarct size and a better preserved myocardial function before hospital discharge than randomization to streptokinase treatment.

Figure 2. Comparison of frequency of 1-month contrast defects between t-PA-treated and PTCA-treated patients in the subset with TIMI grade 3 flow.



The results of the present study extend previous observations and show that after successful IRA recanalization, 1-month tissue level perfusion and regional function are better preserved after PTCA than after t-PA.

Coronary artery recanalization and microvascular integrity. Mounting evidence (1,12) suggests that even with the most aggressive regimens of current pharmacologic approaches (accelerated front-loaded t-PA), early complete TIMI grade 3 reperfusion is achieved in only ~50% of patients, whereas with primary PTCA, IRA patency with brisk flow (TIMI grade 3) is restored in a higher proportion of patients (3). Recent trials (1,21) have documented that TIMI flow grade 2 may not be regarded as successful reperfusion therapy. Thus, one of the major advantages of IRA mechanical dilation is to achieve early and complete recanalization. However, recent studies of MCE, coronary angiography and positron emission tomography have shown (5,22) that about one-fourth to one-third of patients with an AMI had inadequate tissue perfusion ("no-reflow" phenomenon) despite angiographically successful coronary recanalization. In particular, Ito et al. (23) found that a substantial MCE defect may be observed in all patients with TIMI grade 2 reflow after reperfusion and in 16% of patients with TIMI grade 3 reflow. This microvascular dysfunction was previously documented in patients with an AMI undergoing primary PTCA or intracoronary thrombolysis. However, the prevalence of this phenomenon in the subset of patients undergoing intravenous thrombolysis still remains to be determined.

In the present study in a highly selected cohort with similar baseline characteristics, we evaluated the impact on microvascular perfusion of primary PTCA and t-PA therapy for reperfusion after AMI. Our results show that the prevalence of nonperfused segments and the extension of contrast defect at 1 month after reperfusion are higher in patients treated with intravenous t-PA than in those treated with primary PTCA.

In agreement with Ito et al. (23), our data show more extensive microvascular dysfunction at day 30 in the subset of patients with TIMI grade 2 versus TIMI 3 reflow, independent of the reperfusion strategy. However, *the most important finding of the present study* is that 72% of patients in the t-PA-treated group still exhibit microvascular dysfunction despite normal radiocontrast runoff through the IRA compared with 31% of patients in the PTCA group (Fig. 1). Thus, the majority of patients treated conservatively showed at least one nonperfused segment within the risk area at 1 month after AMI, even if TIMI grade 3 reflow through the IRA was reached.

Factors affecting tissue perfusion level. Several theories may be postulated to explain the profoundly different impact on microvascular flow of the two reperfusion strategies. First, the amount of perfusion in infarcted tissue is dependent on many complex, interrelated factors, including the extent of

collateral circulation before recanalization; residual stenosis severity of the culprit artery; vasodilator reserve in the IRA territory; time to recanalization; duration of ischemia, extent of reperfusion injury and loading conditions (22–24).

The high grade residual coronary stenosis observed in our conservatively treated patients may be a strong factor influencing the extent of microvascular dysfunction at follow-up. Even after a clot has been effectively dissolved, the significant residual stenosis in the culprit lesion may play a role in restricting blood flow at rest, thus resulting in continuing ischemia and even ongoing necrosis of the subserved myocardial tissue. Previous studies (25) have suggested that clinical outcome may be worse in patients with >50% stenosis after thrombolysis than in those with low grade residual narrowing, with an increased risk of ventricular dilation and death.

Second, even though all patients included in the study were admitted to the emergency room within 6 h of symptom onset, time to recanalization cannot be exactly assessed in the t-PA–treated group. However, previous studies (1,12) showed a 90-min IRA patency rate (TIMI grade 2 or 3) ranging from 82% to 91% (mean 85%). The time to first balloon inflation in our patients was no longer than 120 min, thus the time to reperfusion would be similar in the two groups of patients. Furthermore, to avoid the effects of unsuccessful IRA recanalization on microvascular integrity, patients were not randomized to the two reperfusion strategies, but were included in the study if, at day 1, primary PTCA was effective and no clinical evidence of failed reperfusion occurred after intravenous t-PA and if at the time of tissue perfusion evaluation, the IRA artery was still patent, with TIMI flow grade 2 or 3.

In conclusion, our study further supports the importance of rapid restoration of a brisk flow, through mechanical removal of the underlying residual coronary stenosis, to prevent microvascular damage.

Microvascular integrity and functional recovery. Only few comparative trials between primary PTCA and thrombolysis have measured left ventricular function at predischarge, and their results were discordant (20,26,27). No difference in this variable was found between the two reperfusion strategies in the Primary Angioplasty in Myocardial Infarction (PAMI) trial (26), whereas in the Zwolle trial (27), both global and regional function were better preserved after PTCA. Some important differences in study design and population may explain these conflicting data. In particular, left ventricular ejection fraction was measured in a different proportion of patients in the two trials, and the prevalence of anterior infarct location was higher in the latter study (36% vs. 49%, respectively).

In the present study, the extent of wall motion abnormalities within the infarct territory was measured before reperfusion and at day 30. The infarct size was similar in both groups before recanalization, but a significant reduction in WMSI was observed only in the PTCA group. The prevalence of anterior myocardial infarction in our study was 69%. As previously suggested (20), the effects on microvascular perfusion and left ventricular function of rapid restoration of flow induced by primary PTCA may be more pronounced in this high risk population. The better preserved myocardial perfusion in the angioplasty group may explain the greater infarct size reduction observed at follow-up. As previously shown by Ito et al. (5), the restoration of myocardial blood flow through a relatively preserved microcirculation may promote the salvage of postischemic myocardium, whereas an inadequate tissue perfusion after successful reperfusion predicts poor functional recovery.

Study limitations. The present report is based on data from a highly selected cohort enrolled after strict inclusion criteria. Accordingly, the results cannot necessarily be transferred to the treatment of patients with AMI in general practice. In particular, because the patients were not randomly assigned to the two treatments, no clinical or prognostic information can be derived from this study. Previous large trials have shown the advantages of primary PTCA over a more conservative treatment for AMI as for the percent of IRA patency and quality of coronary reflow. Conversely, the major goal of the present study was to determine the influence of different successful reperfusion modalities on microvascular dysfunction. In our study, the majority of conservatively treated patients showed at least one nonperfused segment even when TIMI grade 3 reflow was reached; it is therefore possible that in a larger, unselected population this difference could be even more pronounced. Larger randomized trials are necessary to assess the prognostic impact of our preliminary data.

Clinical implications. In the present study, MCE was performed 1 month after AMI because it has been shown (28) that microvascular damage may partially recover during the first weeks after infarction. We and others (5,7,8) have previously found that the extent of MCE-assessed perfusion at 1 month is closely related to the amount of viable myocardium and plays an important role in later functional recovery. Thus, the more preserved microvasculature detected at follow-up in invasively-treated patients may have important clinical implications because the likelihood of functional recovery either spontaneously or after coronary artery bypass graft surgery is significantly higher in this subset of patients (7,8,29).

Contrast echocardiography is low cost and safe and can be performed in the catheterization laboratory, with some additional time. With the introduction of second-generation contrast agents (30) able to produce myocardial contrast enhancement after peripheral vein injection, more information may be derived on the relation between new reperfusion strategies and the extent of microvascular flow.

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