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Duration of Ischemia Is a Major Determinant of Transmurality and Severe Microvascular Obstruction After Primary Angioplasty

A Study Performed With Contrast-Enhanced Magnetic Resonance

Giuseppe Tarantini, MD, PHD,* Luisa Cacciavillani, MD,* Francesco Corbetti, MD,† Angelo Ramondo, MD,* Martina Perazzolo Marra, MD,* Enrico Bacchiega, MD,* Massimo Napodano, MD,* Claudio Bilato, MD, PHD,* Renato Razzolini, MD,* Sabino Iliceto, MD, FACC*

Padua, Italy

OBJECTIVES This study sought to assess the relationship between duration of ischemia and both myocardial transmural necrosis (TN) and severe microvascular obstruction (SMO), by contrast-enhanced magnetic resonance (CE-MR), in patients with acute myocardial infarction (AMI) treated with angioplasty (PCI), and to estimate the risk of TN and SMO with the duration of ischemia.

BACKGROUND The impact of ischemic time on myocardial and microvascular injury is not well characterized in people.

METHODS We performed CE-MR in 77 patients with first AMI, 5 ± 3 days after successful PCI. The AMI was labeled as transmural if hyperenhancement at CE-MR was extended to ≥75% of the thickness in two or more ventricular segments. The SMO was identified as areas of late hypoenhancement surrounded by hyperenhanced tissue. The relationship between ischemic time and CE-MR evidence of SMO or TN was evaluated by logistic regression.

RESULTS Thirteen patients were excluded because of preprocedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 of the infarct-related artery. For the remaining 64 patients, the mean time to treatment was 190 ± 110 min, 45 (65%) patients had TN and 23 (39%) had SMO. Mean pain to balloon time was 90 ± 40 min, 110 ± 107 min, and 137 ± 97 min in patients without TN and SMO, with TN but without SMO, or with both TN and SMO, respectively ($p = 0.001$). Multivariate analysis showed that time delay was significantly associated both with TN (odds ratio per 30 min, 1.37, $p = 0.032$), and SMO (odds ratio per 30 min, 1.21; $p = 0.021$).

CONCLUSIONS In AMI patients with impaired coronary perfusion undergoing PCI, the risk of TN and SMO increases with the duration of the ischemic time. (J Am Coll Cardiol 2005;46:1229–35)

Recent clinical studies have shown that in acute myocardial infarction (AMI), delayed reperfusion results in less myocardial salvage and a higher mortality rate, irrespective of the chosen reperfusion strategy (1,2). In fact, as shown in experimental models, the extent of transmurality (3) and the entity of the no-reflow (4) are strongly dependent on the duration of ischemia before reperfusion, with reduced salvage of myocardium when reperfusion is accomplished after two hours of coronary occlusion. In patients with ST-segment elevation myocardial infarction, myocardial salvage progressively declines as the time between symptoms and therapy increases (2,5). Moreover, a clear relationship between every minute in treatment delay and mortality recently has been shown by De Luca et al. (2). Recent clinical studies in patients with reperfused AMI have shown a close relation among microvasculature obstruction, myocardial viability, left ventricular function, and clinical outcome (6–8). However, although explored in experimental studies, the impact of ischemic time on the extent of myocardial and microvascular injury has not been fully clarified in people. The goals of this study, conducted in patients with AMI treated with primary angioplasty (PCI), were: 1) to address the relationship of duration of ischemia with both myocardial transmural necrosis (TN) and severe microvascular obstruction (SMO) by using contrast-enhanced magnetic resonance (CE-MR), and 2) to estimate the risk of TN and SMO with the duration of ischemia.

METHODS

Between March 2003 and March 2004, a total of 77 patients without prior MI were prospectively enrolled in the study. They were admitted to our department within 12 h of the onset of AMI and underwent successful primary PCI. The AMI was defined by prolonged chest pain with

From the *Department of Cardiac, Thoracic, and Vascular Sciences and the †Department of Radiology, University of Padova Medical School, Padua, Italy. A grant was received from Boehringer Ingelheim.

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JACC Vol. 46, No. 7, 2005
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Abbreviations and Acronyms

AMI = acute myocardial infarction
CE-MR = contrast-enhanced magnetic resonance
MBG = myocardial blush grade
PCI = percutaneous coronary intervention
SMO = severe microvascular obstruction
TIMI = Thrombolysis In Myocardial Infarction
TN = transmural necrosis

ST-segment elevation on the electrocardiogram ≥0.1 mV in two or more contiguous leads, or with new left bundle branch block, or with anterior ST-segment depression caused by posterior infarction at the echocardiogram. All patients received aspirin 250 mg and heparin (70 IU/kg) intravenously before the procedure. Primary PCI with stent was systematically attempted and accomplished with standard techniques. Intravenous abciximab was administered in the cardiac catheterization laboratory at discretion of the interventional cardiologist. Enzymatic infarct size was calculated by the peak release of troponin I obtained by determinations systematically performed on the admission and every 6 h for the subsequent 24 h, and every 12 h for the following 2 days. All patients underwent CE-MR 5 ± 3 days after PCI.

Angiographic data analysis. Two different observers evaluated all coronary angiograms, first in a blinded fashion, then together to reach a consensus regarding Thrombolysis In Myocardial Infarction (TIMI) flow grade, collateral flow, and blush grade, as previously described (9). A successful angioplasty was defined as a combination of postprocedural TIMI flow grade 3 and residual restenosis <30%. Time to treatment was calculated as the interval from the symptom onset to the first balloon inflation. True ischemic time was calculated as the time to treatment in patients presenting at the index angiography (before primary PCI) with TIMI flow grade <3 of the infarct-related artery.

Magnetic resonance data analysis. Patients were examined in a supine position on a clinical 1.0-T scanner (Harmony, Siemens, Erlangen, Germany) using cardiologic software by Siemens with system MRease SYNGO 2002B. All images were acquired using a four-channel phased-array receiver coil during repeated breath holds of varying duration depending on heart rate and patient compliance (12 to 15 s). Images were acquired using a steady-state free-precession sequence (true FISP) in three short-axis views (at the level of the mitral valve, papillary muscles, and apex) and three long-axis views (two, three, and four chambers). Contrast-enhanced images were acquired in the same views 10 min after intravenous administration of a gadolinium-based contrast agent (gadobenate dimeglumine, Multihance, Bracco, 0.2 mmol/kg of body weight). The images were analyzed using a 17-segment model (10) independently by two observers blinded to clinical and procedural characteristics.

To evaluate areas of late enhancement and to differentiate infarcted from noninfarcted myocardium, a segmented gradient echo inversion recovery turbo FLASH sequence was used with the following characteristics: inversion time optimized for each patient, 17 to 21 K-space lines acquisition every 1 or 2 R-R interval (depending on heart frequency), TE 6 ms, flip angle 30°, BW 150 hz/pixel, resolution 134 × 256, typical voxel size of approximately 1.8 × 1.3 × 8 mm depending on the field of view (300 to 360 mm in relation to the patient's size), and slice thickness of 8 mm. Considering the T1 relaxation times of the tissues on the magnetic resonance imaging unit (1.0-T) and the wash-in and wash-out kinetics of extracellular interstitial contrast agents (11), the optimized T1 nullifies the signal from normal myocardium in the images acquired 10 min after contrast medium injection, allowing a clear visualization of the late enhanced infarcted areas, characterized, by definition (12), as a signal intensity at least 400% higher than the signal from normal (remote) myocardium.

Areas of gadolinium enhancement were assessed by visual approach with a scheme based on the spatial extent of delayed enhancement tissue within each segment as reported by others (13). The AMI was labeled as transmural if hyperenhancement was extended to ≥75% of the thickness of at least two contiguous ventricular segments.

We defined SMO (severe microvascular damage in the infarct core) as subendocardial areas of late low or absent signal surrounded by late enhanced tissue (14,15) in at least one ventricular segment.

Statistical analysis. Data are expressed as mean value ± standard deviation for continuous variables, and as frequency with percentage for categorical variables. Differences between means of continuous variables were tested by the

Table 1. Patient Characteristics

Characteristics	Value
Age (yrs)	60 ± 11.5
Men, n (%)	65 (84)
Current smoker, n (%)	41 (53)
Hypertension, n (%)	38 (49)
Diabetes mellitus, n (%)	7 (9)
Previous angina pectoris, n (%)	19 (25)
Previous coronary angioplasty, n (%)	4 (5)
Previous coronary bypass, n (%)	0
Location of myocardial infarction	
Anterior n (%)	39 (51)
Inferior, n (%)	35 (46)
Pain to balloon time, min	190 ± 111
Pre TIMI flow grade 3, n (%)	13 (17)
MBG 2/3, n (%)	55 (71)
Abciximab, n (%)	16 (20)
Stent, n (%)	72 (95)
Troponin I, μg/l	91 ± 90
Left ventricular ejection fraction (%)	59 ± 14
CE-MR image of TN, n (%)	50 (65)
CE-MR image of SMO, n (%)	25 (32)

Data are presented as mean value ± standard deviation or number (%) of patients in group.

CE-MR = contrast-enhanced magnetic resonance; MBG = myocardial blush grade; SMO = severe microvascular obstruction; TIMI = Thrombolysis In Myocardial Infarction; TN = transmural necrosis.

Table 2. Percentage of MBG 2/3, Transmural Necrosis, and Severe Microvascular Obstruction in Patients According to TIMI Flow Grade at Index Angiography

	TIMI Flow Grade <3	TIMI Flow Grade 3	p Value
Patients, n	64	13	
Time to treatment, min	190 ± 110	189 ± 110	0.97
MBG 0/1, n (%)	20 (31)	2 (15)	0.1
Transmural necrosis, n (%)	45 (65)	5 (38)	0.036
Microvascular obstruction, n (%)	23 (39)	2 (15)	0.045
Peak of troponin I, μg/l	101 ± 96	41 ± 60	0.042

Data are presented as mean value ± standard deviation, or number (%) of patients in group.
Abbreviations as in Table 1.

one-way analysis of variance. Frequencies were compared using the chi-square or Fisher exact test analysis when the expected value of cells was <5. A logistic regression analysis was used to evaluate the relationship between time to treatment and (patient) CE-MR evidence of TN or SMO and to calculate odds ratios (for each 30-min delay) after adjustment for characteristics related to the ischemic time. The relationships between ischemic time and patient probability of SMO and/or TN at CE-MR were reported as a continuous function. All MR measurements were performed independently by two observers (M.P.M. and F.C.) blinded to clinical and procedural characteristics and subsequently by one observer (F.C.) one week later. An interobserver and intraobserver concordance of 98% and 99%, respectively, was found in evaluation of TN. In this case, discrepancies were resolved by consensus. By contrast, full agreement was reported for SMO. Comparison of proportions was performed using the chi-square test. Data were analyzed by SPSS 12 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

Clinical and procedural characteristics of the 77 patients enrolled are summarized in Table 1. The mean time to treatment was 190 ± 111 min. Thirteen (17%) patients already had a TIMI flow grade 3 at the index angiography before the primary PCI. Myocardial blush grade (MBG) 2 or 3 was observed in 55 subjects (70%). Collateral circulation (Rentrop 2 or 3) was present only in two patients. Fifty patients (65%) had CE-MR evidence of TN, and 25 (32%) of SMO.

Table 2 summarizes the presence of MBG 0/1, TN, and SMO in patients with or without TIMI flow grade 3. Despite a similar delay in time to treatment between the two groups, the percentages of patients with TN and SMO, as well as the levels of troponin I release, were significantly higher in patients with TIMI flow grade <3. A similar trend, although not yet statistically significant, was observed for MBG 0/1.

When only patients with TIMI flow grade <3 were considered, pain to balloon time (reasonably the expression of the ischemic time in these patients) and peak troponin I levels were positively correlated with the presence of TN and SMO. In fact, the pain to balloon time was progressively longer and troponin I release was progressively greater in patients with both TN and SMO compared with those with TN but not SMO, and those with neither TN nor SMO (Table 3). Three typical examples of TN and/or SMO detected by CE-MR are shown in Figure 1. Among demographic, clinical, and angiographic characteristics of these patients (Table 4), the only variables significantly related to the ischemic time were abciximab use (abciximab, 136 ± 41 min vs. no abciximab, 205 ± 120 min, p = 0.03) and MBG 2/3 (MBG 2/3, 160 ± 93 min vs. no MBG 0/1, 233 ± 116 min, p = 0.01). By contrast, age was not related to the ischemic time, even when analyzed as a continuous variable (p = 0.8).

After adjustment for these confounders, patients with TIMI flow grade <3 showed, for each 30-min delay in reperfusion, the increase of both TN (odds ratio per 30 min, 1.37; 95% confidence interval, 1.03 to 1.8; p = 0.032), and SMO (odds ratio per 30 min, 1.21; 95% confidence interval, 1.03 to 1.4; p = 0.021). Figure 2 illustrates the relation among time to reperfusion and (patient) probability of TN and/or SMO as continuous functions. Total ischemic time was closely correlated with CE-MR evidence of TN and SMO. In addition, a close correlation was observed between the presence of SMO and the evidence of TN at CE-MR (chi-square = 6.2, p = 0.01), with SMO always detected in association with TN.

DISCUSSION

In animal models, the association between duration of the vessel occlusion and both TN (3) and no-reflow extent (4) has been well characterized. To the best of our knowledge, our study first shows a similar relationship in people. After excluding patients with preprocedural TIMI flow grade 3 of

Table 3. Ischemic Time and Enzymatic Data According to the CE-MR Evidence of TN and/or SMO in Patients Without TIMI Flow Grade 3 of Infarct-Related Artery at Index Angiography

	TN−/SMO−	TN+/SMO−	TN+/SMO+
Patients, n (%)	19 (29.7)	22 (34.4)	23 (35.9)
Time to treatment, min*	90 ± 40	177 ± 101	255 ± 145
Peak of troponin I, μg/l†	53 ± 50	110 ± 107	137 ± 97

Data are presented as mean value ± standard deviation, or number (%) of patients in group. Univariate p values among subgroups: *p = 0.001, †p = 0.01.
Abbreviations as in Table 1.

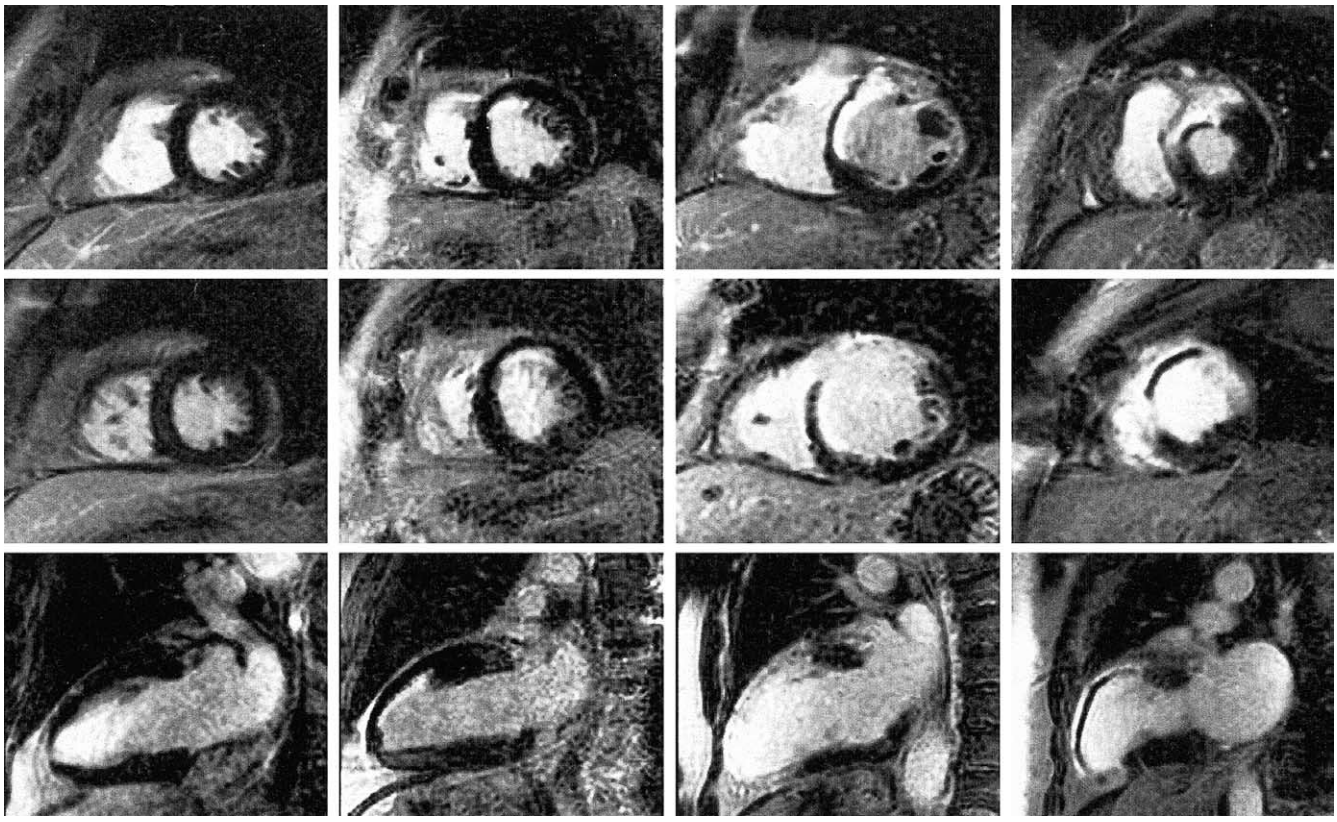

Figure 1. Typical examples of the different myocardial alterations detected by contrast-enhanced magnetic resonance in patients undergoing primary percutaneous coronary intervention at an increasing time delay from the onset of the chest pain. **Upper**, **middle**, **and lower panels** respectively show contrast-enhanced magnetic resonance images obtained at two different short-axis levels and in a long-axis two-chamber plane for four different patients. (Patient A, **left column**) Male, age 76 years; hypertension, history of smoking, dyslipidemia, familiarity of coronary artery disease; electrocardiographic evidence of anterior ST-segment elevation myocardial infarct (STEMI); pain to balloon time: 70 min; troponin I peak: 11.7 ng/ml. After six days from acute event, no signs of necrosis are shown at the late contrast-enhancement magnetic resonance image (MRI) ("aborted" infarct). (Patient B, **left center column**) Male, age 49 years, hypertension, familiarity of coronary artery disease; electrocardiographic evidence of anterior STEMI; pain to balloon time: 170 min; troponin I peak: 38.6 ng/ml. After six days from acute event, MRI shows a nontransmural necrosis in the middle and apical segments of the anterior wall. (Patient C, **right center column**) Male, age 78 years, hypertension; electrocardiographic evidence of anteroseptal STEMI; pain to balloon time: 240 min; troponin I peak: 199 ng/ml. After eight days from acute event, MRI shows a transmural necrosis of the entire anterior wall and of the apical segment of the inferior wall. (Patient D, **right column**) Female, age 73 years; no cardiovascular risk factor; electrocardiographic evidence of septal, anterior and inferior STEMI; pain to balloon time: 310 min; troponin I peak: 258 ng/ml. After seven days from acute event, MRI shows a transmural necrosis of the anterolateral, anterior, and septal wall. In the same area of the infarct, there is evidence of a subendocardial dark zone referred as to severe microvascular obstruction.

infarct-related artery, in the remaining subjects the time from symptom onset to balloon inflation likely represents an indicator of total ischemic time. In this population, we found a continuous relationship among ischemic time and probability of TN and SMO, assessed by CE-MR. In fact, for each 30-min delay in treatment of patients undergoing successful primary PCI, the risk of TN or SMO increases by 37% and 21%, respectively. Although there was also a close correlation between presence of SMO and evidence of TN, it is noteworthy that for any time of reperfusion the probability of transmurality was higher than that of SMO (Fig. 2). In other words, SMO occurs later than TN, suggesting that, from a pathophysiologic point of view, SMO lags behind TN. These results are consistent with those of a recent experimental animal study, which showed that both transmurality (3) and microvascular dysfunction depend on the duration of ischemia and that the extent of no reflow is driven by the extent of infarct size (4). In our study, we did not evaluate the infarct size; however, our results show that in patients with AMI undergoing successful primary PCI, without preprocedural normal flow of infarct-related artery, TN and, more interestingly, SMO are strongly related to the length of ischemia. Similarly, the infarct size expressed as troponin I release (16) was progres-

Table 4. Patient Characteristics and Ischemic Time

Variables	Yes	No	p Value
Age >70 yrs	163 ± 78	198 ± 118	0.3
Male gender	189 ± 117	198 ± 83	0.8
Diabetes	177 ± 99	192 ± 114	0.7
Hypertension	203 ± 120	179 ± 102	0.3
Current smoker	207 ± 133	172 ± 78	0.2
Anterior infarction	201 ± 124	98 ± 16	0.5
Abciximab	136 ± 41	205 ± 120	0.03
MBG 2/3	160 ± 93	233 ± 116	0.01

Data are presented as mean value ± standard deviation.
MBG = myocardial blush grade.

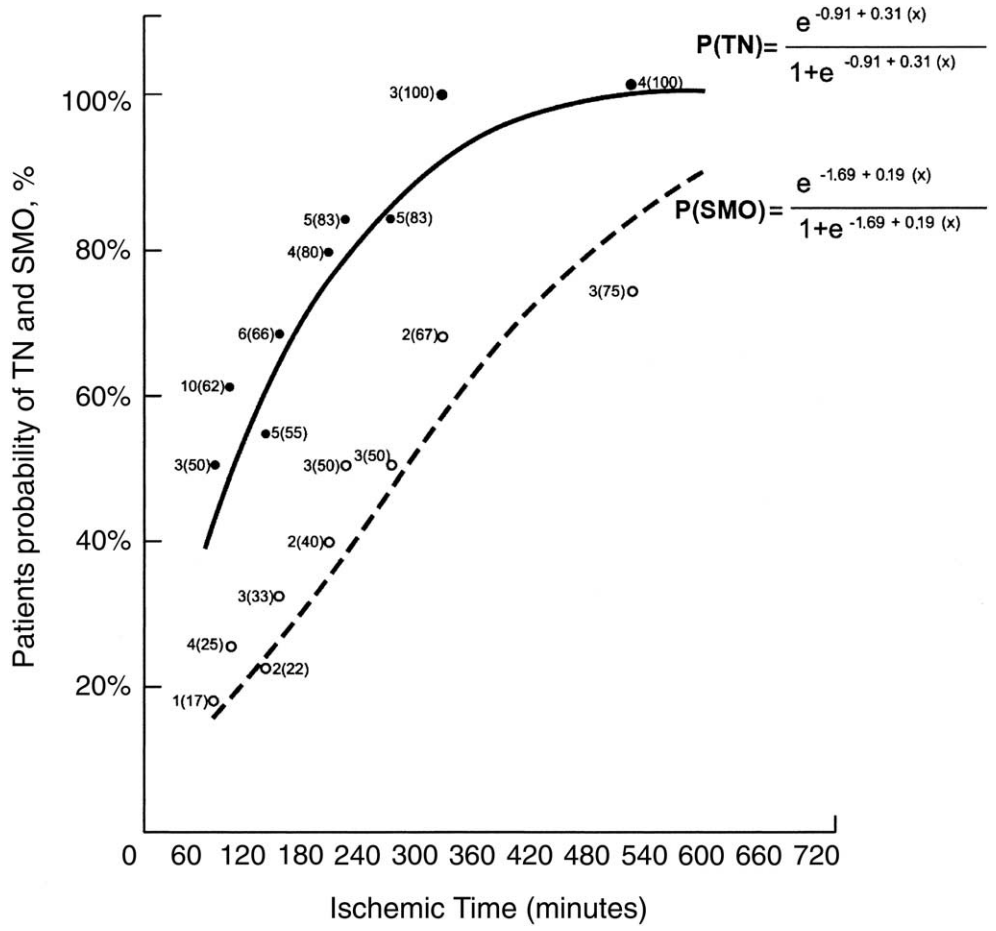

Figure 2. Relationship between ischemic time and in-hospital (patient) probability of transmural necrosis (TN) or severe microvascular dysfunction (SMO) assessed with logistic regression model. The coefficients of both equations have been computed for 30-min intervals. **Filled circles** = observed TN rate expressed in number (%); **open circles** = observed SMO rate expressed in number (%).

sively and significantly greater in patients with both TN and SMO compared with those with TN but not SMO and those with neither TN nor SMO.

Thus, it is not surprising that a longer duration of ischemia corresponds to a more pronounced impairment of myocardial perfusion (assessed by ST-segment resolution or myocardial blush) and, as a consequence, to a larger infarct size and a worse clinical outcome even when optimal mechanical reperfusion is applied (7,17). In other words, restoration of TIMI flow grade 3 epicardial flow by PCI does not guarantee per se the normalization of myocardial perfusion (17). Therefore, although primary PCI, in comparison with thrombolysis, may guarantee a higher rate of recanalization in patients presenting late, it cannot prevent TN and SMO, which are strongly related, even after PCI, to the duration of occlusion. Interestingly, although infarct size is a major determinant of microvascular obstruction for any given delay in time to treatment, both experimental and clinical studies suggested that microvascular obstruction per se is a stronger predictor of worse left ventricular function and postinfarct complications compared with infarct size (7,18). On the other hand, TN seems to delineate viable and nonviable myocardium and predicts recovery of left ventricular function after MI (16).

We defined SMO as late hypoenhancement within a hyperenhanced area. The presence of persistent hypoenhancement within a late hyperenhanced area has been noted before (14,15). Recently, Lund et al. (19) reported a high concordance between MO on first-pass enhancement MR images and SMO on delayed-enhancement MR images defined as late hypoenhancement (correlation coefficient, 0.71). They suggested that the difference could be explained by extensive microvascular damage resulting in persistent hypoenhancement even at late imaging. Here our intention was to report on the severe form of SMO and to focus our analysis on severe cases with persistent contrast filling defects, which recently have been shown to be related to worse remodeling and outcome (8).

It has been shown that the presence of blood flow in the infarct-related artery before PCI is associated with smaller enzymatic infarct size and better outcome (20). Thus, we also analyzed the impact of preprocedural flow on the prognostic role of time delay, and we found that patients with normal flow of the infarct-related artery before PCI

JACC Vol. 46, No. 7, 2005
October 4, 2005:1229–35

had a lower rate of TN, SMO, and, not surprisingly, smaller troponin infarct size than patients without TIMI flow grade 3, despite a similar time delay between the two groups (Table 2). Therefore, from a pathophysiologic point of view, our data further support the prognostic role of early restoration of the flow as a predictor of successful myocardial reperfusion and are in agreement with the observations by others on the relationships between preprocedural TIMI flow grade 3 and a higher rate of postprocedural TIMI flow grade 3, MBG 2 or 3, smaller infarct size, and better outcome (17,20–22).

The predictive value of preprocedural TIMI flow grade 3 would argue its independency from the time to treatment; however, early drug administration was also shown to be associated with higher rates of vessel patency and aborted myocardial infarction (23,24), suggesting the importance of reducing the true ischemic time.

The presence of collateral blood flow is an alternative source of blood supply to a myocardium jeopardized by abrupt occlusion of the vessel, and it has been shown to preserve the myocardium in acute phase of MI, favoring improvement in left ventricular function after successful primary PCI (25). However, coronary angiography, the most commonly used technique for studying collateral circulation, may not be accurate in assessing collateral circulation because most collateral vessels are too small to be angiographically visualized (26). In our study, the limited number (n = 2) of patients with evident collateral circulation does not allow definitive conclusions.

Study limitations. This is an observational study; the patients were enrolled at our institution because of a first AMI and underwent successful primary PCI. Therefore, this population may not be representative of all AMI patients treated with primary PCI.

Our study presents some limitations. First, areas and quantification of transmural extent of necrosis were not identified by software, but were assessed visually. Second, the incomplete coverage of left ventricular myocardium using three short-axis and three long-axis slices only may have led to missing segments with TN and SMO, therefore rating patients as falsely negative for TN or SMO. Similarly, mild MO might have been missed because of application of the sequence at minute 10.

However, the choice of use of a standardized myocardial segmentation according to the American Heart Association (10) limits the potential loss of clinically relevant morphologic information (on a per-patient basis analysis). This point is supported by the fact that troponin I release, a recognized clinical correlate of infarct size (16), was progressively and significantly greater in patients with both TN and SMO compared with those with TN but not SMO and those with neither TN nor SMO (Table 3).

The slope of the relationship between ischemic time and TN or SMO might vary according to the numbers of ventricular segments considered to define the transmural AMI. The design of our study did not allow for infarct sizing; therefore, no conclusive relationship among ischemic time and infarct size and extension of microvascular obstruction can be made.

In our study, abciximab use was administered at the discretion of the interventional cardiologist during or after PCI. To evaluate the impact of true ischemic time on TN and SMO, we restricted our analysis to those patients without an open infarct-related artery at index angiography and who underwent successful PCI. Additional studies are required to determine whether abciximab use may limit SMO beyond TIMI flow grade 3 (coronary patency) after PCI.

Although our results show that ischemic time, probability of TN, and SMO are correlated, the small sample size limits the power and precludes broad generalization into diagnostic terms to predict accurately the patient probability of TN and SMO, and needs confirmation in a larger study. Finally, myocardial infarctions have complex structure with a varying transmural extent, making a transmural/nontransmural division rarely simply one or the other (27). Because of these considerations, caution should be used in making definitive inferences from our results.

Clinical implications. Although primary PCI had been shown to be superior to thrombolytic therapy (28,29), several areas of improvement remain. The potential time delay remains a major drawback to primary PCI. Indeed, among the patients presenting within two hours of the symptom onset enrolled in the CAPTIM study, prehospital thrombolysis resulted in a better outcome compared with that for transfer for PCI (30). A critically important goal of reperfusion is to restore flow of the infarct-related artery as quickly and as completely as possible, but the ultimate goal of reperfusion in ST-segment elevation AMI is to reduce myocardial damage and to improve myocardial perfusion in the risk area. The results of our study suggest that in patients with ST-segment elevation AMI undergoing primary PCI, all efforts should be made to shorten the time from symptom onset and reperfusion, because even small differences in time delay result in a significant increase in TN and SMO.

Although normal flow of the infarct-related artery before PCI may affect myocardial salvage and the extent of microvascular dysfunction, facilitating reperfusion by pharmacologic therapy before PCI needs further investigation. However, from a pathophysiologic point of view, our study supports the growing evidence that strategies aimed to reduce the ischemic time should be strongly implemented to obtain early and optimal restoration of anterograde flow and to reduce the prevalence of transmural necrosis and microvascular dysfunction.

Reprint requests and correspondence: Dr. Giuseppe Tarantini, Department of Cardiac, Thoracic, and Vascular Sciences, Policlinico Universitario, Via Giustiniani, 2, 35128 Padova, Italy. E-mail: giuseppe.tarantini.1@unipd.it.

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