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Impact of Primary Coronary Angioplasty Delay on Myocardial Salvage, Infarct Size, and Microvascular Damage in Patients With ST-Segment Elevation Myocardial Infarction

Insight From Cardiovascular Magnetic Resonance

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Objectives We investigated the extent and nature of myocardial damage by using cardiovascular magnetic resonance (CMR) in relation to different time-to-reperfusion intervals.

Background Previous studies evaluating the influence of time to reperfusion on infarct size (IS) and myocardial salvage in patients with ST-segment elevation myocardial infarction (STEMI) have yielded conflicting results.

Methods Seventy patients with STEMI successfully treated with primary percutaneous coronary intervention within 12 h from symptom onset underwent CMR 3 ± 2 days after hospital admission. Patients were subcategorized into 4 time-to-reperfusion (symptom onset to balloon) quartiles: ≤90 min (group I, n = 19), >90 to 150 min (group II, n = 17), >150 to 360 min (group III, n = 17), and >360 min (group IV, n = 17). T2-weighted short tau inversion recovery and late gadolinium enhancement CMR were used to characterize reversible and irreversible myocardial injury (area at risk and IS, respectively); salvaged myocardium was defined as the normalized difference between extent of T2-weighted short tau inversion recovery and late gadolinium enhancement.

Results Shorter time-to-reperfusion (group I) was associated with smaller IS and microvascular obstruction and larger salvaged myocardium. Mean IS progressively increased overtime: 8% (group I), 11.7% (group II), 12.7% (group III), and 17.9% (group IV), p = 0.017; similarly, MVO was larger in patients reperfused later (0.5%, 1.5%, 3.7%, and 6.6%, respectively, p = 0.047). Accordingly, salvaged myocardium markedly decreased when reperfusion occurred >90 min of coronary occlusion (8.5%, 3.2%, 2.4%, and 2.1%, respectively, p = 0.004).

Conclusions In patients with STEMI treated with primary percutaneous coronary intervention, time to reperfusion determines the extent of reversible and irreversible myocardial injury assessed by CMR. In particular, salvaged myocardium is markedly reduced when reperfusion occurs >90 min of coronary occlusion. (J Am Coll Cardiol 2009;54: 2145–53) © 2009 by the American College of Cardiology Foundation

Current therapeutic strategies in patients with ST-segment elevation myocardial infarction (STEMI) aim for a timely recanalization of the infarct-related artery (IRA) to reduce the progression of the ischemic-necrotic wavefront of myocardial injury and salvage the damaged but still viable myocardium within the area at risk (1,2). In some patients microvascular obstruction (MVO) may occur within the ischemic region in addition to myocardial necrosis, and it is usually associated with greater left ventricular (LV) remodeling and a worse clinical outcome (3–5). Delays in recanalizing the occluded artery in patients with STEMI

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Abbreviations and Acronyms

CMR = cardiovascular magnetic resonance
IRA = infarct-related artery
IS = infarct size
LAD = left anterior descending artery
LGE = late gadolinium enhancement
LV = left ventricle/ventricular
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
MVO = microvascular obstruction
PCI = percutaneous coronary intervention
PPCI = primary percutaneous coronary intervention
SSFP = steady-state free precession
STEMI = ST-segment elevation myocardial infarction
T2w-STIR = T2-weighted short tau inversion recovery
TE = echo time
TR = repetition time

influence the presence and extent of infarct size (IS) and of MVO (5–7), with a strong impact on the rate of cardiac mortality and morbidity (8). Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) imaging represents a well-established and reproducible diagnostic tool to assess irreversible ischemic injury and to visualize the location and transmural extent of IS and MVO within the infarcted region (5,6,9).

T2-weighted short tau inversion recovery (T2w-STIR) imaging is a sequence sensitive to increased myocardial water content, allowing the delineation of myocardial edema after an acute ischemic insult, thus representative of the myocardium at risk. The T2w-STIR hyperintense areas usually include both reversible and irreversible injured myocardium (10–12). However, by the use of a combined T2w-STIR and LGE CMR imaging protocol, salvaged myocardium can be quantified as the difference between the area of increased T2w-STIR signal (myocardium at risk) and the area of LGE (IS), as previously reported (10–14).

The authors of previous studies (1,2,6,7,15–18) evaluating the influence of primary percutaneous coronary intervention (PPCI) delays on IS and myocardial salvage in patients with STEMI reported conflicting results. The present study was designed to determine the influence of time to reperfusion on myocardial damage assessed by CMR in patients with STEMI undergoing PPCI.

Methods

Study population. Between October 2007 and May 2008, 75 consecutive patients with first STEMI undergoing PPCI within 12 h after the onset of symptoms were prospectively enrolled in the study. Creatine kinase and troponin I measurements were systematically performed at hospital admission, every 3 h for the subsequent 24 h, and then every 12 h for the following 2 days. The CMR study was carried out within 5 days from PPCI. A follow-up CMR study to assess LV remodeling was performed at 6 months. Exclusion criteria were unsuccessful PPCI, rescue percutaneous coronary intervention (PCI), facilitated PCI, contraindication to glycoprotein IIb/IIIa inhibitors, non-STEMI, previous MI, previous coronary artery bypass grafting, and contraindications to CMR. Patients with hemodynamic instability at the time of CMR also were excluded. All participants gave written informed consent to the protocol, and the study was approved by the local ethics committee.

PCI and medications. We performed PPCI and stenting of the IRA in all patients according to the clinical protocol used at our institution (3,19). Thrombolysis In Myocardial Infarction (TIMI) flow grade was semiquantitatively scored as previously described (2,19). The number of coronary vessels demonstrating significant coronary artery disease was reported. Collateral flow to the infarct zone was assessed on the initial angiogram before PCI and graded on a scale of 0 to 3 by use of Rentrop classification (20). A successful angioplasty was defined a combination of post-procedural TIMI flow grade 3 and residual stenosis <30%. Time to reperfusion was defined as the interval from the onset of symptoms to the first balloon inflation.

The CMR acquisition protocol. We performed CMR imaging in all patients by using a 1.5-T system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) equipped with SQ-engine gradients (amplitude: 45 mT/m; slew rate: 200 mT/m/ms) and a 12-channel phased-array cardiac coil. After obtaining scout images, cine steady-state free precession (SSFP) CMR images were acquired from patients during short breath holds in the short-axis, 2-chamber, and 4-chamber planes; on short-axis images, the left ventricle was completely encompassed from the base to the apex, from which we acquired a total of 10 to 12 images. Cine SSFP images were obtained by use of the following parameters: repetition time (TR) 51.3 ms, echo time (TE) 1.21 ms, flip angle 80°, 8-mm slice thickness, no interslice gap, matrix of 256 × 256, field of view ranging from 340 to 400 mm, and a voxel size of 1.7 × 1.7 × 8.0 mm.

For T2w-STIR imaging, a breath-hold black-blood segmented turbo spin echo technique was adopted by the use of a triple inversion recovery preparation module (TR 2 R-to-R intervals, TE 75 ms, flip angle 180°, TI 170 ms, slice thickness 8 mm, no interslice gap, field of view 340 to 400 mm, matrix 256 × 256, and a voxel size of 2.3 × 1.3 × 8 mm). Technical details of this sequence are described elsewhere (21). The T2w-STIR images were acquired on short axis planes covering the entire left ventricle during 6 to 8 consecutive breath holds. Each slice was obtained during an end-expiratory breath-hold of 12 to 15 s, depending on the patient's heart rate.

Finally, short-axis LGE images were obtained by use of a segmented inversion recovery technique and acquired 10 to 15 min after injection (Gadolinium-BOPTA, Multihance, Bracco, Milan, Italy; 0.1 mmol/kg body weight at 2 ml/s). Sequence parameters were the following: TR 700 ms, TE 4.33 ms, matrix 256 × 256, flip angle 30°, slice thickness 8.0 mm, no interslice gap, and voxel size 1.7 × 1.4 × 8 mm. The inversion time was progressively optimized to null the signal in the normal myocardium (typical values, 250 to 300 ms) to

ensure matching slice position between T2w-STIR and LGE images, same acquisition planes were adopted. Cine, T2w-STIR, and LGE images were acquired at the same short-axis slice position.

Image analysis. All CMR studies were analyzed off-line by the use of a dedicated workstation (Siemens Argus, Erlangen, Germany). Left ventricular volumes, systolic function, and mass were calculated from the short-axis SSFP cines. Infarcted myocardial mass and MVO were manually traced and calculated from the LGE short-axis images. As reported in Bondarenko et al. (22), myocardial regions was considered infarcted if the IS signal intensity was >5 SDs above the remote myocardium. The MVO was defined as a dark zone within the infarcted segments, usually located in the subendocardium. The mass of myocardial edema was traced and calculated from the T2w-STIR images by the use of a similar threshold-based approach (signal intensity >2 SDs of remote myocardium) (23). Salvaged myocardium was quantified as the difference between the area of increased T2w-STIR signal (area at risk) and the area of LGE (IS) as previously described (10–14). All measurements were normalized to LV mass.

Statistical analysis. Data were analyzed with SPSS software version 15.0 (SPSS Inc., Chicago, Illinois). The continuous variables were calculated as the average value considering the standard deviation, whereas those that were categorical were calculated as percentages. The differences between means of continuous variables at different times to reperfusion were analyzed by 1-way analysis of variance by the use of a linear trend analysis, and a post-hoc analysis with Bonferroni correction was made for differences between groups. The differences between categorical variables were analyzed with the chi-square test of Pearson. A Student *t* test for independent groups was used to assess differences in continuous variables between anterior versus nonanterior infarction, whereas a Student paired-samples *t* test was used to highlight differences in LV parameters after primary PCI and at 6-month follow-up; these tests were made without correction for multiple comparisons. A linear regression analysis was used to evaluate the relationship between time to treatment and CMR extent of MVO, IS, and salvaged myocardium. Differences were considered statistically significant at a 2-sided p value ≤0.05.

Results

Clinical and angiographic data. Seventy patients (89% men, mean age 58 ± 9 years) were studied with CMR 3 ± 2 days after PPCI. There were no differences between the 4 groups. Seventy-five patients were initially recruited, but 5 patients were excluded because of claustrophobia (n = 3) or clinical instability (n = 2). A follow-up CMR was performed in 58 patients; the remaining 12 patients declined. We performed PPCI in left anterior descending artery (LAD) in 43 patients, in the right coronary artery in 26 patients, and in the left circumflex artery in 1 patient. Mean time to reperfusion was 4.4 ± 4.7 h. No events suggesting reocclusion/stenosis were observed between PPCI and CMR examinations.

For the purpose of the study, patients were subcategorized into 4 quartiles on the basis of time from symptom onset to reperfusion: ≤90 min (group I, n = 19), >90 to 150 min (group II, n = 17), >150 to 360 min (group III, n = 17), and >360 min (group IV, n = 17). No differences on baseline clinical and angiographic characteristics were observed in the 4 groups (Table 1). In particular, no statistical differences between groups were observed in relation to incidence of LAD disease, TIMI flow grade 3 before PPCI, and significant collateral circulation.

Time to reperfusion and IS. An infarcted region on LGE images was visualized in all patients and corresponded to the territory distribution of the IRA. Mean IS among 4 groups was 12 ± 8% of LV mass. A significant increase of IS over time was found (8%, 11%, 12%, and 18%, respectively, p = 0.005) (Fig. 1A). The largest increase in IS was observed in patients with the longest time to reperfusion (group IV vs. I, p = 0.002). Time to reperfusion expressed as a continuous variable significantly correlated with IS (r = 0.60, p = 0.0001) (Fig. 2). On a separate analysis on LAD versus non-LAD infarcts, we observed that anterior infarcts were significantly larger than inferior ones. This phenomenon was consistently observed across the 4 reperfusion groups (Table 2).

Time to reperfusion, myocardial edema, and myocardial salvage. Increased signal intensity on T2w-STIR imaging (myocardial edema) was observed in 62 of 70 patients (89%); in the remaining 8 (11%) patients, T2w signal intensity was not homogeneous throughout segments because of the presence of a central hypointense core with peripheral hyperintense rim related to underlying microvascular damage. The mean size of edema among 4 groups was 16 ± 8% of LV mass. In all patients the location of T2w-STIR increased signal intensity corresponded to the territory of distribution of the IRA. The extent of myocardial edema did not changed significantly as time to reperfusion progressed (16%, 15%, 15%, and 19%, respectively, p = 0.37) (Fig. 1B). Conversely, the extent of salvaged myocardium (edematous but not necrotic myocardium) was significantly reduced overtime (8.5%, 3.2%, 2.4%, and 2.1%, respectively, p = 0.003) (Fig. 1C). In particular, a marked reduction in salvaged myocardium was observed when reperfusion occurred area after 90 min of coronary occlusion (group I vs. II, p = 0.0001; group I vs. III, p = 0.0001; group I vs. IV, p = 0.0001), whereas no significant changes were observed between groups II, III, and IV. In late reperfused patients (group IV), an almost complete absence of salvaged myocardium was observed (Fig. 1C). A significant inverse correlation was found between time and salvaged myocardium by linear regression analysis (r = −0.53, p = 0.005).

Time to reperfusion and MVO. Mean size of MVO was 2.1 ± 3.4% of LV mass. The incidence and extent of MVO

Table 1 Patient Characteristics Categorized by Time From Symptom Onset to Reperfusion

Variables	Groups (n = 70 Patients) ≤90 Min (n = 19)	>90–150 Min (n = 17)	>150–360 Min (n = 17)	>360 Min (n = 17)	p Value
Risk factors					
Age, yrs	58 ± 7.3	57 ± 10	57 ± 13	58 ± 11	0.75
Sex, male	15 (78)	13 (76)	10 (58)	9 (53)	0.42
Hypertension	5 (26)	4 (23)	7 (41)	3 (18)	0.15
Diabetes	1 (5)	3 (18)	0 (0)	1 (6)	0.34
Smoking	12 (63)	12 (70)	8 (47)	9 (53)	0.54
Dyslipidemia	4 (21)	6 (35)	4 (23)	2 (12)	0.61
Family history of CAD	5 (26)	6 (35)	3 (18)	3 (18)	0.45
Clinical data					
Time to treatment, h	1.0 ± 0.1	2.4 ± 0.4	5.0 ± 0.9	9.0 ± 3.5	0.001
CK, UI/l	1,806 ± 934	2,012 ± 1,871	2,264 ± 1,544	2,562 ± 1,134	0.34
CK-MB, UI/l	284 ± 218	302 ± 243	311 ± 234	483 ± 486	0.33
Troponin I, ng/ml	8.7 ± 9.9	10.6 ± 11.4	10.9 ± 10.1	11.8 ± 9.2	0.28
Concomitant medications, %					
ACE inhibitors/ARBs	18 (95)	15 (88)	16 (94)	17 (100)	
Beta-blockers	17 (89)	16 (94)	16 (94)	16 (94)	0.89
Statins	19 (100)	17 (100)	17 (100)	16 (94)	
Angiographic data					
Infarct-related artery					
LAD	14 (74)	10 (59)	9 (53)	10 (59)	0.44
LCx	0 (0)	0 (0)	1 (6)	0 (0)	
RCA	5 (26)	7 (41)	7 (41)	7 (41)	
Number of vessels					
1	10 (53)	7 (41)	8 (47)	8 (47)	0.26
2	6 (31)	8 (47)	6 (35)	8 (47)	
3	1 (5)	2 (12)	3 (17)	1 (6)	
TIMI flow grade 3 before PCI	3 (15)	2 (11)	3 (17)	3 (17)	0.84
Collateral flow grade 2 to 3	2 (10)	3 (17)	2 (11)	3 (17)	0.51

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

progressively increased as time to reperfusion increased (0.5%, 1.5%, 3.7%, and 6.6%, respectively, p = 0.039) (Fig. 1D). In particular, the larger MVO area was observed in the latest reperfused group (group IV vs. I, p = 0.034); a weak but statistically significant correlation was observed between time to reperfusion and MVO (r = 0.39, p = 0.005). Furthermore, in patients with MVO, IS was significantly greater than in patients without MVO (16 ± 9.8% vs. 10 ± 6.9%, respectively, p = 0.012).

Time to reperfusion and LV function. Significant increase in LV volumes and reduction in ejection fraction over time was observed (Table 3). However, these changes were not homogeneous because both left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) increased and left ventricular ejection fraction (LVEF) reduced only in the group reperfused the latest (group IV). There were no differences in LVEF across the 4 reperfusion groups between anterior and nonanterior infarcts (Table 2).

At the 6-month follow-up, a significant reduction of LVEDV and LVESV in groups I and II and a significant increased in groups III and IV (Table 4) was observed. A significant increase in LVEF was present only in group I, whereas LVEF was significantly decreased only in group IV (Table 4).

Discussion

In this study we describe the benefits associated with early coronary reperfusion as assessed by CMR in patients with STEMI treated with PPCI. Noninvasive myocardial tissue characterization provided by CMR enabled us to differentiate reversible and irreversible myocardial injury (myocardium at risk and myocardial infarction, respectively) and consequently to determine the presence and extent of salvaged myocardium.

The main findings of this study are that: 1) patients reperfused early (≤90 min) demonstrated smaller IS and microvascular damage and larger salvaged myocardium, whereas patients reperfused later (time to reperfusion >360 min) presented larger IS and MVO and very limited, if any, salvaged myocardium; and 2) the presence and extent of salvaged myocardium markedly decreased when reperfusion occurred after >90 min of coronary occlusion. To the best

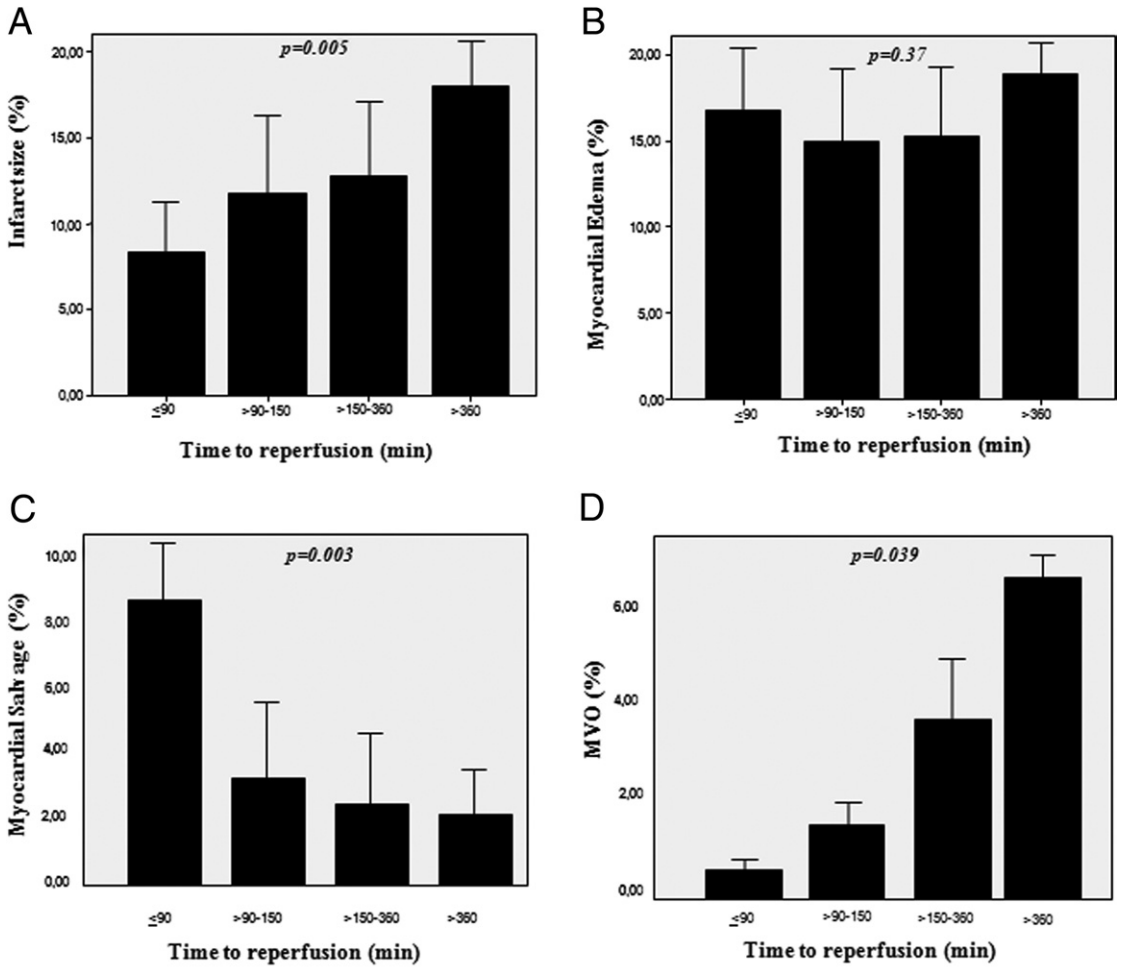

Figure 1 Time to Reperfusion and Cardiovascular Magnetic Resonance Parameters

Bar graphs show the influence of time to reperfusion on infarct size **(A)**, myocardial edema **(B)**, myocardial salvage **(C)**, and microvascular obstruction (MVO) **(D)**. Data are expressed as % left ventricular mass.

of our knowledge, this is the first in vivo, clinical, and noninvasive evaluation of the consequences of early and delayed coronary reperfusion on myocardial damage, as directly visualized by CMR.

Time to reperfusion, myocardial salvage, IS, and MVO obstruction. Reimer and Jennings (1) have demonstrated that approximately one-half of the ischemic myocardium progresses towards necrosis within 40 min of coronary occlusion, one-third of the ischemic myocardium is still salvageable at 3 h, and that the process of myocardial necrosis is complete about 6 h after the onset of coronary occlusion. After this time, the potential for salvage myocardium is considered minimal or absent (1,2). The benefits of reperfusion persist up to 12 h, but these are of decreasing magnitude over time (7–9). According to the "open artery hypothesis," most of the clinical benefits of late recanalization (>6 h) are independent from myocardial salvage and are mostly related to attenuation of LV remodeling processes and reduction of clinical instability (2,7,24).

Multiple randomized clinical trials (6–8) showed a significantly lower rate of mortality among patients achieving TIMI flow grade 3 within 90 min after the onset of STEMI (golden hour). For these reasons, the European Society of Cardiology and American College of Cardiology/American Heart Association clinical guidelines on STEMI recommend PCI within 90 min from first medical contact. Our CMR data confirm this experimental and clinical evidence by demonstrating a progressive increase over time in IS and MVO extent. However, by using CMR we were able to observe, for the first time, that salvaged myocardium consistently reduces after 90 min of coronary occlusion (Figs. 3A and 3B).

Previous studies (1,2,5–7,15–18) in which the authors evaluated the influence of time to reperfusion on IS and salvaged myocardium yielded conflicting results. As previously underlined, Reimer and Jennings (1) demonstrated in

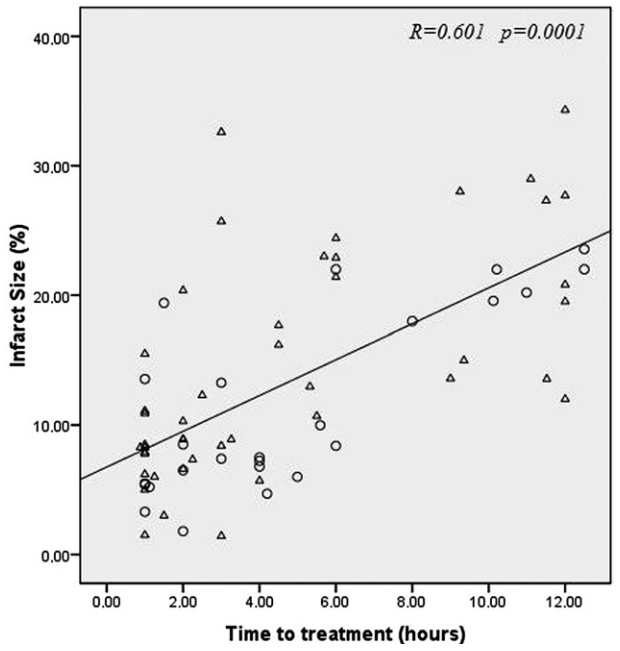

Figure 2 Relationship Between Time to Reperfusion and Infarct Size

Triangles = anterior infarct location; **circles** = nonanterior infarct location.

dogs a substantial reduction of salvaged myocardium in the first hours after coronary ligation. Whereas a reduced efficacy of lytic treatment overtime has been well documented, a recent meta-analysis by Boersma (18) suggests that time delays are largely unimportant in primary PCI. In particular, with clinical data obtained by the use of myocardial scintigraphy, Schomig et al. (16) found no significant relation between time to reperfusion and IS and a constantly high myocardial salvage index in patients treated with PCI even after 12 h from symptom onset. Conversely, by analyzing the T2W-STIR and LGE images, our CMR data support the hypothesis that myocardium potentially salvaged by reperfusion significantly reduces after 90 min of coronary occlusion even in patients treated with PPCI.

The main determinants of MVO are still unclear (3–5,15,24). In agreement with Tarantini et al. (15), we observed a progressive MVO increase over time. In particular MVO was detected only in 6 of 19 patients (31%) treated within 90 min and in 14 of 17 patients (82%) treated after 6 h. Thus, both incidence and extent of MVO are time-dependent phenomenon, as observed for IS. These results are consistent with previous experimental data hypothesizing that the extent of microvascular injury is also driven by the extent of IS (14,15,25).

Finally, the impact of time to reperfusion on LV volumes and LVEF was significantly more pronounced in patients reperfused late (group IV) compared with the other groups (I, II, and III). This finding was confirmed also in the CMR at 6 months, demonstrating a significant increase in LVEDV and LVESV in the later reperfused groups (group III, >150 to 360 min and group IV, >360 min); LVEF significantly decreased only in group IV.

Myocardium at risk and salvaged myocardium. Increased signal intensity in the T2w-STIR images is related to increased water content. In patients with STEMI this phenomenon is likely to represent post-ischemic intracellular edema either related to altered transmembrane sodium gradients or to the inflammatory response to the acute ischemic insult. The authors of recent CMR studies (10–14,24) demonstrated that the increased signal intensity on T2w-STIR images corresponds indeed to the area of myocardium at risk determined histologically. Aletras et al. (10) demonstrated in animal model of 90-min coronary occlusion followed by reperfusion that the area at risk measured by microspheres was comparable with the area of increased signal in the T2w images 2 days later. The increased signal intensity on T2w-STIR images consist of both reversibly and irreversibly injured myocardium. In addition, areas of LGE identified IS with detailed precision compared with histology (10), confirming that IS acutely is not overestimated because of the contribution of edematous areas, which are indeed characterized and quantified only by the T2w images. Therefore, on the basis of the histological evidence that myocardium at risk is identified by the T2w areas and IS by LGE areas, the amount of salvaged myocardium can be derived by subtracting the area of LGE from the T2w area.

Cury et al. (26) recently applied T2w imaging by using a double inversion-recovery with chemical fat saturation and LGE protocol to improve the accuracy in the diagnosis of acute coronary syndrome in the emergency department. The

Table 2 Relationship Among Infarct Location (LAD vs. Non-LAD) and Time to Treatment, Infarct Size, and LVEF

	Groups							
Variables	≤90 Min	p Value	>90–150 Min	p Value	>150–360 Min	p Value	>360 Min	p Value
LAD time to treatment, h	1.0 ± 0.2	0.710	2.5 ± 0.5	0.984	5.2 ± 0.9	0.335	11.5 ± 1.1	0.359
Non-LAD time to treatment, h	1.1 ± 0.2		2.4 ± 0.5		4.5 ± 0.8		10.2 ± 3.1	
LAD infarct size, %	12 ± 3.1	0.050	14 ± 10.1	0.041	16 ± 7.9	0.038	20 ± 9.8	0.002
Non-LAD infarct size, %	6.8 ± 1.5		8.9 ± 3.2		9.7 ± 6.8		10 ± 1.3	
LAD LVEF, %	47 ± 12.4	0.427	44 ± 10.1	0.220	44 ± 5.7	0.147	34 ± 6.0	0.378
Non-LAD LVEF, %	50 ± 10.7		51 ± 9.4		51 ± 7.2		39 ± 7.6	

LAD = left anterior descending artery; LVEF = left ventricular ejection fraction.

Table 3 Influence of Time to Reperfusion on Left Ventricular Function Assessed by CMR

Variables	Groups ≤90 Min (n = 19)	>90–150 Min (n = 17)	>150–360 Min (n = 17)	>360 Min (n = 17)	p Value
LVEDV, ml	128 ± 32	131 ± 37	130 ± 41	153 ± 22	0.03
LVESV, ml	62 ± 22	69 ± 30	68 ± 24	94 ± 21	0.02
LVEF, %	47 ± 10	46 ± 9	47 ± 6	38 ± 7	0.06

CMR = cardiovascular magnetic resonance; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

authors of previous studies (11–15) showed that areas of increased T2 signal intensity are consistently larger than the LGE areas of the irreversible injury. Similarly, in our study, the edematous zone is consistently larger than the infarcted zone but only in patients treated early and progressively reduces with delays on reperfusion evolving in irreversible myocardial damage. The amount of myocardium successfully salvaged dramatically reduces after 90 min of coronary occlusion; thus, clinical benefits of IRA reopening are after this period (2,7,18) are largely not attributable to myocardial salvage.

Milavetz et al. (27) reported the influence of time to reperfusion on myocardial salvage assessed by technetium-99m sestamibi demonstrating that in patients with first anterior MI undergoing successful reperfusion therapy (PPCI or thrombolysis) the greatest degree of myocardial salvage was achieved with an early reperfusion therapy (<2 h). Our data confirm these findings by the use of CMR as an alternative noninvasive imaging modality. The retrospective determination of myocardium at risk, IS—and consequently myocardial salvage—by CMR up to 5 days after reperfusion appears logistically very attractive as compared with the tracer injection before reperfusion therapy required by technetium-99m sestamibi (28). Finally, our study provides additional insight on the association of 4 different time-to-reperfusion intervals and the extent of reversible and irreversible damage.

Study limitations. Despite the limited study population, a relatively high percentage of our patients were treated very early (24% of patients ≤90 min from the symptom onset, 51% within 150 min), which was made possible by an integrated hospital network system activated in our city and region. For the same reason the mean IS detected in our study population was slightly smaller than previously reported. The influence of time to reperfusion on the extent of myocardial salvage IS and MVO needs to be confirmed in larger longitudinal studies.

Currently, there is no consensus on which technique can be used to perform the best MVO quantification (29). With first-pass myocardial perfusion imaging, the area of MVO is larger than using LGE imaging. In our study MVO was assessed in LGE images. Although the size of MVO may be underestimated by use of the LGE sequences, the persistence of MVO in these images is likely to reflect a more severe form of MVO (15). Finally, in this study CMR was performed as part of a research protocol and did not contribute to the care of patients.

Clinical implications. The results of our study suggest that any strategy (30–32) to shorten the delay in the reperfusion of patients with STEMI (i.e., pre-hospital lysis or a direct catheter laboratory notification bypassing the emergency department) is crucial. Although Boersma (18) hypothesizes that that time delays are less important for primary PCI, the present study demonstrated the amount of myocardial salvage reduces significantly already after 90 min of coronary occlusion. Our data might explain the unsatisfactory clinical results of myocardial protection therapy (33). Agents directed toward improving the myocardial reperfusion itself are time-limited to the period when myocardial salvage occurs. Thus, possibly only patients presenting very early after symptom onset may take advantages from cardioprotective drugs.

Finally, this work confirms and emphasizes the important diagnostic role of CMR with LGE and T2w-STIR techniques in providing in vivo characterization of myocardial tissue damage at different temporal stages of coronary reperfusion. The use of CMR can identify and quantify areas of salvaged

Table 4 Left Ventricular Function After Primary Angioplasty and at Follow-Up

Variables	Groups ≤90 Min (n = 15)	p Value	>90–150 Min (n = 14)	p Value	>150–360 Min (n = 16)	p Value	>360 Min (n = 13)	p Value
LVEDV, ml	128 ± 32	0.003	131 ± 37	0.047	130 ± 41	0.005	153 ± 22	0.002
LVEDV follow-up, ml	119 ± 22		121 ± 37		144 ± 42		167 ± 30	
LVESV, ml	62 ± 22	0.062	69 ± 30	0.001	68 ± 24	0.006	94 ± 21	0.003
LVESV follow-up, ml	58 ± 17		56 ± 28		79 ± 38		110 ± 20	
LVEF, %	47 ± 10	0.042	46 ± 9	0.117	47 ± 6	0.980	38 ± 7	0.048
LVEF follow-up, %	55 ± 6		49 ± 10		47 ± 9		34 ± 6	

Abbreviations as in Table 3.

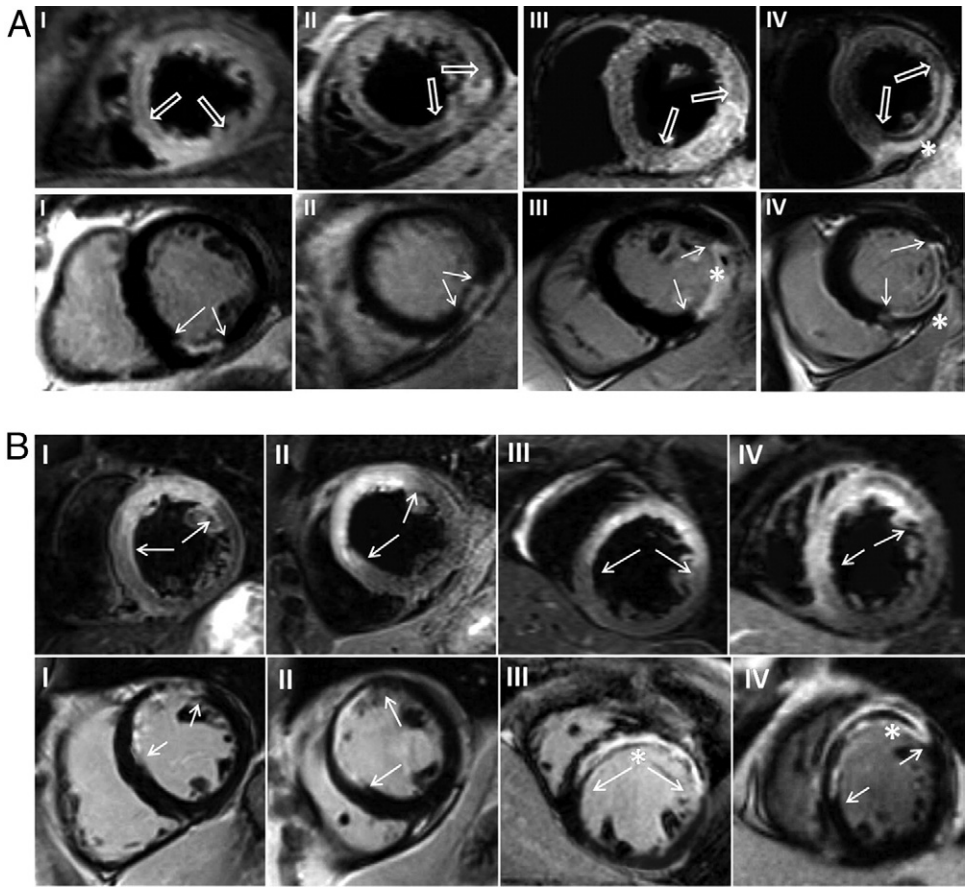

Figure 3 **Influence of Time to Reperfusion on Myocardial Salvage**

(A) Influence of time to reperfusion on myocardial edema and infarct size in inferior myocardial infarctions. Temporal distribution of myocardial edema and infarct size among the 4 groups in patients with inferior myocardial infarction. **(Top)** T2-weighted short tau inversion recovery (T2w-STIR) images; **(bottom)** corresponding late gadolinium enhancement (LGE) images. As time to reperfusion progresses, infarct size **(thin arrows)** and microvascular obstruction (MVO) **(*)** increase. Of note, in group I (early reperfused) the area of edema **(open arrows)** largely exceeds the area of infarct size, demonstrating presence of myocardial salvage; conversely in group IV (reperfused the latest), the area of edema almost corresponds to the infarcted area, suggesting limited myocardial salvage. **(B)** Influence of time to reperfusion on myocardial edema and infarct size in anterior myocardial infarctions**.** Temporal distribution of myocardial edema and infarct size among the 4 groups in patients with anterior myocardial infarction. **(Top)** T2w-STIR images; **(bottom)** corresponding LGE images. As time to reperfusion progresses, infarct size **(thin arrows)** and MVO **(*)** increase, with a parallel myocardial salvage reduction.

myocardium in patients with STEMI treated with PPCI, representing a potentially valuable tool to be used in large clinical trials assessing the efficacy of different reperfusion strategies. Large clinical trials are needed to assess the role of CMR in the risk stratification after acute myocardial infarction and possibly improve patient management.

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Key Words: myocardial salvage ■ myocardial infarction ■ microvascular injury ■ cardiovascular magnetic resonance ■ time to reperfusion.