Relation of Pain-to-Balloon Time and Myocardial Infarct Size in Patients Transferred for Primary Percutaneous Coronary Intervention

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The paradigm of a shorter pain-to-balloon time decreasing extent of infarct size may be not completely true in transferred patients. This study evaluated the influence of pain-to-balloon time on infarct size as assessed by delayed enhancement magnetic resonance imaging in patients transferred from a peripheral hospital to a tertiary center for primary coronary angioplasty (percutaneous coronary intervention [PCI]). Sixty patients (40 men, 64 ± 3 years of age) with first acute myocardial infarction were treated within <168, 168 to 222, 223 to 300, and >300 minutes. A presentation score system including clinical, laboratory, and echocardiographic data was used to classify severity of presentation at admission. Magnetic resonance imaging was performed 6 ± 3 days after PCI. Group 1 had a higher presentation score than did group 2 ($p < 0.02$) and group 3 ($p < 0.02$). Group 1 had a significantly longer delayed enhancement than did group 2 ($p < 0.002$) and group 3 ($p < 0.03$). In conclusion we found that patients with worse presentation are transferred sooner for primary PCI. This approach in these patients does not decrease infarct size likely because of unavoidable delay to reperfusion. This finding suggests a different therapeutic strategy in these patients. **(Am J Cardiol 2007; 100:28–34)**

This study assessed the relation between clinical markers of acute myocardial infarction, pain-to-balloon time and myocardial infarct size, in patients with first ST-segment elevation myocardial infarction (STEMI) and single-vessel coronary artery disease who were transferred from a community hospital to a referral hemodynamic laboratory for primary percutaneous coronary intervention (PCI). We adopted inclusion criteria such as first infarct and single-vessel coronary disease that, although limiting enrollment, would minimize confounding factors related to an already damaged left ventricle that might affect clinical presentation and infarct size.

Methods

Sixty consecutive patients (40 men, mean age 64 years) with STEMI and single-vessel coronary artery disease and no previous infarction or coronary revascularization were enrolled. STEMI was diagnosed on the basis of persistent chest pain lasting >30 minutes and ST-segment elevation ≥1 mm in ≥2 contiguous leads. Eight community hospitals were involved in this study. All patients were first admitted to a community hospital and then transferred to central catheter laboratory for primary angioplasty. Decision to transfer a patient for PCI was independently taken by the community hospital cardiologist. At admission 23 patients had electrocardiographic patterns of anterior (11 anteroseptal and 12 anterolateral), inferior (16), inferolateral (16), and lateral (5) MI. Initially all patients were treated with aspirin and low-molecular-weight heparin. All patients underwent coronary stenting with drug-eluting stents and up-to-date medical therapy consisting of glycoprotein IIb/IIIa inhibitors and clopidogrel initiated during PCI. Mean pain-to-balloon time was 259 ± 157 minutes (range 90 to 700). Patients were subcategorized into 4 quartiles on the basis of pain-to-balloon time distribution: <168 minutes (group 1), 168 to 222 minutes (group 2), 223 to 300 minutes (group 3), and >300 minutes (group 4). Twelve-lead electrocardiography at rest was recorded at first admission in the emergency room, after revascularization, and at discharge. The following parameters were considered: sigma ST-elevation, sum of ST-tract increases in millimeters in each lead at admission; delta ST, the difference in millimeters between sigma ST elevation at admission and after PCI; amd number of Q, QS, and q waves at discharge. Serum cardiac markers (serum creatine phosphokinase activity in units per liter and troponin I assay in nanograms per deciliter) were measured at admission, immediately after PCI, 3, 6, and 12 hours after PCI, and daily after first the 24 hours. Peaks in creatine phosphokinase and troponin I and the area under the enzymatic curve were used as markers of infarct size. Echocardiogram was obtained at admission in the emergency department. A wall motion score (1, normal, to 4, dyskinetic)

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0002-9149/07/$ – see front matter
doi:10.1016/j.amjcard.2007.02.050

Table 1
Presentation score system

	Score			
	1	2	3	4
Age (yrs)	>72	72–66	65–49	<49
Sigma ST (mm)	<7	7–9	10–19	>19
Wall motion score index	<1.23	1.23–1.52	1.53–1.85	>1.85
Troponin at first assay (ng/dl)	<12	12–43	44–160	>160
Site of infarction	Nonanterior	Anterior		

was assigned to each myocardial segment in a 17-segment model[1] and then an echocardiographic wall motion score index was calculated. Ejection fraction was also measured using a modified Simpson rule. A presentation score system was used to categorize factors contributing to the medical decision of primary PCI. This score system included age, sigma ST elevation, troponin at first assay, echocardiographic wall motion score index, and site of infarction (anterior or nonanterior infarction). For each parameter a single score was obtained based on cut-off values derived from quartiles of distribution (Table 1). The presentation score of each patient was the sum of single scores (range 5 to 18). Quantitative coronary angiography was used to evaluate severity of culprit vessel obstruction. An expert operator evaluated coronary blood flow based on visual assessment of the rate of contrast opacification of the infarct artery by assigning a flow grade (0 to 3) before and after PCI in agreement with the Thrombolysis In Myocardial Infarction (TIMI) study group.[2] Imaging protocol consisted of cine magnetic resonance imaging (MRI) to quantitatively evaluate global left ventricular function and contrast-enhanced MRI to determine the location, size, and transmural extent of infarction. MRI was performed using a 1.5-tesla whole-body scanner (GE Healthcare, Milwaukee, Wisconsin). A 4-element (2 anterior and 2 posterior) cardiac phased-array receiver surface coil was used for signal reception. A breath-hold, steady-state, free-precession pulse sequence was used to evaluate global left ventricular function using standard parameters. In each patient 9 to 13 short-axis views (to completely cover the ventricular main axis in end-diastole) and 2 long-axis views (vertical and horizontal long axes) were acquired. For each slice 30 cine frames were acquired. Delayed enhancement (DE) images were obtained 10 minutes after bolus injection of gadobutrol (Gadovist, Schering, Berlin, Germany; 0.2 mmol/kg); images were acquired in the same short-axis and long-axis slices as those used for cine MRI (Figure 1). A fast gradient echocardiographic inversion recovery sequence was used with the following parameters: repetition time 4.2 msec, echo time minimum, flip angle 20°, matrix 256 × 192, number of excitations 1.00, field of view 36 to 42 mm, slice thickness 8 mm, and no interslice gap. Inversion time was optimized to a null signal from normal myocardium. Follow-up MRI examination with the same protocol was performed 3 to 6 months after STEMI. Left ventricular volumes, mass, and ejection fraction were measured using previously validated software (Mass, MEDIS, Leiden, The Netherlands). The ratio between left ventricular end-diastolic volume and mass was chosen as a global remodeling index. We also visually assessed regional ventricular function by wall motion score index. To assess infarct size, extent of DE areas was measured using a semiautomatic, previously validated software.[3] To this purpose we used all short-axis images and 2 additional long-axis images for analysis of the cardiac apex. In each image, boundaries of contrast-enhanced areas were automatically traced and manually corrected when needed. Contrast-enhanced regions, namely infarcted regions, were expressed as grams and as percent of the entire left ventricle. A 17-segment model was adopted where 16 segments were derived from the short-axis images (6 segments at basal, 6 at medial, and 4 at distal level) and the 17th segment, corresponding to the apex, was obtained from the long-axis view. Each myocardial segment was subdivided into 100 radial cordae. Transmural extent of DE was defined as the average number of cordae measured in each segment with >50% extent of DE. Reproducibility of this method has been previously validated.[3] No-reflow area was defined as a hypoenhanced area surrounded by hyperenhancement. Quantification of no-reflow was performed using the same software as for DE. Data are presented as median (with 25th, 50th, and 75th percentiles) or counts and proportions (percentages). Continuous variables are expressed as mean ± 1 SD and categorical variables as percentages. Linear regression analysis by the least square method was used to correlate different variables. Categorical variables were compared by Pearson chi-square test. Two-way analysis of variance or Bonferroni analysis, when appropriate, was used to compare quantitative variables across ≥2 groups.

Results

Clinical characteristic of patients are listed in Table 2. Prevalence of a single risk factor was similar across the 4 groups. A trend toward younger age was detected in patients in group 1 compared with those in groups 2 and 3, whereas a significantly younger age was detected in group 1 compared with group 4. All patients were in Killip class I at presentation. As presented in Table 3, group 1 showed significantly higher troponin at first assay and at peak and a higher echocardiographic wall motion score index than did groups 2 and 3. At discharge numbers of Q and QS waves were larger in group 1. In the entire population presentation score was not correlated to pain-to-balloon time ($p < 0.1$); however, patients in group 1 had a significantly higher presentation score than did patients in groups 2 and 3. No significant difference was present between groups 1 and 4. Presentation score was significantly correlated with global DE and its

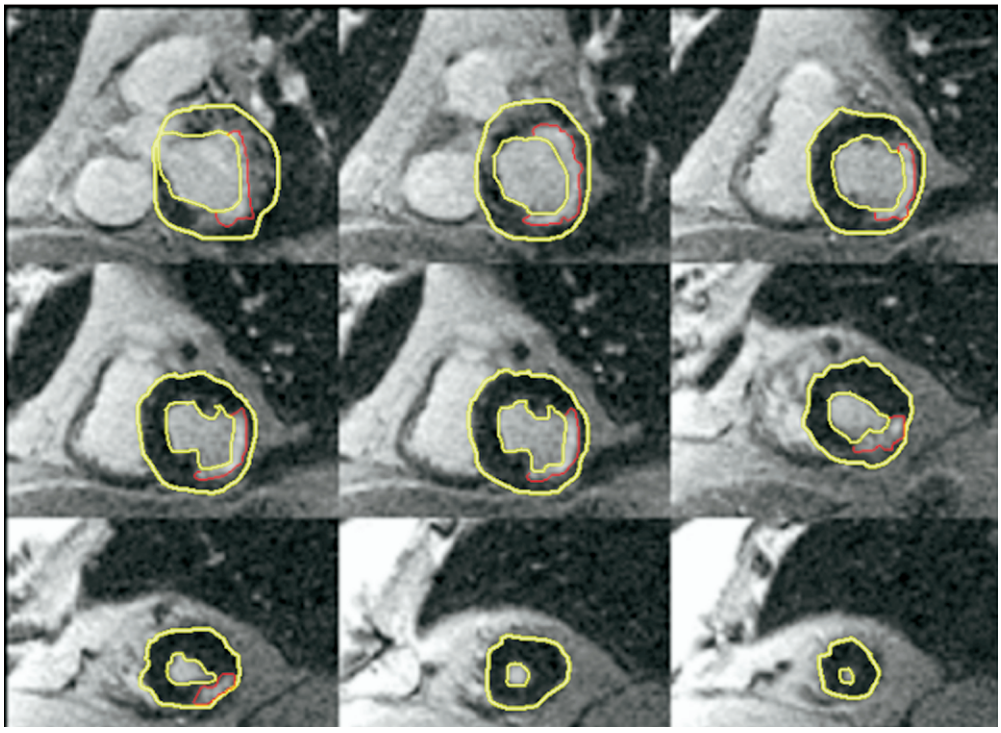

Figure 1. Acute lateral MI limited to the subendocardial layer without no-reflow phenomenon.

Table 2
Patients' characteristics

Variable	Quartile						
	I (n = 15)	p Value (I vs II)	II (n = 15)	p Value (I vs III)	III (n = 18)	p Value (I vs IV)	IV (n = 12)
PCI time (min)	<168		168–222		223–300		>300
Mean age (yrs)	56		66		64	<0.03	70
Door-to-balloon time (min)*	58 ± 16	<0.005	99 ± 37	<0.0001	132 ± 46	<0.0001	236 ± 91
Diabetes mellitus	3 (20%)		3 (20%)		2 (11%)		3 (25%)
Hypertension†	9 (60%)		8 (53%)		5 (28%)		5 (42%)
Dyslipidemia‡	8 (53%)		6 (40%)		12 (67%)		3 (25%)
Smoke	7 (47%)		8 (53%)		8 (44%)		4 (33%)
Obesity§	2 (13%)		5 (33%)		3 (17%)		3 (25%)
No. of risk factors (n ± SD)	2.9 ± 1.1		2.8 ± 1.5		2.5 ± 1.5		2.2 ± 0.4
Previous angina‖	8 (53%)		9 (60%)		9 (50%)		6 (50%)

* Arrival to community hospital.
† Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.
‡ Total cholesterol level >200 mg/dl.
§ Body mass index ≥30 kg/m^2.
‖ Occurring within 1 week before acute MI.

transmural extent (Figure 2). The left anterior descending coronary artery was the most frequently involved artery in groups 1 and 4, whereas the right coronary artery was most frequently involved in groups 1 and 3 (Table 4). No significant differences were found across groups in Thrombolysis In Myocardial Infarction flow grade, before and after PCI, in the portion of the vessel involved (basal-medial-distal) and in the prevalence of nonocclusive lesions. All patients completed the MRI study without adverse effects. MRI findings are presented in Table 5 and Figure 3. Group 1 showed greater impairment of wall motion than did group 2. Global extent of DE was significantly greater in group 1 than in groups 2 and 3. In the entire population, involvement of the left anterior descending artery correlated with a significant larger extent of DE (23.1 ± 10.2% vs 14.1 ± 10.8%, p <0.012). However, considering patients in group 1 only, global DE was not significantly different in patients with and without involvement of the left anterior descending coronary artery (25.3 ± 9.7% vs 16.5 ± 7.8%, p <0.2). Considering patients with involvement of the right coronary artery or left circumflex artery, group 1 had greater global

Table 3
Laboratory and instrument findings

Variable	Quartile						
	I (n = 15)	p Value I vs II	II (n = 15)	p Value I vs III	III (n = 18)	p Value I vs IV	IV (n = 12)
Cardiac enzymes							
Peak CPK (U)	3,168 ± 1,695	<0.004	1,316 ± 826		1,741 ± 2,091		2,907 ± 2,999
Troponin at first assay (ng/dl)	240 ± 200	<0.05	37 ± 312	<0.03	24 ± 32		90 ± 158
Peak troponin 1 (ng/dl)	300 ± 217	<0.03	156 ± 165	<0.02	111.5 ± 152		137 ± 225
ECG at admission							
Sigma ST elevation (mm)	14.5 ± 8.9		12.7 ± 7.9		10.9 ± 8.9		11.3 ± 8.5
ECG at discharge							
No. of Q and QS waves	4.1 ± 1.4	<0.03	2.8 ± 1.7	<0.03	2.6 ± 1.7		3.7 ± 1.9
No. of Q waves	0.9 ± 1.2		0.4 ± 1		0.8 ± 1.2		1.5 ± 2.5
No. of QS waves	2.3 ± 1.8		1.3 ± 1.3	<0.02	0.7 ± 0.9		1.7 ± 1.5
Delta ST elevation (mm)	10.6 ± 7.1		9.9 ± 7.7		8.6 ± 9.2		6.7 ± 6.4
Echocardiogram at admission							
Wall motion score index	1.67 ± 0.2	<0.05	1.4 ± 0.4		1.48 ± 0.5		1.58 ± 0.4
Ejection fraction (%)	44.8 ± 7.7		49.8 ± 7.8		47.5 ± 8.1		40 ± 15.2
Presentation score	10.4 ± 1.5	<0.02	8.1 ± 2.7	<0.03	8.3 ± 2.7		8.7 ± 2.6

CPK = creatine phosphokinase; ECG = electrocardiogram.

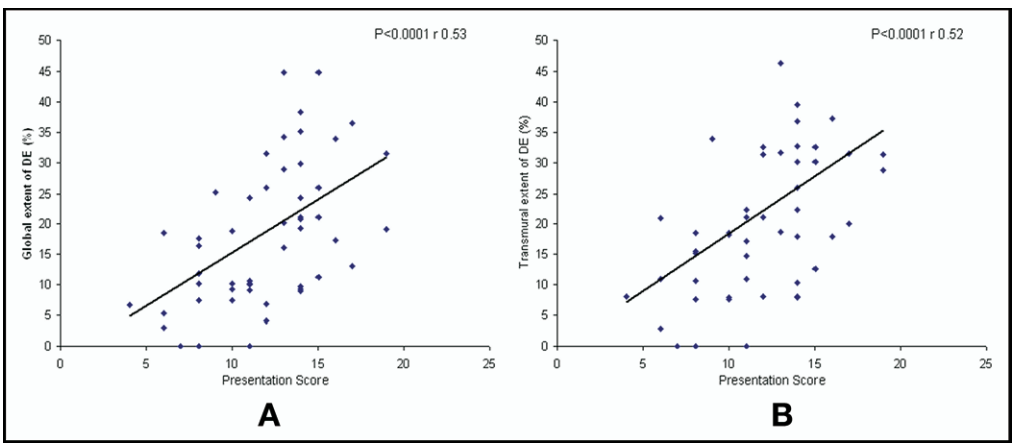

Figure 2. Correlation between presentation score and global *(A)* and transmural *(B)* extents of DE.

DE (17.7 ± 8.0% vs 6.8 ± 4.2%, p <0.011) and transmural DE (22.2 ± 9.6% vs 7.4 ± 4.8%, p <0.005) than did group 2. Presence of no-reflow phenomenon tended to be greater in group 1 than in groups 2 and 3 and less than in group 4 (Table 5). When group 1 was excluded from analysis, patients with no-reflow had a significantly longer pain-to-balloon time than did those without (389 ± 182 vs 264 ± 121 minutes, p <0.03). Nonetheless, excluding group 1, a linear correlation was found between pain-to-balloon time and global DE (r = 0.51, p <0.001). Follow-up cardiac MRI was obtained in 36 unselected patients within 145 ± 40 days after revascularization. Results are presented in Table 5 and Figure 1. Group 1 still had greater global DE and a larger number of segments involved compared with group 2. Further, group 1 had larger end-diastolic and end-systolic volumes and worse remodeling than did groups 2 and 3 (Table 5). Excluding group 1 from analysis, a linear correlation was found between pain-to-balloon time and global DE at follow-up (r = 0.66, p <0.01).

Discussion

In the present study we enrolled patients with first STEMI and single-vessel disease that was treated with primary PCI and stenting in a tertiary center after their transfer from a peripheral hospital. An apparent paradox was found because patients with earlier treatment (<168 minutes from pain onset) had larger infarcts than did patients treated at an intermediate time (169 to 300 minutes) and infarcts no different from the those treated after 300 minutes. Presence of no-reflow areas also tended to be greater in group 1 than in groups 2 and 3, but the difference not significant likely because of the limited number of patients with no-reflow. Follow-up results confirmed more severe infarcts in group 1 based on larger size and more severe ventricular remodeling compared with patients with longer pain-to-balloon time. Although a higher prevalence of anterior infarction was evident in group 1, this factor only partly influenced the results. Considering only patients with right or left circumflex

Table 4
Coronary angiographic findings

Variable	Quartile						
	I (n = 15)	p Value I vs II	II (n = 15)	p Value I vs III	III (n = 18)	p Value I vs IV	IV (n = 12)
IRA							
Left anterior descending	9 (60%)	<0.03	3 (20%)	<0.03	4 (22%)		6 (50%)
Right coronary or left circumflex	6 (40%)	<0.03	12 (80%)	<0.03	14 (78%)		6 (50%)
Total occlusion of IRA	12 (80%)		11 (73%)		13 (72%)		8 (67%)
Partial occlusion of IRA	3 (20%)		4 (27%)		5 (27%)		4 (33%)
Proximal stenosis	2 (13%)		2 (13%)		2 (11%)		1 (8%)
Medial stenosis	10 (67%)		11 (73%)		9 (50%)		7 (58%)
Distal stenosis	4 (27%)		2 (13%)		7 (39%)		4 (33%)
TIMI flow grade before PCI*							
0	10 (66%)		9 (60%)		14 (78%)		8 (66%)
1	2 (13%)		1 (7%)		2 (11%)		1 (8%)
2	2 (13%)		4 (27%)		0		1 (8%)
3	1 (7%)		1 (7%)		2 (11%)		2 (17%)
TIMI flow grade after PCI*							
0	1 (7%)		1 (7%)		2 (11%)		0
1	0		0		0		0
2	1 (7%)		2 (13%)		2 (11%)		2 (17%)
3	13 (87%)		12 (80%)		14 (78%)		10 (83%)

* Visual assessment of rate of contrast opacification of infarct artery.
IRA = infarct-related artery.

Table 5
Cardiovascular magnetic resonance (CMR) findings

Variable	Quartile						
	I (n = 15)	p Value I vs II	II (n = 15)	p Value I vs III	III (n = 18)	p Value I vs IV	IV (n = 12)
CMR I examination							
Day after acute MI	6.7 ± 4.3		7.0 ± 3.3		5.3 ± 1.6		6.5 ± 2.9
Global DE (%)	21.9 ± 10	<0.002	9.3 ± 5	<0.03	14.2 ± 10		25.2 ± 13
Global DE (g)	33.7 ± 22	<0.001	12.6 ± 8		16.2 ± 14		45.4 ± 34
DE segments	9 ± 2	<0.003	5 ± 2	<0.02	4 ± 3		9 ± 3
Transmural DE (%)	24.4 ± 10	<0.002	11.1 ± 8	<0.03	18.2 ± 11		27.8 ± 16
No-reflow (%)	45.4		20		16.7		77.8
Extent of no-reflow (%)	5.3 ± 4		2.8 ± 4		3.7 ± 2		6.1 ± 7
Wall motion score index	1.53 ± 0.3	<0.005	1.32 ± 0.2		1.50 ± 0.3		1.77 ± 0.4
Ejection fraction (%)	46.5 ± 11		54.2 ± 12		46.8 ± 12		47.2 ± 13
CMR II examination							
No. of patients	10		9		9		8
Days after PCI	148 ± 33		149 ± 28		140 ± 34		140 ± 5
End-diastolic volume (ml)	182 ± 31	<0.04	148 ± 37	<0.002	121 ± 30		165 ± 30
End-systolic volume (ml)	93 ± 26	<0.05	58 ± 11	<0.004	51 ± 9		74 ± 11
Ejection fraction (%)	51 ± 3		57 ± 8		63 ± 8		56 ± 4
Δ end-diastolic volume	23 ± −31		−17 ± −51	<0.05	−24 ± −27		8 ± −43
Δ end-systolic volume	12 ± −24		−11 ± −25	<0.02	−30.2 ± −16		1 ± −24
Global DE (%)	15.1 ± 6	<0.01	5.7 ± 2		10.6 ± 7		17.4 ± 5
Global DE decrease (%)	11.88 ± 53		51.7 ± 14		26.0 ± 55		49.9 ± 20
Mass (g)	136 ± 14		137 ± 15		126 ± 29		129 ± 14
End-diastolic volume/mass	1.37 ± 0.2	<0.01	0.9 ± 0.1	<0.003	0.98 ± 0.1		1.2 ± 0.3

Δ = change from first examination.

coronary artery occlusion, group 1 was still characterized by larger infarcts compared with groups 2 and 3.

The presentation score system assessed severity of clinical condition at the first medical visit, which could have influenced transfer time and thus pain-to-balloon delay. Presentation score showed an indirect correlation with time

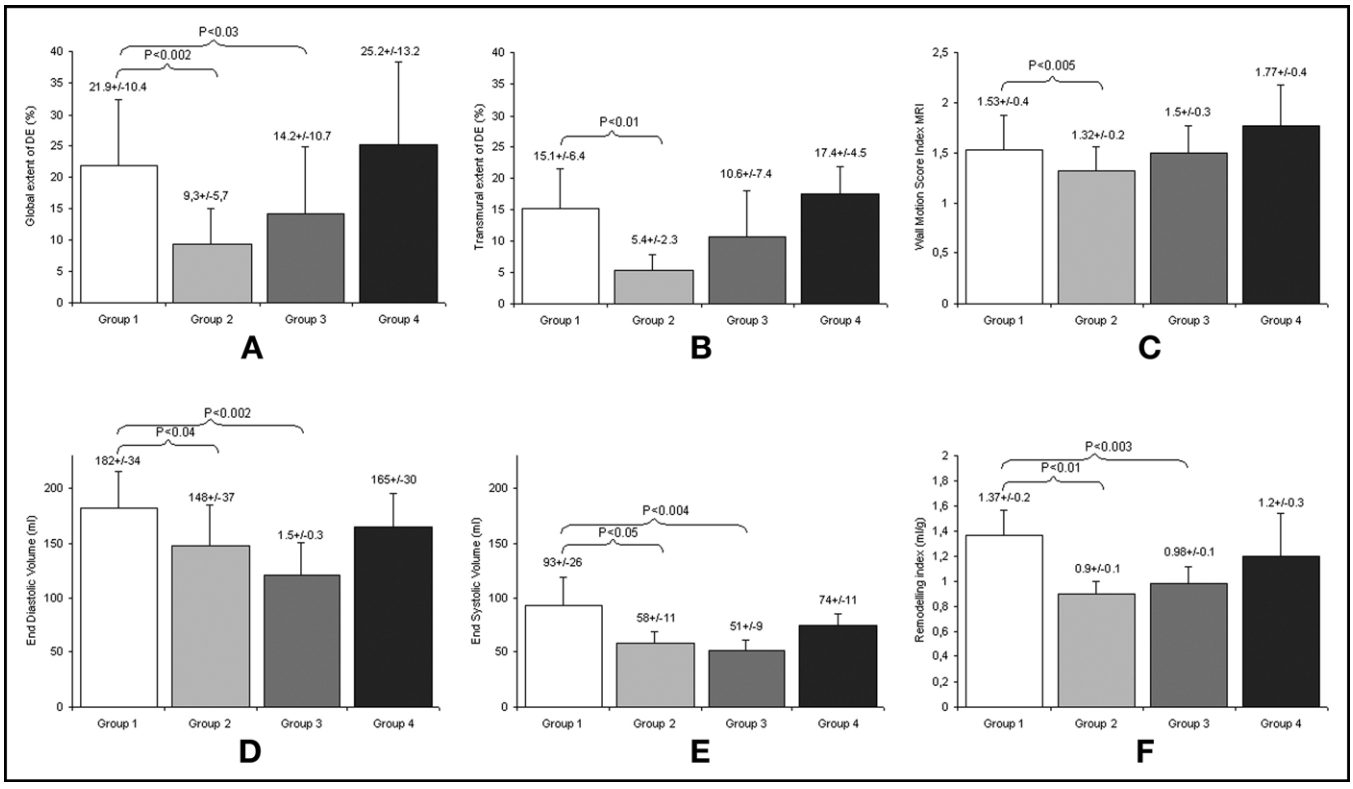

Figure 3. Global extent of DE (percentage) a few days after primary PCI *(A)* and at follow-up *(B)* in the 4 quartiles. *(C)* Wall motion score index at first MRI. End-diastolic *(D)* and end-systolic *(E)* volumes (milliliters) at follow-up. *(F)* Ratio between end-diastolic volume and left ventricular mass (milliliters per gram), used as index of remodeling, at follow-up.

to PCI but a direct correlation with global and transmural extents of DE. Thus the larger extent of MI in patients with a shorter pain-to-balloon time likely reflected a selection occurring at the level of the community hospital. Patients in group 1, with the shortest time to PCI, had a higher presentation score than did patients in group 2 and 3, including more severe electrocardiographic alterations, higher levels of serum markers of myocardial necrosis, and greater regional ventricular dysfunction on first echocardiogram.

The results of our study are in accordance with those of Schomig et al.[4] They assessed extent of MI by single-photon emission computed tomography in patients with STEMI treated with primary PCI or thrombolysis. Patients were clustered into tertiles of pain-to-balloon time: lower (<165 minutes), middle (165 to 280 minutes), and upper (>280 minutes). Although patients scheduled for thrombolysis showed a positive correlation between time to PCI and infarct size, in patients treated with PCI, the lower tertile had infarcts larger than those in the middle tertile (10.1% vs 9.4%) but smaller than those in the upper tertile (11.1%). In contrast to that study, our patient population was selected on the basis of more strict criteria such as first STEMI and single-vessel disease and using cardiac MRI, presently considered the gold standard for assessment of left ventricular volume and mass (expressed in grams), and DE for a more precise definition of the necrotic area compared with nuclear techniques.[5,6] A limitation of the present study was the limited number of patients studied. However, infarct size in this study was assessed by cardiac MRI, which, compared with other imaging modalities, limited variance of measurements, thus ensuring statistical significance with a relatively smaller sample.[7–10] In addition, population sample was highly selected, consisting only of patients with first acute MI and 1-vessel coronary artery disease. A few days after STEMI, infarct size assessed by a DE technique can be overestimated because of tissue edema within the necrotic area; DE regions with time show progressive shrinkage due to thinning of the infarcted wall, scar retraction, and absorption of edema. In our study, we observed a mean decrease of 33% in DE extent at follow-up (160 ± 35 days) with no differences in relative decrease in global DE across quartiles. At this time the final infarct size is accurately assessed.[11] A possible limitation of the present study is lack of validation of the scoring system used to assess clinical severity at first aid presentation. However, it is noteworthy to say that, in contrast to others, the system we used included an echocardiographic wall motion score index, which is a rapid, diffuse, and highly reproducible method to assess extent of MI.[11]

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