JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 5, NO. 11, 2012

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2012.06.022

Time-Dependent Detrimental Effects of Distal Embolization on Myocardium and Microvasculature During Primary Percutaneous Coronary Intervention

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Objectives The authors sought to investigate the impact of distal embolization (DE) on myocardial damage and microvascular reperfusion, according to time-to-treatment, using contrast-enhanced cardiac magnetic resonance (CE-CMR).

Background DE, occurring during primary percutaneous coronary intervention (p-PCI), appears to increase myocardial necrosis and to worsen microvascular perfusion, as shown by surrogate markers. However, data regarding the behavior of DE on jeopardized myocardium, and in particular on necrosis extent and distribution, are still lacking.

Methods In 288 patients who underwent p-PCI within 6 h from symptom onset, the authors prospectively assessed the impact of DE on infarct size and microvascular damage, using CE-CMR. The impact of DE was assessed according to time-to-treatment: for group 1, <3 h; for group 2, ≥ 3 and ≤ 6 h.

Results DE occurred in 41 (14.3%) patients. Baseline clinical characteristics were not different between the 2 groups. At CE-CMR, patients with DE showed larger infarct size ($p = 0.038$) and more often transmural necrosis compared with patients without DE ($p = 0.008$) when time-to-treatment was <3 h, but no impact was proven after this time ($p =$ NS). Patients with DE showed more often microvascular obstruction, as evaluated at first-pass enhancement, than patients without DE (100% vs. 66.5%, $p = 0.001$) up to 6 h from symptom onset.

Conclusions These findings suggest that the detrimental impact of DE occurring during p-PCI on myocardial damage is largely influenced by ischemic time, increasing the extent of necrosis in patients presenting within the first hours after symptom onset, and having limited or no impact after this time window. (J Am Coll Cardiol Intv 2012;5:1170–7) © 2012 by the American College of Cardiology Foundation

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Manuscript received February 16, 2012; revised manuscript received June 14, 2012, accepted June 21, 2012.

Distal embolization (DE) of macroscopic debris in the coronary circulation, as detected by coronary angiography, has been reported in about 14% of patients undergoing primary-percutaneous coronary intervention (p-PCI) for ST-segment elevation myocardial infarction (STEMI), accounting in most of them for impaired microvascular perfusion and larger myocardial damage (1). However, several randomized trials assessing the use of mechanical adjunctive devices aiming to reduce DE have reported conflicting evidences in terms of myocardial reperfusion and myocardial salvage (2). Indeed, even when the p-PCI is performed with respect for coronary microcirculation by use of protection devices on top of triple antiplatelet therapy, angiographically detectable DE may still occur in up to 6% of patients with a poorer outcome (3). These results have raised concerns, not only on the effectiveness of mechanical devices in preventing DE during p-PCI, but also, and more importantly, on the impact of DE by itself on myocardial and microvascular damage (4). The restoration of an adequate coronary flow represents only the first step toward successful myocardial reperfusion and myocardial salvage in STEMI. In fact, the effectiveness of reperfusion therapy depends on several factors, including the duration of ischemia (5), the presence of residual coronary flow by either antegrade flow (6) or collateral circulation (7), and the extent of risk area (8). Thus, it could be argued that the detrimental impact of DE may be strongly influenced by these factors and mainly by duration of ischemia and myocardium viability at time of flow restoration (8–10). We recently reported on the time-dependent impact of angiographically detectable DE during p-PCI on myocardial reperfusion and myocardial necrosis, as evaluated by myocardial blush and troponin I release, respectively (11). However, data regarding the behavior of DE on jeopardized myocardium, and in particular on necrosis extent and distribution, are still lacking. In the last decade, contrast-enhanced cardiac magnetic resonance (CE-CMR) has shown great potential in detecting myocardial scar after myocardial infarction, as well as in assessing the extent and distribution of necrosis (12,13). Indeed, this tool has been useful to study the presence of microvascular damage in the context of necrotic scar (12–15). The aim of the present study was to assess the impact of DE during p-PCI, on either myocardial or microvascular damage according to ischemic time, by CE-CMR.

Methods

Study population. We analyzed data from 288 subjects included in an ongoing prospective registry. All patients undergoing p-PCI, within 6 h from symptom onset, and CE-CMR at our institution were enrolled. Inclusion criteria were continuous chest pain for at least 20 min and within 6 h of symptom onset and the following: 1) ST-segment elevation ≥1 mm (0.1 mV) in 2 or more contiguous leads on the 12-lead electrocardiogram; 2) persistent ST-segment depression in precordial leads V_1 to V_4, with or without ST-segment elevation in inferior or lateral leads; or 3) new-onset left bundle branch block. Exclusion criteria were the use of adjunctive mechanical devices (both thrombectomy catheters and distal protection devices), previous myocardial infarction, electric or hemodynamic instability during hospitalization, and contraindication to CE-CMR. p-PCI was performed with a standard technique by femoral or radial approach according to physician choice. The infarct-related artery (IRA) was the only target of the procedure, and coronary bare-metal stents were used in all cases. The procedure was considered successful if Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the target vessel and a residual stenosis <20% at target site were obtained. Before the procedure, all patients received aspirin 250 to 500 mg intravenously, thereafter 100 to 325 mg/day; heparin (70 U/kg) was given to maintain the activated clotting time >250 s. Clopidogrel was given as soon as possible after hospital admission at a bolus dose of 300 to 600 mg and then at a dose of 75 mg once a day. Abciximab was given according to the judgment of the operator in the catheterization laboratory. All patients gave written informed consent for the procedure. The study complies with the Declaration of Helsinki, and the ethics review board of our institution approved the study.

Abbreviations and Acronyms

CE-CMR = contrast-enhanced cardiac magnetic resonance
DE = distal embolization
IRA = infarct-related artery
ISI = infarct size index
LGE = late gadolinium enhancement
p-PCI = primary percutaneous coronary intervention
PMD = persistent microvascular damage
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis in Myocardial Infarction

Angiographic analysis. Coronary angiograms were acquired digitally (Integris 5000, Philips Medical Systems, Best, the Netherlands). The angiographic analysis was performed offline by 2 experienced operators blinded to clinical data (11). TIMI flow grade and myocardial blush grade were assessed as previously described (16,17). Intracoronary thrombus at baseline was angiographically identified and scored in 5° according to TIMI thrombus score (18). To better define the thrombus burden in case of IRA occlusion, the angiographic pattern of coronary occlusion, when present, was defined on baseline angiogram as follows: 1) cutoff pattern, when there was an abrupt occlusion of the epicardial vessel; 2) tapered occlusion, when there was a vessel tapering just before the occlusion; and 3) persistent dye pattern, when there was dye staining just proximally and/or distally to the occlusion (11). Quantitative coronary analysis was performed at baseline and after procedure, using the Coronary Quantification Package (Philips Medical Sys-

tems) as previously described (11). DE was defined as a distal filling defect with an abrupt occlusion in distal IRA or in 1 or more peripheral coronary branches of the IRA, distal to the PCI site; in particular, we did not consider as DE the occurrence of TIMI flow impairment, at any stage of the procedure, without evidence of a distal filling defect (11).

CE-CMR image protocol. The patients were examined by 1.5-T scanner (Harmony, Siemens, Erlangen, Germany) implemented with cardiological software (MRease SYNGO 2002B, Siemens). The CE-CMR examination was acquired 5 to 8 days after revascularization. Electrocardiogram-gated breathhold cine images were acquired using a segmented steady-state free-precession pulse sequence (true fast imaging with steady state precession [TrueFISP]) in multiple short-axis views every 8 mm by encompassing the left ventricle from base to apex; vertical and horizontal long-axis views were also acquired. Typical in-plane resolution is 1.6 × 1.9 mm 2, with slice thickness = 8 mm; TE = 1.75 ms, TR = 3.5 ms, flip angle (FA) = 60°, matrix = 256 × 256, slice thickness = 8 mm, gap = 2 mm. Rest first-pass myocardial perfusion was performed during administration of a gadolinium-based contrast agent (Multihance, 0.2 mmol/kg, Bracco, Milan, Italy), using a single-shot saturation recovery gradient echo pulse sequence. Three short-axis slices were obtained per heartbeat, every 10 mm, covering the infarct area as seen during cine imaging (90° pre-pulse, TR/TE/FA 2.5 ms/1.3 ms/20°, slice thickness = 10 mm, matrix = 128 × 256, number of excitations = 1).

Late gadolinium enhancement (LGE) images were acquired 10 to 15 min after contrast administration (19), using a 2-dimensional segmented inversion recovery gradient echo pulse sequence, with slice position identical to the cine images, including long-axis views. Sequence parameters were the following: TR = 450 ms, TE = 1.31 ms, (FA) = 15°, slice thickness = 8 mm, gap = 2 mm. The inversion time was set to null the signal of viable myocardium (typical range: 250 to 300 ms).

CE-CMR image analysis. Cine, first-pass perfusion, and LGE images were acquired during the same imaging session and matched using slice position; finally, the images were analyzed using a 17-segment model (20,21). On all short-axis cine slices, the endocardial and epicardial borders were outlined manually on end-diastolic and end-systolic images. First-pass perfusion was evaluated qualitatively according to the 17-segment model (22). Persistent microvascular damage (PMD) was finally evaluated on LGE images as the presence of a hypoenhancement region, with decreased signal intensity (15,23). Extent of necrosis was judged as transmural if LGE extended to ≥75% of thickness of the myocardial wall in 2 or more segments (20). For analysis of transmural extent of infarction, the 2 most basal and most distal slices were excluded, because segmental evaluation at these levels is not considered to be reliable due to the left ventricular outflow tract and partial volume effect, respectively. The infarct size index (ISI) was quantified by manually drawing short-axis slices and is expressed as percentage of left ventricular mass. The presence of PMD was included in the infarcted area. All CE-CMR measurements were performed independently by 2 observers who were blinded to clinical and procedural data.

Measures of outcome. Major adverse events occurring during the hospitalization, including death, nonfatal reinfarction, and stroke, were collected. Diagnosis of nonfatal reinfarction was based on typical chest pain and/or new ST-segment changes with troponin I level re-elevation (11). The troponin I levels were reported as micrograms/liter, and were assessed every 6 h in the first 48 h after admission, and then twice daily up to discharge (11). Peak value release from 8 serial measurements up to 48 h after admission was reported (11). Stroke was defined by development of new cognitive or neurological deficits confirmed by computed tomography or magnetic resonance imaging. Two-dimensional echocardiography was performed in all patients pre-discharge.

Statistical analysis. Categorical data are expressed as numbers and percentages, and were compared using the chi-square or Fisher exact test, as appropriate. Continuous variables are expressed as mean ± SD for normally distributed variables, and as median (25th to 75th percentiles) for not normally distributed variables, and compared using the analysis of variance and Mann-Whitney *U* tests, respectively. The potential predictors of transmural necrosis were evaluated 1 variable at a time in a univariable logistic regression model. The potential predictors were age, diabetes, ischemic time, multivessel disease, patent IRA at baseline, presence of collaterals, final TIMI flow grade 3, abciximab use, and occurrence of DE. Variables that showed significant association with transmural necrosis on univariable analysis ($p < 0.10$) were entered in a multivariable logistic regression model, and a $p < 0.05$ was considered statistically significant. The results of the univariable and multivariable analyses are reported as p values, odds ratios, and 95% confidence intervals. To assess the impact of DE on myocardial and microvascular damage according to time-to-treatment, defined as time from symptom onset to first balloon inflation, patients were divided into 2 groups as follows: group 1, including 146 patients treated <3 h from symptom onset; and group 2, including 142 patients with symptom onset-to-balloon time ≥3 and ≤6 h. Because baseline clinical and angiographic characteristics did not differ between groups, a secondary analysis to compare CE-CMR measurements and DE occurrence was performed in these groups, using the chi-square test for categorical variables and analysis of variance or Mann-Whitney *U* test for continuous variables, respectively. A p value <0.05 with the 2-tailed test was considered statistically significant. Intraobserver and interobserver reproducibility of CE-CMR measurements were assessed using the Pearson correlation analysis. Statistical analysis was carried out by SPSS software package, version 16.0 (SPSS, Chicago, Illinois).

Results

Out of 288 patients enrolled, 41 (14.3%) showed DE and 247 (85.7%) did not. Baseline clinical findings were similar between patients with DE and patients without DE (Table 1). Particularly, pain-to-balloon time did not differ between patients with and those without DE (Table 1). No sex-based differences were detected (Table 1).

After dividing patients into 2 groups according to ischemic time, DE appeared not to be time dependent, occurring in 20 of 146 (13.7%) patients treated before 3 h and in 21 of 142 (14.8%) patients treated between 3 and 6 h ($p = 0.78$). Angiographic analysis at baseline revealed that patients in the DE group had a higher rate of occluded IRA (Table 2). Indeed, in the presence of an occluded IRA, patients in DE group showed in almost two-thirds of cases a "cutoff" pattern, whereas the tapered pattern was more frequent in patients without DE (Table 2). Patients in the DE group also had larger thrombus burden as assessed by TIMI thrombus score, longer lesion, and larger reference vessel diameter compared with patients without DE (Table 2). Abciximab was given more often in patients with DE (Table 2). At the end of procedure, patients experiencing DE had worse TIMI flow grade and myocardial blush, than did patients without DE (Table 2). Procedural success occurred in 30 of 41 (73.2%) patients with DE and in 234 of 247 (94.7%) patients without DE ($p < 0.0001$).

Relationship between DE, ischemic time, and myocardial damage on CE-CMR. At CE-MR, ISI was significantly larger in patients with DE than in patients without, particularly in those treated within 3 h (Fig. 1A). However, after this time, as the ISI of patients without DE increased, it did not differ between patients with and without DE (Fig. 1A). Moreover, myocardial necrosis was more often transmural in patients showing DE than in patients who did not (Fig. 1B). Particularly, the occurrence of DE significantly impacted the transmural extent of necrosis in patients treated within the first 3 h from symptom onset: transmural necrosis was detected in 84.6% of patients with DE and in 51.6% of patients without DE, respectively ($p = 0.025$) (Fig. 1B). After this time, the transmural extent of myocardial necrosis was no longer significantly affected by DE: transmural necrosis was detected in 84.6% and in 64.3% of patients, respectively ($p = 0.15$) (Fig. 1B). Patients experiencing DE showed more often PMD, as compared with patients without DE (Fig. 1C), when time-to-treatment was within 3 h; however, the impact of DE on severe microvascular damage was no longer appreciable when time-to-treatment was longer. Indeed, patients with DE showed more often microvascular obstruction, as evaluated in first-pass images, than patients without DE, showing statistically significant differences at both time points (Fig. 1D, Table 3). In particular, patients experiencing DE developed microvascular obstruction in all cases, whereas patients without

Table 1. Baseline Characteristics

	DE (n = 41) (14.3%)	No DE (n = 247) (85.7%)	p Value
Age, yrs	61 (55–70)	60 (50–67)	0.49
Male	36 (87.8%)	204 (82.6%)	0.41
Hypertension	22 (53.7%)	123 (49.8%)	0.65
Dyslipidemia	22 (54.5%)	111 (44.7%)	0.29
Diabetes mellitus	8 (19.5%)	40 (16.2%)	0.60
Smoke	30 (73.2%)	154 (62.3%)	0.18
Familiar history	18 (43.9%)	122 (49.5%)	0.51
Previous angina	11 (26.8%)	69 (27.9%)	0.05
Pain-to-balloon time, min	185 (120–305)	180 (131–285)	0.13
Troponin I peak, μg/l	112 (58–187)	68.5 (26.3–143.3)	0.01
Pre-discharge 2D echo			
EDVI, ml/m^2	66.1 ± 11.9	61.4 ± 13.6	0.14
ESVI, ml/m^2	33 ± 11.5	31.4 ± 11	0.66
LVEF, %	51.5 ± 6.8	49.9 ± 8.7	0.45

Values are median (25th to 75th percentile), n (%), or mean ± SD.

2D = 2-dimensional; CABG = coronary artery bypass graft; DE=distal embolization; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table 2. Angiographic Characteristics

	DE (n = 41) (14.3%)	No DE (n = 247) (85.7%)	p Value
Infarct-related artery			0.82
Left anterior descending	23 (56.1%)	133 (53.8%)	
Circumflex artery	4 (9.8%)	23 (9.4%)	
Right coronary artery	14 (34.1%)	91 (36.8%)	
Multivessel disease	17 (42%)	128 (52%)	0.29
Collateral flow (Rentrop 2/3)	9 (22%)	57 (23%)	0.83
Occlusion pattern			0.001
Patent IRA (TIMI flow grade 2/3)	7 (18.2%)	66 (26.6%)	
Cutoff	26 (63.6%)	73 (29.7%)	
Tapered	4 (9.1%)	81 (33.2%)	
Persistent dye	4 (9.1%)	27 (0.11%)	
TIMI thrombus score ≥3	37 (90.9%)	183 (74.2%)	0.035
QCA before PCI			
Lesion length	19.3 (15.7–23.3)	16.7 (13.5–21.7)	0.023
RVD, mm	3.17 (2.75–3.56)	2.78 (2.4–3.14)	<0.0001
DS, %	100 (99.9–100)	100 (94–100)	0.013
MLD, mm	0 (0–0.01)	0 (0–0.62)	0.022
QCA post PCI			
RVD	3.24 (2.71–3.5)	3 (2.58–3.35)	0.038
DS, %	11 (4.5–15.5)	10 (5–15)	0.52
MLD, mm	2.78 (2.46–3.14)	2.73 (2.41–3.05)	0.382
TIMI flow grade 3 after PCI	30 (72.7%)	234 (94.7%)	<0.0001
MBG 2/3 after PCI	11 (27.3%)	172 (69.6%)	<0.0001
Abciximab	28 (70%)	87 (35.3%)	<0.0001

Values are n (%) or median (25th to 75th percentile).

DS = diameter stenosis; IRA = infarct-related artery; MBG = myocardial blush grade; MLD = minimal lumen diameter; QCA = quantitative coronary angiography; RVD = reference vessel diameter; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

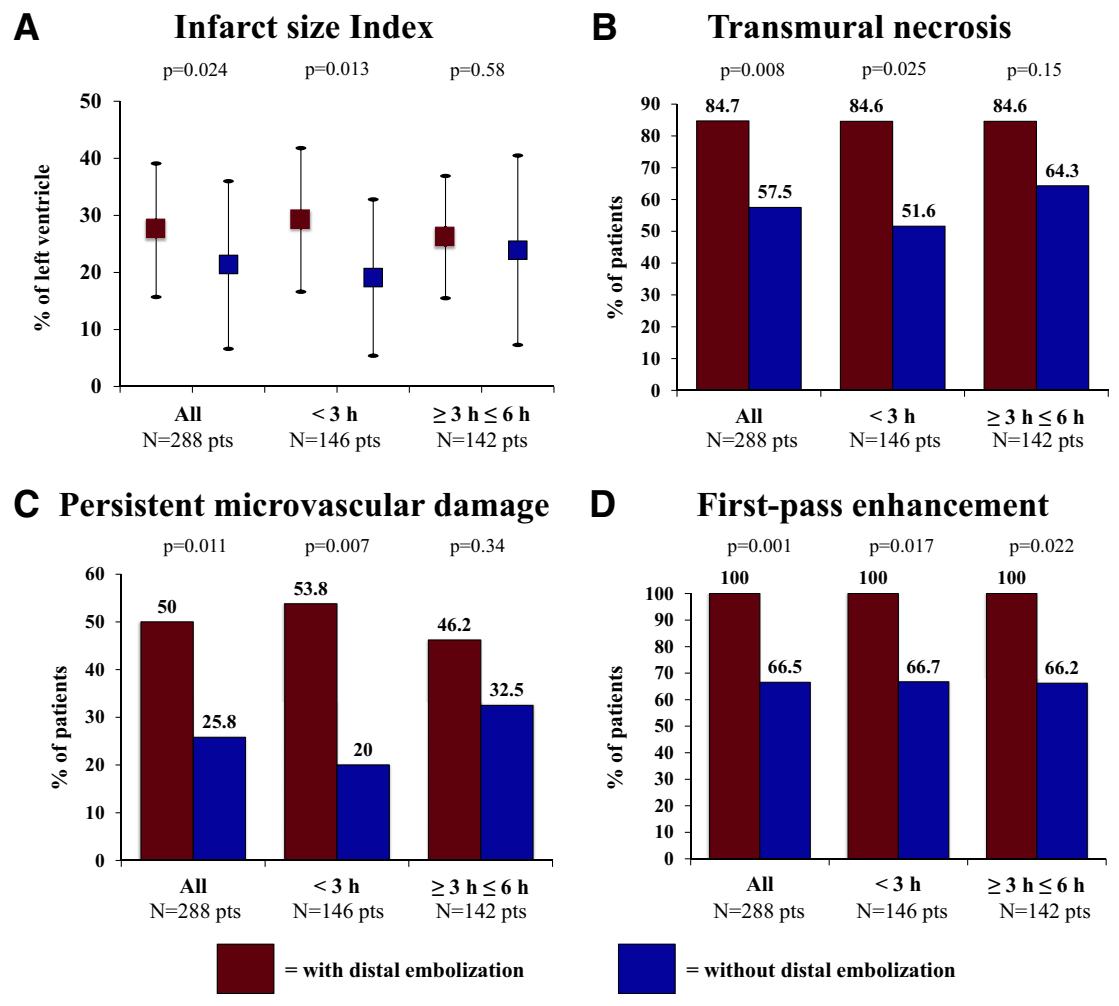

Figure 1. Impact of DE on Myocardial and Microvascular Damage According to Ischemic Time

Infarct size index **(A)**, presence of transmural necrosis **(B)**, persistent microvascular damage **(C)**, and first-pass enhancement **(D)** at CE-CMR in patients with **(red bars)** and those without **(blue bars)** distal embolization (DE), according to ischemic time. CE-CMR = contrast-enhanced cardiac magnetic resonance.

DE showed this in about two-thirds of cases. Examples of CE-CMR findings in terms of myocardial and microvascular damage in patients with and without DE according to time-to-treatment have been represented in Figures 2 and 3. Correlation indexes (r) of transmural necrosis/microvascular damage and ISI measurements were 0.94 and 0.94 for inter-observer variability and 0.95 and 0.95 for intraobserver variability, respectively. At univariable analysis, the patency of IRA at baseline, the occurrence of DE, and time-to-treatment correlated with the presence of transmural necrosis at CE-CMR. Multivariable analysis identified time-to-treatment and occurrence of distal embolization as independent predictors of transmural necrosis (Table 3). Troponin I peak values were significantly higher in the DE group than in patients without DE (Table 1). In-hospital events were not different between groups: 6 (2.0%) patients died, 1 (2.4%) in the group with DE and 5 (2.0%) in the group without DE ($p = 0.88$); heart failure occurred in 9 (21.9%) with DE and 38 (15.5%) without DE ($p = 0.36$), reinfarction occurred in 2 (4.9%) patients with DE and in 6 (2.4%) patients without DE ($p = 0.30$), re-PCI occurred in 3 (9.7%) and in 5 (4.4%) ($p = 0.21$) patients with and without DE, respectively; no patients experienced stroke.

Discussion

Detrimental impact of distal embolization on myocardial and microvascular damage. Experimental and clinical studies have shown that DE complicating p-PCI may affect myocardial reperfusion and increase myocardial necrosis in the setting of STEMI (1,24). However, the impact of this phenomenon may be difficult to address in the clinical setting, because myocardial reperfusion represents a complex process, and the

Table 3. Univariable and Multivariable Analysis: Predictors of Transmural Necrosis at CE-CMR

	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Collateral circulation	1.51	0.78–2.92	0.22	—	—	—
Age, 1/yr	0.99	0.97–1.02	0.81	—	—	—
Patent IRA	0.62	0.36–1.07	0.08	0.73	0.41–1.29	0.28
Distal embolization	2.57	1.06–6.19	0.03	2.51	1.02–6.17	0.04
Final TIMI flow grade 3	0.67	0.25–1.82	0.44	—	—	—
Pain-to-balloon time (30 min)	1.06	1.01–1.11	0.01	1.06	1.01–1.12	0.01
Diabetes mellitus	1.14	0.52–2.50	0.74	—	—	—
Abciximab	0.89	0.65–1.26	0.26	—	—	—
Multivessel disease	0.78	0.46–1.32	0.36	—	—	—

CE-CMR = contrast-enhanced cardiac magnetic resonance; CI = confidence interval; OR = odds ratio; other abbreviations as in Table 2.

impairment of microcirculation has a multifactorial etiology (25). Moreover, the effectiveness of myocardial reperfusion and myocardial salvage seems largely time dependent, with myocardial necrosis increasing as time-to-treatment increases (8–10). Recently, we were able to demonstrate a time-related impact of DE occurring during p-PCI on myocardial reperfusion and myocardial necrosis, as evaluated by myocardial blush and troponin I release, respectively (11). In particular, DE, assessed as angiographic distal filling defects, seems to impair myocardial reperfusion and to increase myocardial damage in patients treated early after symptoms onset, having limited relevance or even no impact on reperfusion and infarct size in the late comers, among whom many patients may have already developed transmural infarction at the time of IRA reopening (11). Accordingly, the present study was able to demonstrate, for the first time by means of CE-CMR, that DE has a detrimental effect on both myocardial and microvascular damage, increasing the extent of necrosis and impairing microvascular perfusion. Moreover, our results confirm and extend the notion that the impact of DE on myocardial damage appears time dependent: DE significantly impairs myocardial damage within the first hours after symptom onset, but it seems not to have a major impact as ischemic time increases. Indeed, it is important to remark that patients experiencing DE in our study not only had larger areas of necrosis, as assessed by ISI, but also had more severe damage, as shown by the occurrence of transmural necrosis and persistent microvascular damage (13). Interestingly, our study also demonstrates that patients with DE showed in almost all cases microvascular obstruction, as evaluated by first-pass images. However, DE seems to exert a major impact on microvascular perfusion even behind the first 3 h after symptom onset.

Time-dependent effect of adjunctive mechanical and pharmacological therapy in STEMI. It seems very important to speculate on the discrepancy observed with regard to the different time-related impact of DE on reperfusion and myocardial

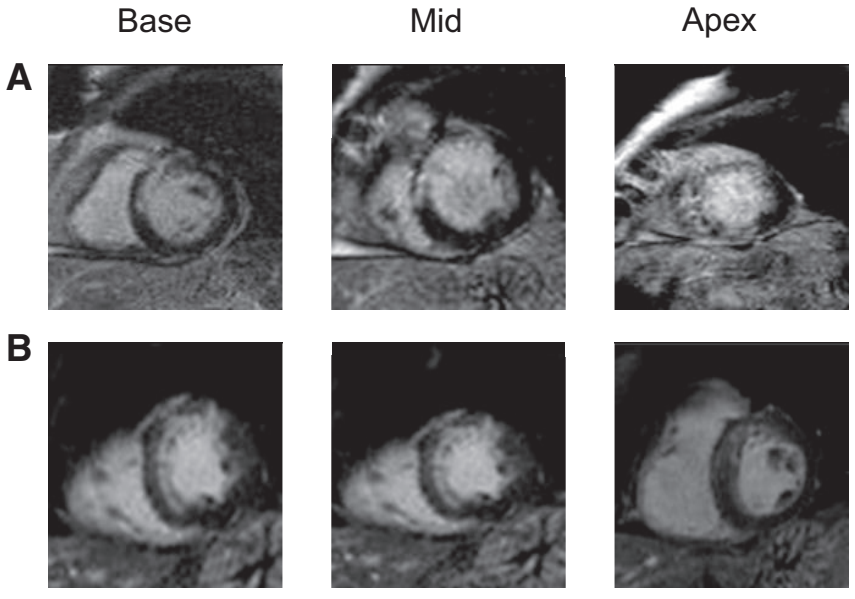

Figure 2. CE-CMR Findings in the "Early Comers" (<3 h) According to DE

When distal embolization occurred in patients treated early after symptoms onset (within 3 h), it was significantly related to transmural necrosis and microvascular damage. **(A)** Patient with 120 min of pain-to-balloon delay, final Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 complicated by distal embolization in the LAD, the corresponding CE-CMR shows transmural necrosis with evidence of severe microvascular damage. **(B)** Pain-to-balloon time 135 min, final TIMI flow grade 3 without distal embolization, CE-CMR shows not-transmural necrosis without microvascular damage. LAD = left anterior descending coronary artery; other abbreviations as in Figure 1.

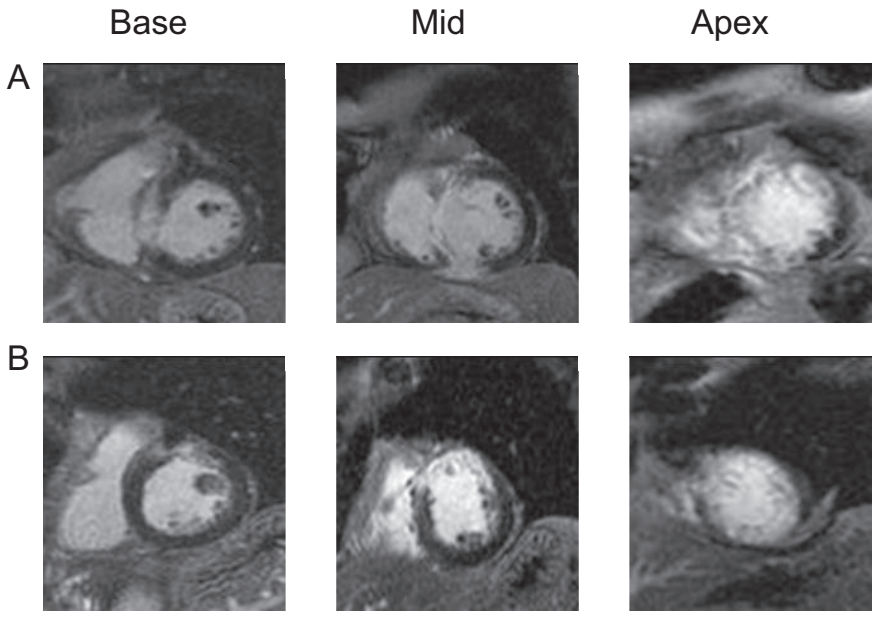

Figure 3. CE-CMR Findings in the "Late Comers" (≥3 h) According to DE

(A) Pain-to-balloon time was 240 min, final TIMI flow grade 3, with distal embolization; the corresponding CE-CMR shows transmural necrosis with severe microvascular damage. **(B)** Pain-to-balloon time was 300 min, final TIMI flow grade 3, without angiographic distal embolization; CE-CMR shows transmural necrosis with severe microvascular damage. Abbreviations as in Figures 1 and 2.

damage, respectively. These observations are consistent with previous experimental and clinical data, showing that both reperfusion and infarct size are time dependent, and that microvascular damage lagged behind myocardial necrosis (8,9). Indeed, these data compare well with those reported in our previous study, showing that the impact of DE on myocardial reperfusion and myocardial necrosis, as evaluated by myocardial blush and troponin I release, respectively, are time dependent but with a different time window (11). In this regard, it is also interesting to note that our data appear in agreement with previous observations on the time-dependent effect of adenosine administration during p-PCI, which was able to reduce the extent of myocardial necrosis and clinical adverse events when given in the first 3 h after symptoms onset, but having no effect beyond this time (26). These observations provide the proof of concept in agreement with the evidence that every pharmacological or mechanical therapy, aimed to reduce the extent of myocardial damage in the setting of myocardial reperfusion, may have no major effect in the late comers due to the already transmural extent of necrosis at time of coronary reopening in these patients. Indeed, the results of our study also offer some opportunity to speculate on the conflicting results of randomized clinical trials evaluating the role of thrombus aspiration devices during p-PCI (2). In fact, many of these trials showed a significant impact of adjunctive devices in improving myocardial reperfusion in STEMI, as assessed by surrogate markers (2). However, in most of these studies, the benefit in terms of myocardial reperfusion did not result in a significant improvement in myocardial salvage nor in clinical outcome (2). Nevertheless, because most of these trials included patients treated in a broad time window (2), even beyond the first hours after symptom onset (mostly up to 6 or even 12 h), this apparent discrepancy could be partially explained in some of them by the time-dependent detrimental effects of DE on myocardial damage. In fact, enrolling patients beyond the first hours may nullify the capability of adjunctive devices in improving myocardial reperfusion, because in late comers, this does not translate into significant myocardial salvage.

Study limitations. Some limitations of our study should be taken into account, in order to place our findings in the proper perspective. First of all, our study was designed to investigate the impact of DE occurring during p-PCI on myocardial reperfusion and necrosis by CE-CMR; thus, excluding patients presenting contraindication to CE-CMR, as well as patients with previous myocardial infarction, our experience may not reflect the real-world population of STEMI. Moreover, at the time the study was performed, abciximab was administered to a relatively small number of our patients, probably making the potential beneficial effects of this drug on DE insufficiently felt. By contrast, it is important to emphasize that abciximab, as administered in downstream fashion at the operator's discretion, was given more often in patients with DE. Therefore, the occurrence of DE per se may have drawn

abciximab administration in some cases, rendering it impossible to draw conclusions about the effect of abciximab on the distal embolization phenomenon. Finally, because our study was designed to investigate the predictors and the impact of DE occurring during p-PCI, as evaluated by coronary angiography, we detected only the macroembolization phenomenon, without drawing any conclusion concerning the impact of the microembolization phenomenon.

Conclusions

Our findings suggest that the detrimental impact of DE occurring during p-PCI on myocardial damage is largely influenced by ischemic time, increasing the extent of necrosis mainly in patients presenting within the first hours after symptom onset, having limited or no impact after this time window. These observations may partially explain the disappointing results coming from randomized clinical trials evaluating the effects of thrombus aspiration devices on myocardial reperfusion and necrosis, which enrolled patients in a broad time window. Besides, it should be emphasized that in early comers, particularly in the presence of significant thrombus burden, thrombus aspiration should be strongly considered in p-PCI, to optimize myocardial reperfusion and to maximize myocardial salvage. However, as suggested by the present study, the definite role of thrombus aspiration during p-PCI should be evaluated in further randomized trials enrolling patients in the proper time interval and by using CE-CMR to assess the real impact of thrombus aspiration on myocardial salvage.

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Key Words: distal embolization ■ myocardial damage ■ myocardial infarction ■ primary percutaneous coronary intervention.