Ability of mechanical reperfusion to salvage myocardium in patients with acute myocardial infarction presenting beyond 12 hours after onset of symptoms

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Background The ability of primary percutaneous coronary intervention (PCI) to salvage myocardium in patients with acute ST-segment elevation myocardial infarction (STEMI) presenting >12 hours after symptom onset is questionable. The aim of this study was to assess the ability of primary PCI to salvage myocardium in patients with STEMI presenting between 12 and 48 hours after the symptom onset.

Methods In the BRAVE-2 trial, 365 patients with acute STEMI presenting between 12 and 48 hours from the symptom onset were randomized to an invasive (PCI) or a conservative treatment strategy. Two-hundred sixty-one patients enrolled in 2 centers had scintigraphy before randomization and 5 to 10 days later and constitute the cohort of the present study. Salvage index (proportion of initial perfusion defect salvaged) was the primary end point of this study.

Results There were 131 patients randomly assigned to the invasive treatment and 130 patients assigned to the conservative treatment. Initial perfusion defect (median [25th-75th percentiles]) did not differ between groups (17.0% [9.0-28.5] vs 16.0% [9.0-37.5] of the left ventricle; $P = .99$). The final infarct size, measured in the follow-up scintigraphy, was significantly smaller in patients assigned to the invasive treatment than in those assigned to the conservative treatment (8.0% [2.0-16.0] vs 12.0% [3.2-25.0] of the left ventricle; $P = .004$). Salvage index was 0.44 (0.13-0.80) in the invasive group versus 0.23 (0.0-0.50) in the conservative group ($P < .001$).

Conclusion Primary PCI leads to significant myocardial salvage in patients with STEMI presenting between 12 and 48 hours after symptom onset. (Am Heart J 2006;152:1133-9.)

Information available indicates that percutaneous coronary interventions (PCIs) are effective even when performed in patients with acute myocardial infarction after 12 hours from symptom onset.[1,2] Experimental[3] and clinical[4-6] studies have demonstrated that ischemic but viable myocardium can persist for >12 hours after the coronary occlusion or onset of symptoms. Thus, all these studies indicate that in patients with ST-segment elevation acute myocardial infarction (STEMI) there is a potential for myocardium salvage even after the first 12 hours from the symptom onset given the appropriate reperfusion approach is used.

The BRAVE-2 trial[7] included patients with STEMI presenting between 12 to 48 hours after symptom onset. The trial demonstrated that patients treated by primary PCI show smaller infarct size compared with patients who received conservative therapy. The aim of this study was to assess the ability of primary PCI to salvage myocardium in patients with STEMI presenting between 12 and 48 hours after the symptom onset.

Methods

Patients and treatments

The BRAVE-2 trial[7] was a randomized, multicenter trial that included STEMI patients presenting between 12 to 48 hours from the onset of chest pain recruited between May 2003 and

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Table I. Baseline characteristics of patients with initial scintigraphy and those without initial scintigraphy

Characteristic	With initial scintigraphy (n = 261)	Without initial scintigraphy (n = 104)	*P*
Age, median (IQR), y	65.8 (54.7-73.8)	67.1 (59.2-73.4)	.50
Women	68 (26.1)	27 (26.0)	.98
Arterial hypertension	179 (68.6)	69 (66.3)	.68
Diabetes	61 (23.4)	26 (25.0)	.63
Current smoker	94 (36.0)	36 (34.6)	.64
Hypercholesterolemia	132 (51.0)	61 (59.0)	.16
Prior myocardial infarction	28 (10.7)	5 (4.8)	.08
Body mass index, median (IQR), kg/m^2	26.7 (24.5-29.4)	27.7 (25.2-30.4)	.19
Infarct localization			.89
Anterior	99 (37.9)	38 (36.5)	
Inferior	98 (37.5)	38 (36.5)	
Lateral	64 (24.5)	28 (26.9)	
Killip class			.97
I	213 (81.6)	85 (81.7)	
II	48 (18.4)	19 (18.3)	
Heart rate, median (IQR), beat/min	73 (61-84)	75 (62-90)	.24
Blood pressure, median (IQR), mm Hg			
Systolic	140 (120-150)	135 (120-150)	.32
Diastolic	80 (70-85)	80 (70-85)	.50
Pain onset to admission time interval, median (IQR), h	22.5 (14.0-39.5)	23.0 (15.0-32.5)	.93
Pain onset to randomization time interval, median (IQR), h	23.3 (15.9-40.2)	23.5 (16.4-34.3)	.70
Final infarct size (% of left ventricle)	10.0 (1.0-22.0)	10.0 (3.0-21.7)	.99

Data are presented as number of patients (percentage) unless otherwise specified. *IQR*, Interquartile range.

December 2004. The study included 365 patients aged 18 to 80 years with diagnosis of STEMI: chest pain episode lasting ≥20 minutes between 12 to 48 hours before presentation and ST-segment elevation ≥0.1 mV in ≥2 adjacent limb leads or ≥0.2 mV in ≥2 contiguous precordial leads or new pathologic Q waves on surface electrocardiogram. Detailed exclusion criteria as well as the details of assignment to either a conservative or invasive strategy were reported in the primary study.[7] Briefly, using a computer-generated randomization sequence, we randomly assigned patients to one of the treatment arms: invasive or conservative. All patients received a loading dose of clopidogrel (300-600 mg) or ticlopidine (500 mg) and 500 mg of aspirin as well as an intravenous bolus of heparin. Patients assigned to the conservative group received an intravenous infusion of unfractionated heparin or subcutaneous low-molecular-weight heparins for at least 24 hours. Patients assigned to invasive arm received abciximab (ReoPro, Lilly Pharma Produktion, Hamburg, Germany) during and after the procedure as an intravenous bolus of 0.25 mg/kg of body weight followed by a 12-hour infusion of 0.125 μg/kg per minute.

All patients in this study received clopidogrel 75 mg/d or ticlopidine 500 mg/d for at least 4 weeks and aspirin 200 to 325 mg daily, indefinitely. Other drugs used were β-blockers, angiotensin-converting enzyme inhibitors, and statins.

Scintigraphic study

Two participating centers (Deutsches Herzzentrum, Munich, Germany, and Division of Cardiology, Careggi Hospital, Florence, Italy) had logistic facilities to perform a scintigraphic examination before randomization without significant delay in study protocol and patient treatments, and had participated in the BRAVE-2 trial myocardial salvage substudy. The BRAVE-2 trial eligible patients who consented to participate in the study underwent tracer (technetium Tc 99m sestamibi) injection before randomization. Thereafter, single-photon emission computed tomography (SPECT) image acquisition was obtained immediately in patients randomized to conservative strategy and after reperfusion in patients randomized to invasive strategy. A follow-up SPECT study at rest was performed 5 to 10 days later. The methods of data acquisition and processing as well as infarct size measurement have previously been described in detail.[8] Three parameters were obtained: area at risk (perfusion defect in the initial scintigraphy), final infarct size (perfusion defect in the follow-up scintigraphy), and myocardial salvage index (area at risk minus final infarct size divided by initial perfusion defect). The first 2 parameters were expressed as percentage of the left ventricle. All studies were processed and measured in the scintigraphic core laboratory by experienced operators who were blind to group assignment and to which scan was performed before and which after.

Definitions and study end point

Classification of anterograde coronary flow in the infarct-related artery was done according to TIMI classification.[9] Collateral circulation was quantified according to Rentrop et al.[10]

After discharge, trained personnel blinded to patient's allocation performed detailed telephone interviews at 30 days after randomization with each patient. For each event reported, evidence was sought from hospital case records or family physician. Myocardial salvage index, or the proportion of initial perfusion defect salvaged by reperfusion and calculated by paired scintigraphic studies, was the primary end point of this study.

Table II. Baseline characteristics of patients randomized to invasive or conservative strategy

Characteristic	Invasive group (n = 131)	Conservative group (n = 130)	*P*
Age, median (IQR), y	65.7 (57.7-74.2)	66.0 (54.4-73.7)	.73
Women	34 (26.0)	34 (26.0)	.97
Arterial hypertension	89 (68.0)	90 (69.0)	.82
Diabetes	29 (22.0)	32 (25.0)	.63
Current smoker	45 (34.0)	49 (38.0)	.57
Hypercholesterolemia	68 (52.0)	64 (49.0)	.66
Prior myocardial infarction	14 (10.7)	14 (10.8)	.98
Prior aortocoronary bypass surgery	7 (5.3)	10 (7.7)	.44
Body mass index, median (IQR), kg/m^2	26.6 (24.8-29.1)	26.9 (24.2-29.7)	.80
Infarct localization			
Anterior	51 (39.0)	48 (37.0)	.83
Inferior	48 (37.0)	50 (38.0)	.86
Lateral	32 (24.0)	32 (25.0)	.92
Killip class			
I	107 (81.7)	106 (81.5)	.91
II	24 (18.3)	24 (18.5)	.91
Heart rate, median (IQR), beat/min	72 (61-83)	74 (61-84)	.31
Blood pressure, median (IQR), mm Hg			
Systolic	140 (120-150)	135 (120-150)	.32
Diastolic	80 (70-86)	80 (70-85)	.65
Pain onset to admission time interval, median (IQR), h	22.0 (14.1-40.3)	22.8 (13.8-38.3)	.84
Pain onset to randomization time interval, median (IQR), h	22.5 (15.7-40.9)	23.7 (15.9-39.6)	.84

Data are presented as number of patients (percentage) unless otherwise specified.

Statistical analysis

Sample size calculation was performed based on the primary end point of the study. In patients assigned to the invasive strategy, we expected to achieve at least a 0.10 absolute improvement in myocardial salvage index. Choosing a 2-sided α level of .05 and power of 90%, 122 patients in each group were needed. The overall number of patients enrolled was expanded to 260 to accommodate for possible missing paired scintigraphic studies.

All analyses were done based on the intention-to-treat principle. Because most of the continuous data were not normally distributed, they are presented as median (interquartile range). Categorical data are presented as counts or proportions (percentage). The differences between the groups were assessed using the χ^2 test or the Fisher exact test for categorical data, and the nonparametric Wilcoxon rank sum test for continuous data. A 2-tailed *P* value of less than .05 was considered to indicate statistical significance. Statistical analysis was performed using S-Plus version 4.5 statistical package (S-PLUS, Insightful, Seattle, WA) for the statistical analyses.

Results

Patients' characteristics

Of 365 patients of the BRAVE-2 trial, 261 recruited in the predefined 2 centers had initial scintigraphy and they constitute the cohort of this study. No significant differences between the patients with initial scintigraphy and those without initial scintigraphy were observed (Table I). Of 261 patients included in the study, 131 received invasive treatment and 130 received conservative treatment on a randomized basis. Baseline demographic and clinical characteristics of the patients treated invasively and conservatively are shown in Table II. All baseline characteristics appear to differ little among patients treated invasively versus those treated conservatively.

The angiographic and procedural characteristics of patients who were assigned to the invasive group are shown in Table III. After diagnostic angiography, 120 patients (91.6%) underwent coronary stenting, 6 patients (4.6%) had plain balloon angioplasty, 3 patients (2.3%) were sent to aortocoronary bypass graft surgery, and 2 patients (1.5%) received no interventional treatment because of an open infarct-related artery without significant stenosis in angiogram. At the time of angiography, 71 patients (54%) had residual blood flow (TIMI flow grade $\geq$1) in the infarct-related artery. Moreover, some degree of collateral circulation (collateral grade $\geq$1) was observed in 40 patients (31%) in the invasive group.

Scintigraphic data

Follow-up SPECT imaging was performed in 257 patients (97.5% of the entire study sample) after a median of 8.1 days (6.9-9.5 days) after randomization. Four patients in the conservative group did not undergo follow-up SPECT imaging. The reasons were refusal in 2 patients and technical reasons (failure of dedicated gamma camera) in 2 patients. In the conservative group, 11 patients (8.5%) underwent unplanned PCI before performing the follow-up SPECT imaging. This was due

Table III. Angiographic and procedural characteristics

Characteristic	Invasive group (n = 131)
Infarct-related coronary artery	
Left main coronary artery	1 (0.8)
Left anterior descending artery	49 (37.0)
Left circumflex coronary artery	37 (28.0)
Right coronary artery	41 (31.0)
Venous bypass graft	3 (2)
Initial TIMI flow grade	
0	60 (46.0)
1	10 (8.0)
2	37 (28.0)
3	24 (18.0)
Collateral grade	
0	91 (69.0)
1	24 (18.)
2	10 (8.0)
3	6 (5.0)
Infarct-related vessel size, median (IQR), mm	2.67 (2.42-3.11)
Initial diameter stenosis, median (IQR), %	100.0 (67.0-100)
Treatment strategy	
Stents	120 (91.6)
Balloon angioplasty	6 (4.6)
Aortocoronary bypass surgery	3 (2.3)
Medical therapy	2 (1.5)
Final TIMI flow grade	
0	0 (0)
1	7 (5.3)
2	11 (8.0)
3	113 (86.0)
Final diameter stenosis, median (IQR), %	8.2 (4.5-12.8)

Data are presented as number of patients (percentage) unless otherwise specified.

to recurrent angina in 7 patients, clinical congestive heart failure in 2 patients, patient's preference in 1 patient, and attending physician's decision in 1 patient.

Scintigraphic data are shown in Table IV. The amount of myocardium at risk or initial perfusion defect did not differ significantly among the patients in the invasive or conservative group. Final infarct size measured in the follow-up scintigraphy was significantly smaller in patients assigned to the invasive treatment versus those assigned to the conservative group. Myocardial salvage index, or the proportion of the initial perfusion defect salvaged by the time of follow-up scintigraphy, was almost 2 times greater among patients in the invasive group compared with patients in the conservative group (Table IV).

In the invasive group, salvage index was calculated in groups with (TIMI flow grades 2 and 3; 61 patients) and without (TIMI flow grades 0 and 1; 70 patients) residual anterograde blood flow in the infarct-related artery. Salvage index was 0.44 (0.15; 0.70) in the group with TIMI flow grades 0 and 1 versus 0.43 (0.11; 0.85) in the group with TIMI flow grades 2 and 3 (P = .88). In patients with TIMI flow grade 0 and 1, salvage index was calculated for patients with (Rentrop grades 2 and 3; 13 patients) and without (Rentrop grades 0 and 1; 57 patients) collateral circulation. Salvage index was 0.60 (0.39; 0.80) in the group with Rentrop collateral grades 2 and 3 versus 0.39 (0.12; 0.66) in the group with Rentrop collateral grades 0 and 1 (P = .07).

Table IV. Scintigraphic data

	Invasive group (n = 131)	Conservative group (n = 130)	P
Area at risk, % of LV	17.0 (9.0-28.5)	16.0 (9.0-37.5)	.99
Final infarct size, % of LV	8.0 (2.0-16.0)	12.0 (3.2-25.0)*	.004
Myocardial salvage index	0.44 (0.13-0.80)	0.23 (0.0-0.50)*	<.001

Data are presented as medians (25th-75th percentiles).
*Calculated in 126 patients who had the follow-up scintigraphic examinations.

In the invasive group, anterior infarct location (odd ratio 0.72, P = .016) emerged as the only independent predictor of myocardial salvage at stepwise multiple linear regression analysis, which included all the baseline clinical and angiographic variables, and time intervals.

Clinical outcome

Thirty-day clinical outcome is shown in Table V. One-month follow-up rate was 100%. During this period, death, reinfarction, or stroke occurred in 3 patients (2.3%) in the invasive group and 6 patients (4.6%) in the conservative group (P = .30). One patient for each group died after follow-up scintigraphy. Major bleeding complications were observed in 3 patients (2.3%) of the invasive group and 1 patient (0.8%) in the conservative group (P = .32). During 30-day period, target vessel revascularization was required in one patient (1%) in the invasive group and 42 patients (32%) in the conservative group (P < .001).

Discussion

The treatment of patients with acute STEMI arriving to hospital beyond 12 hours after symptom onset, but without symptoms of ongoing ischemia, represents a challenging and unresolved issue. At present, there is limited evidence-based rationale in favor of a reperfusion strategy in patients presenting later than 12 hours after symptom onset without persisting ischemia symptoms, and current guidelines are not in favor of an invasive treatment in these patients.[11,12] The BRAVE-2 trial was the first study to show that patients with STEMI presenting between 12 and 48 hours after symptom onset and treated with mechanical reperfusion (mostly coronary stenting) had smaller infarct size than patients treated conservatively.[7]

Table V. Clinical outcome at 30 days

Characteristic	Invasive group (n = 131)	Conservative group (n = 130)	*P*
Death, myocardial infarction, or stroke	3 (2.3)	6 (4.6)	.30
Death	1 (0.8)	1 (0.8)	.99
Myocardial infarction	2 (1.5)	4 (3.1)	.40
Stroke	0	1 (0.8)	.31
Major bleeding	3 (2.3)	1 (0.8)	.32
Minor bleeding	11 (8.4)	1 (0.8)	.003
Blood transfusion	5 (3.8)	1 (0.8)	.10
Thrombocytopenia	1 (0.8)	0	.32
Target vessel revascularization	1 (0.8)	42 (32.3)	<.001

Data are presented as number of patients (percentage).

The present study shows that an invasive strategy in patients with acute STEMI presenting 12 to 48 hours after symptom onset is associated with an almost 2 times greater myocardial salvage as compared with the currently recommended conservative strategy. Thus, data from this study demonstrate that myocardial salvage is an important mechanism by which mechanical reperfusion offers benefit in patients with STEMI presenting beyond 12 hours from symptom onset.

Persistence of viable myocardium >12 hours from coronary occlusion has been demonstrated[3-6] and related somehow to the residual blood flow to the area at risk. Incomplete occlusion or intermittent reopening,[13] and other factors such as ischemic preconditioning,[14] residual blood flow in the infarct-related artery,[6] or recruitment of collaterals[15,16] may prevent complete necrosis and preserve viable myocardium. Other studies have demonstrated the existence of stunned or hibernating myocardium at the area at risk[17,18] and that hibernating myocardium may recover contractile function and that time window to salvage viable myocardium and ameliorate adverse left ventricular remodeling may be extended to weeks if collateral circulation is present.[19] In fact, our study also showed that patients with preserved collateral circulation showed a strong trend toward a greater myocardial salvage compared with patients with absent collateral circulation. Other investigators have demonstrated an association between persistence of blood flow in the infarct-related artery and reduced apoptotic cell death at the site of myocardial infarction[20] and that reperfusion reduces overall apoptotic cell death although accelerates the apoptosis on nonsalvageable cells.[21] Furthermore, imaging studies with fluorodeoxyglucose[22] or rest-distribution thallium[23] have demonstrated that residual viable myocardium after acute myocardial infarction is associated with increased mortality if patients were treated medically compared with revascularized patients. Thus, evidence available shows that viable myocardium is still present at the site of infarction even late after symptom onset. The present study demonstrated that mechanical reperfusion salvages a greater proportion of this viable myocardium compared with conservative treatment. The results of the present study are consistent with those reported from the STOPAMI-3 Study Investigators that documented that mechanical recanalization (coronary angioplasty or stenting) provides a substantial myocardial salvage (myocardial salvage index of 0.52) in patients with AMI considered ineligible for reperfusion therapy because of presentation after 12 hours of symptom onset.[24]

The present trial was not powered to draw conclusions on clinical outcome, and the patient population was relatively small and at low risk because of exclusion criteria. However, we expect a greater invasive-strategy clinical benefit in patients at higher risk.

The enrollment of patients with prior myocardial infarction might potentially represent a limitation of our study. However, the incidence was not only equal in the 2 groups, but was also low in absolute terms. Moreover, after excluding patients with prior myocardial infarction from myocardial salvage analysis the results did not change.

The additive beneficial effects of abciximab in patients with STEMI treated with mechanical reperfusion, although difficult to quantify, deserve consideration. Abciximab enhanced myocardial salvage when used in conjunction with PCI in patients with acute STEMI presenting within 12 hours.[25,26]

An interesting and not fully understood finding of this study is that myocardial salvage was also evidenced in the patients who underwent conservative treatment, although half as much as in patients who received mechanical reperfusion. Specifically, in patients treated conservatively, the salvage index values showed that one fifth to one fourth of the area at risk was salvaged. The exact factors that enabled the myocardial salvage in these patients remain largely unknown. One factor might be the efficacy of conservative therapy to salvage ischemic myocardium. Previous studies have demonstrated that aspirin[27] and β-blockers[28] improve survival in patients with acute myocardial infarction. It has experimentally been demonstrated that beta-adrenergic blockade early after coronary occlusion results in substantial enhancement of the salvaged myocardium achieved by reperfusion.[29] Furthermore, clinical studies have demonstrated that heparin[30] and clopidogrel,[31] both part of therapy in conservatively treated patients, increase the patency rates in the infarct-related artery. Spontaneous or therapy-facilitated coronary reopening and subsequent reperfusion might result in myocardial salvage in patients treated conservatively. In patients with STEMI presenting within the first 12 hours from the symptom onset, the presence of some residual blood

flow in the infarct-related artery was observed in nearly 34% of patients.[32] In the present study, initial angiography in patients treated invasively showed that 54% of the patients had some residual blood flow in the infarct-related artery, demonstrating that the proportion of patients with preserved blood flow in the infarct-related artery is increased with the increase in time from the symptom onset. Although we have no data on the residual blood flow in patients treated conservatively, the randomized design of the study allows anticipation of similar rates of spontaneous or therapy-facilitated coronary reperfusion among patients treated conservatively as well.

Conclusion

An invasive strategy based on coronary stenting with adjunct use of abciximab leads to a substantial myocardial salvage in patients with acute STEMI presenting between 12 and 48 hours after the symptom onset.

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