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Efficacy of primary PCI: the microvessel perspective

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KEYWORDS

Microvascular perfusion;
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The outcome of patients with acute myocardial infarction (AMI) is critically dependent on adequate reperfusion at the tissue level. Primary percutaneous coronary intervention (PCI) achieves full patency of the infarct-related vessel in >90% of the patients with AMI. Despite the restoration of large-vessel flow, tissue perfusion in area at risk frequently continues to be compromised. To optimize microvascular reperfusion and clinical outcomes, additional measures are needed. Thus far, mechanical approaches to improve distal perfusion, such as the use of distal protection devices, have not been shown beneficial. Among the pharmacological approaches, high-dose adenosine infusion holds promise but has to be proved by further clinical studies. Glycoprotein IIb/IIIa receptor blockade with abciximab has a documented efficacy in improving microvascular flow, contractile recovery, and patient survival after primary PCI in AMI. In addition to the inhibition of platelet aggregation, prevention of pro-inflammatory heterotypic platelet interactions may contribute to the beneficial effect of this drug.

Illusion of TIMI grade 3 flow

The treatment strategy for acute myocardial infarction (AMI) is rapidly evolving. Early and complete reperfusion has become the main goal of treatment. Restoration of unimpeded flow through the occluded coronary artery [i.e. thrombolysis in myocardial infarction (TIMI) grade 3 flow] is the prerequisite for survival benefit and recovery of contraction in the infarct area.^{1–3} Thus, until recently, TIMI grade 3 flow was considered to be predictive of optimal clinical benefit. However, it is becoming increasingly clear that restoration of large-vessel patency alone does not suffice to achieve the best outcome.

Despite the restoration of large-vessel flow, tissue perfusion in the area at risk frequently continues to be compromised, as shown by myocardial contrast echocardiography (MCE),^{4,5} flow velocity measurements,^{6–10} and assessment of TIMI frame counts^{11,12} or myocardial blush.^{13,14} Persistent microcirculatory impairment is associated with poor recovery of contractile function^{4–10} and adverse clinical outcomes.^{4,11–14} Thus, restoration of

large-vessel patency does not mean complete perfusion recovery, and perfusion of the microvasculature is an additional prerequisite for obtaining optimal recovery.

Adjunctive therapies to improve microvascular reperfusion

The extent of microvascular perfusion deficits in the presence of TIMI grade 3 flow varies among patients^{4–14} and is a predictor of myocardial recovery^{4–10} and clinical outcomes.^{4,11–14} Therefore, the treatment for AMI should include attempts to correct microvascular perfusion as well as large-vessel perfusion.

Mechanical approaches

Since the early days of primary percutaneous coronary intervention (PCI), the fate of the occlusive thrombus material that is destructed by primary PCI has been a matter of concern. Systematic evaluation revealed angiographic evidence of distal embolization in 9–15% of the patients after primary PCI for AMI,^{15–17} but the true incidence of distal embolization may be considerably higher

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as suggested by autopsy studies¹⁸ and experience with distal protection devices.^{15–17} Distal embolization carries an increased risk of poor clinical outcomes; in a recent study, it was associated with an eight-fold increase in 5-year mortality.¹⁶

On the basis of these findings, distal embolization of plaque and thrombus material is considered to be a major cause for insufficient reperfusion, despite a fully patent infarct-related artery. Hence, it was hypothesized that distal protection devices that prevent embolization during primary PCI may improve distal perfusion.

This concept, however, could not be proved in randomized studies. The first of these trials was the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberalized Debris (EMERALD) study on distal balloon occlusion and aspiration.¹⁹ EMERALD study randomized 501 patients to distal protection or usual care. Visible debris that otherwise would have entered the distal circulation could be removed in 73% of the patients of the study group. Nevertheless, neither the primary endpoint ST-segment resolution nor any of the secondary endpoints including myocardial blush showed any significant benefit of distal protection when compared with usual care.

Concurrent results were obtained in the randomized controlled Protection Devices in PCI Treatment of Myocardial Infarction for Salvage of Endangered Myocardium (PROMISE) study.²⁰ PROMISE study evaluated the effects of the filter wire on myocardial perfusion, as determined by the maximal blood flow velocity across the recanalized infarct-related artery. The study enrolled 200 patients with myocardial infarction (69% ST-elevation) within 48 h (median 6.9 h) after onset of pain. Adenosine-induced flow velocity in the recanalized infarct artery was 34 ± 17 cm/s with the filter and 36 ± 20 cm/s without ($P = 0.46$). Infarct size measured by magnetic resonance imaging was $12 \pm 9\%$ of the LV with the filter and $10 \pm 9\%$ without ($P = 0.33$). Hence, the filter did not improve reperfusion or reduce infarct size after primary PCI. The consistent results of EMERALD and PROMISE suggest that irrespective of the technology, distal protection does not improve reperfusion after primary PCI in myocardial infarction to a clinically detectable degree.

Pharmacological approaches: adenosine

Various pharmacological approaches to improve reperfusion have been tested. These included antioxidants to mitigate reperfusion-associated oxidative stress,²¹ rheological agents to improve blood viscosity,^{22,23} and anti-inflammatory agents.^{24,25} However, none of the clinical trials yielded convincing results. More recently, peri-interventional administration of adenosine has received much attention. In animal models of infarction, adenosine attenuates the no-reflow phenomenon and limits neutrophil activation and reperfusion injury.^{26,27} A clinical study of 54 patients suggested that adenosine as adjunct to primary percutaneous transluminal coronary angioplasty (PTCA) ameliorated flow and prevented the no-reflow phenomenon.²⁸ However, the effect of adenosine was less convincing in the adequately powered

clinical trial Acute Myocardial Infarction Study of Adenosine (AMISTAD II).²⁹ In this study, 2118 patients with evolving anterior STEMI receiving thrombolysis or primary angioplasty were randomized to a 3-h infusion either of adenosine 50 or 70 $\mu\text{g}/\text{kg}$ per minute or of placebo. Clinical outcomes in patients with STEMI undergoing reperfusion therapy were not significantly improved with adenosine. Nevertheless, infarct size was reduced with the 70- $\mu\text{g}/\text{kg}$ per minute adenosine infusion, and this finding correlated with fewer adverse clinical events. The investigators of AMISTAD concluded that a larger study limited to the 70- $\mu\text{g}/\text{kg}$ per minute dose was warranted.

Pharmacological approaches: GP IIb/IIIa receptor blockade with abciximab

Previous investigations on experimental models of myocardial infarction documented the pre-eminent role of platelets in limiting blood flow during reperfusion in AMI.³⁰ By occlusive thrombus formation, distal embolization of small aggregates, and release of vasoconstrictive mediators, platelets interfere with both large-vessel patency and microvascular flow.³⁰

The effect of abciximab on microvascular reperfusion was investigated in the first 200 patients enrolled in the ISAR-2 (Intracoronary Stenting and Antithrombotic Regimen-2) trial (Figure 1).⁹ After 2 weeks, patients in the abciximab arm showed a significantly improved recovery of peak-flow velocity (as measured using the Doppler wire) in the occluded coronary artery when compared with that of patients in the conventional treatment arm [mean increase in peak-flow velocity within 14 days (95% CI): 18.1 (13.6–22.6) cm/s vs. 10.4 (5.4–15.4) cm/s; $P = 0.024$; Figure 1]. As quantitative coronary angiography did not reveal any difference in angiographic outcome between the two treatment groups, the beneficial effect of abciximab reflected improvement in microvascular function.

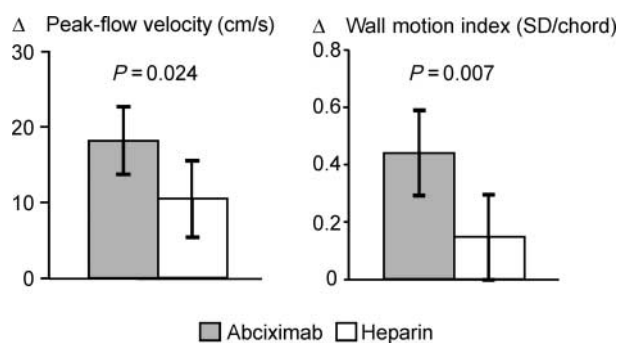


Figure 1 Increase between 14-day follow-up and initial post-interventional study in papaverine-induced peak-flow velocity in the recanalized and stented infarct-related artery (left panel) and in wall motion index within the infarct region (right panel). Columns represent the mean difference. Error bars indicate the 95% CI. Error bars not including zero indicate that the change between initial study and follow-up is statistically significant at the 0.05-level. P-values above the columns refer to the difference between the two treatment groups. (Reproduced with permission from Ref. 9)

kinase activation stimulated by PSGL-1 ligation.^{47,51} Leukocyte activation by stimulated platelets is further enhanced by CD40L-dependent signal transduction.⁵² *In vitro*, the binding of activated platelets to myeloid leukocytes induces the expression of pro-inflammatory cytokines, oxidative burst, and an increased surface expression of tissue factor and Mac-1.⁵³⁻⁵⁶ Mac-1 is known to play a key role in leukocyte-dependent reperfusion injury.⁵⁷⁻⁵⁹

Abundant platelet-leukocyte aggregates have been found in the peripheral blood of patients with AMI.⁵⁴ GP IIb/IIIa receptor blockade with abciximab in these patients reduces platelet-monocyte interaction by decreasing the mass of platelets attached to monocytes.⁴² Through this mechanism, abciximab decreases Mac-1 surface expression on circulating monocytes.⁶⁰ This effect is complemented by the direct Mac-1-blocking properties of abciximab. In addition, cell culture experiments have shown that abciximab can prevent firm adhesion of platelets to activated endothelial cells by blocking both GP IIb/IIIa and the vitronectin receptors.³⁴ The inhibitory effect of abciximab on heterotypic platelet interactions during ischaemia and reperfusion has been confirmed by experiments in isolated guinea pig hearts, in which abciximab improved the recovery of contractile function.⁶¹ These studies demonstrate the functional importance of heterotypic platelet interactions during ischaemia and reperfusion.

A recently published clinical study is consistent with a beneficial effect of the attenuation of pro-inflammatory platelet-endothelium interaction. Aymong *et al.*⁶² demonstrated that abciximab can attenuate endothelial dysfunction. Using the Doppler wire, the investigators studied acetylcholine-mediated coronary blood flow in 48 patients who underwent stenting either with abciximab or without abciximab and a control group of 31 patients who did not undergo coronary intervention or receive drug therapy. Acetylcholine-induced vasodilation was significantly impaired after stenting without abciximab (41% increase in flow vs. 70% in the control group), whereas in patients treated with abciximab during the intervention, the blood flow response to acetylcholine was normal (83% increase in flow). The beneficial effect of abciximab on endothelium-dependent vasodilator responses may be interpreted as a consequence of the inhibition of platelet-endothelium interactions.

Clinical relevance of improved reperfusion by abciximab

Experimental and mechanistic clinical studies suggest a beneficial effect of abciximab on reperfusion after primary PCI in acute myocardial studies. **Five larger randomized clinical studies addressed the clinical relevance of this effect. These studies included RAPPORT (ReoPro and Primary Percutaneous Transluminal Coronary Angioplasty Organization and Randomized Trial),⁶³ ISAR-2 trial,⁶⁴ ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up),⁶⁵ CADILLAC (Controlled**

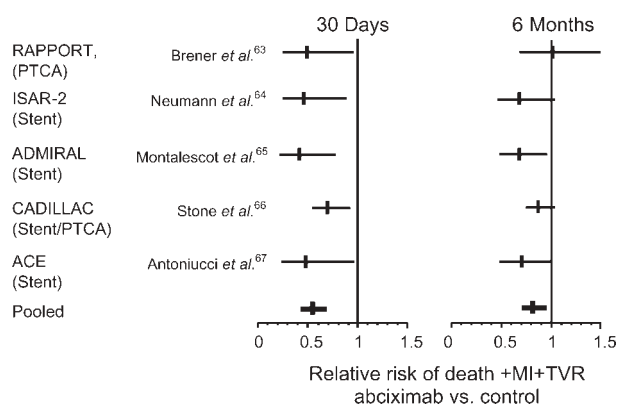


Figure 2 Meta-analysis of five major studies on abciximab during PCI for AMI. MI, recurrent myocardial infarction; TVR, target vessel revascularization.

Abciximab and Device Investigation to Lower Late Angioplasty Complications),⁶⁶ and ACE (Abciximab Carbostent Evaluation).^{67,68} With respect to combined endpoint of death, recurrent myocardial infarction, and target vessel revascularization at 30 days, each of these trials showed a significant benefit of abciximab over control (Figure 2). At 6 months, all point estimates for the triple endpoint favour abciximab, but statistical significance was obtained in ADMIRAL and ACE only. Nevertheless, pooled analysis reveals a significant benefit of abciximab (Figure 2).

Concerning the hard endpoints, death, and non-fatal re-infarction, **a meta-analysis on abciximab for primary PCI, which also included smaller studies, was published recently.⁶⁹ This meta-analysis revealed a significant reduction by abciximab in the 30-day incidence of re-infarction when compared with that of control group (1.0 vs. 1.9%; $P = 0.03$). Most importantly, when compared with the control group, abciximab was associated with a significant reduction in 30-day mortality (2.4 vs. 3.4%; $P = 0.047$) and long-term (6-12 months) mortality (4.4 vs. 6.2%; $P = 0.01$). Thus, peri-interventional administration of abciximab for primary PCI affords a sustained clinical benefit with improved survival.**

Conflict of interest: none declared.

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Editorial

How should we evaluate an open artery in STEMI patients?

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This editorial refers to 'Ageing, impaired myocardial perfusion, and mortality in patients with ST-segment elevation myocardial infarction treated by primary angioplasty'[†] by G. De Luca *et al.*, on page 662, and 'Combined prognostic utility of ST-segment recovery and myocardial blush after primary percutaneous coronary intervention in acute myocardial infarction'[‡] by P. Sorajja *et al.*, on page 667

Acute ST-elevation myocardial infarction (STEMI) is a major cause of mortality and morbidity. After plaque rupture and intracoronary thrombus formation, ischaemia causes damage to myocytes and coronary microcirculation soon after occlusion. In the 1980s, mortality reduction with thrombolytic therapy generated a new standard of care for medical treatment of patients with STEMI. However, fibrinolytic therapy is limited by inadequate epicardial patency, and subsequently it has been shown that mechanical revascularization of the infarct-related coronary artery offers an even greater clinical benefit to patients with STEMI. Thus, the goal of reperfusion treatment in patients with STEMI is to re-establish a patent infarct-related epicardial artery as soon as possible.

The Thrombolysis In Myocardial Infarction (TIMI) group has categorized epicardial coronary flow into four grades (0–3) to standardize the angiographic characterization of reperfusion. The restoration of TIMI flow grade 3 (normal epicardial flow) in patients with STEMI is associated with improved survival and enhanced recovery of left ventricular function. This observation has led to the 'Open artery theory' explanation that restoration of TIMI flow grade 3 has been used as the gold standard for reperfusion success.

However, the angiographic picture only gives an acute image of the flow in the epicardial artery and, therefore, a normal TIMI flow grade does not necessarily mean that

microvascular flow and myocardial perfusion have been normalized. When epicardial reperfusion occurs and blood flow to the infarct area is regained, reperfusion injury is caused by neutrophil infiltration, free radicals, and activation of the complement system. Especially after percutaneous coronary intervention (PCI), it is reasonable to believe that microemboli are pushed away distally, causing microvascular obstruction limiting distal tissue perfusion even after opening of the epicardial artery. Distal embolization in patients treated with primary angioplasty is visible on the coronary angiogram in ~15% of patients.¹ Embolization is related to reduced myocardial reperfusion, more extensive myocardial damage, and a poor prognosis. Thus, it is a very significant oversimplification to only evaluate the TIMI flow of the epicardial artery in STEMI patients. The clinical importance of distal tissue perfusion has been demonstrated in several studies that have used surrogate markers such as ST-segment resolution, myocardial contrast echocardiography, and magnetic resonance imaging.^{2–4} After primary PCI, TIMI-3 is restored in >90% of the patients with STEMI, whereas distal microvascular flow and myocardial perfusion are normalized to a much less degree. The lack of myocardial reperfusion in spite of restored TIMI-3 flow has been called the 'no-reflow' phenomenon. It is therefore clearly appreciated that an open epicardial artery is a necessary but insufficient condition of a distal perfusion.

The higher mortality rate observed in older patients with STEMI has been explained by a higher frequency of comorbidities, such as previous atherosclerotic disease, higher prevalence of hypertension and diabetes mellitus, and impaired left ventricular function. In the study by De Luca *et al.*,⁵ reperfusion was evaluated by the use of ST-segment resolution and myocardial blush in patients with STEMI, treated with primary PCI. They observed a clear and significant relationship between age and reperfusion even after adjustment for baseline confounding factors. Because myocardial perfusion is strongly associated with survival, this is an important observation. However, the CADILLAC study group³ did

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Beyond Epicardial Reperfusion

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The pathogenesis of an acute myocardial infarction consists of the rupture of atherosclerotic plaque, followed by a sudden thrombotic coronary occlusion. Pioneering studies performed more than 40 years ago, even before there was full recognition of the underlying pathobiology, showed that nonselective intracoronary fibrinolysis can restore perfusion to the jeopardized vascular territory.¹ Primary percutaneous coronary intervention (PCI) has now emerged as the optimal mode of reperfusion therapy, if performed by an experienced team within 90 minutes after the first medical contact. Primary PCI results in patency of the occluded artery in almost all patients and in normalization of epicardial perfusion, according to Thrombolysis in Myocardial Infarction (TIMI) grading, in more than 90% of patients.²

Despite the general success of primary PCI, approximately 15% of patients have inadequate myocardial perfusion in the absence of angiographic evidence of mechanical vessel obstruction. This “no-reflow” phenomenon may be due to microvascular damage after myocardial ischemia, to cell necrosis and regional inflammatory responses induced by reperfusion, or to both. In addition, microvascular obstruction may be caused by the embolization of atheromatous and thrombotic debris, either spontaneously or after mechanical dilation of the culprit lesion (Fig. 1). This inadequate myocardial perfusion is clinically relevant, since it is associated with larger myocardial infarcts, greater impairment of left ventricular function, and a worse clinical outcome than those in patients with adequate perfusion.³

These clinical observations have led to intensive research on the salvage of viable myocardium with the use of adjuvant pharmacologic therapy in the setting of primary PCI. The Abciximab before Direct Angioplasty and Stenting in Myocardial In-

farction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial⁴ showed a favorable clinical outcome when platelet aggregation was inhibited with the use of a glycoprotein IIb/IIIa inhibitor, if administered before primary stent implantation in the coronary artery. In daily clinical practice, an antiplatelet and anticoagulation regimen consisting of aspirin, clopidogrel, and heparin serves as standard adjuvant pharmacotherapy in patients undergoing primary PCI, whereas the administration of a glycoprotein IIb/IIIa inhibitor is recommended in patients showing poor ST-segment resolution or evidence of a no-reflow phenomenon.

Mechanical thrombectomy and embolic protection devices are logical therapeutic approaches to treat or prevent microembolization. However, randomized trials have failed to show a beneficial effect of these devices on myocardial reperfusion, infarct size, or clinical outcome.^{5,6} The Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) (NCT00168792) trial⁷ tested the use of adjuvant fibrinolytic therapy with tenecteplase before primary PCI. This trial was stopped prematurely owing to a higher incidence of cardiac complications and stroke in the tenecteplase group than in the group that did not receive tenecteplase. Consequently, the optimal aggressive pharmacologic strategy to be used as an adjunct to primary PCI remains undefined.

In this context, the study by Sezer et al.⁸ in this issue of the *Journal* is of particular interest. The investigators evaluated the effect of intracoronary streptokinase immediately after successful PCI on myocardial perfusion in patients who also received a standard medical regimen including aspirin, heparin, clopidogrel, and a glycoprotein IIb/IIIa inhibitor. The local administration of streptokinase has the advantage over systemic fibrinolytic

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The role of thrombectomy and embolic protection devices

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KEYWORDS

Primary PCI;
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Thrombectomy;
Myocardial perfusion

In recent years, it has been demonstrated that restoration of normal coronary flow in the infarct-related artery is not equivalent to the restoration of myocardial perfusion through cardiac microcirculation. Among patients with ST-segment elevation myocardial infarction (STEMI) who undergo primary percutaneous coronary intervention (PCI), distal embolization and slow-flow and no-flow phenomenon occur in ~30% of patients. In these patients, PCI results are less satisfactory, with lower thrombolysis in myocardial infarction (TIMI) or myocardial blush grade (MBG) values, lower rate of a complete resolution of ST-segment elevation, lower left ventricular ejection fraction, and poorer long-term outcome. Studies **investigating the usefulness of thrombectomy systems in STEMI showed** a similar proportion of patients with TIMI (flow grade 3) in the infarct-related artery in thrombectomy treated patients and control groups. **Some small studies** with thrombectomy systems or distal protection devices **showed encouraging results with preventing slow-flow, no-reflow, and distal embolization, as measured by improved myocardial perfusion by angiography and improved ST-segment elevation resolution after PCI.** Large, multi-centre studies did not confirm **clinical benefit.** New European Society of Cardiology PCI guidelines do not give definitive recommendations regarding the use of embolic protection devices for this group of patients. More randomized trials are needed. **However, thrombectomy may be very effective in the situation of large thrombus bulk when present after first balloon catheter inflation.** It could be also potentially effective with easy to use thrombectomy system for replacing balloon pre-dilatation before stenting, if studies could prove clinical benefit of such concept for primary PCI.

Introduction

In recent years, it has been demonstrated that restoration of normal coronary flow in the infarct-related artery is not equivalent to the restoration of myocardial perfusion through cardiac microcirculation. After conventional primary percutaneous coronary intervention (PCI) with stent implantation and GPIIb/IIIa blockade, the normal myocardial perfusion expressed on angiography

by the myocardial blush grade (MBG) 3 is seen in one-third of patients. In other two-third cases, impaired microcirculatory perfusion is observed (MBG grade 0 to 2), accompanied by only partial (30–70%) or no (<30%) resolution of ST-segment elevation in electrocardiogram.¹ Conversely, it is recognized that complete resolution of ST-segment elevation (>70%) in resting electrocardiogram is a good indicator of restoration of myocardial perfusion. Accordingly, patients with impaired microperfusion have increased early and late mortality, larger irreversible myocardial injury, and consequently higher incidence of adverse remodelling of the left ventricle leading to heart failure.²

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Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction

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Aims Although recognized as an important feature of atherosclerotic coronary disease, little is known about the frequency and prognostic importance of distal embolization during primary angioplasty for acute myocardial infarction.

Methods and Results As part of a randomized trial of thrombolysis vs primary angioplasty, 178 patients with acute myocardial infarction were treated with primary angioplasty. In these patients the occurrence of distal embolization after angioplasty was assessed. Embolization was defined as a distal filling defect with an abrupt 'cutoff' in one of the peripheral coronary artery branches of the infarct-related vessel, distal to the site of angioplasty. We analysed myocardial blush grade, ST-T segment elevation resolution, enzymatic infarct size and left ventricular ejection fraction in patients with and without distal embolization. Clinical information was collected for a mean of 5 years. Distal embolization was present in 27 patients (15.2%). Mean age and gender were not different from patients without distal embolization. Angiographic success (thrombolysis in myocardial infarction flow grade 3 and residual stenosis <50%) after primary angioplasty was less frequently observed in patients with distal embolization (70% vs 90%, $P<0.01$). Myocardial blush and ST-T segment elevation resolution after angioplasty were reduced when distal embolization was present. Patients with distal

embolization had a larger enzymatic infarct size (mean cumulative lactate dehydrogenase measured over 72 h, 1612 vs 847, $P<0.05$) and a lower left ventricle ejection fraction at discharge (42% vs 51%, $P<0.01$). Long-term mortality was higher in patients with distal embolization (44% vs 9%, $P<0.001$).

Conclusion Distal embolization in patients treated with primary angioplasty is visible on the coronary angiogram in 15.2% of patients. It is related to reduced myocardial reperfusion, more extensive myocardial damage and a poor prognosis. Additional pharmacological interventions and/or mechanical devices should be studied to prevent and/or treat distal embolization.

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Key Words: Primary coronary angioplasty, myocardial infarction, distal embolization, myocardial reperfusion, myocardial blush grade, ST-T segment elevation resolution.

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Introduction

Treatment of patients with acute myocardial infarction aims at early and sustained restoration of flow in the infarct related coronary artery. However, the objective of reperfusion therapy is not merely to restore flow in

the epicardial artery, but to reperfuse the myocardium at risk^[1]. The 'no-reflow' phenomenon, characterized by inadequate flow at tissue level despite a reopened epicardial coronary artery, was first described in animals^[2]. Many reports have now documented this phenomenon during acute myocardial infarction in man, by contrast echocardiography^[3], Doppler flow measurements^[4], nuclear techniques^[5], and magnetic resonance imaging^[6]. These myocardial areas of 'no-reflow' may be caused by microvascular disruption, endothelial dysfunction, myocardial oedema and by plugging or embolization by thrombotic or atheromatous debris.

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