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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 (thrombolyis 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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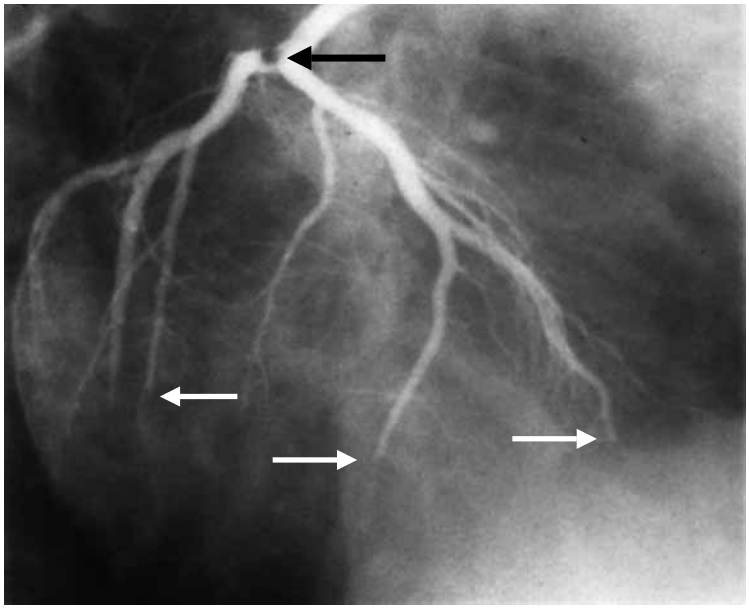

Figure 1 **Contrast injection in the left coronary artery in the right superior oblique view. There is a large filling distal defect in the proximal circumflex artery (black arrow) which was the culprit lesion, whereas several distal vessels show an abrupt cut-off (white arrows), suggesting distal embolization.**

The incidence and relative clinical importance of these various mechanisms are unknown. Distal embolization may be a particular complication of treatment with fibrinolytic agents or primary angioplasty during myocardial infarction[7].

The presence of distal embolization can sometimes be visible on the angiogram after angioplasty[8]. However, distal embolization has not been studied systematically in a large group of patients with acute myocardial infarction. An example of a patient with acute myocardial infarction and distal embolization is shown in Fig. 1. Although small embolizations cannot be seen on the coronary angiogram when distal embolization is visible, it gives us the opportunity to study its clinical sequelae, and estimate the lower limit of the incidence of distal embolization. Therefore, we re-evaluated the angiograms of 178 patients treated with primary angioplasty for acute myocardial infarction[9], to study the incidence and clinical sequelae of angiographic evidence of distal embolization.

Methods

Patients

The study protocol was reviewed and approved by the Medical Ethics Committee of our institution, and clinical results of the study have been reported previously[9]. Upon admission, all patients were intravenously treated with at least 300 mg aspirin and at least 10 000 IE heparin. None of the patients were treated with coumadine, ticlopidine, clopidogrel or a glycoprotein IIb-IIIa receptor antagonist. All patients were treated with intravenous nitroglycerin. Patients randomized to primary angioplasty form the study population of this investigation: a total of 194 patients were randomly assigned to undergo primary angioplasty. After angiography, nine patients were treated conservatively, seven were referred to urgent coronary-artery bypass grafting, whereas the remaining 178 patients underwent primary angioplasty of the infarct related vessel. The infarct-related vessel was dilated, with standard techniques.

Successful angioplasty was defined as Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow and a residual stenosis less than 50% after the angioplasty procedure. Catheterization laboratory events and angiographic data have been described[10]. Distal embolization was defined as a distal filling defect with an abrupt 'cut-off' in one of the peripheral coronary branches of the infarct related artery, distal to the angioplasty site. The presence of distal embolization and the myocardial blush grade was assessed on the angiogram made immediately following the primary coronary angioplasty by two experienced investigators who were blinded to all other data apart from coronary angiogram[11]. All angiograms allowed the assessment of angiographic evidence of distal embolization.

Patients with no-reflow were included in the group with distal embolization. In 28 patients the coronary angiograms did not allow assessment of the myocardial blush grade. Assessment of ST-T segment elevation resolution was performed, as described by Schröder and colleagues[12], before and 1 h after primary coronary angioplasty. The results of electrocardiographic signs of myocardial reperfusion have been reported

previously[13]. In 20 patients an ECG was missing or ST-T segment elevation resolution could not be interpreted because of a new bundle-branch block, the use of a ventricular pacemaker or sustained idioventricular rhythm. Infarct size was estimated by measuring serial lactate dehydrogenase (LDH) activity. Cumulative enzyme release from five to seven serial measurements up to 72 h after symptom onset (=LDH Q72) was calculated, without knowledge of the randomization outcome or clinical data. All patients who survived the initial days were scheduled for pre-discharge left ventricular ejection fraction measurement[9]. The multiple-gated equilibrium method was used after in vivo labelling of red cells with 99m-Tc-pertechnetate. A gamma camera (General Electric, Milwaukee, U.S.A.), with a low-energy, all-purpose, parallel-hole collimator was used. The global ejection fraction was calculated automatically by a computer (Star View, General Electric) with the PAGE™ program. Follow-up information was obtained in September 1998, after a mean of 5 ± 2 years.

Statistical analysis

Primary end-points were death and the combined incidence of death and non-fatal reinfarction. Secondary end-points were myocardial blush grade, ST-T segment elevation resolution, enzymatic infarct size, and left ventricular ejection fraction at discharge. Differences between group means were tested by two-tailed Student's t-test. A chi-square statistic was calculated to test differences between proportions, with calculation of relative risks and exact 95% confidence intervals. Fisher's exact test was used if there was an expected cell value of less than 5. Survival functions were calculated, using the Kaplan–Meier product limit method[14]. The Mantel–Cox (or log-rank) test was applied to evaluate the differences between survival functions. Statistical significance was defined as a *P*-value of less than 0·05. Multivariate analysis was performed by fitting Cox' proportional hazards model[15]. In the multivariate analysis, adjustments were made for differences in age, gender and infarct location.

Results

Of the 178 patients who underwent primary angioplasty of the infarct related vessel, patency of the infarct-related vessel was achieved in 170 patients (90%). Radionuclide left ventricular ejection fraction was measured before discharge in 173 patients (98%). Distal embolization was present in 27 patients (15·2%). Clinical characteristics of patients with and without distal embolization are shown in Table 1. There were no differences between the two groups in age, gender, incidence of diabetes, hypertension, smoking and ischaemic time. Distal embolization was more often observed in patients with anterior myocardial infarction location and in patients with previous myocardial infarction and there was a trend in this direction in patients with multivessel disease. Outcome measures of patients with and without distal embolization are summarized in Table 2. Long-term survival of patients with and without distal embolization is shown in Fig. 2, whereas survival without reinfarction is shown in Fig. 3. Patients with distal embolization had an increased risk of death of 44% compared to 9% in patients without distal embolization ($P<0·001$). The two groups differed considerably with regard to myocardial blush grade and ST-T segment elevation resolution. Patients with distal embolization had impaired myocardial reperfusion in comparison with patients without distal embolization, as shown in Table 3. Furthermore, patients with distal embolization had a larger enzymatic infarct size (1612 ± 1008 vs 847 ± 631, $P<0·005$) and a lower left ventricular ejection fraction at discharge (42 ± 14 vs 51 ± 9, $P<0·005$). After correction for differences in baseline characteristics, distal embolization was associated with a relative risk of death of 8·6 (95% confidence interval 3·7–20·1), after a follow-up of 5 years.

Table 1 Clinical variables and outcome measures of patients with and without distal embolization

	Distal embolization		*P*
Clinical variables	No (n=167)	Yes (n=27)	
Age (years)	59 ± 11	63 ± 12	0·1
Male (%)	136 (81)	24 (89)	0·42
Anterior MI (%)	60 (36)	17 (63)	0·01
Diabetes (%)	13 (8)	3 (11)	0·47
Hypertension (%)	30 (18)	6 (22)	0·6
Previous MI (%)	28 (17)	10 (37)	0·02
Smoking (%)	64 (38)	9 (33)	0·7
Multivessel disease (%)	105 (63)	22 (81)	0·08
Ischaemic time (min)	191 ± 215	218 ± 239	0·6

MI=myocardial infarction; ischaemic time is defined as time from symptom onset to first balloon inflation.

Table 2 Outcome measures of patients with and without distal embolization

Distal embolization			*P*
Clinical variables	No (n=167)	Yes (n=27)	
Outcome			
Patency (%)	151 (92)	19 (73)	0·009
LVEF (%)	51 ± 9	42 ± 14	0·005
LDH Q72	847 ± 631	1612 ± 1008	0·001
Mortality* (%)	15 (9)	12 (44)	<0·001
Death or recurrent MI*	24 (14)	14 (52)	<0·001

MI=myocardial infarction; LVEF=left ventricular ejection fraction; LDH Q72=enzymatic infarct size, *=during long-term follow-up (5 years).

Discussion

This is the first study reporting the incidence and clinical significance of angiographically visualized distal

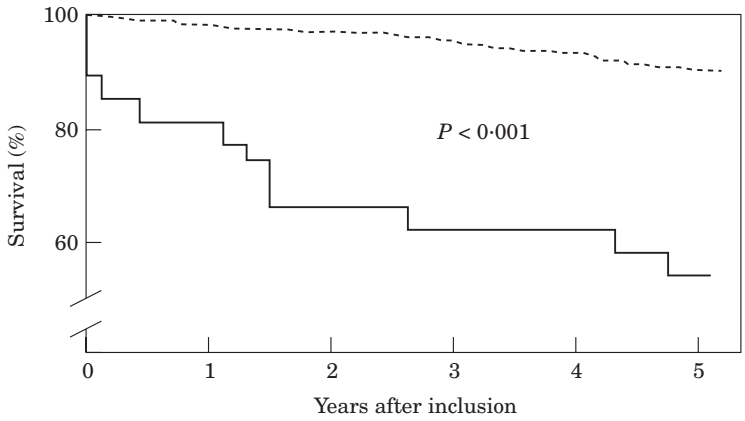

Figure 2 **Long-term survival in patients with (——) or without (– – –) distal embolization ($P<0·001$).**

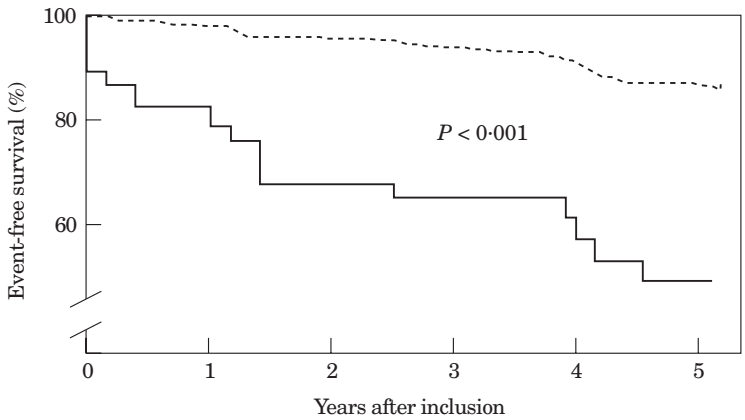

Figure 3 **Long-term survival without re-infarction in patients with (——) or without (– – –) distal embolization ($P<0·001$).**

embolization in patients with acute myocardial infarction treated with primary angioplasty. It confirms the clinical importance of impaired myocardial reperfusion in patients with acute myocardial infarction even when epicardial flow is restored. In our study, distal embolization during primary angioplasty was visualized on the coronary angiogram in 15·2% of patients. Angiographic success (TIMI flow grade 3 and residual stenosis <50%) after primary angioplasty was less frequently observed in patients with distal embolization. However, the majority of patients with distal embolization (73%) had TIMI 3 flow in the epicardial infarct related artery. Distal embolization was more often observed in patients with anterior infarct location and was related to more extensive myocardial damage and a worse prognosis. Patients with distal embolization more often had a reduced myocardial blush grade and had less ST-T segment elevation resolution after angioplasty, suggesting reduced microvascular reperfusion of the myocardium at risk. Both a reduced myocardial blush grade and absence of resolution of the ST-T segment elevation are associated with a larger myocardial infarction and worse outcome[11–13,16].

Table 3 ***Clinical evidence of myocardial reperfusion***

Distal embolization			*P*
Clinical variables	No (n=167)	Yes (n=27)	
Blush grade			
0 (%)	0 (0)	7 (28)	<0·001
1 (%)	24 (17)	10 (40)	<0·01
2 (%)	78 (55)	8 (32)	<0·05
3 (%)	39 (28)	0 (0)	<0·05
Not available*	26	2	
ST-T segment elevation			
Normalization (%)	90 (60)	2 (9)	<0·001
50% resolution (%)	45 (30)	12 (55)	<0·05
No resolution (%)	14 (9)	8 (36)	<0·001
Not available §	18	2	

*=not available for assessment of myocardial blush grade.
§=Assessment of ST-T segment elevation resolution was not possible due to new bundle-branch block, the use of a ventricular pacemaker or sustained idioventricular rhythm.

Angiographically visible distal embolization will be the lower limit of the incidence of embolization during and following reperfusion therapy, as the occurrence of

small embolizations can easily be missed on the angiogram. Saber *et al.*[17] found convincing evidence of distal embolization in patients who died after thrombolysis or primary coronary angioplasty, but so far there is no information available as to what proportion of survivors after acute myocardial infarction actually have distal embolization during myocardial infarction.

Using intracoronary contrast echocardiography, Ito *et al.* showed that at least 25% of acute myocardial infarction patients did not have tissue perfusion even when brisk epicardial flow at angiography was present[3]; distal embolization will be one of the mechanisms involved. During elective angioplasty, the incidence of distal embolization seems to be low, but has been associated with the occurrence of enzyme release after successful angioplasty and myocardial infarction[18,19]. In our study, distal embolization is more frequently observed in myocardial infarction with anterior location, may be related to the fact that the left anterior descending artery has a larger myocardial perfusion area and has more distal branches, and thus distal embolization may become visible more easily, in comparison to the other epicardial coronary vessels. However, in daily practice many cardiologists have the impression that the right coronary artery is more prone to thrombotic complications, so this finding in our study may be attributed to chance. In our study, a previous myocardial infarction and the presence of multivessel disease showed a trend towards a relation with the occurrence of distal embolization. This may indicate that patients with more extensive coronary artery disease have an increased risk of distal embolization.

The most important finding in our study is a relative risk of 8.6 for death after 5 years of follow-up, after correction for baseline characteristics in patients with distal embolization. This implies that additional preventative measures and/or treatment may be of clinical benefit in patients with distal embolization after acute myocardial infarction. Several mechanical techniques have been studied to protect against distal embolization during interventional procedures. These include thrombus aspiration[20–23] transluminal extraction atherectomy[24] and ultrasound fibrinolysis[25]. Most of these devices have been studied during elective angioplasty procedures of venous saphenous vein grafts. As an alternative to a mechanical approach, additional pharmacotherapeutic measures have been developed that may play an important role in the prevention and treatment of distal embolization. It has been suggested that the beneficial effects of the use of platelet glycoprotein IIb/IIIa receptors during angioplasty may be due to a reduction in the occurrence of distal embolization[26].

Neumann *et al.*[27] assessed intracoronary Doppler flow velocity in patients undergoing stenting for acute myocardial infarction, randomized to abciximab plus low-dose heparin or standard-dose heparin alone. They showed an improved flow velocity after administration of a glycoprotein IIb/IIIa inhibitor. Vasodilatation by nicorandil may improve myocardial tissue perfusion[28], but it has not been established whether this effect can also be observed in patients with distal embolization. Information about the effects of other vasodilators, antiinflammatory agents or metabolic support with glucose insulin–potassium infusion in patients with distal embolization are not yet available.

Some limitations of our study should be taken into consideration to place our findings in proper perspective. The presented data are from a post-hoc analysis of a randomized trial of thrombolysis vs primary angioplasty. At the time the study was performed, intracoronary stents and glycoprotein IIb/IIIa inhibitors were not yet used, and the potential beneficial effect on distal embolization could not be studied. Coronary angiography can only demonstrate the lower limit of the incidence of distal embolization, as very small embolizations may occur without becoming visible due to the limit of image resolution.

In conclusion, distal embolization during primary angioplasty occurs in at least 15·2% of patients treated with primary angioplasty for acute myocardial infarction. It is associated with reduced microvascular reperfusion of the myocardium as suggested by reduced myocardial blush grade and ST-T segment elevation resolution. It is a strong predictor of more extensive myocardial damage and a poor prognosis. Additional pharmacological interventions and /or mechanical devices should be studied to prevent or treat distal embolization.

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