Recovery of Myocardial Perfusion in Acute Myocardial Infarction After Successful Balloon Angioplasty and Stent Placement in the Infarct-Related Coronary Artery

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Objectives. This study sought to investigate changes in myocardial perfusion after direct percutaneous transluminal coronary angioplasty (PTCA) in acute myocardial infarction (MI).

Background. After initially successful recanalization of the infarct-related artery, coronary perfusion may deteriorate as a result of reocclusion, distal embolization of platelet aggregates formed at the dilated plaque or microvascular reperfusion injury. This change could offset the benefit from early intervention.

Methods. The study included 19 patients in whom the infarct-related artery was successfully recanalized by PTCA with Palmaz-Schatz stent placement within 24 h after the onset of pain. Basal and papaverine-induced coronary blood flow were assessed by Doppler flow velocity measurements and quantitative coronary angiography. In addition, basal and adenosine-induced myocardial blood flow were measured by nitrogen-13 ammonia positron emission tomography (PET).

Results. Immediately after completion of the intervention, the average coronary flow reserve (CR) in the recanalized vessel was 1.56 ± 0.51; it increased to 2.04 ± 0.65 at 1 h (p = 0.013) and to 2.66 ± 0.72 at 2 weeks after reperfusion (p = 0.008, n = 16). PET studies in 12 patients revealed that perfusion defect size and CR in the infarct region (2.19 ± 0.89 vs. 2.33 ± 0.86) did not change significantly between day 2 after recanalization and 2 weeks. However, we found significant (p < 0.03) increases in basal (by 26%) and adenosine-induced (by 40%) blood flow in the infarct region.

Conclusions. Despite the persistence of a perfusion defect after successful recanalization of the occluded artery in acute MI, CR of the infarct region improves in most patients within 1 h and further improves within 2 weeks.

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Recanalization of the occluded coronary artery in acute myocardial infarction (MI) does not afford a substantial clinical benefit if coronary blood flow continues to be compromised (1). After thrombolysis, residual stenoses are the most obvious cause for depressed coronary blood flow after recanalization of the infarct-related artery. Direct percutaneous transluminal coronary angioplasty (PTCA) as the therapeutic approach in acute MI minimizes the residual stenosis after recanalization (2,3), and the angiographic result may be further improved by adjunctive stent placement (4).

However, postischemic microvascular incompetence may still compromise myocardial blood flow after direct PTCA in acute MI (5–8). Myocardial perfusion may even deteriorate further during the early reperfusion period because of partial reocclusion of the infarct-related artery, distal embolization of platelet aggregates formed at the dilated plaque, or microvascular reperfusion injury due to cardiac inflammatory responses (9–15).

To address this question, we examined patients with acute MI undergoing successful direct PTCA with adjunctive stenting and serially measured Doppler flow velocity in the infarct-related artery to assess changes in coronary blood flow during the 1st h and at 2 weeks after reperfusion. In addition, we performed perfusion imaging by positron emission tomography (PET) 24 to 72 h and 2 weeks after direct PTCA.

Methods

Patient selection. The study included 19 patients with acute MI who were successfully treated by direct PTCA. All patients had presented within 24 h after the onset of pain. The indication for intervention in patients presenting >12 h after the onset of pain was persistent angina. We did not include 1) patients with residual anterograde flow or angiographically visible collateral blood supply of the distal infarct-related

Abbreviations and Acronyms

APV	=	averaged peak velocity
CK	=	creatine kinase
CR	=	coronary flow reserve
ECG	=	electrocardiogram, electrocardiographic
EF	=	ejection fraction
LV	=	left ventricular
MI	=	myocardial infarction
PET	=	positron emission tomography
PTCA	=	percutaneous transluminal coronary angioplasty
QCA	=	quantitative coronary angiography

coronary artery, 2) patients who were in hemodynamically unstable condition (systolic blood pressure <100 mm Hg) or who had substantial pulmonary congestion (rales more than halfway up the lung fields), or 3) patients with previous MI. Tables 1 and 2 show the baseline clinical, angiographic and hemodynamic characteristics of the study patients. Patients with interfering noncardiac diseases, such as inflammatory disorders, malignant neoplasm or infection, were not eligible for the study. The study was approved by the institutional ethics committee for human subjects. Written informed consent was obtained from all patients.

Interventional procedures and postinterventional management. Before the study, all patients with acute MI had been given intravenous bolus injections of heparin (5,000 IU), aspirin (1 g), metoprolol (5 mg, 1 to 3 times), and morphine (5 mg, 1 to 2 times), depending on individual response. Before coronary angiography an additional dose of heparin (10,000 IU) was given intraarterially. PTCA and Palmaz-Schatz stent placement (Johnson&Johnson Interventional Systems) were performed as described earlier (4,16).

After the intervention, seven patients received the vitamin K antagonist phenprocoumon (Marcumar, Hoffmann-La Roche, Grenzach-Wyhlen, Germany) and overlapping intravenous heparin. In addition, these patients were treated with aspirin (100 mg twice daily). Due to changing concepts of antithrombotic therapy after coronary stenting (17), 12 patients received combined antiplatelet therapy with ticlopidine (2 × 250 mg) plus aspirin (2 × 100 mg) instead of anticoagulant agents. Post-MI surveillance included repeated electrocardiographic (ECG) recordings and serial creatine kinase (CK) measurements. In all study patients, we administered angiotensin-converting enzyme inhibitors and beta-blocking agents.

Study protocol. Immediately after completion of stent placement and 1 h after the initial reperfusion, we performed blood flow velocity measurements in the infarct-related coronary artery and quantitative coronary angiography (QCA). Thereafter, we determined blood velocities in the least diseased coronary artery, which served as a control vessel. Finally, we measured left ventricular (LV) end-diastolic pressure through a pig-tail catheter and obtained a left ventriculogram. Perfusion imaging by PET was performed in 12 patients 24 to 72 h after reperfusion. Patients were followed up at 2 weeks after the intervention. We performed QCA and single-plane ventriculography and repeated the flow velocity measurements in the infarct-related artery and the control vessel; final PET studies were scheduled the day after these studies.

Quantitative angiography. Coronary angiography and single-plane left ventriculography in the 30° right anterior oblique view were performed with a digital angiography system and images were stored on digital tapes (Hicor, Siemens, Erlangen, Germany). Angiograms were analyzed off-line on a digital angiographic work station (AWOS, Siemens). Automatic edge detection enabled absolute measurement of coronary diameters (16,17). Global LV ejection fraction (EF) was determined by using the area-length method (18). To quantify regional LV wall motion we used the centerline method (19). Within the region of interest, the mean wall motion of one half of the most abnormally contracting contiguous chords was determined to yield the wall motion index of that region (19). This result was expressed in standard deviation (from normal) per chord (SD/chord). In addition, we determined the number of chords within the region of interest showing hypokinesia ≥−1 SD.

Coronary flow velocity measurements. Coronary flow velocities were measured with the 0.014 in. (0.036 cm) floppy Doppler wire (FloWire, Cardiometrics) and analyzed by the FloMap system (Cardiometrics), as described and validated by Doucette et al. (20).

After completion of PTCA and stent placement we exchanged the angioplasty guide wire for the Doppler wire. By

Table 1. Baseline Characteristics of 19 Study Patients

Male/female ratio	14/5
Age (yr)	59.0 ± 10
Range	37 to 83
Active smokers	7 (36.8%)
Hypercholesterolemia	13 (68.4%)
Systemic hypertension	9 (47.4%)
Diabetes mellitus	1 (0.53%)
Medication before admission	
Aspirin	5 (26.3%)
Beta-blockers	4 (21.1%)
Calcium channel antagonists	2 (10.5%)
Nitrates	3 (15.8%)
ACE inhibitors	2 (10.5%)
Diuretic agents	1 (5.2%)
CAD	
Single-vessel	12 (63.2%)
Double-vessel	3 (15.8%)
Triple-vessel	4 (21.0%)
Infarct-related coronary artery	
Left anterior descending	11 (57.9%)
Left circumflex	2 (10.5%)
Right	6 (31.6%)
Peak creatine kinase concentration (U/liter)	1,502 ± 1,091
Hours from pain to intervention (median; quartiles)	4; 3,8

Unless otherwise indicated, data presented are mean value ± SD or number (%) of patients. ACE = angiotensin-converting enzyme; CAD = coronary artery disease.

Table 2. Quantitative Angiographic and Hemodynamic Data in 19 Patients

	Completion of Intervention	1 h After Reperfusion	2 Weeks After Reperfusion	p Value
Target lesion				
Reference diameter (mm)	3.16 ± 0.44*	3.30 ± 0.42	3.26 ± 0.43	0.005
Minimal lumen diameter (mm)	2.97 ± 0.45	3.08 ± 0.54	3.01 ± 0.40	0.071
Diameter stenosis (%)	6.09 ± 5.92	6.51 ± 6.20	5.79 ± 7.51	0.77
Global LV EF (%)	n.d.	51.92 ± -13.15	57.15 ± -17.66	0.23
Severity of infarct-related wall motion abnormality (SD/chords)	n.d.	-2.61 ± 1.41	-1.50 ± 1.50	0.003
Infarct area with -1 SD hypokinesia (chords)	n.d.	37.25 ± -20.38	25.88 ± -22.32	0.012
Systolic blood pressure (mm Hg)	113.05 ± 20.87	118.0 ± 21.3	107.06 ± 16.89	0.28
Diastolic blood pressure (mm Hg)	75.42 ± 11.01	76.2 ± 11	65.2 ± 10.1*	0.001
Pulse rate (beats/min)	81.11 ± 13.47	81.84 ± 14.51	72 ± 15.11*	0.021
LV EDP (mm Hg)	n.d.	24.21 ± 8.56	16.88 ± 5.60	0.001

*Significantly different ($p < 0.05$) from the two other measurements. Data presented are mean value $\pm$ SD. EDP = end-diastolic pressure; EF = ejection fraction; LV = left ventricular; n.d. = not determined.

placing its tip just proximal to the site of recanalization, we ensured that the sampling volume corresponded to the site of occlusion, thus assessing flow to the entire area at risk. In one patient, in whom occlusion had occurred immediately distal to a patent side branch, we advanced the tip of the Doppler wire just beyond the branching point.

Doppler flow velocity spectra were analyzed on-line to determine time-averaged peak velocity (APV), and ECG as well as blood pressure were monitored continuously. To determine coronary flow reserve (CR), we gave intracoronary bolus doses of papaverine (10 mg). Before the next measurement, we waited until APV had returned to baseline. Basal and maximal APV after intracoronary papaverine were documented by video printout. Immediately after each measurement of basal or maximal APV we performed QCA for assessment of residual stenosis and of vessel diameter (D) within the sample volume, that is, 5 mm distal to tip of the Doppler wire. Doppler-derived flow (Q) was calculated as (20)

$$Q = (0.5 \times APV) \times (\pi D^2)/4.$$

Intracoronary papaverine induced a variable decrease in mean aortic pressure by $3.4 \pm 8.1\%$. We therefore calculated CR as the ratio of peak flow after papaverine (Q_p) and basal flow (Q_b) with adjustments for differences between basal mean arterial pressure (MAP_b) and mean arterial pressure at peak flow (MAP_p), thus obtaining:

$$CR = (Q_p/Q_b) \times (MAP_b/MAP_p).$$

PET studies. Perfusion imaging with N-13 ammonia was performed as described previously (21,22), using an ECAT 951R/31 (Siemens) whole body scanner. After the transmission data acquisition, 20 mCi of N-13 ammonia was injected intravenously and PET acquisition was initiated (12×10 s, 6×30 s, 3×300 s). After a further period of 30 min, adenosine (0.14 mg/kg per min) was infused intravenously for 5 min. At the 2-min mark of this infusion, a second injection of 20 mCi of N-13 ammonia was administered and PET acquisition was repeated.

Image data were analyzed by using short-axis images. Myocardial region of interest was defined on the basis of rest perfusion abnormalities. In addition, a region of interest was placed over remote myocardium to obtain reference information. The ratio of maximal flow to rest flow is the myocardial flow reserve. The extension of perfusion defects was determined by comparing regional relative tracer uptake with control data obtained in healthy volunteers using the polar map approach and a threshold of 2.5 SD.

Statistical analysis. Results are reported as mean value $\pm$ SD, unless otherwise indicated. The Kolmogorov-Smirnov test showed that the perfusion data were not normally distributed. Analyzing the perfusion data, differences between two matched samples by Wilcoxon matched pairs signed rank test and those between more than two matched samples were tested by the Friedman test followed by Wilcoxon matched pairs signed rank test. Otherwise, differences were analyzed by analysis of variance followed by the Scheffé test or by paired t test, as appropriate. Linear regressions were calculated by the least square method. A p value <0.05 in the two-tailed test was regarded as significant.

Results

Direct PTCA with stent placement was successfully completed in all patients, resulting in minimal residual stenosis (Table 2). In all patients the angiographic result was stable throughout the study period (Table 2), and there was no clinical, ECG or enzymatic evidence of infarct extension. Within 2 weeks extent of hypokinesia and wall motion index of the infarct region improved significantly and LV end-diastolic pressure decreased significantly (Table 2). Moreover, diastolic blood pressure and pulse rate at follow-up were slightly but significantly lower than in the initial study.

Two patients with an uncomplicated clinical course refused angiographic follow-up and in one diabetic patient we did not perform angiographic follow-up because of a temporary rise in serum creatinine after direct PTCA. Twelve of the 16 patients
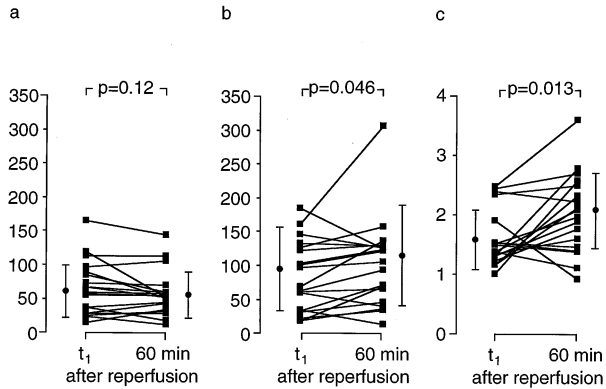
Figure 1. Plot of changes in basal coronary flow (**panel a**), papaverine-induced coronary flow (**panel b**) and CR (**panel c**) in the infarct-related artery within the 1st h of reperfusion as assessed by Doppler wire in 19 patients. Mean values (**circles**) $\pm$ SD (**vertical bars**) are also shown; p values indicate level of significance for difference between t_1 min and 1 h after reperfusion. t_1 = immediately after completion of PTCA and stenting (21 $\pm$ 8 min after initial recanalization).

who completed the angiographic and Doppler wire studies consented to have both PET studies.

Coronary blood flow. After completion of PTCA and stenting, the first Doppler flow velocity measurements were obtained at 21 $\pm$ 8 min after reperfusion. Between this time and 1 h after reperfusion, basal blood flow in the infarct-related artery did not change significantly (Fig. 1a), whereas the papaverine-induced flow increased significantly (Fig. 1b). On average, CR in the infarct-related coronary artery increased significantly during the 1st h of reperfusion (Fig. 1c).

Six patients showed an early decrease in CR. These patients tended to have a higher peak CK concentration than the others. Changes in Doppler flow CR in the infarct-related artery within the 1st h of reperfusion showed a significant inverse correlation to peak CK concentration but were not related to the time between onset of pain and intervention (Fig. 2). There were no significant (p > 0.3) differences in contractile recovery between patients with an early decrease and an early increase in CR, as assessed by the decrease either in number of chords with hypokinesia (12.9 $\pm$ 17.6 vs. 8.8 $\pm$ 13.6) or in severity of wall motion abnormality (1.33 $\pm$ 1.41 vs.

Figure 2. Plot of changes in CR between 21 min and 1 h after reperfusion, as assessed by Doppler wire measurements in 19 patients as a function of peak CK concentration (**left panel**) and as a function of time from the onset of pain to reperfusion (**right panel**). Regression lines, regression coefficients r and p values of the linear regression are also shown.
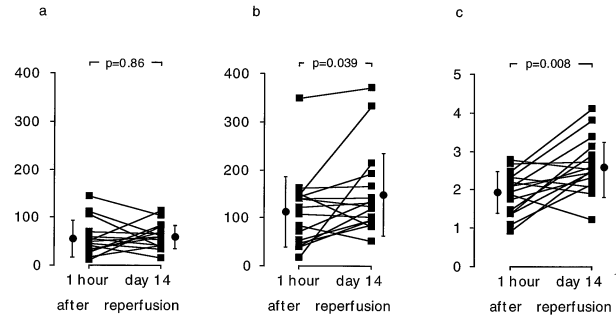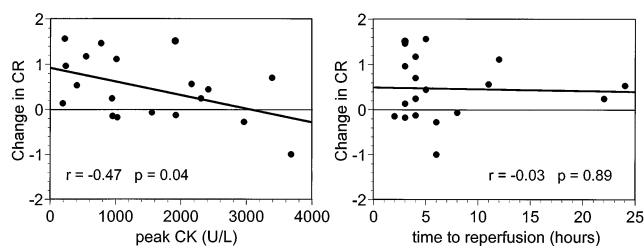

Figure 3. Plot of changes in basal coronary flow (**panel a**), papaverine-induced coronary flow (**panel b**) and CR (**panel c**) in the infarct-related artery between 1 h and 14 days after reperfusion, as assessed by Doppler wire measurements in 16 patients. Mean values (**squares**) $\pm$ SD (**vertical bars**) are also shown. p values indicate level of significance for difference between 1 h and 14 days after reperfusion.

0.73 $\pm$ 0.92). Nor did we find a significant relation between early changes in CR and subsequent change in either number of chords with hypokinesia (r = −0.10, p = 0.71) or severity of wall motion abnormality (r = −0.09, p = 0.74).

We performed angiographic follow-up 14.4 $\pm$ 2.8 days after the initial study. Between 1 h after reperfusion and follow-up, mean CR in the infarct-related artery showed significant further improvement (Fig. 3), which could be attributed to a significant increase in papaverine-induced flow (Fig. 3). At follow-up, CR correlated with the extent of regional LV dysfunction, as assessed by the number of chords with hypokinesia (r = −0.52, p = 0.038) and the wall motion index (r = 0.69, p = 0.003).

In the control vessels, average CR was 2.27 $\pm$ 0.80 at 1 h after reperfusion and did not change significantly until follow-up at day 14 (2.48 $\pm$ 0.93).

Perfusion imaging. The first PET study was performed 41 $\pm$ 21 h after recanalization of the infarct-related artery and the second 16.3 $\pm$ 3.3 days after the intervention. Sizes of the perfusion defects, both under rest conditions and after adenosine infusion, did not differ significantly (p > 0.5) between the two PET studies (rest perfusion defect [% of LV circumference]: 25 $\pm$ 23% vs. 26 $\pm$ 95%, p = 0.72; adenosine-induced perfusion defect: 24 $\pm$ 23% vs. 27 $\pm$ 21%, p = 0.52). Moreover, in both perfusion studies, sizes of the rest and adenosine-induced perfusion defects did not differ significantly (p > 0.67). Adenosine-induced perfusion defect sizes on day 2 correlated with global LV EF (r = −0.89, p = 0.001), number of chords with hypokinesia (Fig. 4) and wall motion index (r = −0.66, p = 0.020) at follow-up.

Between the two PET studies, we found a significant increase in adenosine-induced blood flow in the infarct region (Fig. 5b). Due to a concomitant increase in basal blood flow in the infarct region (Fig. 5a), we did not find significant changes in infarct region CR between the two PET studies (Fig. 5c).

CR values, determined by PET and Doppler wire at follow-up day 2, did not differ significantly (p = 0.26). In the PET studies, average CR of the control regions did not change
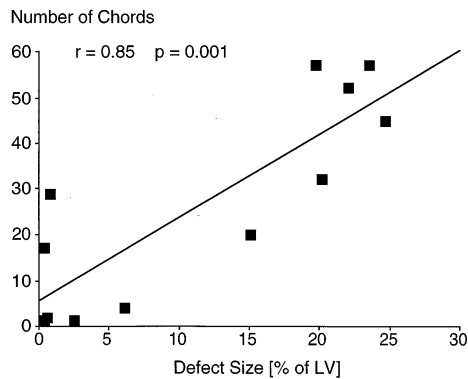
Figure 4. Plot of number of chords with hypokinesia (≥−1 SD) at follow-up as a function of adenosine-induced perfusion defect sizes at day 2 as assessed by PET in 11 patients. Regression line, regression coefficient r and p value of the linear regression are also shown.

significantly during the study period (2.78 ± 1.63 vs. 2.53 ± 0.95, p = 0.89).

Discussion

We investigated changes in CR after successful recanalization of the infarct-related coronary artery by direct PTCA with Palmaz-Schatz stent implantation. Our major finding was early and sustained recovery of CR as the prevailing feature after successful catheter intervention. Within 1 h of reperfusion, average CR in the recanalized infarct-related artery increased from 1.5 to just >2, and during the subsequent 14 days improved further to 2.6. This change in CR is driven by an increase in papaverine-induced blood flow and not by a decrease in basal flow. Our findings thus indicate substantial recovery of flow capacity within the reperfused area or extension of the area with relevant reperfusion, or both. At follow-up, both perfusion imaging and Doppler measurements showed CR values that were not significantly different from those in the control region. Most of the recovery beyond 1 h

Figure 5. Plot of changes in basal myocardial blood flow (**panel a**), adenosine-induced myocardial blood flow (**panel b**) and CR (**panel c**) in the infarct region between day (d) 2 and day 16 after reperfusion, as assessed by PET studies in 12 patients. Mean value (**circles**) ± SD (**vertical bars**) are also shown. p values indicate level of significance for difference between day 2 and day 16 after reperfusion.
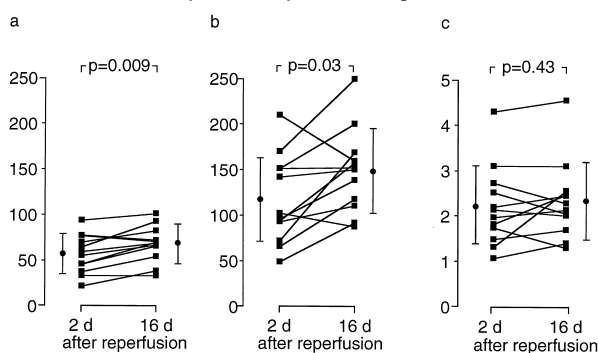
appears to occur during the 1st 2 days. This view is suggested by the results of perfusion imaging, demonstrating no substantial changes in CR of the infarct region or in perfusion defect sizes between day 2 and follow-up.

Despite this remarkable recovery of CR, perfusion imaging demonstrated depressed absolute flows within the infarct region. Previous studies in canine MI (23,24) showed preserved flow in the subepicardial layers and depressed flow in the subendocardial layers during reperfusion. Similarly, our results may be explained by the coincidence of regions with no or low reflow and regions with rapid recovery of flow reserve and eventual near normal flow. Accordingly, extension of the layer with near normal flow may account for the increases in basal and adenosine-induced myocardial blood flow between day 2 and follow-up (25,26). The spatial resolution of the PET technique may not suffice to verify such inhomogeneities of microvascular flow within the infarct region.

Perfusion patterns could be related to variables of regional LV function. CR in the infarct-related artery at follow-up correlated with concomitantly determined measures of infarct size and severity of wall motion abnormality. Moreover, perfusion defect sizes at day 2 correlated with ventriculographic measures of infarct size at follow-up. These findings support the concept that recovery of vascular function within the area at risk is spatially linked to viable myocardium (25,26).

In six patients, the prevailing pattern of early changes in CR deviated. In these patients we found a decrease in CR within 1 h of reperfusion, which may be interpreted as evidence of reperfusion injury. Patients with an early decrease in CR tended to have larger infarcts than the other patients, and early recovery of CR was inversely correlated to peak CK concentration. Early deterioration in CR did not have a detectable impact on functional recovery of the infarct region. These findings may be explained by assuming that early deterioration in CR is due to collapse of perfusion capacity within an area of irreversibly damaged myocardium (25,26).

Comparison with previous studies. Since the initial description of ischemic microvascular injury, commonly referred to as the "no reflow phenomenon" (27), several studies in the dog model (12–14) have provided evidence of microvascular reperfusion injury. These studies demonstrated progressive deterioration of myocardial blood flow (12,13) and flow reserve (14), assessed by tracer microspheres (12–14) or PET (13), as well as progressive perfusion defects demonstrated by fluorescent dyes (12) or perfusion imaging (14). These changes occurred as early as 1 h after perfusion (12,13). Contrary to these findings in the dog, myocardial perfusion did not deteriorate within the 1st h of reperfusion in most of our patients. Several factors may account for this difference. In animals, substantial extension of tissue injury during reperfusion has not been observed after periods of ischemia >120 to 180 min (5). However, reflecting the usual clinical setting, the duration of ischemia in our patients was >180 min. It thus may not fall into the time window during which reperfusion injury can occur. Moreover, to an unknown extent, the adjunctive pharmacologic interventions, such as administration of aspirin,

heparin and morphine, may have helped to prevent reperfusion injury.

To our knowledge, changes in coronary blood flow within 1 h of reperfusion have not been previously investigated in patients with MI. Several clinical studies (7,8,28,29) investigated subacute changes in myocardial blood flow after reperfusion in MI, but these studies included patients who had undergone thrombolysis without definition of degree of residual stenosis. After thrombolysis, early deterioration of blood flow appears to be considerably more frequent than with minimal residual stenosis and a stable angiographic result, as in our study (8). Moreover, one previous study (28) reported substantially lower CR in the infarct region than that of our patients, a finding that must be attributed to the high degree of residual stenosis after thrombolysis (28,30). Nevertheless, two previous studies (7,31) also found improvement of myocardial blood flow in the infarct region within 2 or 4 weeks after reperfusion. Similar to our study, the extent of early perfusion defects, assessed by myocardial contrast echocardiography, was predictive of subsequent functional recovery (31).

Limitations of the study. Apart from microvascular function, myocardial blood flow is affected by heart rate and loading conditions. Although we have no reason to assume that hemodynamic conditions changed significantly within the 1st h of reperfusion, there were significant decreases in LV end-diastolic pressure, pulse rate and diastolic blood pressure between the initial study and follow-up. To an unknown extent, these changes may have affected changes in coronary flow during the study period.

Conclusions and clinical implications. To our knowledge this study provides first evidence of early and sustained improvement of CR in the infarct region after meticulous optimization of vessel patency. It shows that in areas of the infarct region with salvaged microcirculation further recovery of coronary perfusion can be expected during the early period after MI. This perfusion pattern is consistent with postischemic vascular stunning that gradually resolves (31,32). The study does not refute the concept of microvascular reperfusion injury, but it does not yield any evidence of its relevance in the clinical setting. In the minority of our patients with an early decrease in pharmacologic CR, functional recovery of viable myocardium was not impaired by comparison with that of the other patients. Consistent with earlier histologic studies (25,26), it is therefore tempting to speculate that relevant deterioration of vascular function during reperfusion does not occur within areas of viable myocardium. The findings of our study suggest that the clinical impact of microvascular reperfusion injury and no reflow may be less than what might have been expected on the basis of previous animal experiments (12–14).

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