Importance of flow/metabolism studies in predicting late recovery of function following reperfusion in patients with acute myocardial infarction

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Aims Positron emission tomographic imaging is known to be a reliable indicator of viable myocardium in chronic heart disease. Its value in acute myocardial infarction has not been studied extensively.

Methods and results Sixty-two patients receiving thrombolytic therapy were studied. Myocardial tissue flow and metabolism were measured at 5 days and 3 months. Recovery of left ventricular function was investigated with echocardiography or radionuclide ventriculography. In eight patients, normal flow was found in the infarct area at 5 days with no significant changes in flow, metabolism or function over the next 3 months. In 54 patients, impaired regional myocardial blood flow in the infarct zone was observed at 5 days. In 39 patients, there was a matching positron emission tomographic pattern, while in 15 the pattern was mismatched. None of the patients with a TIMI flow grade <3 revealed recovery of left ventricular function. In seven out of 11 patients with TIMI 3 flow and a mismatching pattern, additional angioplasty was performed with functional improvement in six.

Conclusions Recovery of ventricular function is exclusively found in patients with a TIMI flow grade 3. Patients with a positron emission tomographic mismatching pattern reveal functional recovery only after subsequent angioplasty (Eur Heart J 1997; 18: 954–962)

Key Words: Myocardial infarction, thrombolysis, positron emission tomography, viability, stunning, functional recovery.

Introduction

Positron emission tomography is a valid method for detecting viable myocardium in patients with chronic coronary artery disease[1-5]. In the setting of acute myocardial infarction, there is controversy about the usefulness of the match/mismatch model for predicting myocardial viability[6,7]. Studies in patients with a recent myocardial infarction who did not receive thrombolytic therapy and with evidence of tissue viability in the infarct territory, have demonstrated a great variability in recovery of left ventricular function[8,9]. More recently, studies were published dealing with regional blood flow and metabolism in patients who received thrombolytic therapy for an acute myocardial infarction[10,11]. In these studies, however, long-term follow-up data are lacking.

In a recent study performed by our group it was shown that the presence of adequate myocardial tissue perfusion early after successful thrombolysis was essential for recovery of function at late follow-up[12]. These findings were obtained at early angiography in a small and highly selected group of patients with TIMI flow grade 3 reperfusion. In order to further evaluate the usefulness of flow/metabolism studies in the prediction of functional outcome after thrombolysis a larger, unselected group of consecutive patients with acute myocardial infarction was studied.

Materials and methods

Patient population

Patients with an acute myocardial infarction of less than 6 h duration were prospectively studied. All patients had chest pain lasting at least 20 min and ST segment elevation of ≥1 mm in two or more contiguous leads. Patients with cardiogenic shock were excluded. One of the following intravenous thrombolytic therapies was given: recombinant staphylokinase with intravenous
Coronary angiography and ventriculography

Coronary angiography and was performed between 24 h and 5 days after the initiation of thrombolytic therapy. Patency of the infarct-related artery was determined according to TIMI criteria of reperfusion[13].

Assessment of left ventricular function

Patients underwent either two-dimensional echocardiography or radionuclide ventriculography at 5 days and 3 months for follow-up evaluation of left ventricular function. Echo data were displayed using polar maps. The polar maps represent the 16 segments seen using parasternal long axis, parasternal short axis, apical four-chamber and apical two-chamber views. Wall motion in each segment was scored visually by an experienced observer who was unaware of the clinical and positron emission tomographic findings. Wall motion scores were 1 for normal, 2 for hypokinetic and 3 for akinetic or dyskinetic segments. For each patient, the infarct area was indicated manually on the polar maps. The mean wall motion score was calculated at 5 days and 3 months. Function was considered to have improved at 3 months if the mean regional wall motion score of the infarct area had decreased by 1 point. Radionuclide angiography was performed after injection of red blood cells labelled with 20 mCi of 99mTc. Ten minutes after injection, an equilibrium gated nuclear angiogram was acquired over 10 min with the patient positioned under the gamma camera in a left anterior oblique position at 45° for visualization of the septum, apex and posterolateral wall. A low-energy, all-purpose collimator was used. The study was repeated in an anterior position at 70° for visualization of the lateral wall, apex and left part of the inferior wall, and in an anterior position for visualization of the lateral wall, apex and right part of the inferior wall. End-diastolic and end-systolic regions of interest were determined automatically by convolving the end-diastolic left ventricular region as a centre. This is done because no anatomical landmarks are visible in scintigraphic studies. The centre remains the same during the whole cardiac cycle. The regions use overlapping image information (a region also uses half of the two adjacent regions). Regional ejection fraction is calculated using the regional analogue of (EDV - ESV)/EDV[16,17]. Function was considered to have improved at 5 months if the mean regional ejection fraction increased by more than 5%.

Positron emission tomography

Positron emission tomography was performed in all patients at 5 days and 3 months. All patients were studied using the hyperinsulinaemic euglycaemic clamp technique[18]. After positioning the patient in the whole-body tomograph (CTI-Siemens 931/8, Knoxville, Tennessee, U.S.A.), a transmission scan of 15 min was performed. 20 mCi of 13NH3 in 5 ml saline was infused at a rate of 10 ml. min⁻¹. Acquisition was started at the injection time. Serial images of myocardial tracer uptake were acquired for 10 min (12 frames of 10 s, four frames of 30 s and three frames of 120 s). Fifty minutes later, allowing physical decay of 11N activity, 10 mCi of 18FDG was injected as an intravenous bolus, and serial images were recorded for 70 min (eight frames of 15 s, four frames of 30 s, two frames of 60 s, two frames of 120 s and six frames of 600 s).

A three-dimensional delineation of the left ventricular wall was used to correct the images for incomplete recovery and spill-over due to the limited spatial resolution, and to construct a polar map for every frame of the dynamic study[19,20]. The polar maps were divided in 33 regions: one apical region and four rings of eight regions each.

Flow and metabolic indices were computed for the polar maps of the last frame. A flow index was calculated as the ratio of 12NH3 uptake in the infarct region and the 13NH3 uptake in the region with the highest uptake (reference region). The reference region for 18FDG was identical to that used as the flow reference. A metabolic index was defined as the ratio of glucose utilization in the infarct region and that in the
Statistical analysis

Values are expressed as mean ± 1 SD. A paired t-test was used for intra-group comparisons. For comparisons between multiple groups, analysis of variance (ANOVA) was used, followed by post hoc testing (Tukey HSD). Differences were considered significant at P<0.05.

Results

Clinical characteristics

A total of 62 patients was studied. There were 54 male and eight female subjects. Baseline characteristics are summarized in Table 1. In all patients, the diagnosis of an acute myocardial infarction was confirmed by enzymes and ECG changes. All patients received thrombolytic therapy. During the study period (3 months), three patients had a reinfarction, confirmed by enzymes and ECG changes. None of the patients died or suffered a stroke. In 24 patients, additional revascularization (PTCA) was performed after the first positron emission tomography investigation at 5 days. The decision with regard to angioplasty was not affected by the positron emission tomography studies at 5 days.

Regional myocardial blood flow and glucose metabolism

All 62 patients had undergone positron emission tomography studies and coronary angiography by 5 days. Follow-up measurements of flow and metabolism at 3 months were obtained from 59 patients. Three patients refused a follow-up positron emission tomography investigation. Normalized regional \(^{13}\)NH\(_3\) uptake, glucose uptake, positron emission tomography pattern (normal flow, match or mismatch) and angiographic findings are summarized in Table 2. Changes of normalized \(^{13}\)NH\(_3\) uptake in relation to positron emission tomography pattern and TIMI grade is summarized in Fig. 1. Mean normalized \(^{13}\)NH\(_3\) and FDG uptake at 5 days and 3 months are also plotted on Fig. 2.

Eight patients (13% of all patients) revealed normal flow values at 5 days (89 ± 12 ml.min\(^{-1}\).100 g\(^{-1}\)). Absolute glucose values in these patients averaged 45 ± 12 µmol.min\(^{-1}\).100 g\(^{-1}\). TIMI flow grade 3 was observed in seven patients and grade 2 in one patient (patient 1 in Table 2). Absolute flow and metabolism values at 3 months were 86 ± 7 ml.min\(^{-1}\).100 g\(^{-1}\), 100 g\(^{-1}\) and 51 ± 15 µmol.min\(^{-1}\).100 g\(^{-1}\), respectively. Neither normalized \(^{13}\)NH\(_3\) nor glucose uptake values had changed significantly at 3 months (Fig. 1).

Fifty-four patients (87% of all patients) showed reduced myocardial tissue flow at 5 days. Thirty-nine (63% of all patients) of them revealed a concordant decrease of flow and metabolism in the infarct area (positron emission tomography match). In 21 of these, TIMI 3 flow was present and flow and metabolism values at 5 days averaged 57 ± 13 ml.min\(^{-1}\).100 g\(^{-1}\) and 32 ± 10 µmol.min\(^{-1}\).100 g\(^{-1}\) respectively. At 3 months, absolute flow was 67 ± 19 ml.min\(^{-1}\).100 g\(^{-1}\), while absolute metabolism averaged 40 ± 18 µmol.min\(^{-1}\).100 g\(^{-1}\). Both normalized \(^{13}\)NH\(_3\) (P<0.001) and glucose uptake values (P<0.05) had improved significantly at 3 months (Fig. 1). In the 17 patients with a positron emission tomography match pattern and a TIMI flow grade <3, regional myocardial perfusion was 53 ± 12 ml.min\(^{-1}\).100 g\(^{-1}\) at 5 days and 60 ± 17 ml.min\(^{-1}\).100 g\(^{-1}\) at 3 months, while glucose metabolism averaged 30 ± 9 µmol.min\(^{-1}\).100 g\(^{-1}\) at 5 days and 36 ± 16 µmol.min\(^{-1}\).100 g\(^{-1}\) at 3 months. \(^{13}\)NH\(_3\) uptake in this group improved significantly (P<0.05) while FDG uptake also tended to be higher at 3 months (P=ns) (Fig. 1).

In 15 patients (24%) impaired myocardial blood flow was associated with preservation of metabolism at 5 days (positron emission tomography mismatch). TIMI flow grade 3 was present in 11 of these 15 patients. Absolute flow values were 59 ± 13 ml.min\(^{-1}\).100 g\(^{-1}\) at 5 days and 67 ± 16 ml.min\(^{-1}\).100 g\(^{-1}\) at 3 months. A significant improvement in \(^{13}\)NH\(_3\) uptake was noted.

Table 1 Clinical characteristics

| Age (years) | 64 ± 11 |
| Diabetes (%) | 10 |
| Smoking (%) | 49 |
| Hypertension (%) | 37 |
| Hypercholesterolaemia (%) | 29 |
| Family history of CAD (%) | 20 |
| Previous MI (%) | 5 |
| Systolic blood pressure (mmHg) | 128 ± 23 |
| Diastolic blood pressure (mmHg) | 78 ± 14 |
| Heart rate (beats.min\(^{-1}\)) | 69 ± 14 |
| Previous CABG (%) | 4 |
| Time from onset to treatment (min) | 184 ± 97 |

CAD=coronary artery disease; MI=myocardial infarction; CABG=coronary artery bypass grafting.
Changes in flow and metabolism values were observed at 43 ± 11 umol. min⁻¹. 100 g⁻¹ at 3 months. FDG uptake values did not change significantly (\( P=\text{ns} \)). In the four patients with a TIMI flow <3, no significant changes in flow and metabolism values were observed at 3 months.

<table>
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<tr>
<th>Patient</th>
<th>BF 5 days</th>
<th>BF 3 months</th>
<th>Gu 5 days</th>
<th>Gu 3 months</th>
<th>PET 3 months</th>
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Impaired myocardial blood flow

PET match

Table 2 continued on next page

Comparison of flow and metabolism values between the three groups at 3 months revealed a significant difference of flow and metabolism between the normal flow group and both match and mismatch groups (ANOVA, Tukey HSD, \( P<0.01 \)) (Fig. 2). Although the difference was not significant, flow and metabolism values at 3 months in the mismatch group tended to be

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Table 2 continued from previous page

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| BF = normalized regional myocardial blood flow in the infarct territory; Gu = normalized regional myocardial glucose uptake in the infarct territory; PET = positron emission tomography pattern; nf = normal flow; mi = mismatch; m = match; IRA = infarct related artery; RCA = right coronary artery; LCX = left circumflex coronary artery; LAD = anterior descending coronary artery; TIMI = TIMI grade of reperfusion; PTCA = percutaneous transluminal coronary angioplasty; RS = residual stenosis after PTCA; ns = not significant; FI = functional improvement; y = yes, n = no.

Figure 1  Evolution of regional myocardial blood flow in relation to the positron emission tomographic pattern and TIMI flow grade. The three subplots represent evolution of regional myocardial blood flow in regions with normal flow, positron emission tomography match and mismatch at 5 days, respectively.
Figure 2  Intergroup comparison of regional myocardial blood flow and metabolism at 5 days and 3 months. The two upper plots represent comparison of normalized $^{15}$NH$_3$ uptake at 5 days and 3 months between the normal flow group, the positron emission tomography match and the positron emission tomography mismatch groups. A significant difference in $^{15}$NH$_3$ uptake was found between the normal flow group and both match and mismatch groups. The two lower plots represent a similar comparison for normalized FDG uptake. No significant difference in FDG uptake was found between the three groups at 3 months. 1 = normal flow at 5 days; 2 = positron emission tomography match pattern at 5 days; 3 = positron emission tomography mismatch pattern at 5 days.

higher than those of the match group. Since patients were divided in groups according to flow and metabolism data at 5 days, no statistical analysis was performed on these data.

At 3 months, 12 patients revealed normal flow values. Forty-two patients had a match pattern 3 months after the acute event. Eight patients showed a mismatch pattern, none of whom suffered a reinfarction. Four had a mismatch pattern at 5 days while the other four had a match pattern 5 days after the infarction (patients 10, 12, 39, 46, 51, 54, 55, 60 in Table 2). Flow values did not change significantly in these patients.

Left ventricular function

Follow-up of left ventricular function was obtained from 53 patients. Nine patients refused a control study. Thirty-three patients underwent two-dimensional echocardiography, whereas 20 underwent radionuclide ventriculography both at 5 days and 3 months after the acute event. Changes in left ventricular function in correlation with TIMI flow grade after thrombolysis and performance of additional revascularization are summarized in Table 2 and Fig. 3. In two patients with normal flow values at 5 days, a further improvement in systolic function was observed at 3 months as compared to 5 days, without additional revascularization.

No significant functional improvement was found in the positron emission tomography match group as a whole. However, six patients with a positron emission tomography match pattern and TIMI flow grade 3 revealed functional improvement at 3 months, regardless of further therapy. Only one of the patients without TIMI 3 showed functional recovery.

In six out of seven patients with a positron emission tomography mismatch pattern and a TIMI flow grade 3 who received additional revascularization, improved regional wall motion was found after 3 months. On the other hand, of the four patients with a mismatch pattern and TIMI flow grade 3 who did not receive additional revascularization no functional recovery was noted. There was a persistent mismatch pattern in two and one suffered a reinfarction. None of
the four patients with a mismatch pattern and a TIMI flow grade <3 showed improved contractility after 3 months. Two of the four suffered a documented re-infarction, the other two revealed a persistent mismatch pattern at 3 months.

**Major end points**

Major end points of the study are given below.

1. Few mismatches were observed in this population of thrombolysed patients (15 out of 62 patients).
2. Statistically significant improvement of flow values was observed in both match and mismatch groups.
3. Functional follow-up was performed in 53 patients. Fifteen revealed improvement of left ventricular function (28%). Of these, 14 had a TIMI flow grade 3 by 5 days after the acute event.
4. Seven of the 11 patients with a mismatch pattern and a TIMI flow grade 3 received additional revascularization, with functional improvement in six.

**Discussion**

The results of this study indicate that only a minority of patients given thrombolytic therapy have normal flow values in the infarct territory at 5 days, confirming our previous observations.

Furthermore, in patients who reveal decreased perfusion in the infarct area, few mismatch patterns (24%) were observed 5 days after the acute event as compared to patients suffering chronic coronary artery disease. Whether this is due to a low incidence of chronic ischaemia after thrombolytic therapy or to altered metabolic pathways of the affected myocardium early after reperfusion is unknown. In a study with porcine hearts, rendered regionally ischaemic for 45 min and reperfused, no major utilization of carbohydrates for oxidative phosphorylation was seen during early reperfusion. In a canine study it was reported that fatty acid was the most important substrate for oxidative metabolism in the presence of reperfusion. Another study revealed enhanced activity of the non-oxidative glycolytic pathway in canine myocardium after a more prolonged occlusion (3 h) followed by reperfusion.

The duration of the occlusion might be important for the occurrence of an altered metabolic pattern and for the duration of the use of these alternative metabolic pathways by the myocytes after reperfusion. Since all patients received thrombolysis within 6 h after the onset of symptoms, the duration of the occlusion of the infarct-related artery might not have been sufficiently long in most patients to result in alterations of glucose metabolism that could still be measured 5 days after the infarction. FDG uptake is known to be a reliable indicator of viability and a good predictor of functional recovery in chronic situations. It was also shown that in chronic myocardial ischaemia there was a good correlation between positron emission tomographic measurements of flow and metabolism and the amount of fibrosis in biopsies from the same myocardial area. Positron emission tomographic mismatches were found in areas containing viable cells whereas in positron emission tomography match areas, significantly more scar tissue was seen. At first sight, functional outcomes in the first few days following reperfusion seem to be more variable. Regardless of the match/mismatch pattern at 5 days, only one of the patients with a TIMI flow grade <3 at early angiography in this study revealed improved contractility, confirming the importance of a TIMI flow grade 3 reperfusion for functional recovery. In contrast, in six out of seven mismatch patients with a TIMI flow grade 3 who received additional revascularization, functional improvement was noted. None of the patients with a mismatch pattern and a TIMI flow grade 3 who did not undergo additional revascularization showed recovery of function. These data strongly suggest that the presence of a mismatch pattern early after an acute myocardial infarction indicates viable but endangered myocardium and that additional revascularization is needed in these patients, even in the presence of a TIMI flow grade 3. Two out of nine patients with normal flow values at 5 days and six out of 21 match patients, all with a TIMI flow grade 3, revealed at least partial recovery. In five of them, no additional revascularization was
performed, suggesting restoration of tissue flow with delayed functional recovery or 'stunning'. This is in agreement with previous findings in patients with a reperfused anterior infarction in whom major functional improvement in the reperfused area was achieved within 14 days of reperfusion[27]. Another study reported marked reduction in 18FDG activity in patients with acute myocardial infarction and preservation of oxidative metabolism, and their data suggested that this pattern might be more common in patients receiving thrombolytic therapy[28].

Three months after the acute event, the mismatch pattern was still evident in four patients and a new mismatch pattern had developed in another four. None of these eight patients showed signs of recovery of contractile function. An important residual stenosis of the infarct-related artery was found after therapy in all eight patients. These data suggest that in some infarct patients, treated with thrombolysis, a mismatch pattern can be found at late follow-up, due to the presence of a persistent and critical stenosis or due to progression of a non-critical lesion, resulting in hibernating myocardium with impaired function in the presence of viable myocardium. In these patients, additional revascularization might lead to improvement of left ventricular function and to the disappearance of the mismatch pattern.

Flow values and glucose utilization values tended to improve in both match and mismatch groups. This might be due to an underestimation of flow by 13NH3, shortly after the infarction. It is known that glutamine synthetase is susceptible to ischaemia[29]. The glutamine synthetase activity might still be attenuated at the time of the first positron emission tomography investigation. However, another study, in which 18O-labelled water (independent of glutamine synthetase) was used to measure blood flow, also revealed a temporary reduced flow early after reperfusion[30]. A good linear relationship was found between myocardial flow measured with microspheres and with 13NH3 in a large flow range, including necrotic myocardial regions, in spite of the presumed dependence of 13NH3 uptake on cell integrity[29,31]. Moreover, in our study, not only flow values but also glucose utilization values improved significantly 3 months after the acute event. An alternative explanation is that, due to development and recruitment of collaterals, the perfusion level of the infarct area rises at later time points. Finally, retraction of scar tissue in the infarct area might also result in higher flow values as measured with positron emission tomography.

**Study limitations**

It is known that TIMI flow grade can change after a myocardial infarction. Spontaneous recanalization, restenosis or reocclusion can occur. Therefore, one of the study limitations is that coronary angiography was performed at different time points (between 24 h and 5 days) after myocardial infarction. No significant correlation was observed between the time of angioplasty and the anterograde flow grade. Another limitation is the fact that no correlation was performed between TIMI flow grade, perfusion and metabolism, as assessed by positron emission tomography and the severity of underlying left ventricular dysfunction, due to the use of different techniques for evaluation of left ventricular function, which made it difficult to perform correlations without further subdividing patients into even smaller groups. Therefore, this study focused on the evolution of left ventricular function in relation to the initial positron emission tomography results, being clinically the most important question.

It can be concluded that in this population of patients with acute myocardial infarction who received thrombolytic therapy, recovery of function of the infarct area was found only in patients with TIMI flow grade 3. Patients with a positron emission tomographic mismatch pattern who received additional revascularization showed functional recovery at late follow-up, indicating the usefulness of viability assessment with positron emission tomography in the setting of acute myocardial infarction. In some of the patients with normal flow or a positron emission tomographic match pattern at 5 days, improvement of function was found at 3 months, presumably due to delayed functional recovery or stunning. Myocardial blood flow improved significantly in both match and mismatch areas.

**References**


