Early Assessment of Regional Myocardial Blood Flow and Metabolism in Thrombolysis in Myocardial Infarction Flow Grade 3 Reperfused Myocardial Infarction Using Carbon-11–Acetate

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OBJECTIVES
The aim of this study was to investigate the prognostic value of carbon-11–acetate (acetate) positron emission tomography (PET) after successful reperfusion of myocardial infarction (MI).

BACKGROUND
Acetate PET allows the measurement of both myocardial flow and oxidative metabolism. The prognostic value of acetate measurements performed early (within 24 h) after Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 reperfused MI is unknown.

METHODS
In 18 patients with TIMI flow grade 3 reperfusion of their first MI, a dynamic acetate study was performed within 24 h of the acute event. At five days, nitrogen-13–NH3 (NH3) and fluorine-18–labeled fluorodeoxyglucose (FDG) PET studies were performed. Infarct-related areas were classified as “PET viable” or “PET nonviable,” as assessed with NH3 and FDG, according to previously established criteria. At five days and three months, radionuclide angiography was performed for evaluation of left ventricular (LV) function.

RESULTS
In infarct-related regions, myocardial blood flow, FDG uptake and oxygen consumption were decreased, compared with remote regions. However, oxygen consumption values, as measured with acetate in both PET-viable and PET-nonviable areas, as assessed with NH3 and FDG, were not significantly different (p = NS). A significant linear correlation was observed between global LV ejection fraction at three months and oxidative metabolism in the infarct-related area (r = 0.8, p < 0.0001). Multivariate analysis revealed that oxidative metabolism measurements in reperfused myocardium was the only significant predictor for recovery of LV function at three months (p < 0.05).

CONCLUSIONS
Measurement of oxidative metabolism early after TIMI flow grade 3 reperfusion of MI offers important prognostic value concerning LV function at follow-up. (J Am Coll Cardiol 2001; 37:30–6) © 2001 by the American College of Cardiology

Several studies have investigated the possible use of acetate as a tracer of both regional myocardial perfusion (due to its high first-pass extraction fraction in the myocardium) and regional myocardial oxygen consumption (1–4). Acetate is extracted by myocytes and converted to carbon-11–acetyl coenzyme A within the mitochondria, which then enters the tricarboxylic acid cycle. Carbon-11 activity is cleared in the form of carbon dioxide. Initial high uptake of acetate depends on myocardial blood flow, suggesting that early images may be useful to study myocardial blood flow (2). Studies in isolated, perfused rat hearts have demonstrated biexponential carbon dioxide clearance (5). Both the slope of the rapid clearance phase of this biexponential decrease and the decay constant of a restricted monoexponential fit correlate linearly with myocardial oxygen consumption under varying work load conditions (5,6). More recently, different compartment models, based on the biochemical transport steps of acetate, were presented (7,8).

In a previous study measuring myocardial tissue flow in patients with infarcts shortly after successful thrombolysis, recovery of left ventricular (LV) contractile function at follow-up was highly dependent on the absence or presence of adequate myocardial tissue reperfusion (9). The aim of the underlying study was to investigate the predictive value of acetate perfusion and oxidative metabolism measurements for the restoration of LV function in the acute stage of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 reperfused myocardial infarction (MI).

METHODS
Patients with a first acute MI of <6 h duration with one- or two-vessel disease and TIMI flow grade 3 reperfusion at 90 min were prospectively and consecutively included. Only patients with typical chest pain of >30 min and with ST segment elevation of >0.1 mV in two or more limb leads or >0.2 mV in two or more contiguous precordial leads were enrolled. Patients received thrombolytic therapy according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) protocol (10,11). All patients underwent coronary angiography at 90 min after the start of thrombolytic therapy. A control angiogram was obtained at five days. The angiograms were read by two independent, experienced angiographers. The potency of...
the infarct–vessel related area was scored according to the TIMI criteria of reperfusion (12). In all patients, positron emission tomographic (PET) acetate (within 24 h), ammonia (NH₃) and fluorine-18–fluorodeoxyglucose (FDG) (at five days) measurements were performed. Radionuclide angiography was performed both at five days and three months. In addition, an acetate scan was performed in 10 normal volunteers. The study was approved by the Ethical Committee for Human Research of the University of Leuven.

**Positron emission tomography.** The acetate and NH₃/FDG studies were performed with a whole-body PET scanner (model 931-08/12, CTI Siemens, Knoxville, Tennessee). A cyclotron (cyclone 10/5, Ion Beam Applications, Louvain la Neuve, Belgium) and chemical processing equipment were used to produce acetate, NH₃, and FDG. Before each study, a rectilinear scan (2 min) was obtained to position the heart within the field of view. A transmission scan (15 min) using a germanium-68 ring source was performed for photon attenuation correction. Finally, an emission scan was acquired after injection of the tracer (acetate, NH₃ or FDG).

**Image acquisition. NH₃/FDG.** Five days after the acute MI, myocardial blood flow and metabolism were measured with NH₃ and FDG.

Myocardial perfusion was evaluated using NH₃: 740 MBq of NH₃ in 5 ml saline followed by a 20–ml flush of saline was slowly infused at a constant rate of 10 ml/min. Acquisition was started simultaneously with the injection of NH₃. In each patient, 20 dynamic frames were recorded (12 × 10 s, 4 × 30 s, 3 × 2 min, 1 × 10 min). Regional myocardial utilization of exogenous glucose was evaluated with FDG. The metabolic studies were performed using the euglycemic hyperinsulinemic clamp technique (13,14). The tracer dose of 370 MBq was injected after stabilization of the glucose level between 85 and 95 mg% and not earlier than 50 min after NH₃ injection to allow isotope decay. In each patient, four frames were recorded starting 30 min after injection of FDG (4 × 10 min). The time required for image acquisition of the combined NH₃ and FDG study was 21 to 3 h.

**ACETATE.** In each subject, a dynamic acetate study was performed within 24 h after the onset of symptoms. The tracer dose of 740 MBq of acetate, diluted with 0.9% saline to a volume of 5 ml was injected in a bolus. In each patient, 22 dynamic frames were recorded (8 × 30 s, 6 × 60 s, 8 × 120 s). Total acquisition time was 26 min.

**Data analysis. NH₃/FDG.** The frames of the perfusion studies were reconstructed using a Hanning filter with a cut-off frequency of 0.3. A summed frame was constructed using frames 18 to 20. The long axis of the LV was indicated manually on the summed frame. The myocardial image was resampled into 16 radial slices. The radial slices were delineated using an algorithm developed in our department (15,16). The delineation was used to construct a polar map (17). In the patients with MI, two regions of interest (remote and infarct-related regions) were defined on the polar map of the NH₃ study. The first, representing remote myocardium, was defined as the perfusion territory of a non-infarct-related artery (according to angiographic findings) without significant coronary artery stenosis (according to angiographic findings). This region was manually drawn on the basis of previously established criteria, depending on the coronary anatomy as seen on the angiogram (18). Finally, the remote region was automatically copied to the other polar maps (FDG and acetate). The same procedure was followed to define the infarct-related region: the territory of the infarct-related artery was defined on the NH₃ polar map, depending on the coronary anatomy as seen on the angiogram (18). The infarct region was manually drawn within the territory of the infarct-related artery, on the basis of a simple visual estimation of the infarct zone. The infarct region was automatically copied to the other polar maps. A flow index was calculated as the ratio of the averaged counts in the infarct region divided by the counts in the remote area.

The frames of the metabolic study were reconstructed using a Hanning 0.4 filter. A summed frame was constructed. The creation of radial slices, delineation maps, polar maps and regional time-activity curves was done in exactly the same way as for the flow studies. The remote and infarct regions for FDG were the same as for NH₃. A metabolic index was defined as the ratio of the averaged counts in the infarct region to that in the remote region.

On the basis of values obtained in normal volunteers, the myocardium was supposed to demonstrate a “PET-viable” pattern if the flow index was >0.8 or if the ratio of the metabolic and flow indexes was >1.2 (19,20).

**ACETATE.** Polar maps of every frame were constructed in the same way as for the NH₃ and FDG images. In normal subjects, a single region enclosing the entire polar map was drawn. For patient studies, we used the same two regions as defined in the analysis of the NH₃ and FDG images. Absolute blood flow (ml/min per g) and oxidative metabolism (1/min) were calculated using a three-compartment model (7). In this model, rate constant $K_1$ estimates the product of blood flow and first-pass extraction fraction (herein simply called blood flow); rate constant $k_2$ is proportional to the oxygen consumption. For linear regression analysis, acetate perfusion and metabolic indexes were used.
The acetate perfusion index was defined as the ratio of blood flow in the infarct region to that in the remote region. The acetate metabolic index was defined as the ratio of oxidative metabolism in the infarct region to that in the remote region.

**Radionuclide angiography.** Radionuclide angiography was performed at five days and three months. Red blood cells were labeled with 740 MBq of technetium-99m. Ten minutes after the injection, an equilibrium-gated nuclear angiogram was acquired during 10 min. A low energy, all-purpose collimator was used. Global ejection fractions were calculated automatically using standard software (Sopha Medical Benelux, Brussels, Belgium). The studies were interpreted by a skilled nuclear medicine physician. Function was considered to have improved if the ejection fraction was 5% higher (ejection fraction units) at three months compared with five days. Ejection fractions were interpreted by a skilled nuclear medicine physician. (Sopha Medical Benelux, Brussels, Belgium). The studies were interpreted by a skilled nuclear medicine physician.

**Extent of infarction left ventricle.**

**Results are given as the mean value ± SD.** To test the hypothesis that the vector mean values from two multivariate groups were equal, multivariate analysis of variance was applied. If the null hypothesis was rejected, simultaneous confidence intervals for the differences between the mean values were computed to identify which of the components were significantly different. For evaluation of the relation between flow measurements with acetate and those with NH\textsubscript{3} and for evaluation of measurements of oxidative metabolism and FDG uptake, linear regression plots were used. Statistical significance was indicated at p < 0.05.

### RESULTS

#### Clinical characteristics.

Eighteen patients were prospectively included in the study protocol (17 men and 1 woman, mean age 54 ± 14 years). Three patients were excluded because C-11–acetate scan could not be scheduled within 24 h. Patients received both an acetate scan at 24 h and a NH\textsubscript{3}/FDG scan at five days after the infarction. Before admission, the patients’ cardiac medications included the following: nitrates (n = 5), angiotensin-converting enzyme inhibitors (n = 1), aspirin (n = 5), beta-blockers (n = 4), calcium channel antagonists (n = 1) and diuretics (n = 1). The infarct-related coronary artery was the left anterior descending coronary artery in eight patients, the right coronary artery in five patients and the left circumflex coronary artery in five patients. All patients with infarcts were medically treated with recombinant staphylokinase or front-loaded alteplase with intravenous heparin, or streptokinase with intravenous or subcutaneous heparin (10,11). Oral aspirin was given to every patient. The mean blood pressure at the time of the acetate scan was 118/78 mm Hg. The mean heart rate was 79 ± 24 beats/min.

In addition, an acetate scan was also performed in 10 male volunteers (mean age 37 ± 12 years, mean blood pressure 124/82 mm Hg, mean heart rate 72 ± 16 beats/min). The volunteers were selected on the basis of the absence of a cardiac history, with a normal clinical investigation, a normal rest electrocardiogram and a normal bicycle stress test. None of the volunteers was taking a cardiac medication.

#### Myocardial blood flow and metabolism (Table 1).

The NH\textsubscript{3} flow index values in the infarct area were 0.65 ± 0.14. Blood flow values measured with acetate in the infarct area

### Table 1. Ejection Fraction, Acetate Flow and Metabolic Index, Ammonia Perfusion Index, Fluorine-18–fluorodeoxyglucose Metabolic Index and Mismatch Index for Each Patient

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>EF at 5 Days (%)</th>
<th>EF at 3 Months (%)</th>
<th>ΔEF (%)</th>
<th>Infarct Extent*</th>
<th>Acetate Perfusion Index</th>
<th>Acetate Metabolic Index</th>
<th>NH\textsubscript{3} Perfusion Index</th>
<th>FDG Metabolic Index</th>
<th>Mismatch Index</th>
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<td>22</td>
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<td>0.49</td>
<td>1.31</td>
<td>0.70</td>
<td>0.45</td>
<td>0.64</td>
</tr>
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</table>

*Extent of infarction left ventricle.

ΔEF = change in ejection fraction (EF); between five days and three months; FDG = fluorine-18–fluorodeoxyglucose; NH\textsubscript{3} = ammonia.
revealed significantly decreased flow, compared with those values in remote myocardium (0.46 ± 0.11 vs. 0.83 ± 0.18 ml/g per min, p < 0.001). Moreover, the patients’ blood flow in remote areas, as measured with acetate, was significantly higher than that in normal volunteers (0.83 ± 0.18 vs. 0.64 ± 0.1 ml/g per min, p < 0.05). Linear regression analysis of the infarct regions revealed a linear relationship between NH4 flow index values and acetate perfusion index values (r = 0.76, p < 0.001).

The FDG metabolic index values in the infarct area were 0.6 ± 0.21. Myocardial oxygen consumption measurements with acetate (as estimated by k2) in the infarct area (0.075 ± 0.02/min) were significantly lower than those values in both remote areas of patients (0.099 ± 0.03/min) and in normal volunteers (0.095 ± 0.03/min) (p < 0.05). A poor, though statistically significant, linear correlation was observed between FDG metabolic index values and acetate metabolic index values (r = 0.5, p < 0.05). A statistically significant linear relationship was found between FDG metabolic index values and NH4 flow index values (r = 0.8, p < 0.01).

**Evaluation of PET-viable and PET-nonviable regions as assessed with NH4 and FDG.** In total, 18 infarct regions were defined, five of which were considered as PET viable and 13 as PET nonviable, as assessed with NH4 and FDG studies, according to previously established criteria (19,20).

**Myocardial blood flow.** In regions with a PET-viable pattern, as assessed with NH4 and FDG at five days, acetate blood flow values were not significantly different from values obtained in normal volunteers (0.57 ± 0.12 vs. 0.64 ± 0.11 ml/g per min, p = NS). In regions with a PET-nonviable pattern, as assessed with NH4 and FDG at five days, myocardial blood flow, as measured with acetate in the early stage, was decreased (0.43 ± 0.10 ml/g per min, p < 0.05 vs. volunteers). Blood flow measured with acetate in remote areas was significantly higher than those values in the patients’ PET-viable and PET-nonviable areas and those values obtained in normal volunteers (0.83 ± 0.18 ml/g per min, p < 0.05 vs. volunteers and patients’ PET-viable or -nonviable regions).

**Myocardial oxygen consumption (as estimated by k2).** The k2 values in PET-viable areas (0.073 ± 0.02/min) and PET-nonviable areas (0.076 ± 0.02/min) were similar (p = NS). Moreover, k2 values in those areas were slightly lower but not statistically significantly different from k2 values in patients’ remote areas (0.099 ± 0.03/min) and in normal volunteers (0.096 ± 0.03/min) (p = NS).

**Functional follow-up.** For functional follow-up, global ejection fractions were measured five days and three months after the infarction, using nuclear angiography. At five days, a poor linear correlation was observed between LV ejection fraction and measurements of flow (acetate: r = 0.4, p = 0.055; NH4: r = 0.5, p < 0.05) and metabolic indexes (acetate: r = 0.5, p < 0.05; FDG: r = 0.34, p = NS) in the infarct area.

At follow-up, linear regression analysis revealed a fairly poor correlation between global LV ejection fraction at three months and the early flow index measurements with acetate (r = 0.6, p < 0.01) and NH4 in the infarct area (r = 0.45, p < 0.05). Similarly, a poor correlation was observed between LV ejection fraction at three months and the glucose metabolic index in the infarct area five days after the acute event (r = 0.5, p < 0.05). However, a good linear correlation was observed between global LV function at three months and the early measurements of the acetate metabolic index in the infarct zone (r = 0.8, p < 0.0001) (Fig. 1). No significant correlation was found between changes in ejection fraction between five days and three months and the early acetate, NH4 or FDG measurements in reperfused myocardium (p = NS).

For further statistical analysis, the patients were classified into two groups: group 1 = patients with normal LV function at five days or significant improvement of LV function at follow-up; group 2 = patients with impaired LV function at five days and without recovery of LV function. Multivariate analysis revealed that oxidative metabolism in reperfused myocardium was the only significant predictor for recovery of LV function at three months in this study group (p < 0.05 vs. NH4 uptake and FDG uptake) (Fig. 2). Significantly higher values of oxidative metabolism were found in reperfused myocardium in group 1 (0.83 ± 0.12) compared with group 2 (0.48 ± 0.12, NS). The FDG uptake in the infarct area also tended to be higher in group 1 (0.67 ± 0.23) compared with group 2 (0.48 ± 0.12, p = NS), but this difference did not reach statistical significance. No significant difference was found between the two groups in terms of myocardial blood flow.

**Discussion**

**Myocardial blood flow and metabolism.** In this study, only patients with TIMI flow grade 3 reperfused MI were studied. Interestingly, persistent and relatively severe flow reductions were observed in the infarct area of several patients, despite successful thrombolysis early after the onset of acute symptoms. This “no reflow” phenomenon has been described previously and was attributed to a disrupted microvasculature (9). Absolute blood flow in the remote areas of the patients with infarcts was significantly higher than that in normal volunteers. However, oxidative metabolism, which is indicative of myocardial oxygen demand, was not enhanced significantly. Therefore, the improved blood flow in remote myocardium probably did not result in a compensatory improved contractile function.

Acetate kinetic properties allow noninvasive characterization of regional myocardial oxygen consumption in ischemic myocardium (21). In a study by Gropler et al. (22), marked reduction in FDG activity, with preservation of oxidative metabolism, was observed in viable myocardial tissue after acute MI. It was postulated that this pattern might be more common in patients receiving thrombolytic therapy. In our study, which was performed exclusively in patients under-
going successful thrombolysis, similar observations were made. Oxygen consumption values in PET-viable areas were not statistically different from those values in PET-nonviable areas, hereby challenging the classic "PET viable" and "PET nonviable" classification, as assessed with NH$_3$ and FDG in the early stage after reperfusion therapy. In the acute and subacute period after MI, NH$_3$ and FDG might not be the most accurate tracers to determine whether functional recovery will occur. In a previous study, significant improvement of flow values, as measured with NH$_3$ at five days and three months after MI, have been reported in TIMI flow grade 3 reperfused MI (23). One hypothesis for

Figure 1. Linear regression plots comparing ejection fractions (EF) at five days and three months with the acetate perfusion index, acetate metabolic index, NH$_3$ perfusion index and FDG metabolic index. glob. EF 5d = global ejection fraction at five days (%); glob. EF 3m = global ejection fraction at three months (%); fdg = fluorine-18–fluorodeoxyglucose (FDG); perf. = perfusion; met. = metabolic; nh3 = ammonia (NH$_3$).
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