Single photon emission computed tomography with technetium-99m hexakis 2-methoxyisobutyl isonitrile in acute myocardial infarction:

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METHODS

Single Photon Emission Computed Tomography With Technetium-99m Hexakis 2-Methoxyisobutyl Isonitrile in Acute Myocardial Infarction Before and After Thrombolytic Treatment: Assessment of Salvaged Myocardium and Prediction of Late Functional Recovery

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Single photon emission computed tomography (SPECT) with technetium-99m hexakis 2-methoxyisobutyl isonitrile was investigated as a method to evaluate the results of intravenous thrombolytic treatment in 14 patients (11 men and 3 women) with acute myocardial infarction admitted to the coronary care unit within 4 h of the onset of symptoms. All patients received an injection of 740 MBq of the tracer before starting the thrombolytic therapy, and isonitrile tomography was performed 3 to 4 h later. The tomographic study was repeated 5 days after the acute event. The results of thrombolytic treatment were independently evaluated taking into account the clinical, electrocardiographic (ECG) and enzymatic data and the findings of left ventricular and coronary angiography. Furthermore, all patients were studied with two-dimensional echocardiography on admission, 5 days later and 1 month later.

The site and extent of the perfusion defects on admission scintigraphy were consonant with the ECG and echocardiographic findings. A good correlation could be established between the 5 day scintigraphic estimate of infarct dimension and the enzymatic infarct size ($r = 0.907$, $p < 0.00002$). The comparison between pre- and postthrombolytic treatment images enabled the identification of successful and unsuccessful reperfusion even in patients whose other noninvasive findings were inconclusive. Finally, the reduction in defect size predicted late functional improvement that was demonstrated by echocardiography performed 1 month later ($r = 0.89$, $p < 0.00005$).

The results of the study suggest the feasibility and the possible usefulness of isonitrile tomography in demonstrating the presence and size of myocardial damage and in assessing the extent of myocardial salvage after thrombolytic therapy in acute myocardial infarction.

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At the beginning of the 1980s (1,2), coronary angiography performed during the first few hours of myocardial infarction revealed that thrombosis is present in the coronary artery supplying the ischemic zone and may be considered the cause of myocardial infarction in the large majority of patients. This observation led to widespread interest in thrombolytic therapy of acute myocardial infarction. In the following years, several clinical trials (3–6) provided convincing evidence that this therapy improves survival, especially if initiated within the first few hours of the onset of symptoms. This favorable outcome was related to the limitation of the extent of infarct size and consequent improvement in left ventricular function (7–15).

On the basis of these data, early thrombolytic therapy has become standard treatment for patients with acute myocardial infarction. However, because it is difficult to predict and estimate the effectiveness of therapy in one subject, important clinical problems related to the evaluation of the results of thrombolytic therapy in the individual patient remain unsolved. These problems involve assessment of the extent of ischemic myocardium in the acute phase of infarction, evaluation of the final amount of myocardial necrosis after thrombolytic treatment and identification of the effects of reperfusion in terms of reversibly damaged ischemic myocardium (16).

To permit evaluation of the effectiveness of thrombolytic treatment, an ideal imaging method should be able to detect

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the involved area before and after treatment (16,17). It would then be possible to estimate the amount of myocardium at risk as well as the area of definitively damaged myocardium and, consequently, the extent of myocardial salvage. In theory, myocardial perfusion scintigraphy with thallium-201 performed before and after treatment might be a suitable technique to achieve these results, and several reports (18–26) have already described its value. However, the use of thallium-201 is subject to several limitations: low emission energy with a high attenuation of the photons by the extracardiac tissues, prolonged half-life and unfavorable decay modality (which preclude use of high activity doses) and early redistribution (which implies that the images should ideally be obtained immediately after the injection, thus interfering with the immediate start of thrombolytic therapy). Furthermore, in most nuclear medicine laboratories, thallium-201 is not available at all times.

In the last few years, a new class of radiopharmaceutical agents has been developed, namely, the technetium-99m–labeled isonitrile derivatives (27–29). Experimental data (30) with technetium-99m hexakis 2-methoxyisobutyl isonitrile indicate that this tracer accumulates rapidly in myocardial cells in direct proportion to regional blood flow and remains trapped in the viable cells without significant redistribution. These features make it possible to inject this agent before beginning thrombolytic therapy and to obtain scintigraphic images of the preintervention myocardial perfusion up to 3 to 4 h later (16,17,31). Thus, myocardial perfusion scintigraphy can be performed without interfering with the time-dependent therapy.

The present study was designed to investigate if single photon emission computed (SPECT) tomography with technetium-99m hexakis 2-methoxyisobutyl isonitrile can be used to evaluate the results of thrombolytic therapy in individual patients with acute myocardial infarction in terms of estimation of final infarct size, identification of successful versus unsuccessful reperfusion and assessment of the extent of myocardial salvage.

Methods

Study patients. The study group included 14 patients (11 men and 3 women, mean age ± SD 57.4 ± 10.9 years) admitted to our coronary care unit for chest pain suggestive of acute myocardial ischemia. The pain lasted >30 min and was not relieved by the sublingual administration of nitrates. In all patients, the diagnosis of acute myocardial ischemia was confirmed by electrocardiographic (ECG) changes showing ST segment elevation ≥0.1 mV at the J point in at least two limb leads or ≥0.2 mV in at least two precordial leads. Patients were included only if the following requirements had been fulfilled: 1) there was no history of previous myocardial infarction or other cardiac disease; 2) there were no contraindications for thrombolytic treatment; 3) thrombolytic therapy could be initiated within 4 h of the onset of symptoms; 4) complete and adequate visualization of endocardial wall motion could be obtained with two-dimensional echocardiography performed immediately after admission; and 5) informed consent had been obtained from the patient.

Study protocol. After blood sampling for cardiac enzymes and coagulation, a two-dimensional echocardiogram was performed. In the meantime, patients received an injection of 740 MBq of technetium-99m hexakis 2-methoxyisobutyl isonitrile (Cardiolite) that had been prepared as soon as the city emergency ambulance coordination center informed the emergency room physician that a patient with suspected myocardial infarction was being transported to the coronary care unit. After pretreatment with 5 to 10 mg of atenolol intravenously and 325 mg of aspirin orally, intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) (Actylise) was started. The drug was administered over 3 h at doses of 50, 20 and 20 mg at each successive hour, with an initial bolus of 10 mg (total dose 100 mg). At the end of the plasminogen activator infusion, intravenous heparin at 25,000 to 30,000 U/24 h and nitroglycerin at 2 to 4 μg/min were started. Apart from these drugs, standard therapy for acute myocardial infarction, including opiates for pain, antiarrhythmic drugs and diuretic agents, was used when necessary.

Within 3 to 4 h of starting thrombolytic therapy, patients were taken to the nuclear medicine department to undergo SPECT tomography. The transport of the patient and his or her stay in the nuclear medicine department were arranged to ensure close supervision by a cardiologist and two experienced nurses, constant ECG monitoring and easy availability of all resuscitation resources. Five days later, patients underwent repeat SPECT imaging; a two-dimensional echocardiogram was performed on the same day.

In the period between the start of thrombolytic therapy and day 5 after admission, serial determinations of serum creatine kinase isoenzyme (MB CK) activity and serial ECGs were performed. Blood samples were drawn every hour for the first 12 h, every 3 h for the subsequent 12 h, every 6 h for the next 2 days and every 12 h until day 5. Twelve lead ECGs were performed every 30 min during rt-PA infusion and for the next 2 h; subsequent ECGs were performed at the same time intervals as blood samples were drawn.

After giving informed written consent, patients underwent left ventriculography and coronary angiography within 1 week of admission to the hospital. One month after hospital admission (15 to 20 days after discharge) patients were reexamined and a 12 lead ECG and two-dimensional echocardiogram were repeated.

The study protocol was approved by the Committee for the Clinical Experimentation in our institution.

Noninvasive assessment of reperfusion. According to standard criteria (32–36), reperfusion was considered to have occurred when all the following findings were present in a strict temporal relation with thrombolytic therapy: abrupt or rapidly progressive relief of chest pain, reduction of ST segment elevation with rapid return to the isoelectric line and early peaking of serum MB CK level (within 12 h of treatment onset).

Enzymatic and electrocardiographic evaluation. Creatine kinase isoenzyme activity was measured using an immunologic method with starter reagent (Monotest MB CK NAC-act.). Using the values of the MB CK curve, infarct size was estimated as described by Sobel et al. (37) and expressed as MB CK gram-equivalents.

Twelve lead ECGs were recorded using a Hewlett-Packard 4700A cardiograph. The evolution of the ECG pattern was monitored by taking pathologic Q wave development into account. The ECG performed on the fifth day and after 1 month were scored according to the 29 point QRS scoring system proposed by Wagner et al. (38).

Two-dimensional echocardiography. Two-dimensional echocardiograms were performed using an Aloka SSD-720 echocardiograph equipped with a 3 MHz frequency Aloka ASU 32-3-M mechanical transducer. Patients were studied in the left lateral decubitus position. In each study, parasternal long- and short-axis views and apical two and four chamber views were obtained; in subjects in whom these views are suboptimal, the subxiphoid window was used. Images were registered on a Panasonic NGV 10 videorecorder to enable an accurate study and the definition of the evolution pattern in each patient. For the purpose of wall motion analysis, the left ventricle was subdivided into 11 segments according to a modification of the method proposed by Edwards et al. (39), with the apex considered as a single segment. The wall motion pattern of each segment was visually analyzed by two independent observers who were unaware of patient identity, temporal sequence in which images were acquired and results of other clinical and graphic data. The wall motion of each segment was classified as normal or abnormal on the basis of visual impression. The segment was recognized as asynergic if >50% of its extent exhibited abnormal wall motion (hypokinesia, akinesia, dyskinesia). For each study, an asynergic area extent score was obtained. This was calculated as the ratio between the number of segments with abnormal wall motion and the number of all segments examined. The Spearman rank correlation coefficient between the estimates of the two observers was 0.78 ($p < 0.01$).

Left ventricular and coronary angiography. Angiography was performed using either the brachial or the femoral approach. Monoplane left ventricular angiograms were obtained in 30° right anterior oblique and 45° to 60° left anterior oblique projections. To measure left ventricular wall motion, end-diastolic and end-systolic endocardial contours were, respectively, traced in the projected cine film, using the frames with maximal and minimal ventricular volume from a normal sinus beat not preceded by a premature beat. Wall motion pattern was evaluated visually for the presence of regional asynergy (hypokinesia, akinesia, dyskinesia). Coronary angiograms were recorded in multiple projections, including cranial and caudal views of the left coronary artery. The infarct-related vessel was identified on the basis of the location of: 1) ST elevation on the ECG, 2) perfusion defect on the scintigram, 3) asynergic wall motion on the echocardiogram and ventriculogram, and 4) coronary vessel anatomy; the vessel was subsequently evaluated for patency according to the Thrombolysis in Myocardial Infarction (TIMI) criteria (40). Patency was considered present when grade 2 or 3 perfusion was recognized. Left ventricular wall motion and infarct-related coronary artery perfusion status were independently assessed by two observers who were unaware of patient identity and other clinical and graphic data. In all cases, complete interobserver agreement was achieved.

Single photon emission computed tomography. SPECT imaging was performed using a double-head gamma camera (Rotacamera, Siemens) equipped with ultrahigh resolution collimators, with a 15% window about the 140 keV of the technetium-99m emission photopeak. The gamma camera was interfaced with a computer (Hewlett-Packard A900) and the acquisition was performed in step and shot mode, 360° rotation arc, 90 projections each lasting 10 s, on 64 × 64 matrices. Tomographic images were reconstructed with an iterative algorithm (seven iterations) using the conjugated gradient method (41) and taking into account the spatial system response to compensate for resolution losses due to depth (42). The cast of transaxial slices was then used to generate oblique sections, rearranged along the vertical and horizontal long axes and the short axis of the left ventricle (43). Computation time for an entire study was about 3 h. Previous experience using phantoms with our acquisition and reconstruction procedure gave a value of 8 mm for the full width half maximum of the point spread function at a depth comparable with that of the heart (42). A visual example of the difference in resolution power of our method with respect to the conventional filtered backprojection is shown in Figure 1.

The myocardial wall/chamber and myocardial wall/lung count ratios in a midventricular slice (short axis) were, respectively, 5.9 ± 0.3 and 3.55 ± 0.7 (mean values ± SD), with a count density in the normally perfused myocardium of 11,230 ± 3,820 counts/cm^3. After a qualitative overview of the images to identify the site of the area involved, quantification of the amount of myocardial tissue included in the perfusion defects was made using the short axis view images with a method similar to that employed by Tamaki et al. (44). The original 1 pixel thick sections (dimensions of the pixel in the 64 × 64 matrix = 6 × 6 mm) were added to obtain 6 (or,

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Figure 1. Thoracic transaxial tomographic slices at midventricular level. **Left**, Reconstruction using the filtered backprojection (Hann filter, cutoff frequency 0.5 cycles/pixel). **Right**, Reconstruction with the iterative algorithm according to our method. The improvement in image quality is easily appreciable when the reduced thickness of the ventricular walls and the sharp contrast between uptaking myocardium and background are considered.

when necessary, 7) 3 pixel thick slices (slice thickness 18 mm). They were subsequently interpolated in an expanded 256 × 256 matrix (dimensions of the pixel 1.5 × 1.5 mm). Because of the features of the tracer and of the acquisition and reconstruction procedures, images of good quality could be achieved with high target to background ratio and clear-cut contrast between perfused and nonperfused territories. Therefore, the subtraction of a fixed percent of the maximal radioactivity to help identify the myocardial edges was not performed.

Regions of interest defining the contours of both the perfused myocardium and the uptake defect areas were manually drawn by visual inspection using a computer-assisted procedure, and the included number of pixels was automatically calculated (Fig. 2). Manual drawing also allowed us to eliminate small artifacts by regularizing the profiles of the perfused regions. The contours of the uptake defect areas were drawn so as to complete the shape of the ventricular wall, taking into account the curvature of the left ventricle and the thickness of surrounding perfused regions. Particular care was used for the inferior wall because of the possibility of significant spillover from splanchnic structures, which may be encountered in some instances. After adding together the pixels of the normal myocardium and uptake defects of all the slices, the number of three-dimensional image elements (voxel) was multiplied by the volume of each element: 1.5 × 1.5 × 18 mm = 40.5 mm^3. The resulting volume was finally multiplied by the specific weight of the heart muscle (1.05 g/cm^3). The size of the perfusion defect area could, therefore, be expressed both as amount in grams of involved tissue and as a percent of total left ventricular mass. Each set of images was evaluated independently by two observers, and the mean of the two values was employed for the final evaluation. Interobserver variability never exceeded 5%. The estimated extent of perfusion defects on both the admission and 5 day studies was compared, and the variation was expressed as percent of the initially involved area.

Statistical analysis. Comparison of the enzymatic and scintigraphic infarct size and of scintigraphic and echocardiographic results was performed by using both the Pearson correlation coefficient and linear regression. The level of significance was fixed at $p < 0.05$.

Results

Clinical course. The delay between the onset of symptoms and admission to the coronary care unit ranged from 1 to 3 h (mean 1.9 ± 0.7). The delay between admission to the coronary care unit and start of thrombolytic treatment after technetium-99m hexakis 2-methoxyisobutyl isonitrile injection ranged from 15 to 35 min (mean 22.3 ± 5.6). Before being transported to the nuclear medicine department to perform the first scintigraphic study, two patients (cases 2 and 15) had episodes of sustained ventricular tachycardia that were abolished by intravenous administration of lidocaine. No complications occurred that could be attributed to patient transport to the nuclear medicine department or to scintigraphic image acquisition. During the stay at the nuclear medicine department, one patient with inferior infarction (Case 6) developed high grade atrioventricular (AV) block that was treated by temporary ventricular pacing. One patient (Case 10) died on the third day after admission because of cardiogenic shock resulting from extension of the infarction and, thus, could not be evaluated. No other patient had recurrence of chest pain or a new ischemic attack or was subjected to resuscitation maneuvers after admission.

Clinical, graphic and angiographic findings (Tables 1 and 2). Table 1 shows the evolution of symptoms, ECG changes and cardiac enzymes after thrombolytic treatment. On the basis of these data and taking into account the previously mentioned criteria, reperfusion could be inferred in 3 of the

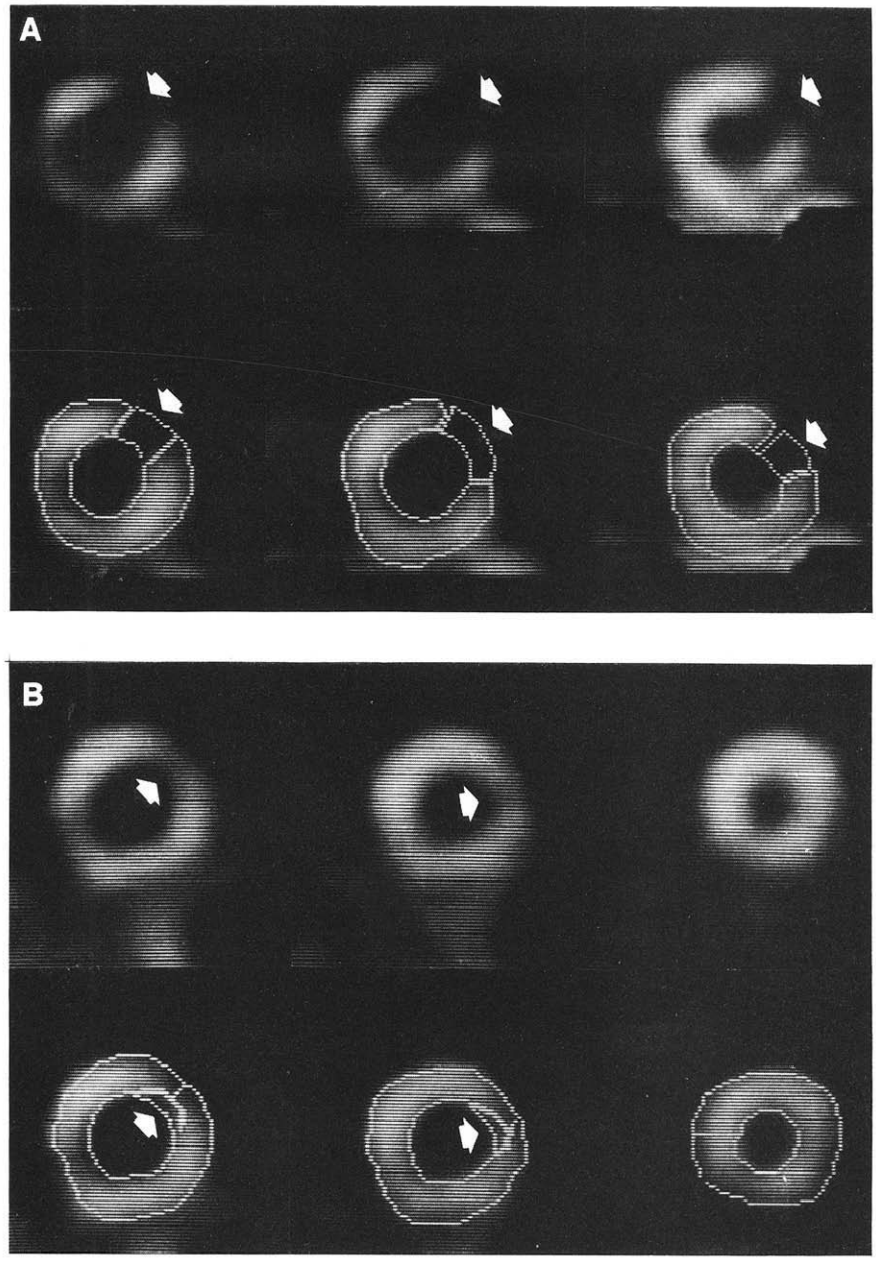

Figure 2. Patient 12. Short-axis images (**from left to right**: basal, midventricular and subapical slices). **A**, in the prethrombolytic treatment images, a clearcut anterolateral perfusion defect is shown (**top row, arrows**). **B**, In the 5 day images, a noteworthy reduction in the defect can be appreciated (**top row, arrows**). In the respective **bottom rows**, the computer-assisted, manually drawn perfused and nonperfused areas (**arrows**) are shown.

13 patients (Cases 1, 5 and 7), whereas the findings in another 3 patients (Cases 3, 4 and 8) allowed us to assume the absence of significant reflow. In the remaining seven patients, data were conflicting and no reliable conclusion about the occurrence of reperfusion could be drawn.

The evolution of ECG changes after admission showed the appearance of abnormal Q waves in 11 patients, reversion to normal in 2 patients (Cases 1 and 12) (Table 2).

Two-dimensional echocardiography performed immediately after admission demonstrated one or more asynergic segments in all patients (Table 2). In the 5 day echocardiogram, a reduction in asynergic area extent score as compared with the admission pattern was noted in only one patient (Case 1).

Left ventriculography showed a clear wall motion abnormality of the involved area in 11 subjects and a normal pattern in only 2 patients (Cases 1 and 12); according to the coronary angiographic findings, the infarct-related vessel was patent in 9 patients (Cases 1, 4, 5–7, 9, 11, 12 and 14) and closed in 4 (Table 2).

The results of the delayed evaluation (1 month after the acute episode) demonstrated no variations in the ECG pattern in 12 patients; in only 1 patient (Case 7) was a reduction in QRS score observed (Table 2). In contrast, echocardiography showed a clear reduction in the extent of wall motion abnormalities in seven patients (Cases 1, 5–7, 9, 11 and 12), with a decrease in asynergic area extent score ranging from 33% to 100%; in the remaining six patients the wall motion pattern was unchanged (Table 2).

Scintigraphic evaluation (Table 3). In the first scinti-

Table 1. Clinical Features and Evolution of Symptoms, Electrocardiographic Changes and Cardiac Enzymes After Thrombolytic Treatment in 14 Patients

Case No.	Age (yr)/ Gender	Time Intervals (h) between: Onset of Symptoms and Start of Treatment	Start of Treatment and Relief of Pain	Start of Treatment and Beginning of ST Normalization	MB CK Peak (units)	Time to MB CK Peak After Start of Treatment (h)	Enzymatic Estimate of Infarct Size (MB CK gram equivalents)
1	56/M	1	1	1	55	6	9.5
2	58/M	2	5	5	456	9	65
3	65/M	2	6	3	401	15	41
4	61/M	3	6	Never	200	15	39
5	58/M	2	1	2	350	4	37.8
6	64/M	1	2	Never	170	9	30
7	37/F	2	1	2	510	4	27
8	58/M	3	4	Never	91	21	25
9	63/F	1	2	1	111	15	14.3
10	80/M	2	4	Never	158	18	—
11	60/M	2	2	6	300	9	30.6
12	46/M	1	1	4	88	18	9.5
13	59/F	2	4	5	429	12	46.3
14	39/M	3	4	6	153	12	33

F = female; M = male; MB CK = serum creatine kinase MB isoenzyme.

graphic study, all patients presented with a clear perfusion defect. The location and extent of the defect were consonant with the ECG and echocardiographic findings. In the 5 day scintigraphic study, seven patients (Cases 1, 5, 6, 7, 9, 11 and 12) showed a remarkable reduction in the perfusion defect, with a decrease in involved left ventricular mass ranging from 51% to 73% in comparison with the initial images (Fig. 3). In contrast, the other six patients had only a negligible reduction in the extent of the perfusion defect, with a decrease ranging from 1% to 8% of the initial defect size (Fig. 4). Infarct size estimated on the basis of the 5 day scintigraphic images was compared with the amount of necrotic tissue measured using the MB CK curves and a good correlation was found ($r = 0.907$, $p < 0.00002$) (Fig. 5).

The percent decrease in the perfusion defect size between the first and second scintigraphic studies showed a good correlation with the reduction of the asynergic area extent score evaluated by comparing the results of the admission echocardiographic examination with those of the delayed control study performed 1 month after the acute episode ($r =$

Table 2. Electrocardiographic, Echocardiographic and Angiographic Findings in 14 Patients

Case No.	Electrocardiogram: Involved Leads (admission)	QRS Score: 5 Day	QRS Score: 1 Month	Echocardiographic Asynergic Area Extent Score: Admission	5 Day	1 Month	% Decrease (1 month vs. admission)	Ventriculography and Coronary Angiography: LV Wall Motion Pattern	Status of Infarct-Related Vessel
1	V_1–V_3	0	0	0.18	0	0	100	Normal	Patent
2	II, III, aVF	8	8	0.09	0.09	0.09	0	Abnormal	Occluded
3	V_2–V_5	3	3	0.27	0.27	0.27	0	Abnormal	Occluded
4	V_1–V_4	9	9	0.18	0.18	0.18	0	Abnormal	Patent
5	V_1–V_3	4	4	0.45	0.45	0.09	80	Abnormal	Patent
6	V_1–V_4	2	2	0.27	0.27	0.18	33	Abnormal	Patent
7	V_2–V_4	3	2	0.36	0.36	0.18	50	Abnormal	Patent
8	II, III, aVF	3	3	0.18	0.18	0.18	0	Abnormal	Occluded
9	II, III	6	6	0.36	0.36	0.18	50	Abnormal	Patent
10	V_1–V_4	—	—	0.27	—	—	—	—	—
11	V_1–V_3	2	2	0.27	0.27	0.09	66	Abnormal	Patent
12	I, aVL	0	0	0.09	0.09	0	100	Normal	Patent
13	II, III, aVF, V_4, V_5	5	5	0.18	0.18	0.18	0	Abnormal	Occluded
14	II, III, aVF, V_5, V_6	4	4	0.18	0.18	0.18	0	Abnormal	Patent

LV = left ventricular.

Table 3. Results of Single Photon Emission Computed Tomography With Technetium-99m Hexakis 2-Methoxyisobutyl Isonitrile in 14 Patients

Case No.	Site of Uptake Defect	Admission		5 Day		% Decrease of Defect Extent Between Admission and 5 Day Images
		Estimate of Involved Myocardium (g)	% of Left Ventricular Mass	Estimate of Involved Myocardium (g)	% of Left Ventricular Mass	
1	Anteroseptal	29	17.9	7.9	4.9	73
2	Inferolateral	67.3	23.2	65.6	22.7	2
3	Anterolateral and apex	33.2	16	31.5	15.2	5
4	Anteroseptal and apicolateral	52.3	32	49.4	30.2	6
5	Anteroseptal and apex	55.2	41.7	27.3	20.6	51
6	Anteroseptal and apex	49.8	38.7	20.8	16.1	58
7	Anteroseptal and apex	39.5	28.7	12.6	9.2	68
8	Inferolateral	25	17.6	23.8	16.7	5
9	Inferolateral	22.6	19.8	9	7.8	61
10	Anteroseptal and apex	48	29	—	—	—
11	Anteroseptal and apex	79.5	36.7	34.7	16	56
12	High lateral	20	8.6	7.4	3.2	63
13	Inferolateral and apex	42.4	18.4	38.9	16.9	8
14	Inferolateral	41.2	18.1	40.9	17.9	1

0.89, $p < 0.00005$) (Fig. 6). When the percent decrease in the perfusion defect size was compared with the echocardiographic evolution in the individual patients, only one of the seven patients with a significant decrease in perfusion defect size showed a reduction of asynergic area extent score on the 5 day echocardiogram, whereas in all these patients echocardiography performed 1 month later demonstrated a reduction of wall motion abnormalities. In contrast, in the six patients who had a limited or negligible reduction in perfusion defect size, there was no echocardiographic improvement in left ventricular wall motion, even after 1 month (Fig. 7).

Discussion

Advantages of technetium-99m isonitrile scintigraphy. Technetium-99m hexakis 2-methoxyisobutyl isonitrile offers significant advantages over thallium-201 for myocardial perfusion imaging to evaluate thrombolytic therapy: higher emission energy, shorter half-life, higher administrable activity and absence of any significant redistribution, even several hours after administration (30). The absence of any significant redistribution allows one to inject the radiopharmaceutical agent before starting thrombolytic therapy and to perform scintigraphy even 3 to 4 h later without interfering with the treatment and at a time when the patient's condition is relatively stabilized. In our study, the time lapse between admission to the coronary care unit and start of intravenous rt-PA infusion ranged from 15 to 35 min and in no case could the delay be attributed to the tracer reconstitution or injection procedure. The delay in scintigraphic acquisition reduces the potential problems associated with patient transport to the nuclear medicine department, which is necessary when SPECT imaging is employed.

Life-threatening arrhythmias dependent on acute myocardial ischemia or reperfusion are more likely to occur in the first few hours after admission (45). In two of our patients, sustained ventricular tachycardia occurred before the planned time of the first scintigraphic study. Only in Case 6, a patient with inferior myocardial infarction and AV block, was an intervention (cardiac pacing) outside the coronary care unit necessary to correct bradycardia.

Perfusion defect in the scintigraphic study performed before thrombolytic treatment as expression of the ischemic area at risk. Perfusion defects were present in all patients on the scintigrams performed after the injection of technetium-99m isonitrile before the start of thrombolytic treatment. The location of the defects was consonant with the ECG and echocardiographic results. Experimental data support the reliability of the perfusion defect estimated from the isonitrile images as an indicator of the size of myocardium at risk after coronary occlusion. In dogs undergoing permanent or 2 h coronary occlusion followed by reperfusion, the size of the scintigraphic perfusion defect during occlusion corresponded to the occluded vascular bed quantified by a postmortem technique that included nonoccluded coronary artery dye perfusion (46). Li et al. (47) showed a high correlation coefficient ($r = 0.96$) between tissue technetium-99m isonitrile content and coronary flow assessed using labeled microspheres in dogs during coronary occlusion, with perfusion defects in the myocardial regions corresponding to the abnormal distribution of the microspheres. In 38 patients with coronary artery disease, Dilsizian et al. (48) demonstrated that isonitrile imaging accurately predicts cor-

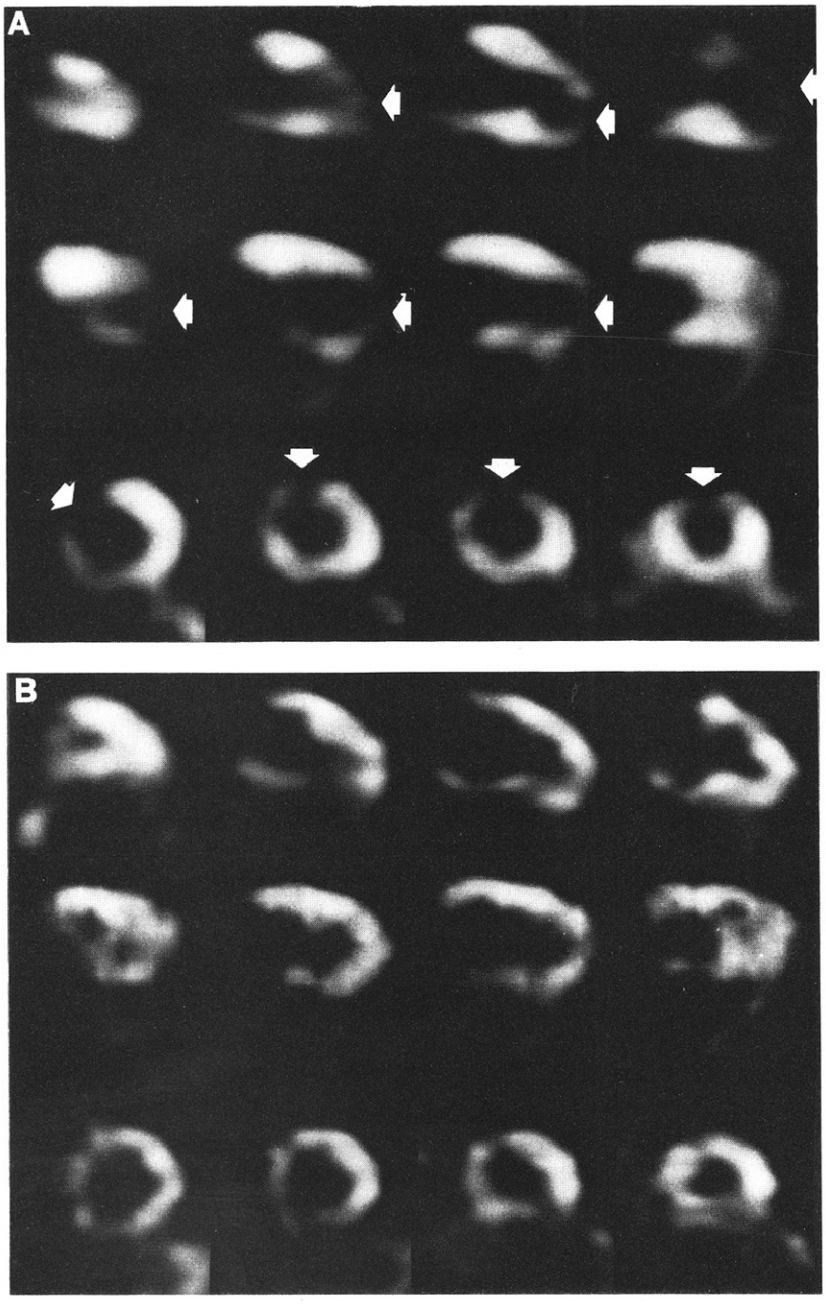

Figure 3. Patient 1, Admission (**A**) and 5 day (**B**) tomographic images. **Top row**, Vertical long-axis view from lateral (**left**) to septal (**right**) wall. **Middle row**, Horizontal long-axis view from anterior (**left**) to inferior (**right**) wall. **Bottom row**, Short-axis view from basal (**left**) to subapical (**right**) wall. The anteroseptal perfusion defect present in **A** (**arrows**) has almost completely disappeared in **B** (73% decrease).

onary occlusion with poor collateral flow; on the basis of their results, they suggested that this method could be useful in evaluating patients with acute myocardial infarction. In our study, the size of the perfusion defect calculated on the basis of SPECT imaging, varied from 8.6% to 41.7% of the left ventricular mass, indicating a wide range of myocardium at risk.

Perfusion defect in the post-thrombolytic scintigram and final infarct size. Experimental data (47,49,50) obtained in dogs that underwent prolonged coronary occlusion followed by reperfusion are conflicting with respect to the possibility that early isonitrile imaging would accurately reflect regional coronary flow and myocardial viability in the reperfused myocardium. Consequently, the real extent of myocardial infarction could not be precisely quantified by scintigraphic evaluation performed immediately after treatment. Therefore, to avoid an erroneous estimate of the extent of the infarcted area, scintigraphy performed after thrombolytic treatment must be performed with some delay after the intervention. Our decision to perform the second scintigraphic study 5 days after the acute event was based on the arbitrary assumption that 5 days is an adequate amount of time for this technique to ensure an accurate assessment of infarct size. It is possible that a shorter time delay may be sufficient; experimental data by Verani et al. (46) demonstrated good evaluation of infarct size using tomographic

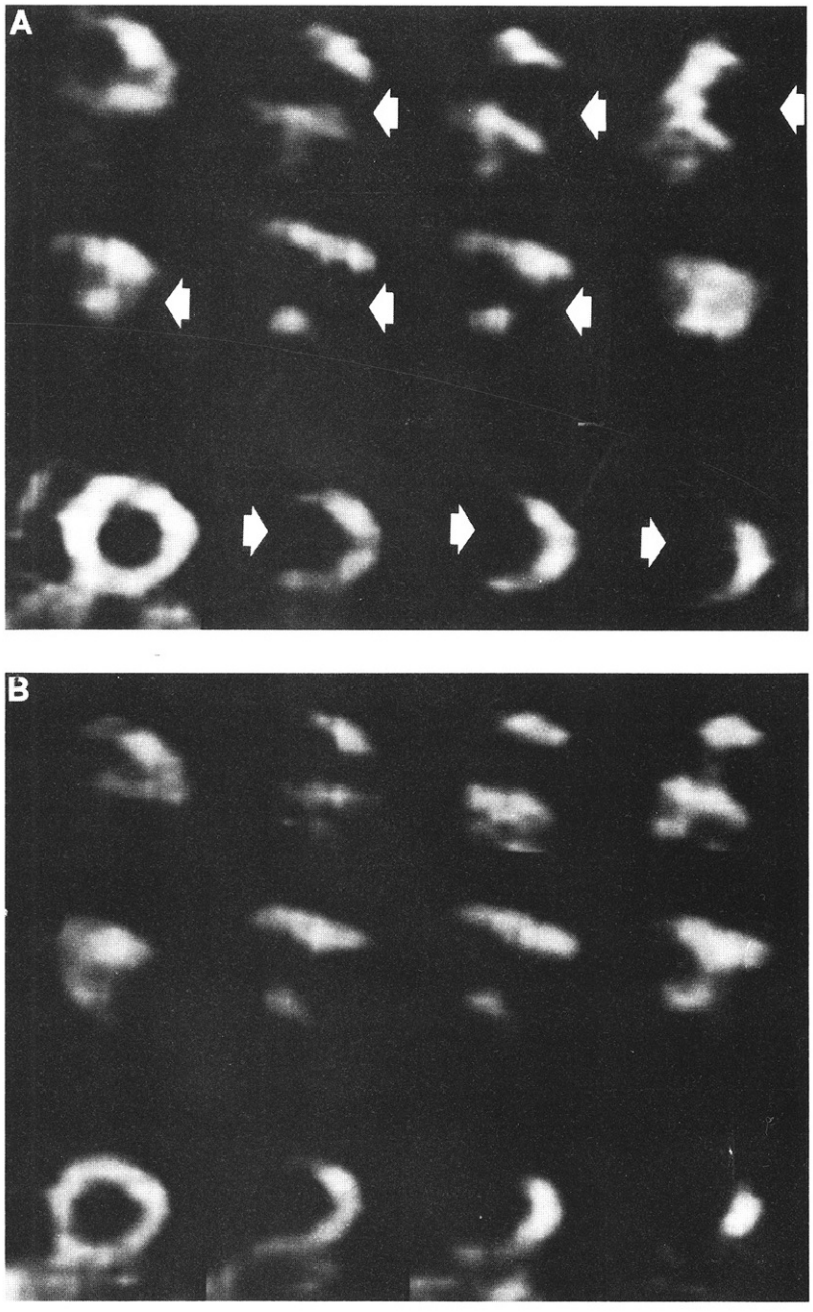

Figure 4. Patient 4. Same image sequence as in Figure 3. A large uptake defect involving the septal, anterior and apical walls is shown (**arrows**). No significant changes from admission (**A**) to 5 day imaging (**B**) occurred (6% decrease).

scintigraphy performed 48 h after reperfusion. In contrast, Grégoire et al. (51) showed a progressive reduction in scintigraphic defect score from a first tomographic study at 24 h to a later study after 7 days in patients with acute myocardial infarction who received thrombolytic therapy. Therefore more frequent scintigraphic control studies are needed to further define the optimal time for final infarct size quantification. On the basis of the available data, however, 5 days after the acute event may be a reasonable compromise that combines early evaluation and accurate assessment of infarct size.

In our study, perfusion defects were present in all patients in the scintigraphic study performed 5 days after admission. Seven patients showed a significant reduction in the extent of the defect when compared with the initial size: the reduction of the involved left ventricular mass ranged from 51% to 73%; in the remaining six patients, only a minimal reduction (varying from 1% to 8%) of the extent of the perfusion defect could be demonstrated. Infarct size determined on the basis of the postthrombolytic treatment scintigrams showed a good correlation with the amount of necrotic tissue evaluated using the MB CK curve.

Our results in humans agree with those of an experimental study in dogs (46), which showed that in the latter study,

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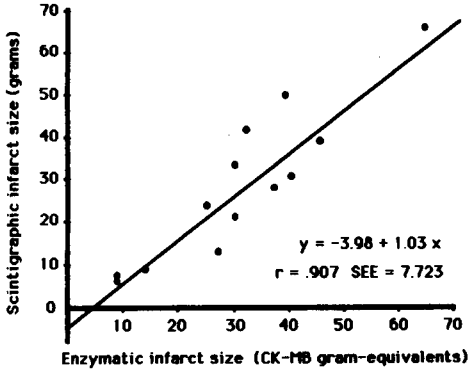


Figure 5. Correlation between enzymatic (CK-MB) and scintigraphic infarct size in 13 patients.

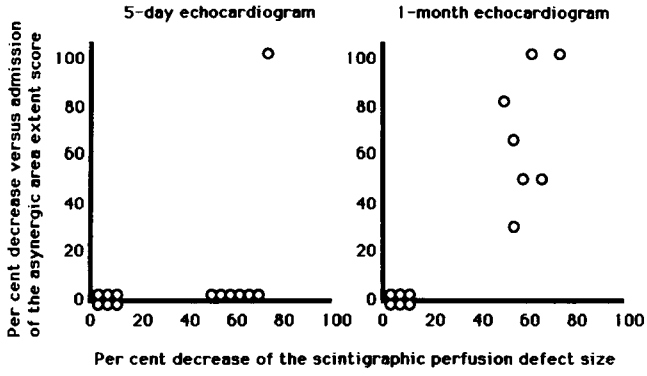
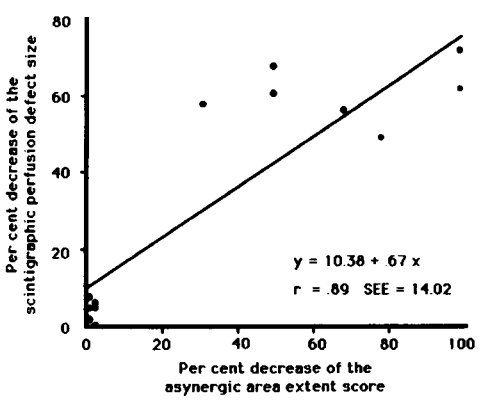


Figure 7. Evolution of the asynergic area extent score in the 5 day (**left**) and 1 month (**right**) echocardiogram compared with the percent decrease in the scintigraphic perfusion defect size in 13 patients.

myocardial imaging with technetium-99m hexakis 2-methoxyisobutyl isonitrile reliably evaluated infarct size, especially when the perfusion defect was estimated using SPECT imaging, which is less influenced by the overlap of normal and abnormal myocardium than is planar imaging. In another study in humans by Gibbons et al. (52), the extent of hypoperfused myocardium calculated on the basis of SPECT imaging performed 6 to 14 days after acute myocardial infarction correlated significantly with the ejection fraction at rest and with the regional wall motion score in the infarct segments, indicating its validity as a measure of infarct size.

Decrease in scintigraphic defect size, reperfusion and assessment of salvaged myocardium. If the perfusion defect on the initial scintigrams can be assumed to reflect the extent of myocardium at risk and the residual perfusion defect on the scintigram obtained 5 days later can be considered as an estimate of infarcted myocardial tissue, then the difference between the original perfusion defect and the residual defect is the scintigraphic expression of the amount of salvaged myocardium. This correspondence has been experimentally demonstrated in another study (46) in which the amount of salvaged myocardium calculated on the basis of scintigraphic data corresponded to the difference between the myocardial area vascularized by the occluded vascular bed and the anatomic infarct size.

Figure 6. Correlation between the percent decrease in the echocardiographic asynergic area extent score and the scintigraphic perfusion defect size in 13 patients.



Preliminary data in humans suggest the usefulness of technetium-99m isonitrile myocardial tomography in assessing the response to thrombolytic treatment in acute myocardial infarction (52–57). In our study, of the seven patients in whom a remarkable decrease in the perfusion defect was present, reperfusion could be inferred on the basis of noninvasive findings in three; all seven subjects had a patent infarct-related vessel at coronary angiography. In all of these patients, echocardiography performed 1 month later demonstrated a reduction in wall motion abnormalities, with a decrease of 33% to 100% in asynergic area extent score. In contrast, of the six patients who had a limited or negligible reduction in the perfusion defect size, noninvasive findings were suggestive of absent reflow in three, and in four subjects, coronary angiography demonstrated the occlusion of the infarct-related vessel. In these six patients, there was no detectable echocardiographic improvement in left ventricular wall motion, even after 1 month. Our data, which demonstrate a strict correlation between scintigraphic results and myocardial functional recovery, suggest that the decrease in scintigraphic defect size between the pre- and the postthrombolytic treatment scintigraphic images is really an expression of the amount of salvaged myocardium.

Reliability of conventional methods to assess the results of thrombolytic therapy in the individual patient. The importance of the opportunity offered by isonitrile tomography to "measure" the benefit obtained by the individual patient after thrombolytic therapy is emphasized by the absence of other reliable methods. Coronary angiography, apart from its invasiveness, can reliably demonstrate infarct-related vessel patency, but this does not necessarily imply myocardial salvage. In two of our patients, the absence of a significant decrease in perfusion defect, associated with a lack of late functional recovery, was demonstrated in the

presence of a patent infarct-related vessel. In these patients, late reperfusion, which was probably not related to the thrombolytic treatment and was not effective in salvaging myocardium, can be presumed to have occurred.

Other noninvasive techniques proposed for the evaluation of the results of thrombolytic treatment have important limitations. The ECG does not appear to be helpful in the identification of patients in whom significant myocardium salvage occurs as a result of reperfusion. Although several studies (58–61) indicate that statistically significant differences exist for R and Q wave changes between patient groups with successful or unsuccessful reperfusion, the ability to recognize different patterns of evolution on the basis of ECG data is limited in the individual patient (61). In our series, all but two patients developed Q waves after thrombolytic treatment, and an overlap in the QRS score was present between patients in whom scintigraphy showed a reduction in the original perfusion defect and those whose perfusion defect remained unchanged.

The usefulness of the early evaluation of left ventricular function to assess the results of thrombolytic therapy is also limited. Several studies (62–65) that compared function measured before and soon after successful thrombolytic therapy found no early recovery in either regional or global function. Instead, it has been found that return of contractile function in the salvaged tissue may require a long time: the "stunned" myocardium (66) needs this time to repair damaged metabolic processes or to reconstitute high energy phosphate stores (67,68). In our patients, two-dimensional echocardiograms performed 5 days after admission demonstrated the presence of regional asynergy in all but one subject. In these patients, comparison with echocardiograms recorded on admission before thrombolytic therapy failed to reveal any improvement in the asynergic area extent score despite the reduction in scintigraphic perfusion defect size.

Problems related to the imaging techniques. Technical problems encountered in performing an accurate quantitative assessment of the cardiac scintigraphic images cannot be denied. The movements of the heart in the chest as a result of breathing and myocardial wall motion during the cardiac cycle are possible sources of inaccuracy (69). The use of gated scintigraphy has been proposed to overcome this limitation, but its real usefulness has been questioned because of the decrease in collected counts per unit of time (70). In our study, we could not excessively prolong the acquisition time because of the condition of the patients, even though the features of the tracer would have allowed it. Another limitation is caused by the effects of attenuation and scatter on image quality, with ensuing decrease in both counting efficiency and spatial resolution (71,72). However, several nongated tomographic studies (73–75) have demonstrated the reliability of this method for quantitative studies in clinical practice. The possibility of accurate quantification of infarct volume using tomography with technetium-99m pyrophosphate has been demonstrated in dogs by Lewis et al. (76), who found a good correlation with the histologic estimate, and in humans by Corbett et al. (77) and Jansen et al. (78), who showed a high correlation, respectively, with the peak serum CK ($r = 0.83$) and with the enzymatic infarct size based on the MB CK curve ($r = 0.89$).

In our protocol, the bias produced by the limitations just mentioned and by the partial volume effect (79) is partly reduced by the fact that we assessed volumes and not tracer concentrations, that the involved tissue was also expressed as a percent of left ventricular mass and that we compared two estimates in the same subject and, therefore, under similar acquisition and reconstruction conditions. Furthermore, the features of our reconstruction technique must be considered. Previous experience (42) using phantoms and brain tomography demonstrated the higher image quality of our modified iterative algorithm as compared with the filtered backprojection that is usually employed. Even if these results cannot be simply transferred to the imaging of the heart without considering the differences due to the peculiar characteristics inherent in myocardial imaging, the high quality of the images obtained remains a favorable prerequisite for the application of quantitative measurements. The distinct contrast between perfused and nonperfused myocardial tissue permitted easy definition of myocardial contours and uptake defects by computer-assisted manual drawing, with consequent good interobserver reproducibility. In contrast, it must be admitted that our method cannot be considered a common one. Even if it does not require particularly sophisticated hardware, the procedure is certainly time-consuming and its routine use cannot be recommended.

Analysis of regional wall motion on left ventricular angiograms and two-dimensional echocardiograms was performed on the basis of the visual assessment of asynergic segments. Visual evaluation of asynergy has been validated in many previous studies in acute myocardial infarction (65,80,81). Although this type of evaluation may introduce a subjective element, the good interobserver agreement in our study suggests that the results were not significantly affected.

Limitations of the study. It is possible that the perfusion defects on the 5 day scintigrams do not exclusively reflect the extent of myocardial necrosis because a significant amount of tissue, although hypoperfused, may still be metabolically active. Positron emission tomography with ^{18}F-2-deoxyglucose reveals persistent tissue metabolism in a large number of segments with a fixed or partially resolving stress thallium defect. This implies that markers of perfusion may underestimate the extent of viable tissue in hypoperfused myocardial segments (82,83). Nevertheless, the impressive correlation found in our study between 5 day scintigraphic infarct size and enzymatic infarct size suggests that a large amount of myocardial tissue involved in the perfusion defects observed on the 5 day scintigrams was really necrotic.

The use of the enzymatic estimate of infarct size to confirm scintigraphic quantification may not be ideal. However, enzymatic evaluation of infarct size has been demonstrated as having a reliable correlation with anatomic data (84) and has already been employed to validate quantitative myocardial assessment using thallium-201 SPECT imaging (44,85). Although the value of this approach could be partially affected by the effects of reperfusion (86), this appears to be the only reasonable way to validate scintigraphic estimates of infarct size in humans.

The reliability of isonitrile tomography in assessing the effect of thrombolytic treatment on induced reperfusion must be interpreted cautiously. It is possible that the scintigraphic evaluation suggests coronary reopening induced by treatment when, in fact, reperfusion may be induced by the spontaneous activation of fibrinolytic factors or, alternatively, by the recruitment of collateral vessels around a persistent subtotal or total coronary occlusion. This last hypothesis is at least partially undermined by the demonstration at coronary angiography performed within 1 week of infarct-related vessel patency in all seven patients with scintigraphic defect size reduction.

Practical problems. The extensive applicability of this protocol may be limited by practical problems. The need to have the hexakis 2-methoxyisobutyl isonitrile labeled with technetium-99m promptly after patient admission to the coronary care unit requires rapid communication first between the home and the emergency room physician and then between the latter and the nuclear medicine department. In our institution, the admission of a patient with chest pain suggestive of acute myocardial infarction is generally announced in advance by phone by the city emergency ambulance coordination center; therefore, the nuclear medicine department can often be informed even before the patient is admitted to the hospital. Other problems may limit the general applicability of this procedure to patients with acute infarction. Such problems are mainly caused by the inconstant presence of physicians and technicians in some nuclear medicine departments, particularly during evenings and holidays, and the difficulty in organizing the transport of patients with an acute ischemic attack outside of the coronary care unit. However, the availability of mobile gamma cameras could enable at least planar scintigraphic imaging to be performed at the bedside without moving the patient from the emergency room.

Clinical implications. In the present study, we evaluated the ability of technetium-99m hexakis 2-methoxyisobutyl isonitrile SPECT imaging to assess the results of thrombolytic therapy in individual patients with acute myocardial infarction. Although myocardial salvage achieved by reperfusion is often expressed in terms of left ventricular functional recovery, salvage is primarily an anatomic entity defined as the reduction in infarct size from that envisaged should no intervention be undertaken (12,87).

Our data show that the comparison between pre- and post-thrombolytic treatment tomographic images enables assessment of salvaged myocardium and allows identification of successful versus unsuccessful reperfusion, even in patients whose other noninvasive findings are inconclusive. Although these data may not be particularly helpful in acute patient management strategies because the information is obtained well after the time when additional therapeutic options can be considered, their prognostic relevance cannot be denied. Furthermore, the demonstration that it is possible to predict late myocardial functional recovery on the basis of the results of the pre- and post-thrombolytic treatment scintigraphic evaluation enables the early identification of patients in whom improvement of left ventricular function is expected to occur.

Finally, the demonstration of the feasibility of this new approach in assessing the results of thrombolytic therapy opens the way to the possible use of this protocol to evaluate the effect of other therapeutic interventions in patients with acute myocardial infarction by direct assessment of myocardial salvage and residual infarct extent.

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