Serial Changes in Myocardial Perfusion Using Tomographic Technetium-99m-Hexakis-2-Methoxy-2-Methylpropyl-Isonitrile Imaging Following Reperfusion Therapy of Myocardial Infarction

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Resting tomographic myocardial perfusion images using technetium-99m-hexakis-2-methoxy-2-methylpropyl-isonitrile (Tc-Sestamibi) were obtained in 25 patients during their first myocardial infarction. Tc-Sestamibi was injected intravenously before acute reperfusion therapy, and repeated twice, at 18–48 hr, and at 6 to 14 days. Reperfusion was successful in 19 patients. In the patients with successful reperfusion, there was a mean decrease in the amount of hypoperfused myocardium between the initial and second studies (−9% ± 12%, p = 0.004) and a further decrease between the second and final studies (−10% ± 12%, p = 0.002). Nine of these 19 patients (47%) had evidence of significant improvement at the time of the second study. In six patients, significant improvement was not evident until the final study. Although tomographic imaging with Tc-Sestamibi following reperfusion therapy may show improvement in perfusion at 18–48 hr, the full extent of improvement is usually not evident until later.

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W ith the advent of thrombolytic therapy for the treatment of acute myocardial infarction, a noninvasive means of determining patency of the infarct-related artery and of quantitating the results of therapy would be valuable. Regional wall motion and ejection fraction have been used for this purpose, but have recognized limitations (1–3). Thallium scintigraphy has been used before and after thrombolytic therapy to assess the efficacy of reperfusion therapy (4–9). However, imaging

before thrombotic therapy is impractical, as it delays the initiation of therapy by nearly one-half hour.

The recently developed radiopharmaceutical, technetium-99m-hexakis-2-methoxy-2-methylpropyl isonitrile (Tc-Sestamibi), appears promising in the evaluation of myocardial perfusion (10–12). Its accumulation in normal myocardium in direct proportion to blood flow at rest (10,13), and, unlike thallium, its very slow washout permit delayed imaging for up to six hours after the initial administration. The late images still represent the myocardial perfusion at the time of administration. In previous reports from our multicenter study group (14,15), planar and tomographic imaging with Tc-Sestamibi allowed determination of the extent of myocardium at risk in patients with acute myocardial infarction. In these studies, the change in myocardial perfusion determined by Tc-Sestamibi before and after acute intervention has been shown to be useful in assessment of the efficacy of thrombolytic therapy. However, little is known about the time course of recovery of perfusion following reperfusion therapy.

This study was designed to assess the changes in the initial myocardial perfusion defect at two time points (18–48 hr and 6 to 14 days) following thrombolytic therapy and to determine whether the presence and extent of improvement may be predicted at 18–48 hr.

METHODS

Study Population

Twenty-five patients with acute myocardial infarction were enrolled. Data from some of the tomographic images of eleven of these patients (14) and data from the planar images of eight of these patients (15) were included in previous reports. Inclusion criteria were: 1) chest pain of at least 30 min, but less than 12 hr duration and 2) electrocardiographic ST elevation of at least 0.1 millivolts in at least two leads. Exclusion criteria

included: 1) evidence of previous myocardial infarction, 2) any technetium nuclear medicine study within 48 hr of presentation, and 3) clinical instability preventing transport within 6 hr of presentation to the Nuclear Cardiology Laboratory for tomographic imaging.

Clinical Care

All patients were admitted to the Coronary Care Unit and received conventional therapy. Within 12 hr of the onset of pain, 23 patients received acute reperfusion therapy, consisting of tissue plasminogen activator (TPA) in 7 patients, streptokinase in 1 patient, percutaneous transluminal coronary angioplasty (PTCA) in 11 patients, both TPA and PTCA in 3 patients, and both streptokinase and PTCA in 1 patient. Thrombolytic therapy was administered intravenously using conventional regimens (16). Acute reperfusion therapy was not selected for two patients.

All patients underwent cardiac catheterization during hospitalization, 24 within the first 48 hr. Coronary angiography was performed using a standard femoral or brachial approach. Left ventriculography was performed by a simultaneous biplane technique. Percutaneous transluminal coronary angioplasty was performed in 15 patients using previously described techniques (17). The infarct-related artery was identified by analysis of the electrocardiogram, left ventriculogram, and coronary angiogram, and determined to be patent (19 patients) or occluded (6 patients) according to previously established criteria (16).

Radionuclide Studies—Acquisition

Tc-Sestamibi was prepared in advance, four times daily, so as to be immediately available for patient usage. A sterile, non-pyrogenic, lyophilized kit was prepared as previously described (14). Each patient received 20 to 30 mCi of Tc-Sestamibi intravenously prior to the initiation of thrombolytic therapy. Radionuclide acquisitions were performed 1-6 hr (median 4 hr) later using a rotating gamma camera. Thirty images were acquired for 40 sec each, over a 180° arc, beginning 45° right anterior oblique and ending 45° left posterior oblique. Data from these studies are subsequently designated "initial."

A repeat injection of Tc-Sestamibi was given 18-48 hr after the initial dose. In 21 patients, this injection occurred prior to coronary angiography. One to six hours (median 1.5 hr) later, images were acquired in the same projections as used in the acute studies. Data from these studies are designated "18 to 48 hour."

Prior to discharge 6 to 14 days later, Tc-Sestamibi was again administered and images were acquired in a similar manner. Data from these studies are subsequently designated "final."

Resting radionuclide angiography was performed 1 day after the final Tc-Sestamibi study using modified in vivo labeling (18) and previously described techniques (19).

Radionuclide Studies—Processing

Processing of radionuclide studies was performed using previously described techniques (14,20) by an observer blinded to patient treatment and outcome. Short-axis slices of the left ventricle were obtained every pixel (6 mm) and normalized to the peak counts in the heart for each set of images. Circumferential count profiles were generated for representative apical, mid-ventricular, and basal short-axis slices by

identifying the peak counts in every 6° sector around the left ventricle. The ventricle was assumed to consist of a hollow cylinder at the base and mid-ventricle and a hollow cone at the apex. Relative volumes were estimated using the radius of the representative slice and standard geometric formulas. A threshold value of 60% of peak counts in each profile was used to determine the defect size. The defect size was expressed as a percent of the left ventricle that was hypoperfused. This method has been validated in phantom studies ($r = 0.99$) (20), and a similar threshold technique has been validated in an animal model ($r = 0.95$) (21).

As reported previously (14), intraobserver variability for the determination of the percent of hypoperfused left ventricle ranged from -5% to $+5\%$, mean $-1\% \pm 3\%$, $r = 0.97$. The interobserver variability was similar, ranging from -6% to $+3\%$, mean $-1\% \pm 3\%$, $r = 0.98$. Thus, significant improvement in perfusion was defined by a decrease in defect size of $>6\%$, or two standard deviations (s.d.s).

The resting ejection fraction was determined from the resting radionuclide angiogram using standard techniques (19).

Regional wall motion was assessed subjectively on the resting radionuclide angiogram by an observer blinded to the patient's treatment and outcome, using a grading system of 0 to 4 (4 = normal, 0 = akinesia or dyskinesia). A total of 10 segments were graded (3 on the anterior view, 5 on the left anterior oblique view, and 2 on the left lateral view). The wall motion score in the infarct territory was computed as the average of the appropriate segmental scores.

Statistical Analysis

The initial, 18-48 hr, and final hypoperfused regions for each patient were compared using a paired t-test. Comparisons between those with reperfusion and those with persistent occlusion of the infarct-related artery and between anterior and inferior infarcts were made with an unpaired t-test. Linear correlation was performed between the hypoperfused region, the resting ejection fraction, and the regional wall motion score. A p value < 0.05 was considered significant. All values are expressed as mean $\pm$ s.d.

RESULTS

Clinical Course

The clinical characteristics of the patients are shown in Table 1. Twelve patients received intravenous thrombolytic therapy beginning 84-540 min (median 140 min) after the onset of chest pain. Four of these patients also received percutaneous transluminal coronary angioplasty before the 18-48 hr studies. Eleven patients underwent PTCA alone, from 69 min to 12 hr (median 238 min) after the onset of chest pain.

Eight patients received late revascularization therapy between the 18-48 hr and final Tc-Sestamibi studies. This included PTCA in five patients, all with open arteries, and coronary artery bypass grafting in three patients, all with closed arteries.

Extent of Hypoperfused Myocardium

The amount of left ventricle that was hypoperfused on the initial study, prior to therapy, ranged from 9%

TABLE 1
Data Summary for the 25 Patients

No.	Age	Sex	MI location	Early reperfusion therapy*	Infarct-related artery	Arterial status after early therapy	Late revascularization†	Hypoperfused region (%LV)				Late rest EF	Late RWMS
								Initial	18–48 hr	Final	Change		
1	57	M	Anterior	TPA	LAD (prox)	90%	PTCA	58	18	25	−33	43	2.8
2	66	F	Lateral	TPA	RCA (prox)‡	70%	PTCA	49	53	33	−16	55	2.0
					LCF (diffuse)	40%							
3	72	M	Inferior	TPA	RCA (prox)	100%	CABG	9	15	4	−5	58	3.5
4	57	M	Inferior	TPA, PTCA	RCA (dist)	20%	None	21	25	14	−7	44	1.0
5	64	M	Anterior	TPA, PTCA	LAD (prox)	30%	None	58	59	54	−4	23	1.4
6	44	M	Anterior	TPA	LAD (mid)	95%§	PTCA	22	16	22	0	38	2.2
7	56	F	Inferior	TPA	RCA (prox)	95%	None	15	15	0	−15	69	4.0
8	52	M	Inferior	PTCA	LCF (prox)	100%	CABG	11	19	15	+4	44	2.0
9	64	M	Anterior	TPA	LAD (prox)	50%	None	68	59	60	−8	26	0.8
10	67	M	Inferior	None	RCA (prox)	100%	CABG	18	14	14	−4	63	¶
11	47	M	Inferior	None	RCA (prox)	100%	None	14	18	25	+11	57	0.0
12	50	M	Anterior	PTCA	LAD (mid)	10%	None	37	12	16	−21	45	3.8
13	42	M	Anterior	PTCA	LAD (mid)	30%	None	56	47	35	−21	33	1.2
14	59	M	Anterior	PTCA	LAD (mid)	40%	None	46	30	8	−38	53	2.2
15	70	M	Anterior	PTCA	LAD (mid)	30%	None	58	55	52	−6	33	1.2
16	60	M	Anterior	PTCA	LAD (mid)	20%	None	70	67	56	−14	33	1.2
17	77	M	Inferior	PTCA	RCA (mid)	40%	None	26	28	20	−6	43	3.0
18	56	M	Anterior	streptokinase, PTCA	LAD (prox)	50%	None	77	59	47	−30	39	1.4
19	59	M	Inferior	streptokinase	RCA (mid)	100%	None	26	28	25	−1	54	1.5
20	62	M	Inferior	TPA	LCF (dist)	90%	PTCA	38	33	29	−9	63	1.0¶
21	68	M	Inferior	PTCA	LCF (dist)	20%	None	10	9	9	−1	64	2.0
22	87	M	Anterior	PTCA††	OM 1	99%	None	15	3	3	−12	64	4.0
23	72	M	Anterior	PTCA	LAD (prox)	20%	None	74	58	16	−58	45	1.8
24	66	M	Inferior	TPA, PTCA	RCA (mid)	30%	None	30	8	2	−28	53	2.5
25	71	M	Anterior	PTCA	LAD (mid)	40%	PTCA	55	55	32	−23	43	1.2

* Includes therapy within the first 12 hr of the onset of chest pain, performed prior to the 18–48 hr Tc-Sestamibi study.

† Includes therapy performed following the initial Tc-Sestamibi study, but prior to the final study.

‡ Wall motion and perfusion abnormalities present in both inferior and lateral walls.

§ Attempted PTCA led to occlusion of left anterior descending coronary artery and inadequate views of inferior wall because of severe dilatation of right ventricle.

¶ Inadequate views of inferior wall because of severe dilatation of right ventricle.

** RWMS for lateral wall.

†† Artery had spontaneously recanalized (TIMI grade 3 flow); PTCA could not be performed because of vessel tortuosity.

CABG = coronary artery bypass grafting, EF = ejection fraction, LAD = left anterior descending coronary artery, LCF = left circumflex coronary artery, LV = left ventricle, MI = myocardial infarction, OM 1 = first obtuse marginal coronary artery, PTCA = percutaneous transluminal coronary angioplasty, RCA = right coronary artery, RWMS = regional wall motion score, and TPA = tissue plasminogen activator

to 77%. The 18–48-hr study, performed after thrombolytic therapy, demonstrated hypoperfusion ranging from 3% to 67% of the left ventricle. The final study, performed prior to discharge, demonstrated hypoperfusion ranging from 0 to 60% of the left ventricle.

In the 19 patients with successful reperfusion, there was a mean decrease in the amount of the left ventricle hypoperfused between the initial and 18–48 hr studies (−9% ± 12%, p = 0.004), and a further decrease, also significant, between the 18–48-hr and final studies (−10% ± −12%, p = 0.002, Fig. 1). The overall decrease between the initial and final studies was highly significant (−18% ± 14%, p = 0.0001). In three patients (Patients 1, 9, and 11), the improvement in perfusion

was slightly greater at 18–48 hr (7%, 1%, and 4%, respectively), than at the final study. In the six patients with persistent occlusion, there was an insignificant increase in the amount of the ventricle that was hypoperfused at 18–48 hr (1% ± 6%) and at the final study (1% ± 7%) (Fig. 2).
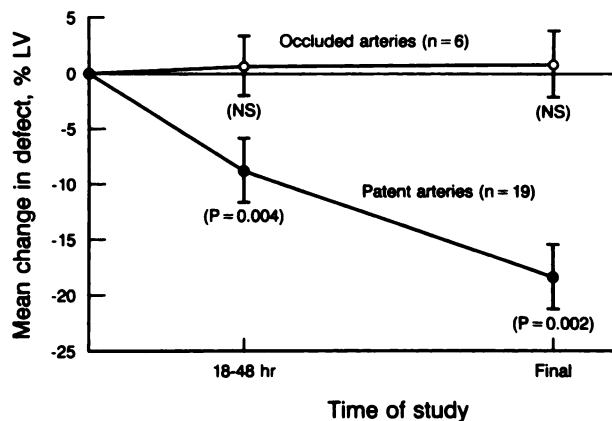
Significant improvement in perfusion, as defined by a decrease in defect size of >6%, occurred in 9 (47%) of the 19 patients with patent arteries between the initial and the 18–48-hr studies. This improvement was sustained in the final study. In an additional six patients, improved perfusion was evident only at the time of the final study. The sensitivity of the 18–48-hr test in predicting final improvement in perfusion was 60% (9
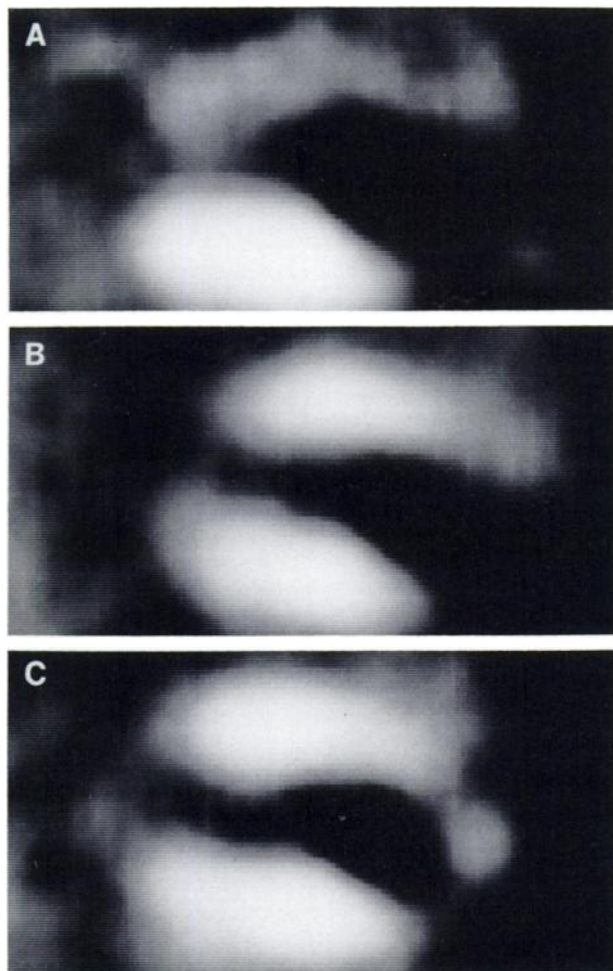
FIGURE 1
Representative serial vertical long-axis images for Patient 23. The anterior wall is at the top of the image, the apex is on the right, and the inferior wall is at the bottom. (A) Initial image before treatment. (B) Image obtained 27 hr later. (C) Image obtained 6 days later. There is improvement in the image at both of the follow-up studies, but a persistent perfusion defect.
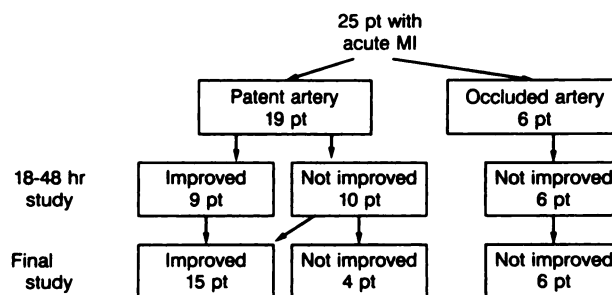

FIGURE 2
The mean change in perfusion defect as a percent of the left ventricle (%LV) at the time of the 18–48-hr and 6–14-day studies is plotted for the 19 patients with patent arteries and the 6 patients with occluded arteries. NS = not significant.

## Correlation of Hypoperfused Myocardium with Ejection Fraction and Regional Wall Motion Score

The percent of hypoperfused left ventricle at the final study correlated significantly (r = −0.77, p = .0001) with the resting ejection fraction by radionuclide angiography. As expected, the correlation improved from the initial to the final Tc-Sestamibi studies (Table 2). The percent of hypoperfused left ventricle also correlated significantly with the regional wall motion score in the infarct segment, both for anterior (r = −0.72, p = 0.003), and inferior infarcts (r = −0.79, p = 0.001). The change in hypoperfused myocardium did not correlate with either the final amount of hypoperfused myocardium (r = 0.09) or the ejection fraction (r = 0.09).

DISCUSSION

In previous studies, planar and tomographic imaging with Tc-Sestamibi has been shown to be useful for assessing myocardium at risk in patients with acute myocardial infarction (*14,15*). Furthermore, the change

of 15 patients); the specificity was 100%. In patients in whom reperfusion therapy failed to restore arterial patency, or in whom reperfusion therapy was not administered, there was no significant improvement in perfusion at the times of the 18–48-hr or the final studies (Fig. 3).

Among the 15 patients in whom a significant improvement in perfusion was demonstrated, there was a trend toward greater final improvement in perfusion in those 9 patients in whom improvement was evident at the 18–48-hr study compared to those 6 patients in whom improvement was not evident until the final study (Fig. 4). This difference was of borderline significance (p = 0.054). The amount of improvement at 18–48 hr correlated weakly with the amount of improvement at the final study, (r = 0.53).

FIGURE 3
This flow diagram relates the patency of the infarct-related artery to subsequent changes in perfusion at 18–48 hr and at the final study.
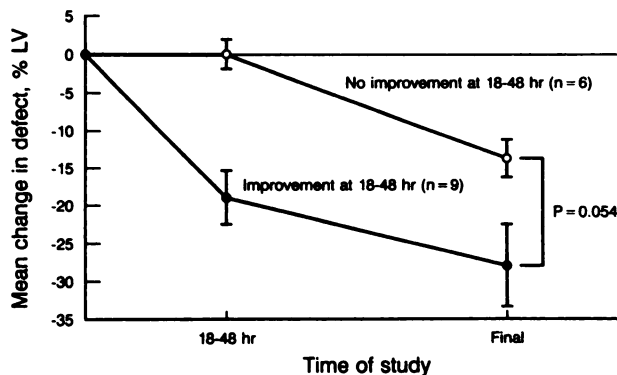
FIGURE 4
The mean change in defect as %LV is plotted at the time of the 18–48-hr study and the final study for 15 patients in whom a significant improvement in patient was demonstrated. The patients are subdivided into the group of 9 patients in whom improvement was evident at 18–48 hr, and the 6 patients in whom improvement was not present until the final study.

in myocardial perfusion determined by Tc-Sestamibi before and after acute myocardial infarction appears to be a promising tool for the assessment of the effect of acute thrombolytic therapy (14).

Although the uptake of Tc-Sestamibi generally parallels that of thallium-201 (^{201}Tl) (22,23), differences have been noted (12). Myocardial accumulation of ^{201}Tl is generally presumed to reflect myocardial viability (7, 24). However, early after reperfusion, the uptake of ^{201}Tl appears to more closely reflect regional blood flow rather than viability (25–27). Thus, early ^{201}Tl uptake may overestimate the extent of improvement in perfusion, although this phenomenon appears to resolve after 48 hr (26). While several preliminary experimental studies indicate that cell viability is necessary for the uptake of Tc-Sestamibi (28–30), another study has suggested that in areas of reperfusion, early Tc-Sestamibi imaging overestimates flow (31).

The current study suggests that the improved uptake of Tc-Sestamibi at 18–48 hr is not due to reactive hyperemia, but instead indicates viable myocardium. In each patient in whom the 18–48-hr study showed a significant increase in perfusion, this increase was maintained at the time of the final study. In only three patients was there evidence of slightly greater improve-

TABLE 2
Correlation of Perfusion Defect with Rest Ejection Fraction*

Time of study	Correlation coefficient	
Initial	r = −0.67	p = 0.0002
18–48-hr	r = −0.68	p = 0.0002
6–14 days	r = −0.77	p = 0.0001

* n = 25 patients.

ment in perfusion at 18–48 hr than at the final study. Although these findings could be interpreted as "reactive hyperemia," the differences were small (1%, 4%, and 7%), and within the 6% reproducibility of the technique in two of the three patients. Further studies are needed to determine whether these findings at 18–48 hr apply to images performed earlier after reperfusion. In addition, the correlation of the perfusion defect with the rest ejection fraction obtained by pre-discharge radionuclide angiogram improved from the time of the initial to the final Tc-Sestamibi studies, suggesting initially ischemic but viable myocardium. Furthermore, the pre-discharge regional wall motion score in the infarct area was inversely correlated with the final amount of hypoperfused myocardium for both anterior and inferior infarctions. Thus, both global and regional function are closely related to the uptake of Tc-Sestamibi on the final images.

A noninvasive means of determining the success of reperfusion therapy in restoring patency of the infarct-related artery and in salvaging myocardium would be very useful. Among the patients in this study with patent arteries, a significant (p = 0.004) decrease in the extent of hypoperfusion was evident at 18–48 hr, although substantial additional improvement occurred later. Among those patients in whom significant improvement in perfusion was demonstrated, there was a trend toward a greater final extent of improvement in those patients in whom improvement was evident at 18–48 hr. However, the amount of improvement in perfusion at 18–48 hr was not a good predictor of the amount of improvement at the final study. In each patient in whom a decrease in the perfusion defect of >6% was noted, arterial patency was demonstrated. Therefore, although the 18–48-hr study was highly specific (100%) in predicting artery patency, its sensitivity was only 60%. A subgroup of the patients reported here also had planar imaging with quantitation of defect size (15). The serial changes in defect size by planar imaging and correlation with arterial patency are in agreement with the present tomographic study. It is possible that further analysis of data may permit prediction of arterial patency with greater accuracy. In addition, it may be possible to appreciate changes earlier after reperfusion by administering a split dose of Tc-Sestamibi (32,33).

This study has a number of limitations. The requirement for frequent kit preparation may limit the widespread application of this technique. Limitations in the validation of the quantitative method, which assumes uniform myocardial shape and thickness, and is based on a static cardiac phantom, have been discussed previously (14). The time intervals between the reperfusion therapy and the two follow-up perfusion studies were variable. Eight patients underwent additional revascularization therapy prior to the final perfusion study, which may have influenced the results.

Despite the limitations, these data demonstrate that tomographic imaging with Tc-Sestamibi is a promising tool for assessing sequential changes in myocardial perfusion following reperfusion therapy. Improvement in perfusion is often evident by 18–48 hr. However, the full extent of improvement is usually not evident until later.

ACKNOWLEDGMENTS

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