

# Thrombolysis in Acute Myocardial Infarction Using Intracoronary Streptokinase: Assessment by Thallium-201 Scintigraphy

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**SUMMARY** Twenty-one patients with acute myocardial infarction, admitted to the hospital within 4 hours after the onset of symptoms, were studied by seven-pinhole thallium-201 scintigraphy before and 1 hour and 24 hours after intracoronary fibrinolysis using streptokinase. The size of the thallium-201 perfusion defect was assessed from myocardial cross sections reconstructed from the original seven-pinhole data and expressed as a fraction of left ventricular circumference.

Recanalization was achieved in 16 patients within  $3.9 \pm 1.6$  hours after onset of symptoms (group A). In these patients, the size of the perfusion defect had decreased from  $36 \pm 17\%$  to  $19 \pm 15\%$  ( $p < 0.001$ ) at 24 hours. No significant change was detected by redistribution at 1 hour after the intervention. In five patients, intracoronary fibrinolysis was unsuccessful, and the vessel remained occluded (group B). The thallium-201 perfusion defect affected  $40 \pm 15\%$  of the left ventricular circumference before the intervention; it remained virtually unchanged at 1 hour ( $37 \pm 16\%$ ) and at 24 hours ( $41 \pm 15\%$ ) after fibrinolysis. The perfusion defect was most reduced in patients with extensive collaterals supplying the ischemic area or with subtotal occlusion of the affected coronary artery.

We conclude that successful intracoronary fibrinolysis may reduce the size of the thallium-201 perfusion defect in many patients with acute myocardial infarction. One important factor in the final result may be the presence of residual coronary flow supplied by extensive collaterals or by subtotal occlusion of the affected coronary artery when reperfusion is achieved around 4 hours after the onset of symptoms.

RECENT REPORTS have shown that rapid recanalization of acutely occluded coronary vessels by intracoronary infusion of streptokinase is feasible.<sup>1-7</sup> However, a crucial question remains to be answered: whether early reperfusion within the time limits of a clinical setting actually preserves myocardial structure, or at least reduces the final size of the necrotic myocardial segment. In this study, thallium-201 (<sup>201</sup>Tl) seven-pinhole tomography was used to follow the time course of the perfusion defect in patients with acute coronary occlusion who underwent intracoronary fibrinolysis.

## Methods

### Patient Selection

Patients were included in the study if they had acute onset of chest discomfort less than 4 hours before hospital admission and electrocardiographic evidence of acute transmural myocardial infarction (ST-segment

elevation with or without pathologic Q waves). Exclusion criteria were recent gastrointestinal bleeding, trauma, surgery or malignant neoplasm. The nature, potential benefits and possible risks of the study were fully explained, and the patients gave written, informed consent.

### Study Protocol

#### Radionuclide Studies

After the initial evaluation, 2.0 mCi of <sup>201</sup>Tl were injected into a peripheral vein. The patient was transferred to the cardiac catheterization laboratory, and while the catheterization team was setting up for the intervention, imaging was begun 10 minutes after the application of the radioisotope. All studies were performed with a mobile gamma camera (Picker Dyna Mo) equipped with a seven-pinhole collimator (aperture size 5.5 mm). The camera head was positioned over the cardiac apex in a 40–45° left lateral projection to align it with the long axis of the left ventricle. A 30% symmetric energy window centered on the 80 keV peak was used. A total of 2.5 million counts was collected, usually in less than 10 minutes. The studies were performed in the catheterization laboratory to avoid a delay.

A second image was recorded after termination of the catheterization. Twenty-four hours later, a second dose of <sup>201</sup>Tl (1.0–1.5 mCi) was injected and a third image was recorded. All scintigraphic data were trans-

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Supported by a grant from the Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg, within the SFB 90-Cardiovasculäres System der Universität Heidelberg.

Presented in part at the 30th Annual Scientific Session of the American College of Cardiology, San Francisco, California, March 1981.

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Received July 15, 1981; revision accepted January 7, 1982.

Circulation 66, No. 3, 1982.

ferred on line to a computer for storage and evaluation (DEC PDP 11/34).

### *Invasive Studies*

Upon completion of the radionuclide studies, the patient received the following premedication intravenously: diazepam, 10 mg; prednisolone, 500 mg; and heparin, 2500 U. Using the femoral approach, left ventricular (LV) angiography and coronary angiography were performed using the Judkins technique. The occluded vessel was identified and a streptokinase infusion was started through the indwelling Judkins catheter; 2000 U/min of streptokinase were delivered selectively to the occluded coronary artery. Control injections of contrast medium were repeated at 15-minute intervals throughout the procedure. If there was no visible progress within the first hour after institution of fibrinolytic therapy, an attempt was made to penetrate the clot mechanically by carefully advancing a guidewire. The streptokinase infusion was terminated 15 minutes after recanalization of the occluded vessel, or upon reaching a maximum total dose of 200,000 U of streptokinase. To prevent reocclusion, heparin (30,000 U/day) was started after the initially prolonged thrombin time had returned to less than twice the control value. The catheter sheath was left in place for 24 hours to prevent major bleeding from the puncture site.

### **Laboratory Findings and ECG Changes**

In addition to routine laboratory tests, blood samples for creatine kinase, glutamic-oxaloacetic transaminase and lactate dehydrogenase were drawn every 12 hours. Twelve-lead ECGs were taken daily.

### **Data Processing and Evaluation (fig. 1)**

#### *Thallium-201 Scintigrams*

Eight cross-sectional planes through the left ventricular myocardium, perpendicular to the long axis, were

reconstructed from the original data stored on magnetic tape using a commercially available computer algorithm.<sup>9, 10</sup> To define the areas with decreased <sup>201</sup>Tl uptake, all reconstructed myocardial cross sections were analyzed by a semiquantitative program described by Vogel et al.<sup>10</sup> In brief, after the geometric center of each cross section is defined, 60 radii are projected outward from this point at equal angular spacing. A search is made along each radius for the peak count rate, which is then normalized to the maximum count rate in each patient. The results are displayed as a circumferential plot over 360°.

Abnormal myocardial sections are identified by comparing each circumferential plot to the lower limit of normal as defined by 15 patients free of cardiac abnormalities (mean  $\pm$  SD), who were analyzed correspondingly. If a section showed decreased thallium-201 uptake, no attempt was made to grade the degree of abnormality. The mean of all cross sections was calculated and expressed as a fraction of LV circumference. Intraobserver variability was  $\pm$  5% and interobserver variability  $\pm$  9%.

### *Invasive Studies*

LV volumes and ejection fractions were calculated according to the area-length method;<sup>11</sup> coronary angiograms were evaluated by an independent observer who was unaware of the results of the radionuclide studies. Coronary collateralization was assessed according to the method described by Hamby et al.<sup>12</sup> In brief, presence of collaterals required visualization of the left anterior descending coronary artery with complete obstruction of the vessel, or visualization of the posterior descending coronary artery in the presence of complete, proximal right coronary artery obstruction. Significant collateral flow was considered present only when there was opacification of the major trunk of the occluded vessel.

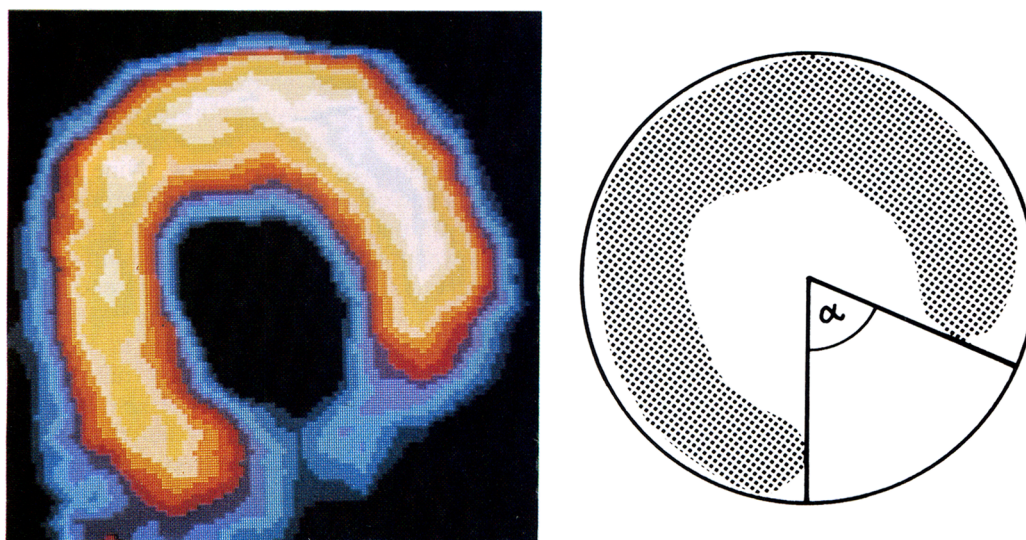


FIGURE 1. Method of assessing size of thallium-201 perfusion defect. After defining the geometric center of each myocardial cross section, the angle ( $\alpha$ ) under which the perfusion defect appeared was measured and expressed as a fraction of the left ventricular circumference.

TABLE 1. Results of the Study

Pt	Age (years)	Lesion		Collat- erals	LVEF (%)	Killip class	$\Delta t$ (hours)	$\Sigma$ Strep (U $\times$ 1000)	Size of $^{201}\text{Tl}$ perfusion defect (% LV)			
		Before	After						24 hours			
Group A												
1	72	LAD	100	90	+	44	I	3.5	200	61	60	44
2	43	RCA	100	90	+	25	I	3.5	180	52	41	22
3	45	LAD	99	90	+	37	I	7.5	120	49	44	18
4	63	RCA	100	90	+	33	III	4.0	140	40	40	6
5	71	LAD	99	90	0	48	II	5.0	200	47	46	19
6	58	LAD	99	90	0	60	I	1.5	240	51	48	13
7	66	RCA	99	75	0	61	I	4.5	125	11	8	3
8	64	RCA	100	90	+	49	I	5.5	200	13	19	8
9	63	LAD	100	90	0	46	I	1.5	60	43	42	38
10	52	RCA	100	50	0	—	II	3.5	200	16	17	0
11	59	RCA	100	75	0	46	I	4.5	175	29	21	19
12	60	LAD	100	95	0	50	I	5.0	200	53	54	50
13	61	LAD	100	90	0	52	I	2.0	200	46	44	36
14	55	RCA	100	90	0	54	I	4.0	100	14	13	6
15	35	LCx	100	75	0	47	I	4.0	200	15	19	7
16	39	RCA	100	75	0	47	I	4.0	180	29	19	12
Mean	55.6					47		3.9	170	36	33	19*
$\pm$ SD	$\pm 11.0$					$\pm 9$		$\pm 1.6$	$\pm 48$	$\pm 17$	$\pm 16$	$\pm 15$
Group B												
17	73	LAD	100	100	0	56	II	—	200	54	52	54
18	43	RCA	100	100	+	60	I	—	200	23	22	22
19	65	LAD	100	100	0	36	III	—	180	27	31	31
20	66	RCA	100	100	?	26	I	—	200	56	55	57
21	46	LAD	100	100	0	41	I	—	200	42	36	40
Mean	58.6					44			196	40	37	41
$\pm$ SD	$\pm 13.2$					$\pm 7$			$\pm 9$	$\pm 15$	$\pm 16$	$\pm 15$

\*Significantly different from before ( $p < 0.001$ ).

Abbreviations: LVEF = left ventricular ejection fraction (before intervention);  $\Delta t$  = time from onset of symptoms to reflow;  $\Sigma$  Strep = total amount of streptokinase used; LAD = left anterior descending coronary artery; RCA = right coronary artery; LCx = left circumflex coronary artery.

### Statistical Analysis

Values are mean  $\pm$  SD. Serial data, such as the size of the perfusion defect, were examined for statistical significance by analysis of variance (Friedman's test). Single comparisons between unrelated data were made by the  $t$  test for unpaired data.

### Results

The results are summarized in table 1.

#### Patients

Twenty-one patients, all males, fulfilled the admission criteria and consented to intracoronary fibrinolysis. Their mean age was 57 years (range 35–73 years). The ECG diagnosis was inferior infarction in 10 patients and anterior, anteroseptal or anterolateral infarction in 11. On admission, two patients (nos. 4 and 19) were in Killip class III and three (nos. 5, 9 and 17) were in class II; the 16 other patients were in class I. Creatine kinase levels, although not part of the admission criteria, were normal in all patients when fibrinolysis was instituted.

#### Invasive Studies (figs 2–4)

Seven patients showed complete occlusion of the left anterior descending coronary artery (LAD) by angiography; three showed subtotal occlusion (99%), with minimal, sluggish flow. Nine patients showed complete occlusion of the right coronary artery (RCA) and one patient showed subtotal occlusion. One patient showed total occlusion of the left circumflex coronary artery (LCX). Five patients had extensive collateral circulation supplying the ischemic segment.

Recanalization was achieved in 16 patients (76%) within an average of 3.9 hours (range 1.5–7.5 hours) after the onset of symptoms. Those 16 patients constitute group A. Fibrinolysis failed to reopen the occluded vessel in five patients (31%). Those patients constitute group B. In group A, the average dose of streptokinase was 170,000  $\pm$  48,000 U in group A; in one patient, fibrinolysis was continued beyond the upper limit of 200,000 U after the vessel had been reopened in order to dissolve residual clot. In group B, the average dose was 196,000  $\pm$  9,000 U; in one patient, fibrinolysis was terminated before reaching





FIGURE 2. Coronary angiogram from patient 4 before thrombolysis. The right coronary artery is totally occluded.

200,000 U because of deterioration of the patient's condition. The LV ejection function before fibrinolysis was moderately depressed in both groups ( $47 \pm 9\%$  in group A and  $46 \pm 11\%$  in group B) (NS).

Among the 21 patients of this study, three patients died during hospitalization. A 73-year-old patient (no. 17) with three-vessel disease and occlusion of the LAD that could not be recanalized died 38 hours after the intervention in cardiogenic shock. A 65-year-old patient (no. 19) with three-vessel disease and new occlusion of the LAD that could not be reopened died 4 days after fibrinolysis in cardiogenic shock. A 66-year-old

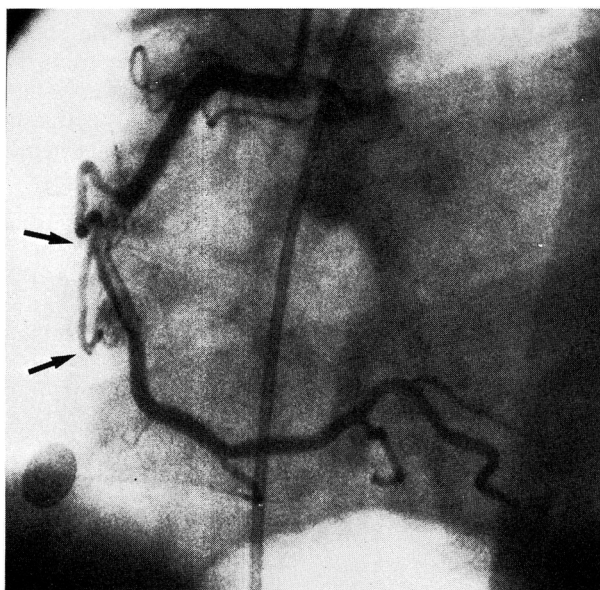


FIGURE 3. Control angiogram after 1 hour of fibrinolytic therapy. There is distal filling of the right coronary artery; however, residual thrombus formations can be identified (arrows).

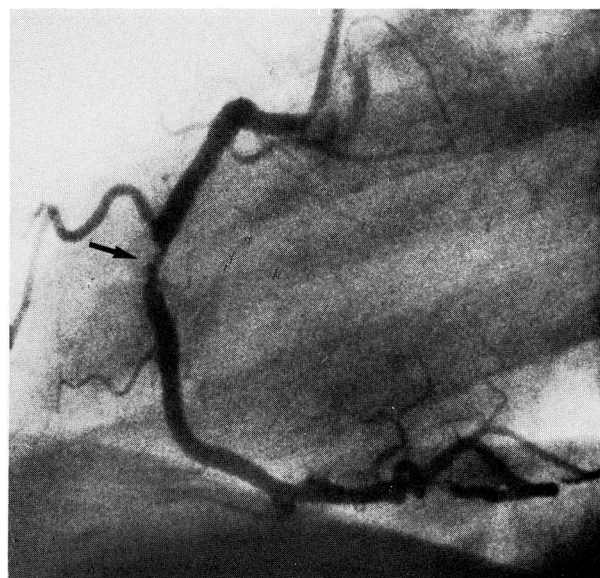


FIGURE 4. Control angiogram obtained at the conclusion of the intervention. All thrombus formations have disappeared; a fixed 75% stenosis remains (arrow).

patient (no. 20) with poor LV function (LV ejection fraction 26%), three-vessel disease, and new occlusion of the RCA that could not be reopened died of sudden cardiac arrest after he had been transferred to a general ward 2 weeks after the intervention. Except for minor bleeding from puncture sites, no complications were encountered.

#### Radionuclide Studies (table 1, figs. 5–7)

Before thrombolysis, a perfusion defect was present on all  $^{201}\text{Tl}$  scintigrams, which corresponded to the site of coronary occlusion and to the wall motion abnormality noted on the LV angiogram. The average size of the underperfused area was  $36 \pm 17\%$  of the LV circumference in group A and  $40 \pm 15\%$  in group B (NS). At 1 hour after fibrinolysis, no change in size of the perfusion defect was detected by  $^{201}\text{Tl}$  redistribution (group A:  $33 \pm 16\%$ , group B:  $37 \pm 16\%$ ). At 24 hours after fibrinolysis,  $^{201}\text{Tl}$  uptake improved significantly in group A ( $19 \pm 15\%$ ) ( $p < 0.001$ ); it had completely normalized in one patient and did not change in four patients. In group B,  $^{201}\text{Tl}$  uptake was virtually unchanged from control ( $41 \pm 15\%$ ) (NS).

#### Factors Related to Reduction of Perfusion Defect Size

To identify factors in the final result of intracoronary fibrinolysis, the reduction in size of the perfusion defect observed at 24 hours was correlated to other variables. No significant correlation was found for the time difference between onset of symptoms and reflow because of the narrow constraints specified by the study protocol ( $r = 0.1$ ), or for the initial size of the perfusion defect ( $r = 0.2$ ). However, in patients 1–8, who had extensive collaterals or subtotal occlusion, the  $^{201}\text{Tl}$  perfusion defect at 24 hours decreased significantly more (from  $41 \pm 18\%$  to  $17 \pm 13\%$ ) compared with patients 9–16, who had poor or no collaterals and total occlusion ( $31 \pm 15\%$  vs  $21 \pm 18\%$ ) ( $p < 0.01$ ).



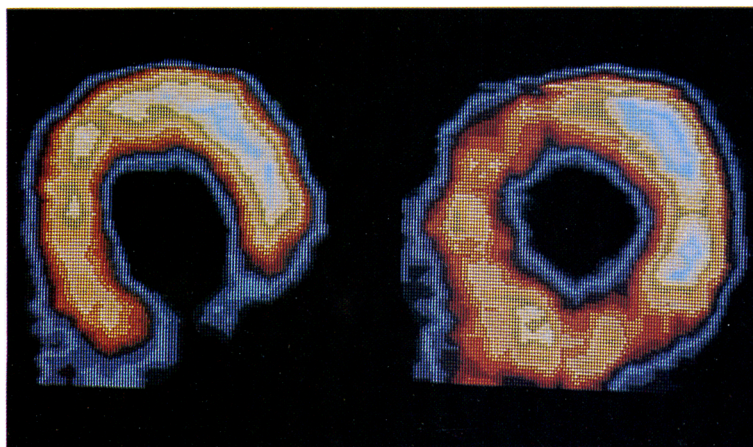


FIGURE 5. Seven-pin-hole thallium-201 scintigram obtained in patient 4 before (left) and 24 hours after (right) successful recanalization. There is total resolution of a large perfusion defect in the inferior aspect of the left ventricular circumference.

### Laboratory Findings and ECG Changes

After the intervention, all patients showed signs of myocardial necrosis. CK levels increased to at least four times the control value, and there were new Q waves or loss of R-wave amplitude on routine ECGs.

### Discussion

Thallium-201 scintigraphy offers a unique dimension in assessing changes of myocardial perfusion and viability in response to therapeutic intracoronary fibrinolysis in evolving myocardial infarction. Two main factors determine the intracellular uptake of  $^{201}\text{Tl}$ : regional blood flow and the integrity and functional status of the myocytes.<sup>13-15</sup> Necrotic tissue fails to accumulate  $^{201}\text{Tl}$ , whereas restoration of flow to an ischemic area, at a time when irreversible damage has not yet supervened, will invariably normalize  $^{201}\text{Tl}$  uptake.<sup>16-22</sup>

Experimental studies in animals<sup>8</sup> and in myocardial cell cultures<sup>23</sup> have shown that myocytes are no longer capable of extracting and storing thallium once they have been damaged irreversibly by anoxia or calcium overload. The initial thallium perfusion defect measured in this study represents a mixture of ischemia and infarcted area, new or old. On reperfusion, previously

anoxic but still viable cells will start to extract thallium from the blood stream, provided they do not suffer reperfusion damage. Hence, changes in  $^{201}\text{Tl}$  uptake early after reperfusion should reflect the amount of ischemic myocardial tissue salvaged.

The results of the present study indicate that there was significant improvement of  $^{201}\text{Tl}$  uptake in many patients with acute myocardial infarction in whom intracoronary streptokinase was successfully used to recanalize the occluded vessel (group A). In contrast, in patients in whom the vessel probably remained occluded, no overall change of the perfusion defect was noted at 24 hours after the intervention (group B). Similar results were reported by Maddahi<sup>7</sup> and Markis<sup>8</sup> in patients undergoing intracoronary fibrinolysis using intracoronary injections of  $^{201}\text{Tl}$ . In group A, the data have a wide scatter, indicating that the results achieved were quite variable. Total or nearly total normalization of  $^{201}\text{Tl}$  uptake was seen in only six patients of group A; hardly any change in size of the perfusion defect was noted in three of these patients.

Several factors may account for these differences: (1) The duration of the ischemia (the time from the onset of symptoms until coronary reflow was established). In this series of patients, however, no significant correlation between the duration of the ischemia

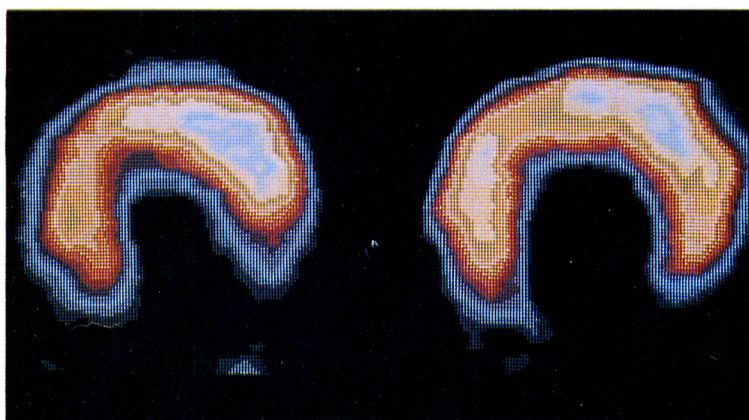


FIGURE 6. Seven-pin-hole thallium-201 scintigram from patient 18 before (left) and 24 hours after (right) unsuccessful intracoronary fibrinolysis. The inferior perfusion defect remains essentially unchanged.

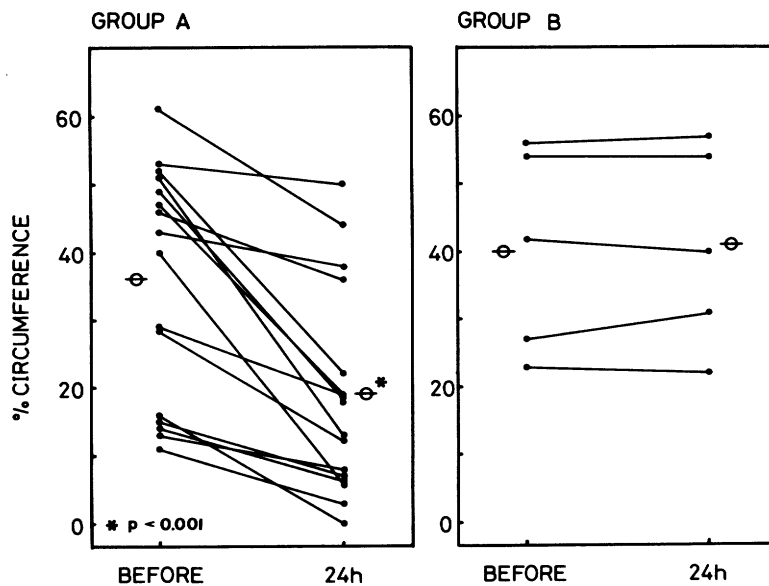


FIGURE 7. Size of thallium-201 perfusion defects before and 24 hours after thrombolysis expressed as a percentage of left ventricular circumference. In 16 patients in whom the intervention was successful (left), there is significant improvement of thallium-201 uptake; very little change is noted in five unsuccessful cases (right).

and improvement of  $^{201}\text{Tl}$  uptake was found ( $r = 0.1$ ) because of the narrow time limits specified by the study protocol. (2) The initial size of the perfusion defect ( $r = 0.2$ ) and the site of the coronary occlusion were not related to the final result, i.e., the reduction of the perfusion defect. (3) If patients were arranged according to the degree of collateralization of the ischemic area, in patients with extensive collaterals or only subtotal occlusion with some residual flow (patients 1–8), improvement of  $^{201}\text{Tl}$  uptake was significantly greater than in those patients in whom only few or no collaterals and total occlusion of the vessel were observed. In patients in whom fibrinolysis failed to reopen the vessel, even the presence of extensive collaterals did not affect the further course of the ischemic segment.

Although the number of patients constituting the study population is quite small, it is striking to note that all early deaths occurred in patients in whom the intervention was unsuccessful, whereas no deaths were observed among patients of group A. Studies on more patients will have to clarify whether successful recanalization is associated with reduction of early mortality.

Our results are in good agreement with experimental findings on the regulation of myocardial metabolism during ischemia and reduction of infarct size. Due to some residual, albeit insufficient, oxygen supply, the development of the energy deficit, i.e., breakdown of energy-rich phosphates (creatine phosphate, adenosine triphosphate) occurs at a slower rate than during total ischemia. As glycolytic flux is likewise reduced, this observation must be attributed to some — although insufficient — aerobic energy production.<sup>24</sup> In support of these metabolic results, Schaper et al.<sup>25</sup> observed a significant prolongation of the period during which a substantial part of the ischemic myocardium may recover during reperfusion, if some residual flow either due to subtotal occlusion of the coronary artery or due to collateral flow is present.

#### Limitations of the Study

Recent investigations have shown that the seven-pin-hole technique is not significantly more sensitive or specific than planar  $^{201}\text{Tl}$  scintigraphy, although contrast is considerably enhanced.<sup>26</sup> We decided to use this technique because of time constraints. Seven-pin-hole scintigraphy requires the recording of only one image, which usually can be accomplished in less than 10 minutes, whereas at least three projections are required with planar imaging. The initial study therefore could be performed while the catheterization laboratory was set up, causing no additional time delay. As the seven-pin-hole technique is very sensitive to patient positioning, great care was taken to align the collimator exactly with the long axis of the left ventricle and to reproduce this position as closely as possible on subsequent studies. All raw data images were screened for clipped edges or off-center position in order to eliminate reconstruction artifacts. In some instances, the position was readjusted and a second picture was recorded. Because of its limited angle aperture of less than  $180^\circ$ , the z-axis resolution of the seven-pin-hole collimator deteriorates with increasing distance from the collimator face, i.e., toward the base of the heart. Thus, the thickness of individual cross sections through the myocardium is not identical at all levels; they are considerably thinner at the apex as compared to the base. This characteristic results in an overrepresentation of the apical levels compared with the base. Another consequence of deteriorating z-axis resolution is the propagation of the perfusion defect into cross sections that do not contain it. The larger the size of the perfusion defect, the greater the propagation of the abnormality; this effect, therefore, tends to exaggerate the reduction of the perfusion defect in the treated group. As the effects of coronary occlusion tend to affect the apical and middle portions of the LV myocardium to a greater extent than the base of the heart, these two effects are likely to cause overestimation of the perfusion defect either by overrepresentation or by

propagation. However, as each patient acts as his own control, and because the reproducibility of the seven-pin-hole recordings are adequate,<sup>25</sup> these technical limitations should not affect the validity of the results.

Another problem is the spontaneous resolution of perfusion defects on <sup>201</sup>Tl scintigrams. Studying patients with acute myocardial infarction who did not undergo an intervention, Wackers et al.<sup>21, 22</sup> noted spontaneous improvement of <sup>201</sup>Tl uptake over time on serial scintigrams. The greatest changes were noted 4–10 days after the onset of symptoms. To minimize this problem, no studies were performed later than 24 hours after the intervention. Judging from the results obtained in group B with unsuccessful intracoronary fibrinolysis, no significant spontaneous change could be observed within this period.

### Clinical Implications

This and other reports<sup>1–8</sup> show the relative safety of intracoronary fibrinolysis in acute myocardial infarction. Additionally, the results demonstrate that successful fibrinolysis can reduce the size of the initial perfusion defect, although the outcome in individual cases is unpredictable and may be variable. The patients who are to benefit most from this intervention are those with some residual flow through a subtotally occluded vessel or by means of extensive collateralization to the ischemic area. Total or nearly total normalization may be expected in these cases. These results are in good agreement with experimental findings. It is not possible to predict the benefit of intracoronary fibrinolysis in any patient with acute myocardial infarction before the invasive study. Further, no fixed time limit between onset of symptoms and admission to the hospital, up to which intracoronary streptokinase may be successful, can be determined. For patients with total ischemia, the 4-hour period chosen arbitrarily in this study seems to be too long, whereas patients with good collateral flow or subtotal occlusion may benefit from this intervention even after a longer time period of regional myocardial ischemia.

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