

A randomized, placebo-controlled trial of intravenous recombinant tissue-type plasminogen activator and emergency coronary angioplasty in patients with acute myocardial infarction

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ABSTRACT To determine the role of tissue-type plasminogen activator (t-PA) and immediate percutaneous transluminal coronary angioplasty (PTCA) in treating patients with evolving transmural myocardial infarction, 50 patients received t-PA (1.25 mg/kg iv over 3 hrs) or placebo according to 3:1 double-blind randomization 3.8 \pm 1.1 hr after onset of symptoms. At emergency coronary arteriography, patency of the infarct-related vessel was demonstrated in 32 of 38 (84%) patients receiving t-PA vs two of 12 (17%) receiving placebo ($p < .001$). Of the 32 patients with recanalization after t-PA, 28 had a residual stenosis of at least 50% and underwent randomization a second time to immediate ($n = 15$) or no PTCA ($n = 13$). Immediate PTCA of the infarct-related vessel was successful in all 15 patients, with reduction of the residual diameter stenosis from $80.8 \pm 8.2\%$ to $32.5 \pm 15.6\%$ ($p < .001$). The incidence of postinfarction angina (≥ 20 min of chest discomfort and reversible electrocardiographic changes) and reinfarction (documented by recurrent creatine kinase isoenzyme elevation) was reduced in the patients receiving t-PA and PTCA (2/15) compared with that in patients receiving t-PA alone (7/13; $p = .006$). At 1 week there was no difference in patency of the infarct-related vessel (12/15 t-PA and PTCA vs 9/13 t-PA only) or in global ventricular functional change between the two groups (0.5 ± 10.4 SD/chord for t-PA and PTCA vs -2.1 ± 8.2 SD/chord for t-PA only). Patients who underwent PTCA had significantly improved infarct-zone regional wall motion 1 week later (0.83 ± 0.94 SD/chord) compared with those who did not undergo PTCA (-0.24 ± 0.73 SD/chord; $p = .003$). These findings support the potential role for emergency PTCA after intravenous administration of t-PA.

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RECENT large, controlled clinical trials in acute myocardial infarction have demonstrated an overall reduction in mortality with the use of early thrombolytic therapy.^{1,2} However, reinfarction and postinfarction ischemia have been observed to be more prevalent in patients so treated.¹⁻³ Although these studies have used intravenous streptokinase, recent data suggest that recombinant tissue-type plasminogen activator (t-PA) is a more effective coronary thrombolytic agent.^{4,5}

Preliminary experience with percutaneous transluminal coronary angioplasty (PTCA) in myocardial infarction suggests that this technique may reduce the frequency of recurrent ischemic events and promote recovery of myocardial function by achieving definitive recanalization of the infarct-related vessel.^{6,7} This study was undertaken to determine the role of emergency PTCA after intravenous thrombolytic therapy, with the major end points of myocardial function and recurrent ischemic events.

Patients and methods

This study was conducted at the University of Michigan Medical Center between September 1985 and January 1986 after approval of the institutional review board. Patients were eligible if they met the following criteria: (1) chest discomfort lasting 20 min or longer, unresponsive to sublingual nitroglycerin, (2) symptom onset less than 6 hr, (3) electrocardiographic

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ST segment elevation of 1 mm or greater in two contiguous leads, (4) age under 75 years, (5) if female, nonmenstruating, and (6) no history of recent trauma, surgery, bleeding diathesis, prior coronary artery bypass grafting, or transmural infarction in the infarct-related artery distribution. Patients with cardiogenic shock, defined as systolic blood pressure under 85 mm Hg, who were unresponsive to volume expansion were excluded. During the study, all patients who met entry criteria were included except for one patient who developed hemoptysis just before informed consent was obtained. After receiving t-PA, one patient was found to have pericarditis and no evidence of myocardial infarction. This patient was not included in the current report.

The study design is represented in figure 1. Patients were randomly assigned to receive either t-PA or placebo (excipient, all components but active drug) on a 3:1 double-blind basis. The dose of t-PA was 0.75 mg/kg over the first hour with 10% given as a bolus, and 0.5 mg/kg over the subsequent 2 hr for a total dose of 1.25 mg/kg over 3 hr. In patients weighing over 80 kg, a maximum dose of 105 mg was used. The t-PA was a predominant single-chain preparation (Genentech, South San Francisco, CA). Forty-four patients in this trial received the study medication at an outlying community hospital and were transported to the University of Michigan cardiac catheterization laboratory via helicopter (n = 26) or ambulance (n = 18).

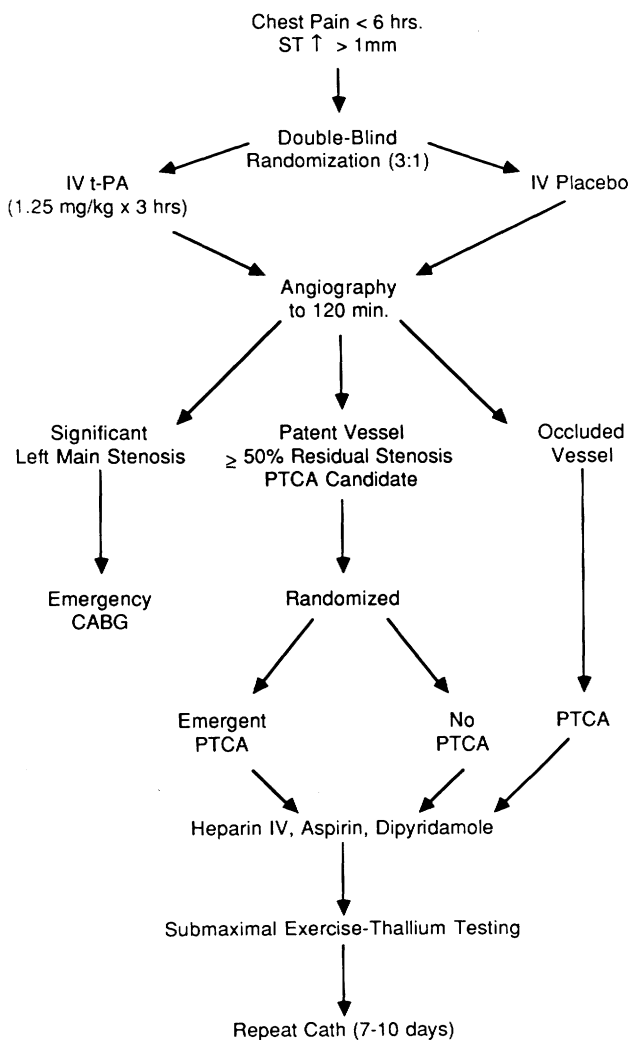


FIGURE 1. Study protocol.

Coronary arteriography and left ventriculography were performed 60 min after initiation of the drug infusion. After the initial angiogram, the randomization code was broken to determine whether the study drug was t-PA or placebo. In placebo-treated patients who had total occlusion of the infarct-related vessel, either intracoronary streptokinase (250,000 U over 60 min) was administered or PTCA was performed, or both. Serial coronary arteriograms were obtained at 60 to 75, 90 and 120 min. The final determination of the patency of the infarct-related vessel was made at 120 min according to the classification of the Thrombolysis in Myocardial Infarction (TIMI) trial.⁴ As defined by the TIMI study group, TIMI grade 0 = "no perfusion" with no antegrade flow beyond the point of occlusion; TIMI grade 1 = "penetration without perfusion" so that contrast fails to opacify the coronary bed distal to the obstruction; TIMI grade 2 = "partial perfusion," so that the contrast filling is delayed or its clearance is delayed but contrast material opacifies the distal coronary bed; and TIMI grade 3 = "complete perfusion," showing a normal pattern of contrast filling clearance.⁴

In those patients receiving t-PA without evidence of thrombolysis, PTCA was performed to restore patency. All patients who demonstrated thrombolysis (TIMI grade 2 or 3) after t-PA were considered for randomization to emergency PTCA, except for those who had: (1) less than 50% residual stenosis, (2) critical left main stenosis or equivalent anatomy, (3) diffuse multivessel disease not amenable to PTCA, or (4) an unidentifiable infarct-related vessel. In all such patients judged suitable for emergency PTCA, a card was pulled that randomly assigned the patient to receive or not receive this procedure. The PTCA was performed in the infarct-related vessel only, but if several lesions were present in this artery they were all approached. Two to three balloon inflations, to a maximum of 8 to 10 bar for a 60 sec interval, were routinely used. Successful emergency PTCA was defined as that achieving a 50% reduction of the initial infarct-related vessel luminal diameter stenosis, with attendant decrease in the translesional gradient to less than 20 mm Hg and resultant TIMI grade 3 flow.

Left ventriculography was performed during the acute study before PTCA. All patients underwent repeat catheterization at 7 to 10 days after admission for determination of patency of the infarct-related vessel and ventricular function. In patients who were restudied before 7 days because of recurrent ischemia, a third catheterization was performed at day 7 to 10 to assess left ventricular function and final patency status of the infarct-related vessel. Patients underwent exercise treadmill testing with single-photon emission tomographic thallium-201 scintigraphy before hospital discharge.

All patients received 5,000 U of heparin at the time of arterial access and an additional 5,000 U just before PTCA if this was part of the acute catheterization. Low-molecular weight dextran was initiated during the catheterization at 50 ml/hr and continued until 500 ml was infused. After catheterization, a continuous heparin infusion of 1000 U/hr was maintained until follow-up catheterization, except for a few hours on the second hospital day when the arterial access sheath was removed. Patients were also treated with 325 mg/day aspirin, 75 mg of dipyridamole three times daily, and 30 mg of diltiazem four times daily. β -Blockers were not initiated during the study period and were discontinued shortly after admission unless required to treat hypertension. Patients received intravenous lidocaine during the first 24 hr of hospitalization.

Recurrent ischemic events during the hospital course were defined as follows: (1) postinfarction angina — recurrent chest pain lasting 20 min or longer with accompanying 2 mm or greater electrocardiographic ST segment elevation or depression in the infarct-related territory; T wave changes were not

considered diagnostic; (2) reinfarction — prolonged chest discomfort with attendant enzymatic confirmation of creatine kinase-MB elevation; (3) exercise-induced angina — submaximal exercise testing before discharge demonstrating reversible thallium-201 uptake in the region of the infarct zone with or without accompanying chest discomfort; and (4) angiographically documented reocclusion of the infarct-related vessel at 1 week, despite lack of clinical stigmata. Patients were considered to reach a clinical end point if either reinfarction or postinfarction angina occurred, at which time such patients were considered for crossover to PTCA or coronary artery bypass surgery. If elective bypass surgery was planned, this was not performed until the 7 day repeat left ventriculogram had been completed. If a patient developed more than one adverse clinical outcome (e.g., reinfarction and postinfarction angina) only the more serious one was tabulated.

Reperfusion time was estimated when this did not occur by angioplasty. In patients with a patent infarct-related vessel on the first angiogram, the time of the angiogram was used. If recanalization occurred during serial angiography, the time of the angiogram demonstrating patency was recorded. Thus the estimated reperfusion time represents a maximum time, corresponding to definite angiographic confirmation.

Stenosis of the infarct-related vessel was determined by calipers and by quantitative angiography using an automated edge detection computer algorithm.⁸ To determine percent diameter stenosis, end-diastolic frames were chosen from the coronary arteriogram that demonstrated the most severe stenosis. These were digitized into 256×256 eight-bit matrices with a cine film projector equipped with a primary beam splitter coupled to a fixed-gain video camera and a video-to-digital converter. Images were stored in the memory of a digital radiographic computer (DPS 4100C, ADAC Laboratories) for subsequent processing. Quantitation of the post-PTCA residual stenosis was difficult because of the characteristic hazy and irregular intimal borders. This usually required some manual input to ensure agreement with the visual and caliper determination. All values reported are the quantitative angiographic results except when it was not possible to use the software analysis because of vessel overlap (five patients) or inadequate film quality for digitization (four patients). For these patients, caliper values were used.

Left ventricular global and regional function were determined blinded to therapy, time of the study, and patient identity. The right anterior oblique ventriculograms were spliced off of the cine film and randomly coded. The ventriculograms were reviewed by two angiographers independently to generate outlines of the end-diastolic and end-systolic cavity. Outlines generated by the first angiographer (A. L.) were used for global and regional analyses, and the second angiographer's (E. T.) outlines were used as a check for interobserver variability. If there was a discrepancy of 3% or more in ejection fraction between the two angiographers, a joint determination of the outlines was performed. Outlines were digitized and stored in the same fashion as were the coronary arteriograms. Technically inadequate ventriculograms, due to either ventricular tachycardia or inadequate opacification, were not included in the analysis. This led to omission of left ventricular function results in three patients, one in the t-PA failure group and two in the combined t-PA and PTCA group. Global ejection fraction was determined by the area-length method.⁹ Regional wall motion for the infarct and noninfarct zones was determined by the centerline chord method^{9, 10} and expressed in standard deviation units per chord. All ventriculograms were analyzed before the code was broken. No changes in the ventriculographic data were made after the code was broken.

Plasma fibrinogen levels were measured in plasma samples obtained from blood collected on 0.01M citrate (final concen-

tration) and 200 kIU/ml aprotinin (Trasylol). The Clauss¹¹ and Merskey¹² methods were used to determine levels of fibrinogen and fibrinogen degradation products, respectively.

Statistical analysis. All values are presented as mean \pm 1 SD unless otherwise stipulated. Analysis of ventricular function data was done for the randomized t-PA only and t-PA plus PTCA groups by the intention-to-treat principle. Differences in patency of the infarct-related vessel between t-PA and placebo groups were established by Fisher's exact test. Differences in left ventricular function between t-PA and placebo plus PTCA groups were determined by unpaired t tests and one-way analysis of variance.

Results

Baseline angiographic and clinical data for the 50 patients receiving the study medication at 3.8 ± 1.1 hr from onset of symptoms are summarized in table 1. There were no significant differences in baseline variables between the 38 patients treated with t-PA and the 12 patients receiving placebo, except for a trend of increased age in the latter group.

The results of infarct-vessel patency, as determined by immediate coronary angiography, are shown in figure 2. At 90 min after t-PA therapy, 27 of 38 patients (71%) demonstrated recanalization of the infarct-related vessel, whereas 32 (84%) were found to have patent infarct-related vessels, (9 TIMI grade 2, 23 TIMI grade 3) at the 120 min infusion point. Of note, five of these patients demonstrated intermittent patency and occlusion during serial angiography, of whom four demonstrated TIMI grade 2 or 3 filling and clearance at 120 min. At follow-up angiography, all five of these patients demonstrated reocclusion.

Of the 32 patients with reperfusion in 120 min, three had less than 50% residual stenosis in the infarct-related vessel. One patient, found to have a patent dominant left circumflex artery related to the infarct with a

TABLE 1
Baseline clinical and angiographic data

	t-PA	Placebo	p value
No. of patients	38	12	—
Age (yr)	52.6 ± 11.3	58.3 ± 10.5	.065
Male/female	29/9	10/2	NS
Time from chest pain to drug (hr)	3.8 ± 1.3	3.7 ± 1.0	NS
Time to reperfusion (hr) ^A	5.4 ± 1.4	5.2 ± 1.5	NS
Infarct vessel			
LAD	20	5	NS
LCX	2	3	.05
RCA	16	4	NS
Multivessel disease	20	6	NS

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

^AEstimated reperfusion time — a maximum time based on angiographic confirmation of patency (see text).

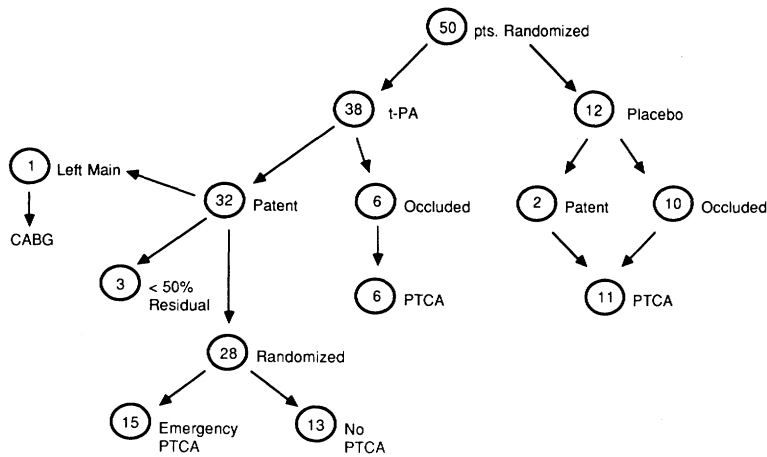


FIGURE 2. Flow chart of patient results and the two randomization outcomes.

90% proximal residual stenosis and total occlusion of the proximal left anterior descending artery, underwent emergency coronary bypass surgery. The remaining 28 patients exhibiting patency of the infarct-related vessel after t-PA were subject to randomization for emergency PTCA.

Baseline data for the 28 patients randomly assigned to either emergency PTCA or medical therapy are shown in table 2. The two groups were not significantly different with respect to age, sex, time from onset of chest pain to initiation of t-PA, location of the infarct-related vessel, or multivessel disease (>50% lesion in a noninfarct vessel).

PTCA was successful in all 15 patients assigned to this therapy, reducing the stenosis from $80.8 \pm 8.2\%$ to $32.5 \pm 15\%$ ($p < .001$). A minimal, localized intimal dissection that did not compromise the lumen occurred in four patients. PTCA was also performed in the six patients who failed thrombolytic therapy with

t-PA. Successful recanalization was achieved in five of the six patients.

In the patients treated initially with placebo, two of 12 (17%) demonstrated patency of the infarct-related vessel at the initial angiogram (72 ± 14 min from onset of infusion). Of the 10 patients with persistent occlusion, intracoronary streptokinase was given in eight and was successful in one patient before PTCA was performed at 43 ± 20 min of therapy. PTCA was attempted in 11 of the 12 patients in the placebo group and was successful in nine.

Hospital course. There were four deaths in the trial. Two of these were placebo group patients who did not have recanalization spontaneously and in whom PTCA was unsuccessful in achieving sustained patency. t-PA thrombolysis failed in one patient, who had only brief reperfusion after PTCA before experiencing reocclusion in the laboratory. The other fatality was in a 73-year-old man who received t-PA 5.2 hr from onset of chest pain and successful PTCA at 7.5 hr but who had a very extensive anterior infarction. All four patients developed cardiogenic shock and recurrent ventricular tachycardia and fibrillation before death. Cumulatively these four deaths occurred among 32 patients in whom PTCA was attempted in the study, representing a hospital mortality of 12.5% in patients in whom shock was not present at baseline.

Adverse clinical events are summarized in table 3. Of 13 patients randomly assigned to t-PA only, five developed postinfarction angina and two others experienced reinfarction. Three of these patients underwent PTCA and two coronary artery bypass surgery. Only one patient of the 15 patients receiving t-PA plus emergency PTCA had postinfarction angina ($p = .04$) and none had reinfarction. Submaximal exercise testing demonstrated provokable infarct zone ischemia in four other patients receiving t-PA and in one receiving com-

TABLE 2
Baseline data: emergency PTCA randomization

	t-PA only	t-PA + PTCA	p value
No. of patients	13	15	—
Age (yr)	53.5 ± 10.5	51.3 ± 15.5	NS
Male/female	8/5	12/3	NS
Time from chest pain to t-PA (hr)	4.1 ± 1.1	3.9 ± 1.4	NS
Infarct vessel			
LAD	5	8	NS
LCX	0	1	NS
RCA	8	6	NS
Multivessel disease	9	9	NS
2-vessel	6	5	NS
3-vessel	3	4	NS
Infarct-vessel residual stenosis (%)	77.9 ± 13	80.8 ± 8.2	NS

Abbreviations as in table 1.

TABLE 3
Adverse clinical outcomes^A

	t-PA only (n = 13)	t-PA + PTCA (n = 15)
Postinfarction angina	5	1
Reinfarction	2	0
Exercise-induced ischemia (infarct zone)	4	1
Reocclusion	4	3
Death	0	1

^AValues reflect patient and not event outcomes. If a patient had more than one event (except reocclusion), only one is tabulated.

bined therapy. The cumulative difference in spontaneous or provokable ischemia between the two groups was 11 of 13 (85%) vs two of 15 (13%), respectively ($p < .001$). Among the six patients in whom t-PA failed and who underwent PTCA, one patient developed early postinfarction ischemia and reocclusion was confirmed within six hour after successful PTCA. In eight of 10 surviving placebo patients who underwent PTCA, one developed ischemia and demonstrated reocclusion. Congestive heart failure, manifested by new requirement for digoxin and furosemide therapy, occurred in 11 patients (eight t-PA [21%] and three placebo [25%]). Of the eight t-PA-treated patients who received digoxin and furosemide, three were randomly assigned to t-PA only (of whom two had reinfarction), two showed no improvement after t-PA therapy, one had less than 50% residual stenosis of the infarct-related vessel, one underwent emergency bypass surgery, and the remaining two were assigned to t-PA and PTCA therapy (of whom one had a prior myocardial infarction and the other had reocclusion).

Subsequent treatment for the 13 patients assigned to t-PA only consisted of the following: three had emergency PTCA, three had elective coronary artery bypass surgery, two were treated medically because of silent reocclusion in one and a less than 50% stenosis at follow-up angiography in another, and five underwent elective PTCA after the final cardiac catheterization.

Repeat cardiac catheterization. All patients underwent repeat coronary arteriography and left ventriculography at 7.8 ± 0.5 days after acute infarction, except for the four patients who died during the first 48 hr and one patient found to have no significant atherosclerotic disease after t-PA. Reocclusion of the infarct-related vessel was demonstrated in four of 13 (31%) patients treated only with t-PA and in three of 15 (20%) t-PA plus PTCA patients ($p = \text{NS}$). Reocclusion was silent in one patient treated only with t-PA and in two patients treated with combined therapy. In four patients

with recurrent chest pain and electrocardiographic changes, reocclusion occurred at 8, 12, 30, and 62 hr after therapy. Of note, in four patients with postinfarction angina in the t-PA only group there was a persistent, high-grade residual stenosis of the infarct-related vessel with sustained patency. Stenosis reduction of the infarct-related vessel for the 28 randomized t-PA patients is shown in figure 3. In the t-PA only group, there was a significant decrease in percent diameter stenosis, as determined by quantitative angiography, from end of the catheterization to repeat study ($77.9 \pm$

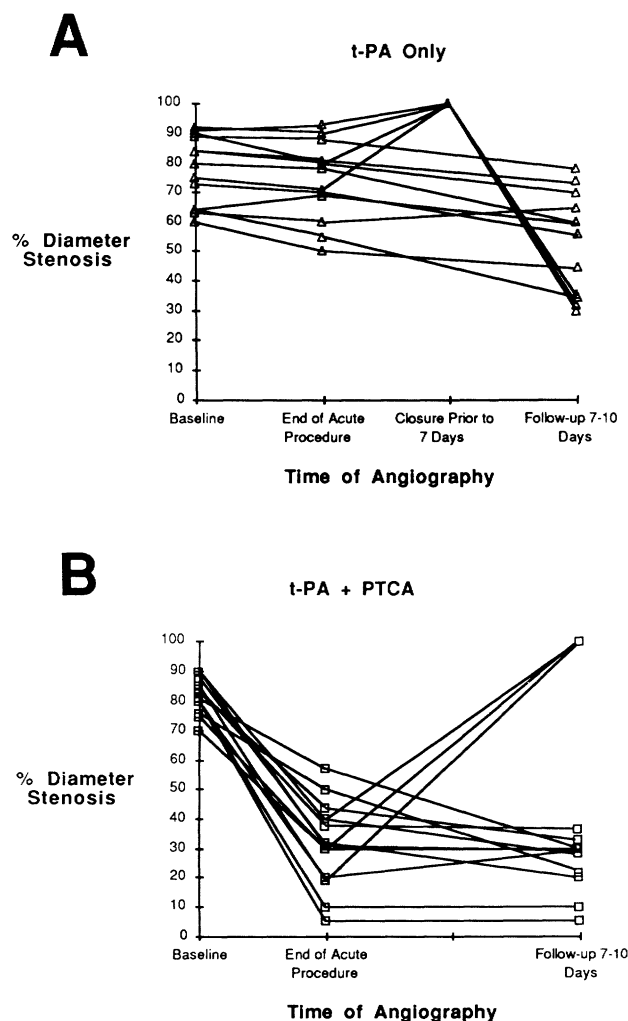


FIGURE 3. A, Infarct-vessel quantitative angiographic results. Percent diameter stenosis is plotted (mean \pm SEM) for the two groups of patients assigned to t-PA. In the patients treated with t-PA only who showed persistent patency, there was a significant decrease in stenosis from the end of the acute procedure to the follow-up study ($76.9 \pm 6\%$ to $62 \pm 7\%$; $p = .03$). Of note, three of four patients who had reocclusion and developed recurrent ischemia underwent immediate PTCA. B, Percent diameter stenosis is plotted for the patients assigned to t-PA and PTCA. There was a significant decrease in acute residual stenosis ($80.8 \pm 8.2\%$ to $32.5 \pm 15.6\%$; $p < .001$) and a trend toward further reduction at 1 week in those patients with sustained patency ($32.5 \pm 5\%$ to $24.4 \pm 4\%$; $p = .07$).

13% vs $62 \pm 24.2\%$; $p < .05$). The 15 patients assigned to t-PA plus PTCA had a reduction in percent diameter stenosis from $80.8 \pm 8.2\%$ to $32.5 \pm 15\%$ ($p < .001$) acutely.

Left ventricular function. Data on global and regional left ventricular function for the t-PA patients are summarized in table 4 and graphically displayed in figure 4. In addition, a group of patients with an occluded vessel who underwent PTCA as primary recanalization therapy (six failed t-PA patients, seven placebo patients without evidence of recanalization) are compared in figure 5. Within these two groups of patients with occluded arteries, there were no significant differences in regional or global functional results. The global ejection fraction did not show evidence of improvement in any of the major subsets of patients (figure 5). There was significant improvement in infarct zone regional function in patients receiving t-PA plus PTCA compared with patients receiving t-PA only ($+0.83 \pm 0.94$ vs -0.24 ± 0.73 SD/chord, respectively; $p = .003$). Patients undergoing PTCA after initial placebo or failed t-PA therapy (occluded arteries) also experienced an improvement in infarct zone wall motion compared with patients treated with t-PA only ($+0.54 \pm 1.45$ vs -0.24 ± 0.73 SD/chord, respectively; $p = .05$). The noninfarct zone showed a significant decrease in motion (day 0 to day 7) only in the patients with occluded arteries (-1.57 ± 2.18 SD/chord) compared with the other t-PA patients (-0.02 ± 1.35 SD/chord; $p = .02$, one-way analysis of variance, figure 5).

Bleeding and hemostatic variables. A transfusion of 2 or more units of packed red blood cells was required to maintain the hematocrit above 30 in 10 (26%) t-PA and two (17%) placebo patients ($p < .05$). A significant

periaccess hematoma was present in 17 (45%) t-PA and six (50%) placebo patients. Upper gastrointestinal bleeding occurred in two and gross hematuria in one t-PA patient. The fibrinogen nadir in t-PA patients was $65 \pm 14\%$ of baseline compared with $77 \pm 6\%$ in placebo patients who did not receive intracoronary streptokinase ($n = 4$). Fibrinogen degradation products were increased to a median 1:4 titer in t-PA patients vs 1:2 in the placebo group.

Discussion

Our results confirm the high thrombolytic efficacy of recombinant t-PA and support the use of emergency PTCA after thrombolysis to lessen the residual stenosis of the infarct-related vessel and to preserve regional left ventricular function.

The 84% patency of the infarct-related vessel achieved with t-PA is higher than previous reports of 56% to 80%.^{4, 5, 13-16} The increased thrombolytic efficacy may in part relate to the preparation used, which is predominantly single chain, and differs from the two-chain form previously investigated^{4, 5, 13-16} with respect to fibrin selectivity and pharmacokinetics. However, the final determination of patency was made at 120 min, which represented an increase from the 90 min patency rate of 71% and involved serial contrast injections, which may promote arterial patency. The placebo recanalization rate of 17% is similar to that of previous placebo-controlled intravenous thrombolytic trials in which acute coronary angiography was performed.^{13, 16}

Recurrent ischemia or infarction were especially frequent in patients assigned to t-PA without emergency PTCA. The rate of postinfarction angina and reinfarction in this group, seven of 13 (54%), is high

TABLE 4
Regional and global left ventricular function

	Randomized t-PA only (n = 13)	Randomized t-PA + PTCA (n = 13)	p value
Baseline			
Infarct zone (SD/chord)	-2.62 ± 1.41	-2.94 ± 0.82^A	NS
Noninfarct zone (SD/chord)	0.19 ± 1.91	0.38 ± 1.38	NS
Global EF (%)	51.7 ± 11.9	52.7 ± 10.9	NS
Day 7			
Infarct zone (SD/chord)	-2.86 ± 1.23	-2.11 ± 1.45^A	.09
Noninfarct zone (SD/chord)	0.10 ± 1.98	0.40 ± 1.70	NS
Global EF (%)	49.6 ± 11.2	53.2 ± 12.9	NS
Change day 0-7			
Infarct zone (SD/chord)	-0.24 ± 0.73	0.83 ± 0.94^A	.003
Noninfarct zone (SD/chord)	-0.09 ± 1.47	0.03 ± 1.33	NS
Global EF (%)	-2.11 ± 8.2	0.5 ± 10.4	NS

^APaired t test of regional wall motion of the infarct zone demonstrated significant improvement ($p = .007$).

compared with the 21% to 35% combined frequency reported in controlled trials with streptokinase.^{1-3, 7} This increase may reflect the heightened thrombolytic efficacy of t-PA compared with streptokinase with preservation of viable but jeopardized myocardium. It may also relate to the relative short half-life (<5 min) of t-PA. This problem may be obviated by the recent finding of Gold *et al.*,¹⁵ in which a prolonged infusion of low-dose t-PA reduced the incidence of reocclusion. In the current study, all patients with postinfarction ischemia underwent urgent repeat angiography, which demonstrated reocclusion in 63% (7/11) of such pa-

tients. The timing of reocclusion was quite variable. Of interest, however, five of nine ischemic events in the series occurred before 24 hr. A key predictor of late reocclusion was transient reocclusion during acute, serial coronary angiography. This finding heralded subsequent reclosure in four of five such patients and may denote an infarct-related vessel with heightened thrombotic tendency.

Emergency PTCA after t-PA was effective in reducing the combined incidence of recurrent ischemia and infarction compared with t-PA alone (1/15 vs 7/13 patients; $p = .006$). The 7 day arterial patency was

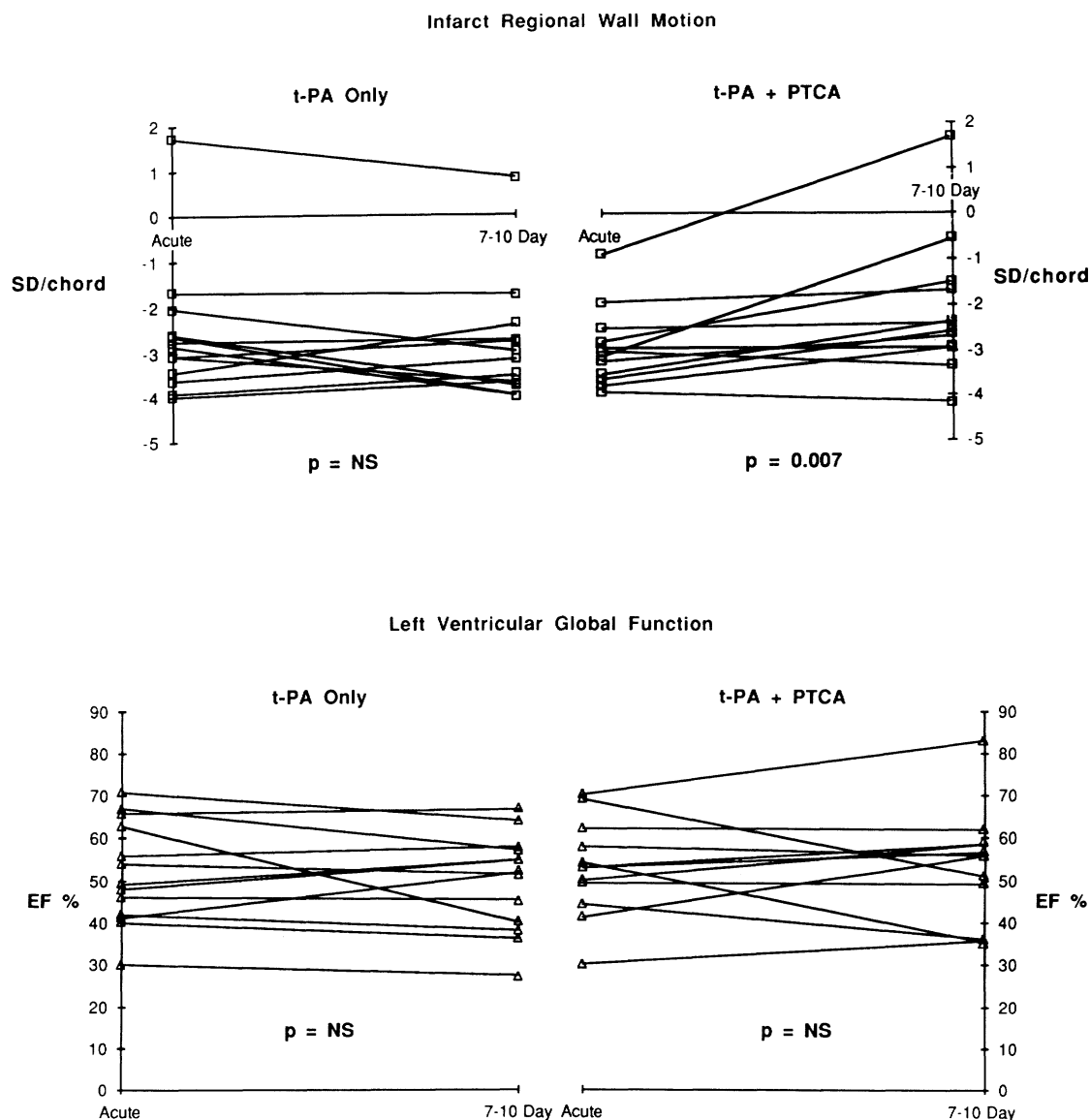


FIGURE 4. A, Regional infarct zone function for the two randomized groups of patients. There was no significant improvement from baseline to repeat (7 to 10 day) left ventriculography in t-PA only patients (-2.62 ± 1.41 to -2.86 ± 1.23 SD/chord). In patients assigned to t-PA and PTCA there was a significant improvement (-2.94 ± 0.82 to -2.11 ± 1.45 SD/chord; $p = .007$). B, Global left ventricular function for the two randomized groups of patients. Neither group demonstrated significant improvement in ejection fraction (EF) from baseline to repeat study. Mean and SD values: t-PA only, $51.7 \pm 11.9\%$ to $49.6 \pm 11.2\%$; t-PA and PTCA, $52.7 \pm 10.9\%$ to $53.2 \pm 12.9\%$.

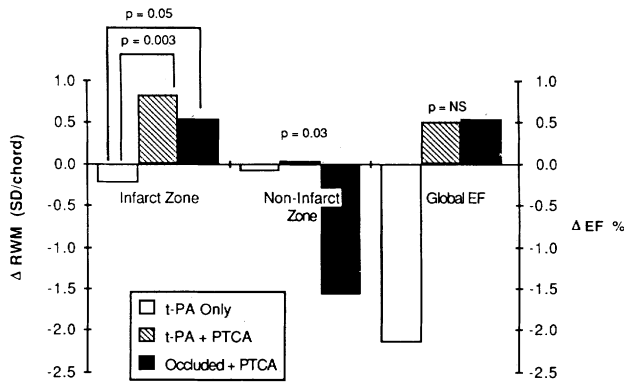


FIGURE 5. Cumulative regional and global function results. Patients with an occluded infarct-related artery who showed recanalization with PTCA demonstrated significant improvement in infarct zone regional wall motion compared with the t-PA only group. Only the non-infarct zone for occluded plus PTCA arteries showed significant regression of hyperkinesis ($p = .02$, one-way analysis of variance). No group demonstrated a significant increase in ejection fraction (EF). Values represented are means; the standard deviations are reported in the text.

increased in the t-PA plus emergency PTCA group (12/15; 80%) compared with the t-PA only group (9/13; 69%), but this difference was not statistically significant. PTCA was successful in primary or augmented recanalization in 28 of 32 (88%) patients who underwent dilatation during the initial catheterization. The 20% incidence of reclosure in the patients who underwent immediate PTCA is consistent with previous reports of PTCA in acute myocardial infarction.^{2, 7, 14} It is, however, disconcerting that PTCA, despite concomitant systemic heparin and anti-platelet therapy, did not yield a higher rate of follow-up patency. It is not known whether reocclusion after successful PTCA in this setting is secondary to rethrombosis, intimal dissection and disruption, or vasospasm. As demonstrated in the current study and corroborated by prior reports,¹⁷ the percent diameter stenosis of the infarct-related vessel lessens over time, which indicates the presence of residual thrombus.

Death ensued in two of the four (50%) patients with unsuccessful PTCA compared with two of 28 (7%) patients with successful emergency PTCA. Extensive myocardial necrosis, manifested by early development of cardiogenic shock in the latter two patients, was most likely responsible for death. Like thrombolysis, the critical early application of PTCA may be required to improve clinical outcome. These deaths in four of 32 (12.5%) patients who underwent PTCA in the current study raise concern that mortality may not be decreased by emergency PTCA.

Regional myocardial wall motion of the infarct zone was augmented by emergency PTCA in the two groups

undergoing the procedure but did not improve in the patients who received only t-PA. The difference in paired regional function in the two groups of patients receiving t-PA followed by PTCA is especially of note because it includes three t-PA only patients who required crossover to PTCA because they reached a clinical end point. These data point out the potential role of PTCA for improving infarct zone wall motion. The mechanism for this observed recovery of regional function after PTCA appears may relate to the reduction of the residual stenosis and increased coronary blood flow through the infarct-related artery.¹⁸

However, global ventricular function was not shown to improve in any major subset of patients. The lack of significant improvement in global ejection fraction after thrombolysis and PTCA may be attributed to the relatively long time in the present study from onset of symptoms to infusion of the study medication (3.8 ± 1.1 hr) or angiographic coronary recanalization (5.6 ± 1.4 hr). In addition, the insensitivity of the measurement of global function after reperfusion due to initial hyperkinesis of the noninfarct zone or to a small infarct region that may not affect global function may account for this finding.

With improved measures to achieve and sustain patency of the infarct-related vessel such as early t-PA and the use of a prolonged maintenance low-dose infusion,¹⁵ the need for emergency catheterization and PTCA might be obviated. However, in the majority of patients, using current clinical and electrocardiographic criteria, we cannot differentiate whether or not recanalization has occurred after intravenous fibrinolytic therapy.¹⁹ Immediate angiography appears to be the only definitive method to determine the status of the infarct-related vessel. Thus the group of patients without myocardial reperfusion after t-PA represents a major potential target for aggressive intervention. The present trial also suggests that there may be improvement in regional myocardial function in patients who had PTCA as the primary method of reperfusion. Although emergency angiography and PTCA is of considerable expense and lacks widespread availability at the community hospital level, we recently reported the safety of helicopter transport and out-of-hospital therapy with t-PA in patients with acute myocardial infarction.²⁰ With rapid interhospital transport, it is potentially feasible to provide emergency PTCA to patients in remote areas.

The results of this pilot study have several important limitations. Although it was a randomized trial, the number of patients was small. Without knowledge of baseline angiographic data before t-PA therapy, we do

not know whether some patients had subtotal occlusion and may have increased likelihood for subsequent functional recovery. Repeat evaluation of left ventricular function was performed at 7 days, which may not take into account further recovery that may occur weeks to months after reperfusion.²¹⁻²³ Although randomization to PTCA depended on an operator-subjective decision, all patients with a significant (>50%) residual lesion and absence of left main equivalent anatomy were indeed randomized.

The optimal timing and patient selection for acute intervention during evolving myocardial infarction remain undetermined. Ongoing large-scale randomized trials of second-generation thrombolytic agents and PTCA will help to further define proper applications of these therapies. However, the results of this randomized pilot study do support the potential adjunctive role of emergency PTCA for immediate reduction of the underlying residual stenosis of the infarct-related vessel and preservation of regional myocardial function.

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