Clinical Trial

Prevention of Coronary Artery Reocclusion and Reduction in Late Coronary Artery Stenosis After Thrombolytic Therapy in Patients With Acute Myocardial Infarction

A Randomized Study of Maintenance Infusion of Recombinant Human Tissue-Type Plasminogen Activator

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Sixty-eight patients with acute "transmural" myocardial infarction presenting within 6 hours (range, 1.3–5.8 hours) of onset of chest pain were given intravenous recombinant tissue-type plasminogen activator (rt-PA) at a dosage of 1 mg/kg during 90 minutes. Coronary angiography at 90 minutes revealed a patent infarct-related coronary artery in 52 patients (76%). These patients were randomized either to treatment by continuous infusion of heparin alone (27 patients) or to treatment by heparin and a maintenance infusion of rt-PA at a dosage of 0.8 mg/kg during 4 hours (25 patients). Coronary angiography was repeated 60 minutes after the start of the maintenance infusion and again after 8–14 days. Acute symptomatic reocclusion of the infarct-related artery occurred during the 1-hour observation period in five (19%) patients treated with heparin alone but in none of the patients treated with rt-PA ($p=0.05$). The measured residual stenosis of the patent infarct-related coronary artery was similar in the heparin-treated and the rt-PA–treated groups at 90 minutes infusion: $66\pm14\%$ versus $68\pm13\%$ diameter stenosis, respectively (mean ± SD) and 1.1 ± 1.1 mm^2 versus 0.82 ± 0.7 mm^2 area ($p=0.35$). At 8–14 days after infusion, residual stenosis was unchanged in the heparin-treated group, but it improved to $55\pm17\%$ ($p=0.001$) and 1.6 ± 1.2 mm^2 ($p=0.003$) in the rt-PA–treated group. At 90 minutes of infusion, residual intraluminal thrombus was observed in 29 of the 52 patients (56%) with a comparably measured distribution in the two groups ($p=0.43$). At 150 minutes, however, the extent of intraluminal thrombus was significantly reduced in the rt-PA–treated group as compared with the heparin-treated group ($p=0.03$). In-hospital ischemic events (symptomatic reocclusion, unstable angina, or cardiovascular death) occurred in 12 patients of the heparin-treated group but only in three patients of the rt-PA–treated group ($p=0.03$). Fibrinogen levels decreased to $65\pm21\%$ of baseline at 90 minutes of rt-PA infusion. During the rt-PA maintenance infusion, fibrinogen fell slightly from 63 ± 26 to $57\pm28\%$ ($p=0.18$). This study shows that after successful reperfusion with 1 mg/kg rt-PA during 90 minutes, a maintenance infusion of 0.8 mg/kg rt-PA during 4 hours prevents acute symptomatic coronary artery reocclusion, and it reduces the frequency of ischemic events and the severity of residual coronary artery stenosis at hospital discharge. (*Circulation* 1988;78:546–556)

Successful thrombolytic therapy of acute myocardial infarction does not always produce stable coronary artery patency. The reported in-hospital reocclusion rate after reperfusion with intravenous streptokinase has ranged from 10% to

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30%.[1-6] Recombinant tissue-type plasminogen activator (rt-PA) has been shown to be a more effective thrombolytic agent than streptokinase[7-9] and to produce less extensive systemic fibrinogenolysis.[10] In multicenter trials, intravenous rt-PA has been associated with coronary reocclusion rates of 10% to 30% despite heparin anticoagulation.[7,8,11]

Because high-grade residual coronary artery stenosis after successful reperfusion is a significant predisposing factor for coronary artery reocclusion,[5,12-14] efforts to prevent reocclusion have included mechanical procedures such as acute coronary angioplasty.[15] However, this procedure commits all patients receiving thrombolytic therapy to acute angiography, which is logistically prohibitive. Moreover, acute angioplasty does not adequately prevent coronary artery reocclusion, which occurs within 1 week in up to 15% of the patients.[15] In a pilot study, we found that a maintenance infusion of rt-PA prevents early coronary artery reocclusion in patients with a high-grade residual stenosis.[14]

This study was performed to confirm and establish, within the framework of a randomized study, the safety and efficacy of a maintenance infusion of rt-PA with respect to early and late in-hospital reocclusion, frequency of ischemic events, residual stenosis of the infarct-related artery at 8–14 days, and the need for emergency interventional procedures.

Patients and Methods

Patient Selection Criteria

Sixty-eight patients were entered into the randomized study between February 1, 1986 and May 15, 1987. The criteria for admission to the study were as follows: 1) chest pain suggestive of acute myocardial infarction of at least 30 minutes duration, less than 6 hours from onset, 2) acute "transmural" myocardial infarction with ST-segment elevation of at least 0.1 mV in two contiguous standard electrocardiographic leads, 3) age less than 70 years, and 4) no contraindications to thrombolytic therapy. Exclusion criteria included previous infarction in the same myocardial zone, cardiogenic shock (systolic blood pressure of <90 mm Hg with signs of systemic hypoperfusion), recent cardiopulmonary resuscitation, left bundle branch block, poorly controlled hypertension with blood pressure of 180/110 mm Hg or greater after initial therapy, recent bleeding, surgery within 21 days, advanced major disease, history of cerebrovascular disease, head or spinal trauma within 6 months, and clouded sensorium or childbearing potential. Written, informed consent was obtained from each patient, and the study design was approved by the hospital committee for human studies and was performed with an Investigational New Drug number granted by the U.S. Food and Drug Administration.

Study Protocol

Patients consenting to participate received standard therapy for myocardial infarction in the emergency room, including sublingual nitroglycerin, intravenous morphine sulfate (5–10 mg), intravenous lidocaine (1–2 mg/min) and oxygen (4 l/min). After initial blood sampling, all patients received intravenous rt-PA at a dosage of 1.0 mg/kg during 90 minutes, with 10% of the total dose being given as a bolus during the first 2 minutes. An intravenous bolus of 5,000 units heparin was given in the emergency room before beginning the rt-PA infusion and was followed by a continuous infusion of 1,000 units/hr during rt-PA infusion. During the initial 90-minute infusion of rt-PA, patients were transferred to the cardiac catheterization laboratory where selective coronary angiography and left ventriculography were performed by the Judkins technique.

Patients with patent infarct-related arteries at 90 minutes of infusion were randomized to receive either heparin alone (1,000 units/hr) or a maintenance infusion of 0.8 mg/kg rt-PA given during 4 hours with a continuous infusion of heparin. Repeat coronary angiography was performed 60 minutes after the start of the randomized maintenance infusion (at 150 minutes), or it was performed earlier if acute reocclusion was suspected on the basis of either chest pain or electrocardiographic ST-segment elevation.

At the completion of the angiographic monitoring period, the 8 French femoral arterial and venous sheaths were left in place, and the patient was transferred to the coronary care unit. Intravenous heparin was continued for 8–14 days at a rate adjusted to maintain the activated partial thromboplastin time at 1½–2 times control. At 24 hours after angiography, heparin was discontinued for 2–4 hours to allow removal of the sheaths, and it was then reinstituted with a bolus of 2,000–5,000 units. For at least 24 hours from the time of angiography, all patients received intravenous nitroglycerin by continuous infusion in a dose selected to reduce the arterial systolic blood pressure by 10% but not below 100 mm Hg. After discontinuation of intravenous nitroglycerin, all patients were maintained on oral isosorbide dinitrate (60–160 mg/day) and diltiazem (120–240 mg/day). Repeat coronary and left ventricular angiography was performed between 8 and 14 days after infarction. Patients who developed chest pain in association with recurrent ST-segment elevation between 150-minute and the 8–14-day angiograms were returned to the cardiac catheterization laboratory for reevaluation of the patency of the infarct-related artery.

Quantitative Coronary Angiography

Reperfusion of the infarct-related artery was quantified by the Thrombolysis in Myocardial Infarction trial (TIMI) criteria and defined as grade 2 or 3.[16]

Persistent occlusion or reocclusion was defined as TIMI grades 0 or 1.

Residual coronary stenosis was quantified by the method of Brown et al,[17] with the use of computer analysis of projected, magnified coronary artery images corrected for pin-cushion distortion. Stenotic and adjacent, normal segments were traced by an observer, blinded with respect to patients' treatment but not to the infarct-related vessel, using the optimal single-plane view or two orthogonal views when there was no overlap. The catheter position was noted on rectilinear coordinates. Vessel and catheter diameters were digitized with a tablet with computer analysis by signal transmission to the University of Washington in Seattle. The tracings were analyzed to calculate the minimal cross-sectional area in square millimeters and residual diameter stenosis in percentage.

Measured assessment of intracoronary thrombus was made according to a predetermined definition. Intraluminal thrombus was defined as a convex filling defect with rounded well-defined edges, which was surrounded on three sides by contrast medium and was graded as absent (grade 0), as occupying less than 50% of the vessel lumen immediately adjacent to the stenosis (grade 2), or as occupying 50% or more of the vessel lumen (grade 3). Probable mural thrombus (grade 1) was defined as an intraluminal lucency with irregular, poorly defined edges. Angiographic assessment of intracoronary thrombus was made by two observers who were blinded with respect to patients' treatment. Differences in grading were resolved by consensus with a third blinded observer.

Wall Motion Analysis

Quantification of left ventricular function was performed with the 30° right anterior oblique contrast ventriculogram that was obtained during initial angiography and again at 8–14 days. The left ventricular ejection fraction was determined by the area-length method of Sandler and Dodge.[18] Regional wall motion was determined by the centerline method of Sheehan et al.[19] Severe hypokinesis was defined as motion that was two or more standard deviations below normal. The length of the severely hypokinetic segment (cm) was then calculated by multiplying the percentage of contiguous hypokinetic chords by the left ventricular end-diastolic perimeter, which was corrected for magnification.

Analysis of Data

Randomization was performed with a closed-envelope system with the sequence defined by a random number generator. This study was initially designed to accrue 90 patients in order to detect, with 0.8 power probability, whether the reocclusion rate was reduced from 25% to 5% but was terminated early because of increased intracerebral bleeding complications reported with a total dose of 150 mg.[20] Fisher's exact test was used to compare proportions in the two randomized patient groups, and Student's t test was used for paired or unpaired values to evaluate two-tailed levels of significance of differences within or between patient groups. For variables that were not normally distributed, a Mann-Whitney test was used to compare patient groups. Stepwise logistic regression analysis was used to assess predictors of reocclusion among the patients treated with heparin. Treatment comparisons of ordered categorical data, such as clot score, were made with the Kruskal-Wallis exact test. Treatment comparisons of time to reocclusion were made with a logrank test. Patients who were not followed up were considered censored for this analysis. Reported data are mean ± SD.

Hemostasis Analyses

Blood samples for determination of fibrinogen, activated partial thromboplastin time and immunoactive rt-PA were obtained before the treatment and at 90 minutes infusion in all patients. In patients randomized to maintenance rt-PA, additional blood samples were taken at 2 and 4 hours after the start of the maintenance infusion. Fibrinogen levels were measured in plasma samples obtained from blood collected on 0.01 M citrate (final concentration) and 200 kIU aprotinin/ml (Trasylol) with a clotting rate assay (Clauss method)[21] as previously modified.[22] This assay is insensitive to therapeutic concentrations of heparin. rt-PA–related antigen levels were measured as previously described.[23] Activated partial thromboplastin time was measured conventionally by the hospital's clinical laboratory.

Sequential Study With a Reduced Dose of rt-PA

The randomized study was terminated when published data indicated that a dose of 150 mg rt-PA may be associated with an increased frequency of intracerebral bleeding as compared with a dose of 100 mg.[20] To make a preliminary assessment of whether 100 mg rt-PA given as 60, 20, 5, 5, 5, and 5 mg during 6 hours was comparable to our weight-adjusted higher thrombolytic and maintenance dosages, we studied 13 patients serially without randomization between June 6 and October 11, 1987. Except for the dosage of rt-PA, the admission criteria and the study protocols were the same as for the randomized study.

Results

Patient Characteristics

Table 1 summarizes the characteristics of all patients entered into the randomized trial. For the 52 reperfused patients, the distribution of baseline characteristics was similar, except that there were more diabetics ($p = 0.046$) and more right coronary artery–related infarcts ($p = 0.019$) in the rt-PA maintenance group. The latter difference disappeared when patients were divided into anterior and inferior infarction groups ($p = 0.27$) because inferior

TABLE 1. Patient Characteristics, Randomized Trial

Characteristics	Persistent occlusion	Reperfusion	
		Heparin maintenance	rt-PA maintenance
Patients (*n*)	16	27	25
Gender (male/female)	14/2	23/4	22/3
Age (yr)	52±9	55±11	55±11
Range	38–68	33–72	26–68
Time to rt-PA (hr)	3.1±1.0	2.9±1.1	3.1±1.0
Range	1.6–5.0	1.3–5.3	1.3–5.8
Locus of occlusion			
LAD	4	16	10
RCA	7	5	13
Cx	5	6	2
Systolic pressure (mm Hg)	128±21	125±26	139±33
Diastolic pressure (mm Hg)	85±13	80±16	85±17
Admission pulse rate (beats/min)	81±12	74±17	75±11
Initial rt-PA dose (mg)	82±16	80±14	83±12
Range	50–100	50–115	60–118
Maintenance rt-PA dose (mg)			67±10
Range	. . .	. . .	48–94
Peak creatine kinase (units/l)	1,500±900	1,200±900	1,300±1,200
Range	470–3,900	200–3,300	80–4,800
Smoker	6	18	14
Previous infarction	0	4	2
Hypertension	7	11	16
Diabetes	3	1	6

rt-PA, recombinant tissue-type plasminogen activator; LAD, left anterior decending coronary artery; RCA, right coronary artery; Cx, left circumflex coronary artery.

infarcts from circumflex disease were more frequent in the heparin-treated group. The time from onset of chest pain to treatment was approximately 3 hours in all groups. The thrombolytic dose in each group was approximately 80 mg. In the rt-PA maintenance group, an additional dose of 67 ± 10 mg was given during 4 hours, resulting in a total rt-PA dose of approximately 150 mg.

Coronary Angiography

Coronary angiography at 90 minutes revealed a patency rate of 76% (52 of 68 patients) in the randomized study. Immediately after randomization, one of the 27 patients in the heparin-treated group died of cardiac rupture. During the 1 hour observation period after randomization, five of the 26 remaining patients in the heparin-treated group, but none of the 25 patients in the rt-PA maintenance group, developed coronary artery reocclusion ($p = 0.05$) (Table 2). Asymptomatic, late reocclusion was detected during follow-up angiography in two patients in the rt-PA–treated group. One patient in the heparin-treated group showed asymptomatic late reocclusion, and one had clinical evidence of late coronary artery reocclusion with recurrence of severe chest pain and ST-segment elevation at 24 hours. Emergency coronary artery bypass surgery was immediately performed, during which time occlusion of the left anterior descending coronary artery was observed.

One patient in the heparin-treated group died in-hospital from ventricular failure before follow-up angiography, and one patient in the rt-PA–treated group refused follow-up angiography. Thus, the overall incidence of reocclusion was seven of 25 (28%) in the heparin-treated group and two of 24 (8%) in the rt-PA maintenance group ($p = 0.01$). Figure 1 shows the proportion of patients with angiographically confirmed reocclusion related to time. There is a marginally significant difference between the two groups by logrank test ($p = 0.07$).

Residual coronary artery stenosis at 90 minutes of infusion (Table 2) was comparable in the heparin and in the rt-PA maintenance groups (66 ± 14% and 68 ± 13%, respectively, $p = 0.6$). At 8–14 days, coronary artery stenosis in patients with persistent patency was unchanged in the heparin-treated group (63 ± 18%, $p = 0.6$) but was reduced significantly in the rt-PA maintenance group (to 55 ± 17%, $p = 0.001$). Similarly, minimal cross-sectional areas did not increase in the heparin-treated group, but the areas increased significantly ($p = 0.003$) from 0.82 ± 0.7 to 1.6 ± 1.2 mm^2 in the rt-PA maintenance group.

Measured assessment of intraluminal thrombus at 90 and 150 minutes of infusion (Table 2) showed that the frequency and extent of residual throm-

TABLE 2. Results of Coronary Angiography

	Randomized study		
	Heparin maintenance	rt-PA maintenance	*p*
Patients (*n*)	27	25	. . .
Acute reocclusion	5 (26)	0 (25)	0.05
Late reocclusion	2 (20)*	2 (24)	. . .
Coronary artery stenosis (%)			
90 min infusion	66 ± 14 (26)	68 ± 13 (25)	0.6
8–14 days			
All patients	72 ± 22 (24)	59 ± 21 (24)	0.04
Patent vessels	63 ± 18 (18)	55 ± 17 (22)	0.18
Δ Percent stenosis			
(8–14 days vs. 90 min)			
All patients	5.0 ± 14 (24)‡	−8.5 ± 16 (24)§	0.003
Patent vessels	−0.9 ± 9 (18)‖	−11. ± 14 (22)¶	0.01
Cross-sectional area (mm^2)			
90 min infusion	1.1 ± 1.1 (24)	0.82 ± 0.7 (25)	0.35†
8–14 days			
All patients	0.9 ± 1.3 (22)	1.4 ± 1.2 (23)	0.20
Patent vessels	1.3 ± 1.3 (16)	1.6 ± 1.2 (21)	0.52
Δ Area			
(8–14 days vs. 90 min)			
All patients	−0.2 ± 0.7 (21)#	0.6 ± 1.0 (23)**	0.0005†
Patent vessels	−0.04 ± 0.8 (15)††	0.7 ± 1.0 (21)§§	0.02†
Residual thrombus (90 min)			0.43
Grade 0	12	10	
Grade 1	8	5	
Grade 2	2	5	
Grade 3	4	5	
Thrombus score			
(150 vs. 90 min)			0.03
No thrombus	8	10	
Improvement	5	7	
Unchanged	4	7	
Deterioration	8	0	
Coronary blood flow (90 min)			0.41
TIMI grade 2	13	9	
TIMI grade 3	14	16	
Coronary blood-flow score			
(150 vs. 90 min)			0.15
Complete flow throughout	12	14	
Improvement	2	2	
Unchanged	6	7	
Deterioration	6	1	
Indeterminate	1	1	

Values are mean ± SD. Values in parentheses are the total number of patients evaluated.
*One patient was documented by angiography and one by emergency coronary bypass surgery.
† Values not normally distributed.
rt-PA, recombinant tissue-type plasminogen activator; TIMI, Thrombolysis in Myocardial Infarction trial.
The *p* values of the randomized study are levels of significance of the difference between data of the heparin-treated and rt-PA maintenance groups. Level of significance of the change (8–14 days vs. 90 min): ‡0.07, §0.02, ‖0.7, ¶0.001, #0.35, **0.005, ††0.86, §§0.003.

bus, as expressed by the thrombus score, was similar in both groups at 90 minutes ($p = 0.43$). However, at 150 minutes, the thrombus score in the rt-PA maintenance group was significantly improved as compared with the heparin-treated group ($p = 0.03$).

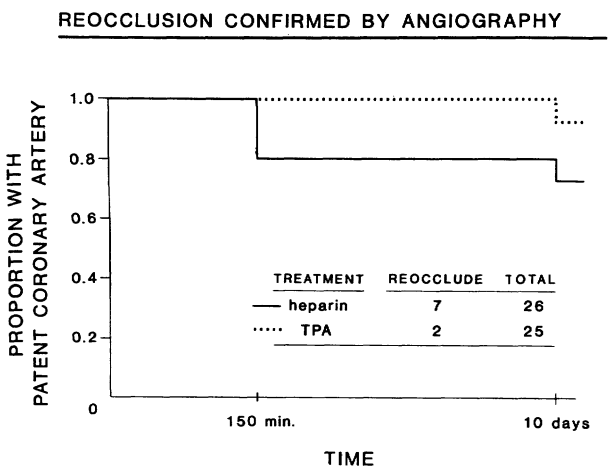

FIGURE 1. *Plot of proportion of patients with patent coronary arteries at each time of angiographic evaluation. TPA, recombinant human tissue-type plasminogen activator.*

Coronary blood flow at 90 minutes of infusion as defined by TIMI grades was not significantly different between the randomized groups ($p=0.41$). There was a tendency for the TIMI grade to decrease between 90 and 150 minutes of infusion more frequently in the heparin-treated group as compared with the rt-PA group, but this difference was not significant ($p=0.15$) (Table 2).

The correlation between acute coronary artery reocclusion (which occurred only in patients randomized to heparin infusion), the percent residual stenosis, the coronary blood flow grade, and the intraluminal thrombus score at 90 minutes of infusion is illustrated in Table 3. In the 25 patients analyzed, the mean residual stenosis was 66±15% (only three patients had a residual stenosis ≥80%); the coronary blood flow grade was 2.6±0.5, and the intraluminal thrombus score was 1.0±1.2. The five patients with acute reocclusion had a higher mean residual stenosis, a lower mean blood flow grade, and a higher mean thrombus score than the 20 patients without reocclusion. Stepwise logistic regression analysis indicated that coronary blood flow grade significantly predicted acute coronary artery reocclusion ($p=0.04$).

Clinical Events

The occurrence of clinical events is summarized in Table 4. Statistical analysis revealed that the frequency of ischemic events (symptomatic reocclusion, unstable angina, and ischemia-related deaths) was significantly higher in the heparin-treated group as compared with the rt-PA maintenance group ($p=0.03$). The death followed intra-aortic balloon pump dependence probably accompanied by ischemic mitral regurgitation and end-organ failure that prevented bypass surgery. There was a significant difference in the occurrence and time of ischemic events between the two treatment groups ($p=0.006$, by logrank test).

Bleeding complications (Table 4) occurred more frequently in the rt-PA maintenance group. This difference was not statistically significant ($p=0.15$).

Left Ventricular Function Analysis

Results of angiographic evaluation of left ventricular function are summarized in Table 5. The global ejection fraction of the reperfused group at 90 minutes of infusion was not different between the randomized groups ($p=0.22$). At 8–14 days after infusion, the global ejection fraction had significantly improved in the nonreoccluding, reperfused group as compared with the persistent occlusion group ($p=0.008$), but patients with continued patency in both randomized groups improved comparably ($p=0.57$).

Results of segmental wall motion were similar. The reperfused patients had comparable hypokinetic segment lengths at 90 minutes infusion, but they improved more significantly at 8–14 days as compared with patients with persistent occlusion ($p=0.003$), and there was no significant difference in the change of the hypokinetic segment lengths between the randomized groups ($p=0.10$) with continued coronary patency.

Hemostasis Analyses

Infusion of 1 mg/kg rt-PA during 90 minutes resulted in a mean steady-state plasma rt-PA level of 1.6–2.0 μg/ml and was associated with a mean decrease of fibrinogen to 63–77% of the preinfusion value (Table 6). The maintenance infusion of 0.8 mg/kg during 4 hours was not associated with a further significant change of the plasma fibrinogen level ($p=0.18$).

Study of a 6-Hour rt-PA Infusion Limited to 100 mg

Compared with the randomized group, the 13 patients in the sequential low-dose rt-PA study showed the same sex distribution (12 men), age

TABLE 3. **Heparin Maintenance Group: Factors Associated With Acute Coronary Artery Reocclusion**

	Reocclusion	Stable patency	*p*
Patients (*n*)	5	20	
Residual stenosis (%)	71±11	65±15	0.37
Coronary blood flow (TIMI grade)	2.3±0.5	2.7±0.47	0.04
Intraluminal thrombus (score)	1.6±1.3	0.85±1.1	0.19

TIMI, Thrombolysis in Myocardial Infarction trial.

TABLE 4. Clinical Events During and After Thrombolytic Therapy

	Persistent occlusion	Randomized study	
		Heparin maintenance	rt-PA maintenance
Patients (*n*)	16	27	25
In-hospital mortality	0	2	0
Bleeding complications			
Patients with bleeding (*n*)	9	6	12
Hematoma at puncture sites	7	5	8
Gingival bleeding	0	0	4
Hematuria	2	1	1
Retroperitoneal bleeding	0	0	1
Transfusion requirement	0	0	1
Ischemic events			
Symptomatic reocclusion	0	6	0
Unstable angina	0	5	3
Ischemia related deaths	0	1	0
Silent reocclusion	0	1	2
Coronary angioplasty during hospital stay			
Before 8–14-day angiogram	6	2	0
After 8–14-day angiogram	0	3	1
Coronary bypass grafting during hospital stay			
Before 8–14-day angiogram	0	2	0
After 8–14-day angiogram	1	2	3

rt-PA, recombinant tissue-type plasminogen activator.

(57 ± 9 years), infarct location (seven anterior, six inferior), and time to rt-PA infusion (2.9 ± 0.7 hours). There was a similar evidence of smoking, previous infarction, hypertension, and diabetes. Mean blood pressure (120 ± 18/80 ± 13 mm Hg) and pulse rate (75 ± 17 beats/min) were comparable. rt-PA was administered as 60, 20, 5, 5, 5, and 5 mg during 6 hours, regardless of the patient's weight.

Coronary angiography at 90 minutes of infusion revealed a patent coronary artery in 12 of the 13 patients (92%). During the 1-hour observation period, two patients reoccluded (Table 7). In addition, three patients developed chest pain and ST-segment elevation during the maintenance low-dose rt-PA infusion. They were readmitted to the cardiac catheterization laboratory, and acute reocclusion was angiographically documented. In four of the five patients with acute reocclusion, the maintenance rt-PA infusion rate was increased fivefold, which caused coronary artery reperfusion within 15 minutes in all patients. The patients then underwent acute coronary angioplasty. Asymptomatic, late

TABLE 5. Angiographic Evaluation of Left Ventricular Function

	Persistent occlusion (*n* = 16)	Randomized study		
		Heparin maintenance (*n* = 27)	rt-PA maintenance (*n* = 25)	*p*
Global ejection fraction (%)				
90 min infusion	61 ± 9 (11)	52 ± 13 (18)	57 ± 10 (16)	0.22
8–14 days	56 ± 13 (9)	60 ± 12 (14)*	58 ± 14 (18)*	0.69
Change	−5 ± 11 (9)†	6 ± 11 (13)†‡	4 ± 8 (15)§	0.57
Hypokinetic segment length (cm)				
90 min infusion	4.9 ± 3 (11)	9.2 ± 5.8 (18)	9.1 ± 5.5 (17)	0.93
8–14 days	6.8 ± 5 (9)	5.8 ± 4.3 (16)*	7.8 ± 4.9 (18)*	0.21
Change	2.5 ± 5 (9)‖	−4.4 ± 3.4 (15)¶	−1.6 ± 5.3 (16)#	0.10

Values are mean ± SD. Values in parentheses are total number of patients evaluated.
rt-PA, recombinant tissue-type plasminogen activator.
*Patients with patency at 8–14 days only.
The *p* values of the randomized study are levels of significance of the difference between data of the heparin-treated and rt-PA maintenance groups. Level of significance of the change (8–14 days vs. 90 min): †0.17, ‡0.07, §0.07, ‖0.13, ¶0.001, #0.23

TABLE 6. rt-PA and Fibrinogen Levels

	Persistent occlusion	Randomized study	
		Heparin maintenance	rt-PA maintenance
Patients (*n*)	16	27	25
Plasma rt-PA antigen concentration (μg/ml)			
90 min infusion	1.6±0.6 (13)	1.9±1.1 (15)	2.0±1.0 (13)
End infusion	. . .	. . .	0.75±0.3 (13)
Fibrinogen level (% of control)			
90 min infusion	65±36 (15)	77±29 (22)	63±26 (20)
End infusion	. . .	. . .	57±28 (19)
Change			−6±17 (19)*

Values are mean±SD. Values in parentheses are total number of patients evaluated.
rt-PA, recombinant tissue-type plasminogen activator.
*Level of significance as compared with zero is 0.18.

reocclusion occurred in one additional patient. Thus, of 12 reperfused patients, six reoccluded before the 8–14-day angiogram. The residual coronary artery stenosis at 90 minutes of infusion and the cross-sectional areas were comparable to those of the randomized rt-PA maintenance groups (Table 7). The thrombus score and coronary blood flow at 90 minutes of infusion were not significantly different from those of the heparin-treated or rt-PA maintenance groups of the randomized study.

Clinical ischemic events were observed in eight of 12 reflowed patients (five symptomatic reocclusions, two unstable anginas, and one ischemia-related death). Bleeding complications occurred in five patients, of whom one required transfusion. End-infusion fibrinogen level was 83±16%, and rt-PA antigen level was 0.25±0.16 μg/ml.

Discussion

The value of thrombolytic therapy for acute myocardial infarction has been established by several large trials (24–26). However, a major problem accompanying this therapy is reocclusion and recurrent ischemia.[5,12–14] Prevention of reocclusion has been attempted by early angioplasty. However, the Trial of Acute Myocardial Infarction (TAMI) study[15] showed an acute reocclusion rate of 15% after angioplasty, and the European multicenter trial demonstrated an increased complication rate.[27] These results and the required commitment of resources for early angioplasty underscore the importance of administration of thrombolytic agents in a manner capable of producing stable coronary patency. The present study was designed to test whether a maintenance infusion of intravenous rt-PA would reduce the frequency of reocclusion and recurrent ischemia, thereby reducing the need for invasive procedures.

We chose a lytic dosage of 1 mg/kg given during 90 minutes because of the previously reported 75% patency rate at this dosage.[28] Studies with wide dosing ranges have demonstrated that a 75% reflow rate at 90 minutes approximates the upper limit for thrombolytic therapy.[29] A maintenance dosage of 0.8 mg/kg given during 4 hours was selected because our pilot studies had demonstrated maintenance blood levels of rt-PA of 0.7±0.5 μg/ml, a level suitable for the prevention of coronary rethrombosis and for continued clot lysis.[30]

TABLE 7. Results of a 6-Hour rt-PA Infusion Limited to 100 mg

Patients (*n*)	13
Coronary patency	
90 min infusion (*n*)	12
Acute reocclusion	
90–150 min (*n*)	2
100–330 min (*n*)	3
Late reocclusion (*n*)	1
Coronary stenosis	
90 min infusion (%)	65±13 (11)
Cross-sectional area	
90 min infusion (mm^2)	1.0±0.6 (10)
Residual thrombus	
(90 min infusion) (*n*)	
Grade 0	5
Grade 1	4
Grade 2	2
Grade 3	1
Coronary blood flow	
(90 min infusion) (*n*)	
TIMI grade 2	6
TIMI grade 3	6
Fibrinogen level (% of control)	
End infusion	83±16% (6)
Plasma rt-PA antigen concentration (μg/ml)	
End infusion	0.25±0.16 (7)

Values are mean±SD. Values in parentheses are number of patients evaluated.
rt-PA; recombinant tissue-type plasminogen activator; TIMI, Thrombolysis in Myocardial Infarction trial.

At 90 minutes after the beginning of rt-PA infusion, the residual stenosis in all randomized reflowed patients was 67 ± 13%. Forty-two percent showed some delayed angiographic washout (TIMI grade 2 flow). Furthermore 31% showed clearly definable intraluminal filling defects (clot thrombus grade 2 or 3).

Maintenance of patients on heparin alone after 90 minutes of rt-PA infusion was associated with a significantly higher incidence of symptomatic, acute reocclusion and increased angina at rest compared with patients on rt-PA maintenance infusion. Furthermore, even when reoccluding patients were excluded, patients maintained on heparin alone did not show a further diminution in average residual percent stenosis during 10 days. During a maintenance infusion of rt-PA at 0.8 mg/kg for 4 hours, the blood level of rt-PA was maintained at 0.75 ± 0.3 μg/ml; acute reocclusion and unstable angina were prevented, and the residual stenosis at 10 days was significantly decreased. In this maintenance group, no patients required acute angioplasty.

Randomized patients in these studies who suffered acute reocclusion had a higher mean residual stenosis, a lower coronary blood flow grade, and a higher intraluminal thrombus score at 90 minutes of infusion than patients with stable patency. The mechanism of acute reocclusion was often observed to be an increase in residual clot size with slowing of coronary washout, which only occurred after the cessation of rt-PA in the heparin-maintenance group.

The stimulus that initiated reocclusion may also have been impairment of coronary runoff. Distal coronary obstruction, possibly related to edema, platelet aggregates, or distal emboli, may produce TIMI grade 2 flow even though residual coronary stenosis at the occlusion site is no longer greater than 80%. Regression analysis showed that the reduction of flow to TIMI grade 2 was more important than residual coronary stenosis in predicting coronary reocclusion. Maintenance rt-PA prevents reocclusion even in the presence of TIMI grade 2 coronary blood flow at 90 minutes of infusion. It is not possible to determine from this study whether maintenance rt-PA infusion prevents reocclusion by continuing thrombolysis or by improving coronary runoff, only that the final common pathway of coronary thrombus growth is prevented.

In association with the prevention of acute reocclusion, maintenance rt-PA at 0.8 mg/kg during 4 hours apparently contributes to remodeling at the site of plaque disruption and coronary occlusion. Indeed, residual stenosis is further reduced, suggesting lysis of mural thrombi, whereas in the heparin group, persistence of stenosis suggests organization of mural thrombus. With further thrombus resolution during rt-PA maintenance, the residual coronary stenosis fell to 55 ± 17% with only four patients showing residual stenosis greater than 70%. At this level of stenosis, recurrent ischemic events were observed in only three of 24 patients, despite presumed underlying plaque rupture.

Left ventricular function analysis confirmed the frequently demonstrated finding that patients with stable reperfusion show better function at discharge than patients with persistent occlusion. No differences were observed between patients with stable reperfusion, whether they were maintained on heparin alone or rt-PA with heparin.

The frequency of acute reocclusion during heparin maintenance is significantly higher (Gold et al[14] and this study) than observed in a similar study by the European Study Group.[11] In the latter study, 40 mg rt-PA was given during 1 hour followed by randomized administration of either heparin or a maintenance rt-PA infusion of 5 mg/hr during 6 hours (with heparin). The overall patency rate at 90 minutes of infusion was 66%. The maintenance rt-PA level was 0.08 μg/ml, which is about one tenth of the level obtained by 0.8 mg/kg during 4 hours. The early reocclusion rate (6–24 hours), however, was only 7% and not different between the groups. One explanation for the difference from our results may be the low lytic dose used, which may have eliminated from analysis patients with the highest tendency to reocclusion by failure to produce reflow.

In the present study, we infused rt-PA at a dose of 1.8 mg/kg during 5.5 hours, which amounted to an average total dose of approximately 150 mg. Despite this, bleeding complications were limited to catheter sites, and fibrinogen levels were well maintained. One patient required transfusion because of a catheter-induced injury. We did not observe intracerebral bleeding. However, with a similar total dose, the TIMI group observed an intracranial bleeding rate of 1.7% in a much larger series of patients.[20] It should be noted, however, that in the TIMI study, rt-PA was not given on a weight basis. Furthermore, the patients received 90 mg rt-PA during the 1st hour, resulting in a much more pronounced depletion of fibrinogen than observed in our present study, in which patients received a mean of 52 mg rt-PA (0.67 mg/kg) during the 1st hour.[31]

A reduction in the total rt-PA dose to 100 mg has been correlated with a lower incidence of intracranial bleeding.[20] The two most widely used infusion regimens are 60, 20, and 20 mg during 3 hours[27] and 60, 20, 5, 5, 5, and 5 mg during 6 hours.[20] We chose the latter for a pilot study in 13 patients because we have previously demonstrated in a nonrandomized series that a 5.5-hour infusion of rt-PA stabilizes the reflowed coronary artery.[14] This infusion regimen, given under angiographic control, was associated with a high patency rate, but the maintenance infusion did not uniformly prevent acute symptomatic coronary reocclusion.

Clearly, the results of the sequential study with a reduced dose of rt-PA, which demonstrated a reocclusion rate of over 40%, have to be interpreted

very cautiously. Indeed, although we found no significant differences in any of the relevant patient characteristics at entry as compared with the randomized study groups, these patients were not allocated under conditions required for valid comparison. In addition, the size of the sequential study group is small and thereby of limited statistical power. Nevertheless, in at least two instances, angiographic evidence was obtained that reocclusion occurred by progressive thrombus enlargement. Furthermore, in four of five patients with acute reocclusion, this was readily reversed by a fivefold increase of the rt-PA infusion rate.

Our findings indicate that it will be necessary to give rt-PA maintenance infusions at a certain minimal level and duration to attain both complete clot lysis and to prevent thrombus reaccumulation on a complex atherosclerotic plaque surface. The major remaining question is whether stable reflow can be consistently obtained when the maintenance rt-PA infusion is reduced below doses given in our randomized trial. It is possible that a total dose of 100 mg rt-PA can be divided into a lytic and maintenance portion that will prevent reocclusion. Recent studies by Guerci et al[32] and O'Rourke and Norris[33] have shown improved left ventricular function using the 60-, 20-, and 20-mg regimen during 3 hours. Therefore, this regimen may be an adequate alternative to infusion of 100 mg during 6 hours.

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