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Regional Wall Motion Improvement After Coronary Thrombolysis With Recombinant Tissue Plasminogen Activator: Importance of Coronary Angioplasty

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To evaluate functional recovery in 20 consecutive patients with acute myocardial infarction who received recombinant tissue-type plasminogen activator, serial two-dimensional echocardiograms were performed before and immediately after tissue plasminogen activator administration and at 1 and 10 days postinfarction. Tissue plasminogen activator was administered intravenously (17 patients) or by intracoronary infusion (3 patients) after angiographic confirmation of total occlusion. Reperfusion, documented by angiography, occurred in 13 of the 20 patients. The mean time from onset of chest pain to thrombolysis was 5.1 ± 1.1 hours. Echocardiograms were evaluated for regional function with a visual semiquantitative scoring system by two independent observers who had no knowledge of patient identity, temporal sequence, therapy or effect of therapy.

There was no immediate or 24 hour improvement in wall motion. At day 10 compared with pretreatment, 28 of 33 reperfused infarct zone segments versus 6 of 20 nonreperfused infarct segments demonstrated improved wall motion ($p = 0.01$). This improvement did not relate to time from onset of chest pain to successful thrombolysis. Of reperfused infarct zone segments in the distribution of coronary artery balloon dilation, 19 of 23 segments exhibited improvement versus 7 of 17 (reperfused, no angioplasty) and 6 of 20 (nonreperfused, no angioplasty) segments ($p = 0.001$). Infarct zone segments reperfused at the time of ongoing chest pain demonstrated functional recovery compared with segments reperfused in the absence of chest pain (18 of 23 versus 10 of 20, respectively; $p = 0.05$).

Thus, in this uncontrolled series, there was echocardiographically detectable improvement in function of reperfused infarct segments 10 days after coronary thrombolysis with recombinant tissue plasminogen activator. The functional recovery occurred predominantly in patients who also had coronary artery balloon dilation or ongoing chest pain, or both, at the time of coronary thrombolysis.

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During the past 5 years, there has been scientific interest in applying thrombolytic therapy to patients with acute myocardial infarction (1–3). With intracoronary streptokinase, recanalization of the acutely occluded coronary artery has been demonstrated to be successful in up to 80% of patients (4–8). Despite reperfusion, however, only a few controlled studies have shown beneficial effects on left ventricular function and many have shown no measurable benefit (5,9–14). Recombinant tissue-type plasminogen activator is a human enzyme that holds promise for the treatment of acute coronary thrombosis by virtue of its relative clot-

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selectivity, short half-life and little potential for antigenicity (15–18). We recently participated in a multicenter pilot study of tissue plasminogen activator in acute myocardial infarction (19). During this study, in addition to determining the coronary thrombolytic efficacy of this agent, we directed our attention to whether successful coronary thrombolysis, together with methods to maintain arterial patency, could affect functional recovery of myocardium.

Methods

Selection of patients. Patients who presented to Johns Hopkins Hospital and the Francis Scott Key Medical Center with chest pain of greater than 20 minutes' but less than 6 hours' duration, associated with 1 mm or greater electrocardiographic ST segment elevation (in one or more leads), were considered for entry into the protocol. Exclusion criteria were: cardiogenic shock, prior coronary artery bypass surgery, bleeding diathesis, prior transmural myocardial infarct, age greater than 70 years, pregnancy or significant hepatic, renal or pulmonary disease.

Coronary arteriography and thrombolysis. After giving informed consent, patients underwent selective coronary arteriography using the Judkins technique. Once arterial access was obtained, heparin (100 U/kg body weight, maximum 10,000 U) was infused intravenously. Coronary angiograms were obtained in the oblique and several hemiaxial projections for both the infarct vessel and the contralateral coronary artery. Total occlusion was confirmed angiographically in 21 of 34 patients so studied. The study drug (tissue plasminogen activator [0.25 to 0.75 mg/kg over 30 to 120 minutes] or saline solution placebo) was administered intravenously to these 21 patients. Thirty minutes after the start of the infusion, the study was unblinded. If placebo had been infused and there was no evidence of recanalization during the placebo infusion (this occurred in three patients), the patient was crossed over to treatment with intracoronary tissue plasminogen activator infusion (0.375 mg/kg over 15 to 30 minutes). In one patient, reperfusion was observed during the placebo infusion. Because this patient never received tissue plasminogen activator, the data are not included in this series (19). The remaining 20 consecutive patients were entered into the protocol. Relevant characteristics are summarized in Table 1.

Coronary angioplasty. All patients who had successful recanalization with tissue plasminogen activator were considered for percutaneous transluminal coronary angioplasty. The criteria for selection were 1) a discrete lesion that appeared amenable to dilation in the infarct vessel and 2) lack of diffuse or severe atherosclerotic disease of the noninfarct-related vessels. Coronary angioplasty was performed at a mean of 22 (±21) hours after successful thrombolysis. It was not performed immediately after thrombolysis in seven of nine patients because of the time required to transfer the patient between hospitals or obtain cardiothoracic surgical backup. All patients with tissue plasminogen activator-mediated thrombolysis were placed on a medical regimen to prevent rethrombosis, consisting of intravenous heparin (1,000 U/h), aspirin (325 mg/day), dipyridamole (75 mg three times/day) and nifedipine (10 mg four times/day). Heparin was continued for the initial 4 to 5 hospital days; antiplatelet and calcium channel antagonist therapy were utilized throughout the hospital course.

Table 1. Patient and Therapy Characteristics

Patients	
Number	20
Age (yr)	
Mean	55 ± 7
Range	(39 to 69)
Sex (male/female ratio)	17:3
Site of infarct (no. of patients)	
Anterior	9
Inferior	11
Drug therapy	
Dose of t-PA (mg)	43 ± 17
Route (no. of patients)	
Intravenous	17
Intracoronary	3
Hours from chest pain to t-PA	4.8 ± 1.5
Hours from chest pain to lysis	5.1 ± 1.1
Successful lysis	
All patients	13 of 20 (65%)
Patients with intravenous t-PA	12 of 17 (71%)

Lysis = coronary artery recanalization; t-PA = recombinant tissue-type plasminogen activator.

Echocardiography. Two-dimensional echocardiography was performed before administration of tissue plasminogen activator, serially every 15 minutes for 2 hours after the infusion was complete and at 24 hours and 8 to 10 days postinfarction. The Hewlett-Packard ultrasonograph (AC-77020) was used for 16 patients and the Diasonics 3400R for the remaining 4 patients. Each two-dimensional study consisted of parasternal long- and short-axis views (the latter at two cross-sectional levels) and apical two and four chamber views. In patients in whom these views were suboptimal, the subxiphoid window was utilized. Using a combination of these views, all studies were technically adequate for scoring regional endocardial wall motion.

For the purpose of analysis, the left ventricle was divided into seven segments (Fig. 1). Each study was recorded on videotape and later scored independently by two observers who were unaware of patient identity, temporal sequence in which the studies were acquired, therapy and effects of therapy (thrombolysis or no thrombolysis, angioplasty or no angioplasty). Each myocardial segment was scored for wall motion using semiquantitative visual analysis grading for dyskinesia, akinesia, hypokinesia and normal motion (20). Improvement was defined by at least one full increase in grade, from akinesia to hypokinesia or hypokinesia to

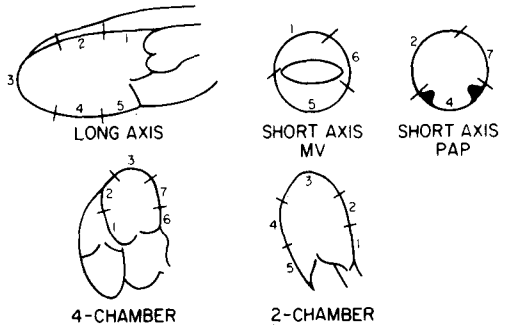

Figure 1. Schematic diagram showing the method used to identify seven myocardial segments from the long- and short-axis parasternal (**above**) and apical four and two chamber (**below**) echocardiographic views. 1 = basal septal, 2 = mid apical septal, 3 = apical, 4 = diaphragmatic, 5 = posterobasal, 6 = superolateral and 7 = inferolateral. MV = mitral valve level; PAP = papillary muscle level.

normal wall motion. The infarct zone was defined by matching echocardiographic territory to the distribution of the occluded coronary artery, as defined by coronary arteriography. The regions not supplied by the totally occluded coronary artery were considered the noninfarct zone. Noninfarct zone segments were not scored for hyperkinesia; when it was present (in 7 of 77 segments), the segment was graded as having normal wall motion. In scoring, there was lack of observer agreement on 14% of segments; this was resolved by joint review of the study and consensus.

Statistical analysis. All values reported are mean ± standard deviation of the mean. Chi-square analysis, with either a 2 × 2 or 2 × 3 contingency table, was utilized to determine whether there was a significant difference between functional wall motion improvement in the reperfused and nonreperfused infarct zones and the noninfarct zone.

Results

Thrombolysis. Coronary reperfusion with tissue plasminogen activator was successful in 13 (65%) of the 20 patients. The time from onset of chest pain to angiographically determined lysis was 5.1 ± 1.1 hours. Tissue plasminogen activator was administered intravenously in 17 patients and by the intracoronary route in 3 patients after no lysis was observed during the 30 minute placebo infusion. Reperfusion was achieved in 12 of the 17 patients who received tissue plasminogen activator intravenously, but in only 1 of the 3 who received the enzyme by intracoronary infusion. The mean dose of tissue plasminogen activator was 43 ± 17 mg (range 0.25 to 0.75 mg/kg over 30 to 120 minutes). In patients with successful reperfusion, recanalization of the infarct vessel occurred 36 ± 10 minutes after the start of tissue plasminogen activator infusion. Six of 13 patients with reperfusion had ongoing chest pain at the time of angiographic recanalization. Visible collateral channels to the distal territory of the infarct vessel were noted in 4 of the 13 patients. Of the six patients who did not exhibit recanalization, three had evidence of collateralization to the infarct vessel. At the time of angiographic lysis, electrocardiographic Q waves and persistent ST segment elevation were present in four and eight patients, respectively.

Percutaneous transluminal coronary angioplasty (Table 2). Nine of the 13 patients in whom reperfusion occurred returned to the catheterization laboratory for coronary angioplasty. At that time, two of the nine patients demonstrated reocclusion, without associated symptoms, despite an intensive medical antithrombotic regimen. In these two patients, dilation of the infarct vessel by angioplasty was unsuccessful. Of the seven patients who had successful infarct vessel dilation by angioplasty, five had normal findings on a predischarge submaximal exercise treadmill test (maximal heart rate 120 beats/min). An equivocal test in two patients led to repeat coronary angiography, which demonstrated a widely patent vessel in both patients. In follow-up, one patient died after a massive stroke that occurred 18 days postinfarction; the other six patients with successful coronary artery dilation are asymptomatic and have returned to work at 9 ± 2 months postinfarction.

Four patients in whom thrombolysis was achieved were not considered candidates for coronary angioplasty for the following reasons: one patient with two vessel disease had two clinical reocclusive episodes within 6 hours after tissue plasminogen activator infusion, manifested by recurrence of chest pain and electrocardiographic ST segment elevation, and underwent emergent surgical revascularization successfully; three patients had severe, diffuse three vessel coronary artery disease, one of whom died of cardiogenic shock and massive hemorrhagic infarction on the fifth day after infarction.

Reocclusion. In addition to the two patients who exhibited "silent" reocclusion detected at the time of attempted coronary angioplasty, the patient who died of cardiogenic shock demonstrated a total left anterior descending artery

Table 2. Results of Coronary Angioplasty After Thrombolysis

Site of dilation (no. of patients)	LAD in 4, RCA in 5
Time postinfarct (hours)	22 ± 21
Success of dilation	7 of 9 (77%)*
Change in percent stenosis	84 ± 6 to 29 ± 7
Predischarge ETT (no. of patients)	Negative in 7 of 7
Follow-up status	Asymptomatic in 6 of 7 patients†; 9 ± 2.1 (mo)

*Of the two patients in whom coronary angioplasty was not successful, both had reocclusion without associated symptoms before the procedure. †One patient sustained a massive stroke 2 weeks after hospital discharge. ETT = submaximal treadmill exercise test; LAD = left anterior descending coronary artery; RCA = right coronary artery.

thrombotic occlusion at autopsy. The other patient who developed recurrent chest pain and ST segment elevation responsive to intravenous streptokinase was demonstrated to have intracoronary thrombus at the time of surgical revascularization.

Regional function: immediate and 24 hours (Fig. 2). The changes in regional function from pretreatment to immediately after treatment and to 24 hours later were similar. At 1 hour after tissue plasminogen activator infusion, no improvement of wall motion was found in 28 of 43 reperfused infarct zone segments compared with 15 of 20 nonreperfused infarct segments and 68 of 77 noninfarct segments (p = NS). One day after tissue plasminogen activator was administered, lack of functional improvement was evident in 30 of 43 reperfused infarct regions, 16 of 20 nonrecanalized infarct segments and in 69 of 77 segments of the noninfarct zone (p = NS). Thus, there was no detectable immediate or 24 hour improvement in regional wall motion after tissue plasminogen activator infusion. The scoring of noninfarct zone segments served as a control and showed no significant change throughout the 10 day study period.

Regional function at 10 days (Fig. 3 to 6). In contrast to the immediate and 24 hour results, wall motion at 10 days was significantly more improved in reperfused infarct zone segments than in nonreperfused segments (improvement in 28 of 43 versus 6 of 20, respectively; $\chi^2 = 6.7$, p = 0.01) (Fig. 3). An example of echocardiographic improvement in segmental motion is shown in Figure 4. The greatest functional improvement of the reperfused infarct segments occurred in the subgroup that underwent both successful thrombolysis and coronary angioplasty (Fig. 5). Regional wall motion improvement was evident in 19 of 23 reperfused infarct segments that were also in the distribution of coronary artery balloon dilation, but in only 7 of 17 "lysis only" and 6 of 20 nonreperfused infarct zone segments ($\chi^2 = 13.3$, p = 0.001). There were no intergroup differences in functional improvement for reperfused versus nonreperfused infarct segments with regard to the presence or absence of pretreatment visible collateral vessels, electrocardiographic Q waves or persistent ST segment elevation (concurrent with tissue plasminogen activator therapy). However, in those patients with ongoing chest pain at the time of coronary thrombolysis, there was greater improvement in the reperfused infarct zone segments in patients with chest pain at 10 days postinfarction (Fig. 6). At 10 days, wall motion improvement was detected in 18 of 23 reperfused infarct segments in patients with chest pain at the time of coronary thrombolysis versus 10 of 20 reperfused infarct segments in patients without chest pain (p = 0.05, Fisher's exact test).

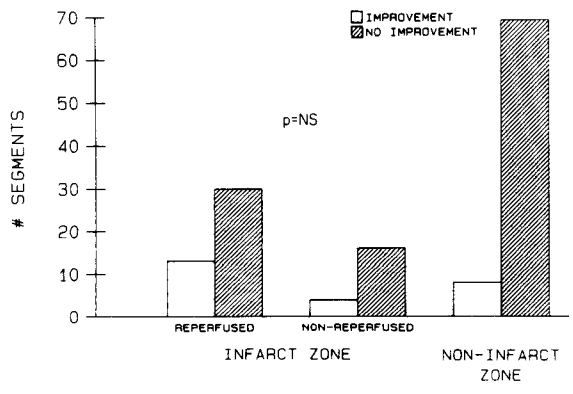

Figure 2. Lack of improvement of segmental wall motion at 24 hours compared with pretreatment. There was no difference between the number of reperfused or nonreperfused infarct segments that exhibited improvement. Minimal change in wall motion (no improvement) was apparent in the noninfarct zone.

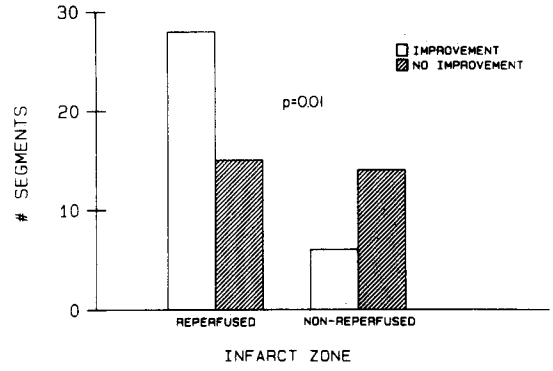

Figure 3. At 10 days, compared with baseline, there is significantly greater wall motion improvement in reperfused than in nonreperfused infarct zone segments.

Functional recovery: lack of time dependency of reperfusion (Fig. 7). There is marked scatter in the change of wall motion score (10 days compared with pretreatment) for all infarct zone segments reperfused within a range of 3 to 7 hours from the onset of chest pain. This suggests that in this small series of patients, no trend was established that correlated early reperfusion with functional recovery of infarct segments.

Discussion

Using two-dimensional echocardiography, we have demonstrated the absence of detectable regional wall improvement immediately and 24 hours after treatment of acute coronary occlusion with recombinant tissue-type plasminogen activator. However, 10 days after treatment, there was an improvement in segmental motion of the reperfused compared with the nonreperfused infarct zones. This occurred chiefly in patients who had both successful plasminogen activator-mediated coronary thrombolysis and angioplasty. In addition, although the time from onset of chest pain to thrombolysis did not correlate with functional recovery, infarct zone segments that were reperfused while the patient had ongoing chest pain exhibited greater improvement in regional wall motion than did those of patients without chest pain at the time of reperfusion.

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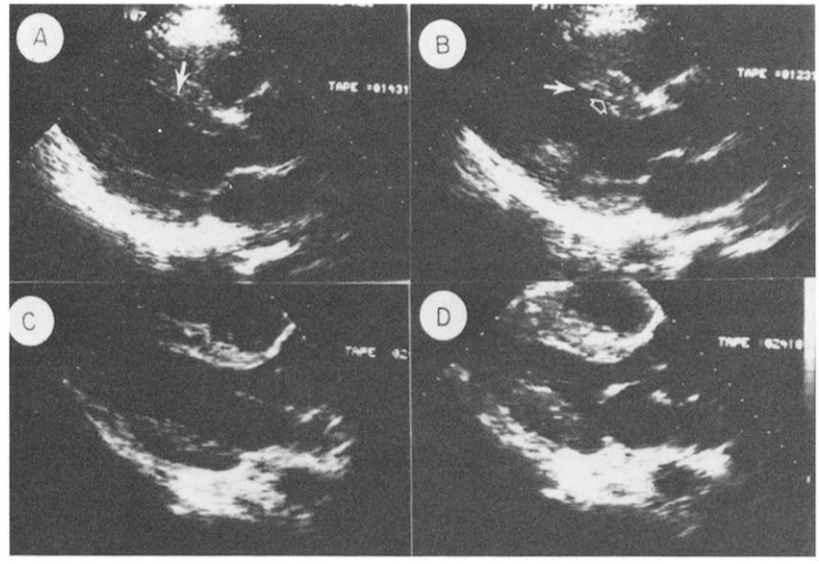


Figure 4. Two-dimensional echocardiograms of a patient who presented with proximal left anterior descending artery occlusion and underwent successful thrombolysis and coronary angioplasty. **A**, Baseline study, parasternal long-axis view in diastole, demonstrates mid- and distal septal deformity (**arrow**). **B**, Corresponding systolic frame shows lack of inward endocardial movement (**arrow**) and hinge point at proximal septum (**arrowhead**). **C**, Study at 10 days postinfarction, parasternal long-axis view in diastole, demonstrates normal cavity configuration. **D**, Corresponding systolic frame demonstrates normal endocardial motion of the mid- and distal septal segments.

Comparison with previous studies. The finding that regional myocardial function is unchanged immediately and 1 day after successful coronary thrombolysis is in agreement with most experimental animal investigations (21–24) and clinical studies (4,12,25) with streptokinase treatment for myocardial infarction. Despite this finding, recent studies using C-11 palmitate positron imaging (26,27) have shown immediate improvement of regional metabolism after tissue-type plasminogen activator in the canine model and in a small clinical series. The lack of early improvement has been attributed to prolonged postischemic ventricular dysfunction or "myocardial stunning" secondary to ischemia-induced biochemical and ultrastructural alterations (21–24). The finding of regional functional improvement at 10 days postinfarction, however, contrasts with the conclusions of several randomized, placebo-controlled studies of intracoronary streptokinase (4,6–9).

Because we found that coronary angioplasty appeared to be the predominant contributory factor to functional recovery, the differences in our observations may be due, in large part, to the incorporation of mechanical revascularization into the study design for all appropriate candidates. In patients with acute myocardial infarction, prior studies of sequential coronary thrombolysis with intracoronary streptokinase and coronary artery balloon angioplasty (28–36) have demonstrated both feasibility and improved angiographic appearance of the infarct vessel acutely and before hospital discharge, but regional functional recovery has not been reported. Recently, Yasuno et al. (37) demonstrated a significant improvement of regional wall shortening after administration of urokinase followed by immediate transluminal coronary angioplasty. Another approach to patients with acute infarction is intracoronary administration of streptokinase combined with acute surgical revascularization, which has been demonstrated (38) to reduce infarct size and improve left ventricular function. Several studies (39–44) have demonstrated improved global and regional

Figure 5. Marked improvement, at 10 days compared with baseline, of infarct zone regional wall motion in the distribution of reperfusion (lysis) and coronary artery balloon dilation (PTCA) compared with segments reperfused without subsequent angioplasty or those not reperfused. In the "lysis only" segments, no overall improvement was noted.

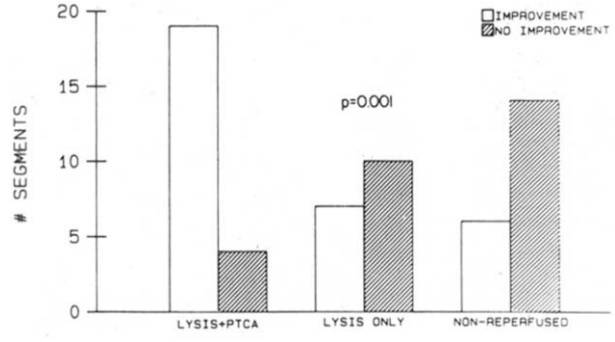
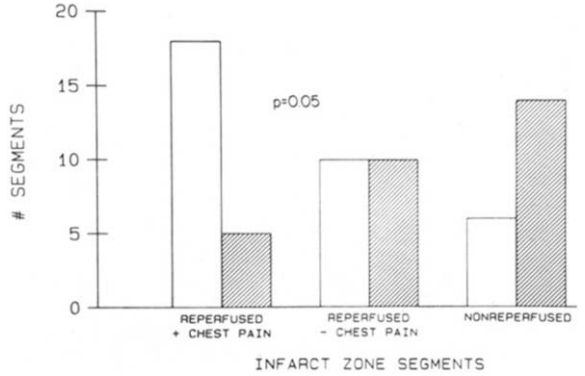


Figure 6. At 10 days, there is significant improvement of wall motion in reperfused infarct zone segments in patients with ongoing chest pain compared with segments in patients without chest pain.



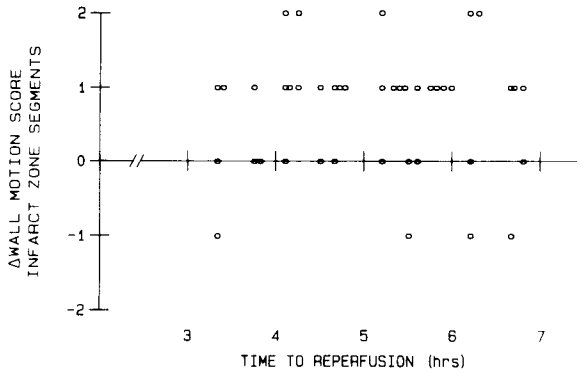


Figure 7. The time to reperfusion is plotted against the change (Δ) in wall motion score (day 10 versus admission) for reperfused infarct zone segments. Marked scatter of regional wall motion is evident throughout the range of 3 to 7 hours from onset of chest pain to coronary thrombolysis.

myocardial function, both systolic and diastolic, after coronary angioplasty in patients with evidence of reversible transient ischemia.

Role of coronary angioplasty. In our study, the importance of coronary angioplasty in promoting functional recovery may relate to at least two factors. First, treatment of the underlying stenosis, which was severe in all patients, abolishes a flow-limiting obstruction and allows "full" coronary revascularization (45), which may be crucial for functional recovery. Indeed, the coronary flow reserve is minimally affected by successful thrombolysis alone, but exhibits significant improvement after sequential coronary angioplasty (46). Second, by dealing effectively with the residual atherosclerotic coronary lesion, there appears to be less propensity for reocclusion after initial recanalization (28–34). In experimental atherosclerotic, thrombotic occlusion, after treatment with tissue plasminogen activator, we found evidence of residual thrombus, which may propagate recurrent thrombosis (47). Careful angiographic studies suggest that the incidence of symptomatic reocclusion after streptokinase therapy without coronary angioplasty is at least 20% before hospital discharge and proportionally higher for more critical lesions (6,30,48–50). Furthermore, as was demonstrated in our series of patients, rethrombosis may also be a "silent" phenomenon. Thus, by further improving coronary blood flow and removing the nidus for rethrombosis, coronary angioplasty may be a key determinant of functional recovery after myocardial infarction. Because benefit was seen despite a mean delay of 22 hours between thrombolysis and angioplasty, this combined approach may prove to be feasible even in hospitals where angioplasty is not immediately available.

Time to reperfusion. In our patients, the duration of chest pain before reperfusion did not appear to be inversely correlated with functional recovery. If in patients the onset of chest pain truly represents the coronary occlusive event, the results in animals are not parallel with our observations (51,52). However, several other clinical studies with streptokinase (53–55) have not found the time interval from onset of chest pain to recanalization to be of predictive value for left ventricular functional improvement.

Perhaps a more important marker of myocardial salvageability is the presence of chest pain at the time lysis is achieved (56). As identified in the current study, there was a greater degree of segmental improvement of infarct zone regions in patients with ongoing chest pain. Other factors such as collateral blood flow or electrocardiographic manifestations did not appear to be related to demonstrable functional recovery. Although other studies have pointed toward particular benefit in patients with subtotal coronary occlusion (6,55,57), these patients were excluded a priori from entry into the current study.

Limitations. Several limitations of our study design are apparent. *First,* this is a small, uncontrolled, consecutive series of patients. It is clear that spontaneous reperfusion may occur in the early phase of acute coronary occlusion (57,58). Similarly, there are spontaneous changes of left ventricular function in the first 24 hours of acute myocardial infarction and throughout the hospital course (59). Clearly, it is possible that some patients who had successful tissue plasminogen activator-mediated thrombolysis may have had early spontaneous reperfusion without this enzyme (56). The study design and analysis of data are similar to many of the initial studies of patients with myocardial infarction treated with streptokinase (12–14,60–62). Although not statistically significant, the difference in site of infarction between patients with and without reperfusion is a function of the small, nonstratified sample size. Thus, interpretation of such a series of consecutive cases must be made with caution (63).

Second, coronary angioplasty was not performed on a randomized basis. The selection criteria for this procedure were successful reperfusion and suitable coronary artery anatomy. Although coronary dilation was associated with significant regional wall motion improvement, this may have been due to the favorable anatomy itself, which may in turn correlate with subsequent functional recovery. Our results indicate that reperfused infarct zone segments without subsequent mechanical revascularization lacked significant wall motion improvement compared with infarct regions not initially reperfused. Thus, it remains possible that coronary angioplasty was the sole factor responsible for improvement. Indeed, a recent study by O'Neill et al. (64) demonstrated that direct coronary angioplasty was superior to intracoronary streptokinase in leading to improved myocardial blood flow and left ventricular function.

Third, the analysis of regional function relied on visual assessment of wall motion on two-dimensional echocardiographic studies, which is a semiquantitative measurement (20). Although analysis of regional wall thickening is more

quantitative, it requires complete definition of endocardial and epicardial outlines, which was not possible in some cases, and does not allow integration of various echocardiographic planes (65). Visual techniques have been validated and utilized in many prior studies of acute myocardial infarction (66,67). Instead of deriving an overall wall motion score index (5,10,25,66,67), we used a high threshold to define wall motion improvement and kept infarct and noninfarct zone segments discrete.

Although the intravenous route was used in most patients, a pretreatment angiogram was required to confirm thrombolytic efficacy of tissue plasminogen activator. Thus, an intrinsic time delay for initiation of therapy, despite intravenous administration, was part of the study design and may have impeded the demonstration of more substantial wall motion improvement.

Implications. Our study points to the important potential role of angioplasty in promoting improvement of regional function after acute coronary artery occlusion. The coronary thrombolytic efficacy of tissue-type plasminogen activator compares favorably with both intracoronary (4–8) and intravenous (10,11,50) streptokinase, but there was little functional recovery in those patients who did not also have successful mechanical revascularization. The salutary properties of tissue plasminogen activator, both its relative fibrin selectivity and its short half-life, may be of particular value in allowing definitive revascularization with coronary angioplasty to be achieved safely. Controlled trials are currently in progress to test the role of second generation thrombolytic agents and angioplasty in acute myocardial infarction.

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