

Original Studies

Applicability of Percutaneous Transluminal Coronary Angioplasty to Patients With Recombinant Tissue Plasminogen Activator Mediated Thrombolysis

Eric J. Topol, MD, Jaan E. Eha, MD, Kenneth P. Brin, MD,
Edward P. Shapiro, MD, James L. Weiss, MD, Mary B. Riegel, RN,
Sidney O. Gottlieb, MD, and Jeffrey A. Brinker, MD

To test the utility and safety of percutaneous transluminal coronary angioplasty (PTCA) after recombinant tissue plasminogen activator (t-PA), we performed the procedure in all suitable candidates with acute myocardial infarction (MI) who had successful t-PA mediated coronary thrombolysis. Twenty consecutive patients with MI received t-PA after coronary angiographic confirmation of total occlusion. Successful recanalization with t-PA was achieved in 13 patients, leaving a residual obstruction of $84 \pm 6\%$ in the nine patients for whom PTCA was attempted at a mean of 21.6 h. Success was achieved in seven patients, leading to a residual lesion of $29 \pm 7\%$. In the two patients for whom PTCA was unsuccessful, total reocclusion occurred prior to the attempt despite therapy with heparin, aspirin, dipyridamole, and nifedipine. All PTCA procedures were uncomplicated. Serial two-dimensional echocardiography at 10 days, compared to admission, demonstrated infarct zone wall motion index improvement in the patients with successful PTCA (group A, 0.83 ± 0.36 to 1.46 ± 0.49) as compared to the 13 patients without thrombolysis or successful PTCA (group B, 0.61 ± 0.26 to 0.66 ± 0.39), ($P < 0.05$). One patient of group A sustained a massive stroke at 2 weeks after hospital discharge. In the remaining six patients, follow-up exercise testing and/or coronary arteriography demonstrated a negative treadmill test and/or patent infarct vessel, respectively. After successful PTCA, no patient had clinical signs of reocclusion, reinfarction, postinfarction angina, or congestive heart failure. At 9.4 ± 2 months, all six patients are asymptomatic and have returned to work. Thus, sequential PTCA after t-PA can

From the Johns Hopkins Hospital and Francis Scott Key Medical Center, Baltimore.

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Dr. Topol is now at the Cardiac Study Unit, S5438 Main Hospital, University of Michigan Hospital, 1405 E. Ann St., Ann Arbor, MI 48109.

Address reprint requests to Jeffrey A. Brinker, MD, 501 CMSC, The Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

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be performed safely and successfully in patients with MI and this approach may be associated with improved regional function and a favorable post-MI course.

Key words: coronary angioplasty, coronary thrombolysis, acute myocardial infarction, regional myocardial function

INTRODUCTION

Since the widespread acceptance of the high frequency and importance of total coronary artery occlusion in the early phase of acute myocardial infarction, various therapeutic strategies have been proposed. Recanalization of the infarct vessel with streptokinase, either by intracoronary or intravenous delivery, has been the most common method utilized to date [1–10]. However, several placebo controlled studies have not shown clear-cut benefit for patients in terms of recovery of left ventricular function [2,4,6,9]. With streptokinase administration, no matter which route is selected, there is attendant fibrinogenolysis and a prolonged lytic state [11–13]. With the introduction of human tissue-type plasminogen activator, produced by recombinant technology, an enzyme with a short half-life (< 5 min) [14,15] and relative fibrin selectivity has become available [16–23].

Besides thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA), either directly or after streptokinase, has been performed in the setting of acute myocardial infarction and various studies point toward the potential advantage of this technique in promoting more complete and sustained infarct vessel recanalization [24–34]. The current study was undertaken to determine the safety, feasibility, and outcome of combined therapy with t-PA and PTCA in patients with acute myocardial infarction.

MATERIALS AND METHODS

Patient Selection

As part of a multicenter pilot trial of t-PA in acute myocardial infarction [18], patients who presented to either The Johns Hopkins Hospital or the Francis Scott Key Medical Center with chest pain of greater than 20 min but less than 6 h duration and associated with ≥ 1 mm of electrocardiographic ST segment elevation (in one or more leads) were considered for entry to the protocol. The exclusion criteria were cardiogenic shock, history of a bleeding diathesis, coronary artery bypass surgery or transmural myocardial infarction, age > 70 years, and significant hepatic, renal, and pulmonary disease.

Angiography and Thrombolysis

Once the above criteria were met, informed consent was obtained. The study protocol was approved by the institutional review boards of both hospitals. Patients underwent selective coronary arteriography, both of the infarct vessel and the non-infarct related arteries, using the Judkins technique. After arterial access was obtained, heparin (100 U/kg, maximum 10,000 U) was administered. Coronary angiograms were obtained in both right and left oblique projections as well as multiple hemiaxial views. Total occlusion of the infarct vessel was confirmed in 21 of 34 patients initially

entered into the study. According to the study design, only those patients with total occlusion were candidates for t-PA therapy. For the first 16 patients entered, there was two to one randomization between t-PA and placebo. In the placebo arm of the study, if no recanalization was observed after 30 min of serial angiography (angiograms were performed every 15 min after the start of study drug to 2 hr), patients were crossed over to intracoronary t-PA (0.375 mg/kg over 15–30 min). Patients initially randomized to t-PA received this enzyme intravenously at dosages from 0.25 to 0.75 mg/kg over 30–120 min. The last five patients who received t-PA in this study were treated on an open basis with 0.75 mg/kg over 120 min. Only one patient in the study achieved reperfusion during the placebo infusion, and no further data regarding this patient are presented here [18]. The remaining 20 consecutive patients who received t-PA, three by intracoronary delivery and 17 by intravenous administration, serve as the study group. Each patient who demonstrated reperfusion was placed on an antithrombotic regimen of heparin (1,000 U/hr), aspirin (315 mg per day), dipyridamole (75 mg three times per day), and nifedipine (10 mg four times per day) immediately after the initial catheterization.

Coronary Angioplasty

All patients with suitable coronary artery anatomy were considered for coronary artery balloon dilatation. The criteria utilized to determine suitability were 1) successful t-PA mediated coronary thrombolysis; 2) a discrete, high grade residual stenosis at the site of prior occlusion; and 3) atherosclerotic disease confined to the infarct vessel or lack of critical, diffuse disease in the noninfarct related coronary arteries. Of 13 patients who exhibited recanalization after t-PA, four patients were not considered candidates for PTCA. The reason for exclusion was severe, diffuse, multivessel disease in all four patients. Coronary angioplasty was performed in the remaining nine patients at a mean of 21.6 hr (range 0.5 hr to 3 days), the time dependent on cardiothoracic surgical backup availability. Angioplasty was performed via the femoral approach using USCI (Billerica, MA) guiding and dilatation catheters and guide wires. The balloon size was selected on the basis of estimated vessel size proximal to the target lesion. In the infarct vessel of each patient, the area of stenosis was dilated with 2–3 balloon inflations (range 4–11 atmospheres). Using caliper measurements, the residual lesion was quantitated as percent diameter stenosis averaging the value in two angiographic views, one in each obliquity.

Evaluation of Regional Myocardial Function

Regional left ventricular function was evaluated using serial two-dimensional echocardiography, performed prior to t-PA, throughout the infusion and for 1 hr after its completion, and at 1 and 10 days after admission. The echocardiograms were reviewed by two observers, independently, and blinded to patient identity, the temporal sequence of study acquisition, therapy, and the effects of therapy. For analysis the myocardium was divided into seven segments, and the infarct zone was matched to the distribution of the infarct vessel, as determined by angiography. The infarct zone comprised a mean of 3.15 segments (range two to five segments) and each segment was scored using semiquantitative visual wall motion analysis. The grading utilized was -1, dyskinesia, defined as paradoxical expansion of endocardial movement; 0, akinesia, or absence of endocardial motion; 1, hypokinesia, defined as reduced inward motion; and 2, normal. A wall motion score index for the infarct zone was calculated

according to a modification of the method of Heger et al [35] by averaging the scores for the two observers, summing the scores for the infarct zone segments, and dividing by the number of segments localized to this zone. This analysis was performed for the echocardiograms obtained prior to therapy and prehospital discharge, approximately 10 days after admission.

Submaximal Exercise Treadmill Testing

All patients who underwent PTCA attempts were exercised on a treadmill with 12-lead electrocardiographic monitoring prior to discharge. The target heart rate utilized was 120 beats/min and the test was stopped for symptoms of ischemia or electrocardiographic ≥ 1 mm ST segment depression in one or more leads. In one patient who developed chest pain of uncertain etiology (atypical quality without accompanying electrocardiographic changes) and another patient who had equivocal ST segment changes during exercise, repeat coronary arteriography was performed.

Postdischarge Follow-Up

The status of each patient who underwent t-PA and PTCA therapy was determined by either direct out-patient examination or via telephone communication with the patient or his attending physician.

Statistical Methods

Unless otherwise stipulated, all values are reported as mean \pm 1 standard deviation of the mean. The infarct zone wall motion indices were compared for the patient groups using a paired t-test, and intergroup differences between admission and day 10 index were tested using a one-way analysis of variance.

RESULTS

Recanalization

Reperfusion of the infarct vessel was evident in 13 out of the 20 patients (65%) who received rt-PA. Relevant data are summarized in Table I. This occurred at 5.1 ± 1.1 hr from the onset of chest pain, utilizing a dose of 43 ± 17 mg of rt-PA. Of

TABLE I. Patient and Therapy Characteristics*

Age	55 ± 5.7 years (range 39–69 years)
Sex	17 male, three female
Time (CP to lysis)	5.1 ± 1.1 hr
Time (CP to drug)	4.8 ± 1.5 hr
Site of occlusion	LAD nine pts; LCx two pts; RCA nine pts
Dose of rt-PA	43 ± 17 mg
Route	IV 17 pts, IC three pts
Successful lysis	13 of 20 pts (65%); 12 of 17 pts (71%) ^a

*CP, chest pain; Drug, study medication; IC, intracoronary; IV, intravenous; LAD, left anterior descending coronary artery; LCx, left circumflex artery; lysis, coronary recanalization; pts, patients; rt-PA, recombinant tissue plasminogen activator.

^aThrombolysis with intravenous recombinant tissue plasminogen activator.

those patients who received the enzyme intravenously (without the delay of a placebo infusion), 12 of 17 achieved thrombolysis. From the start of the infusion, the time to angiographic lysis was 36 ± 9 min. The residual lesion after successful thrombolysis was $84 \pm 6\%$. The site of occlusion was the left anterior descending artery in nine patients, left circumflex artery in two patients, and the right coronary artery in nine patients. The infusion was not accompanied by any untoward effects in 16 patients; in four patients there was evidence of minor bleeding, from the gingiva in two patients, from the ear in one patient, and guaiac positive emesis in one patient. Six of the 20 patients had bleeding around the femoral vascular access sites either while the sheaths were in place or in small, localized hematomas after the sheaths were removed. No patient received a blood transfusion during the course of the study.

Coronary Angioplasty

PTCA was attempted in nine patients (Table II). In two patients reocclusion of the infarct vessel was noted at the time of angioplasty attempt. Both of these patients had been asymptomatic between the time of successful thrombolysis and repeat control angiography for coronary dilatation. Despite multiple attempts to cross the site of total occlusion, a guide wire could not be advanced in one patient and a 2.0 mm low profile dilating catheter could not successfully traverse the other patient's occlusion. In the other seven patients, PTCA was successful. A representative set of angiograms is shown in Figure 1. The residual stenosis was reduced from $84 \pm 6\%$ to $29 \pm 7\%$. The residual transstenotic gradient was less than 15 mm Hg in all of these patients. No complication of the procedure occurred in any of the patients for whom the procedure was attempted. There was angiographic evidence of localized intimal dissection in four of the seven patients.

Hospital Course: Clinical Outcome

Of the patients reperfused, the seven who had successful coronary angioplasty had no evidence of reinfarction, postinfarction angina, congestive heart failure, or reocclusion or need for coronary artery bypass surgery. In the six patients who exhibited recanalization but did not undergo angioplasty (or this procedure was unsuccessful), there was evidence of reocclusion in four patients, reinfarction in one patient, postinfarction angina in three patients, and coronary artery bypass surgery was performed in three patients.

Response to Exercise Testing

Of the patients who had successful rt-PA mediated coronary thrombolysis and PTCA, five of seven had a negative submaximal graded exercise treadmill test. In two of these patients repeat coronary arteriography was performed because of either an equivocal exercise electrocardiogram or atypical chest pain, and both patients demonstrated a widely patent infarct vessel.

Regional Myocardial Function

In the seven patients reperfused and mechanically revascularized, the infarct zone wall motion index significantly improved (from 0.83 ± 0.36 on admission to 1.46 ± 0.49 at 10 days; $P = 0.01$) compared to those patients with successful thrombolysis only (from 0.58 ± 0.25 to 0.80 ± 0.33 at 10 days, $P = \text{NS}$) or those patients without recanalization (from 0.63 ± 0.32 to 0.54 ± 0.42 at 10 days, $P = \text{NS}$). The differ-

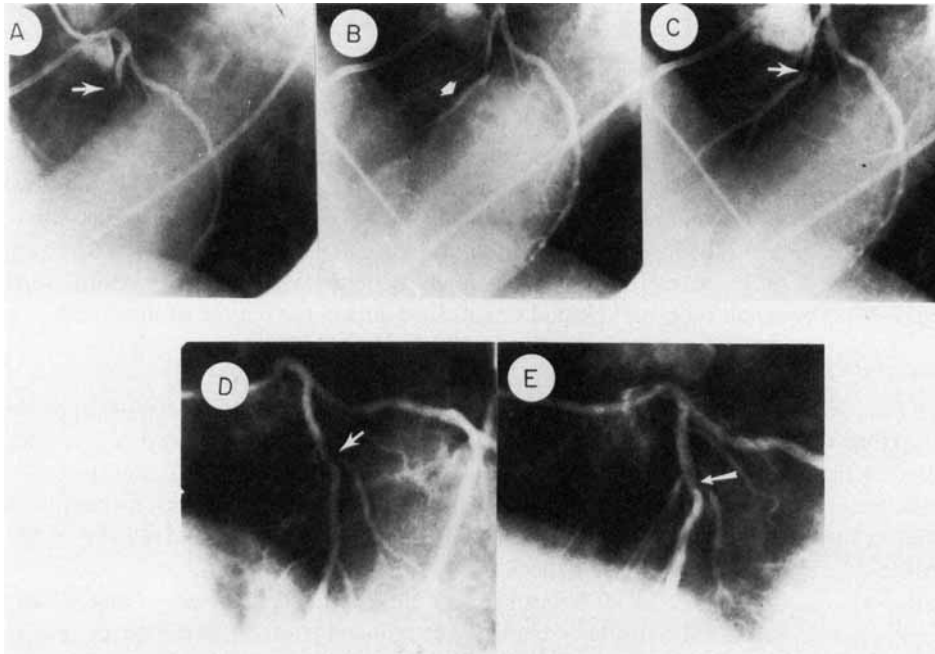


Fig. 1. Serial cineangiograms of the left anterior descending coronary artery from a study patient. A) Left anterior oblique projection shows total occlusion (arrow). B) Midway through the t-PA infusion recanalization is apparent with slow and incomplete filling of the distal vessel (arrow) and residual thrombus at the site of previous occlusion. C) Thirty minutes after completion of the infusion, a high grade residual lesion is evident (arrow). D) Just prior to angioplasty (40 h postinfarct) a persistent high grade stenosis (arrow) is apparent. E) After coronary angiography, a minimal residual lesion is shown with haziness at the site of dilatation (arrow).

ences in baseline infarct zone wall motion indices were not statistically significant (ANOVA). Further, there was significant improvement in the infarct zone index of the patient group with successful thrombolysis and PTCA compared to the other two groups ($F = 5.85$, $P < 0.05$, one way ANOVA; Fig. 2).

Follow-Up

One patient who had successful thrombolysis and PTCA sustained a massive stroke 2 weeks after hospital discharge. The remaining six patients in this group have returned to work and are asymptomatic at 9.4 ± 2 months. One patient became symptomatic with angina 7 months after hospital discharge. Coronary arteriography demonstrated restenosis (90%) of the right coronary artery lesion and this was successfully dilated. Repeat graded exercise testing was negative and the patient is free of symptoms.

DISCUSSION

Our results demonstrate that coronary angioplasty can be performed safely and successfully after tissue plasminogen activator thrombolytic therapy in patients with

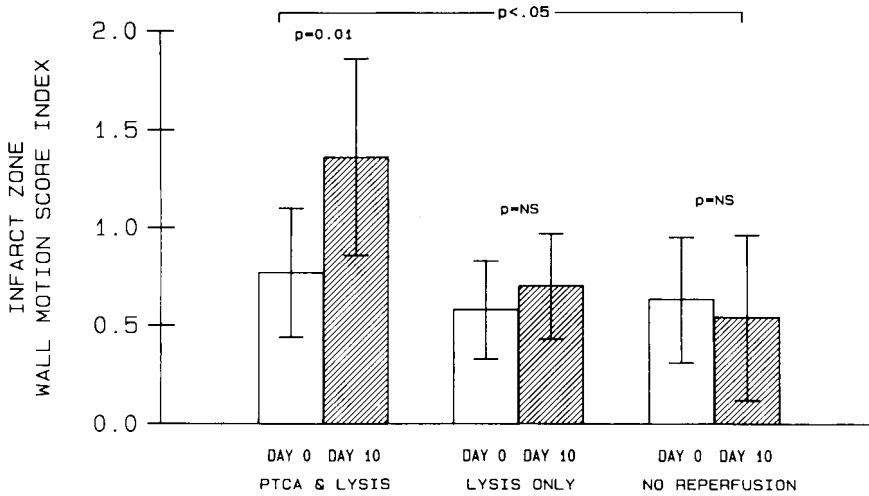


Fig. 2. Regional myocardial function on admission and at 10 days after therapy with either reperfusion with t-PA and sequential PTCA, thrombolysis only or no reperfusion. The infarct zone wall motion index (mean \pm SD) is plotted versus the time of the study for each patient group. There was significant improvement of infarct zone segmental motion only in the patient group with successful t-PA mediated thrombolysis and mechanical revascularization.

acute myocardial infarction. Although this represents a small, uncontrolled series, this combined interventional strategy was correlated with a favorable in-hospital and long-term clinical outcome as well as clear-cut improvement in regional wall motion of the infarct zone.

Rationale for Combination Therapy

The vast majority of patients with acute coronary occlusion who achieve reperfusion after thrombolytic therapy are left with a high grade stenotic lesion [36–38]. The atherosclerotic plaque narrowing has important potential consequences. First, it appears to serve as a nidus for rethrombosis, and the incidence of reocclusion is inversely correlated to the artery cross-sectional area after recanalization [37]. The propensity to reocclude may relate to the adherence of fibrin to the atherosclerotic plaque, as we have previously demonstrated to occur in an experimental atherosclerotic model after therapy with t-PA [39]. The propagation of a thrombus may thus be enhanced under conditions of reduced flow. Second, the high grade atherosclerotic lesion is usually flow-limiting, so that myocardial tissue is still “underperfused” and evaluation of function may be confounded because it is difficult to distinguish accurately infarcted versus ischemic myocardium. In this setting, the effects of coronary angioplasty may be particularly complementary and desirable by virtue of their potential to reduce the propensity for rethrombosis and provide more complete revascularization to the infarct zone.

Comparison With Previous Studies

There are several prior studies of patients with myocardial infarction that confirm the ability of PTCA to achieve a high primary success rate either after thrombolytic therapy or directly [24–34]. Most of these investigations support a diminished inci-

TABLE II. Response to Therapy With rt-PA and PTCA*

Patient No.	Age	Sex	Vessel	Time to lysis (hr) ^a	Time to PTCA (hr)	Dose t-PA (mg)	Route	Residual lesion after lysis (%)
1	69	M	LAD	4.1	12	25	IC	97.5
2	40	M	RCA	5.5	0.6	40	IV	82.6
3	54	F	RCA	5.8	40	62	IV	86.9
4	56	M	RCA	4.2	62	40	IV	81.7
5	68	F	RCA	6.4	38	38	IV	81.4
6	68	F	LAD	6.1	40	17	IV	76.2
7	68	M	RCA	4.6	1	94	IV	85.7
8	39	M	LAD	6.2	1	30	IV	88.1
9	53	M	LAD	3.1	0.75	62	IV	95
Total	57.2	6 M, 3 F	4 LAD, 5 RCA	5.1 ± 1.1	21.6 ± 23	45 ± 23	1 IC, 8 IV	83.9 ± 5.7

*ETT, exercise treadmill test predischarge; IV, intravenous; IC, intracoronary; lysis, coronary recanalization; LAD, left anterior descending coronary artery; RCA, right coronary artery; PTCA, percutaneous transluminal coronary angioplasty; rt-PA, recombinant tissue plasminogen activator.

^aTime from onset of chest pain.

^bIn two patients, control angiography at PTCA attempt revealed total reocclusion and the procedure was unsuccessful.

dence of reocclusion when the two interventions, streptolysis and angioplasty, are combined compared to only thrombolysis. However, only two such studies were randomized [28,34] and the endpoint for all has been angiographic appearance of the vessel either acutely or prehospital discharge. In a recent study, Yasuno et al [33] considered global and regional ventricular function after urokinase and PTCA and demonstrated improvement at 6 weeks postinfarct. And, in a randomized study by O'Neill et al [34], direct coronary angioplasty was superior to intracoronary streptokinase in leading to improved myocardial blood flow and left ventricular function. Prior studies of sequential thrombolysis and angioplasty therapy are summarized in Table III.

Advantages of Thrombolysis With t-PA

The key theoretical advantages of t-PA compared to first-generation lytic agents, streptokinase and urokinase, relate to its fibrin selectivity, short half-life, and lack of antigenicity. Via the intravenous route, the ability of rt-PA to dissolve coronary thrombus has been approximately 75% [18], which compares favorably to the 50–55% efficacy rate of intravenous streptokinase [8,40], and this increased rate of thrombolysis has been associated with a relative sparing of fibrinogen and absence of a systemic lytic state [14,18]. However, it has become clear that too high a dose of t-PA may lead to similar effects as those of streptokinase by virtue of the production of free plasmin [41–43]. The short half-life of this enzyme offers particular advantage for sequential surgical or transluminal balloon coronary revascularization, since these procedures can be accomplished without the hazard of prolonged or severe bleeding. On the other hand, the short time span of fibrinolysis with t-PA may allow more acute rethrombosis in comparison with intravenous streptokinase, which at the doses cur-

TABLE II (Continued)

Residual lesion after PTCA (%)	Localized dissection	Infarct wall motion index		ETT	Follow-up
		Admission	Day 10		
— ^b	No	0.5	0.66	Not done	Successful CABG
35	Yes	1.12	1.4	Negative	Asymptomatic
27.8	Yes	1.25	1.87	Negative	Asymptomatic
36.2	No	0.33	0.83	Atypical chest pain	Repeat angiography—patency, asymptomatic
— ^b	No	0.67	1.33	Negative	Asymptomatic
19.3	No	0.83	2.0	Negative	Asymptomatic
25	No	0.37	1.75	Negative	Restenosis at 9 months; successful repeat PTCA
23.6	Yes	0.82	1.66	Equivocal	Repeat angiography—patency; stroke 2 weeks after discharge
37.2	Yes	1.12	0.75	Negative	Asymptomatic
29.2 ± 7.0	4 yes, 5 no	0.77 ± 0.33	1.36 ± 0.50		

rently utilized (750,000 to 1.5 million units) leads to at least a 24-hr period of a systemic lytic state.

Timing of Coronary Angioplasty

In the present study, PTCA was performed either directly following thrombolysis or after transfer of the patient and/or surgical backup could be provided. It is unclear what represents the optimal timing for PTCA after coronary thrombolysis, assuming that these interventions are done sequentially. In most previous studies, coronary angioplasty was performed immediately after recanalization was established with lytic therapy. But this strategy is not readily transferable to a community hospital that is not set up for coronary angioplasty but has the necessary personnel to administer readily a safe fibrinolytic agent. Several experimental and clinical studies point toward the critical importance of time to the salvage of myocardium [44–46]. The regional wall motion improvement observed in our study did not appear to relate to the time of angioplasty, but clearly this series is too small to make any conclusion. If such a benefit can be confirmed in large, controlled trials, sequential therapy of fibrinolytic and mechanical therapy could be widely applied.

Limitations

In view of the small number of patients in this pilot study, our results must be considered preliminary and will require confirmation and replication in larger, controlled trials that are currently underway. 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 dilatation was associated with significant regional wall motion improvement, this may have been due to the favorable anatomy itself, which may correlate with subsequent functional recovery. Our results indicate that reperfused, infarct zone segments without subsequent PTCA lacked significant wall motion improvement compared to infarct regions

TABLE III. Prior Studies of Coronary Thrombolysis and PTCA*

Reference	No. patients	Lytic agent	Time of PTCA (hr)	Success (%)	Late patency (%)
Meyer et al [24]	21	SK	1	81	Not studied
Gold et al [25]	28	SK	Immediate	71	55 (8–14 days)
Hartzler et al [27]	39	SK	Immediate	87	94 (10 days); 79 (6 months)
Uebis et al [28]	25	SK	Immediate	96	100 (3 days)
Papapietro et al [29]	18	SK	Immediate	72	69 (8–17 days)
Kalbfleisch et al [30]	15	SK	Immediate	93	100 (6 weeks)
Holmes et al [31]	22	SK	Immediate	68	Not studied
Schwarz et al [32]	28	SK	Immediate	89	Not studied
Yasuno et al [33]	32	UK	Immediate	72	66 (42 days)
Pooled results	228	8 SK, 1 UK		81	75 (3–42 days)

*SK, streptokinase; UK, urokinase; late patency, widely patent vessel at repeat angiography; time of PTCA, time after coronary thrombolytic therapy.

not reperfused. Thus, it remains possible that coronary artery dilatation was the sole factor responsible for improvement.

Implications

The exact role of coronary angioplasty in acute myocardial infarction remains unclear but there are numerous advantages that have already been observed. It appears technically preferable to administer a fibrinolytic agent immediately, allowing for the time to set up an invasive cardiology laboratory for coronary angioplasty. Recanalization of the infarct vessel would at least provide a “roadmap” for the dilatation hardware and potentially make the angioplasty procedure safer and easier. Perhaps more important, however, is the prompt restoration of flow, albeit often incomplete, with a chemical means of therapy. The time required to administer an intracoronary agent has been at least 1.5 to 2 hr [1–8,10] from patient identification into a study protocol and would be expected to be at least this long for a PTCA procedure; the optimal timing of this procedure remains undefined. In the interval period of time, thrombolysis could be achieved. Tissue plasminogen activator has several properties that combined with coronary angioplasty *may* make this sequence of interventions the optimal therapy for patients with acute myocardial infarction.

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