THROMBOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION

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Current interest in thrombolytic therapy for patients with acute myocardial infarction is encouraged by the following observations. First, an occlusive coronary artery thrombus is present in the vast majority of individuals with acute transmural myocardial infarction. Second, rapid lysis of these intracoronary thrombi with subsequent reperfusion can be achieved by several available pharmacologic agents. Finally, in animal studies, reperfusion after temporary coronary artery occlusion salvages jeopardized myocardium and reduces infarct size. Since infarct size is a powerful predictor of morbidity and mortality, interventions which reduce infarct size would be expected to improve prognosis following myocardial infarction. Pharmacologic efforts to salvage myocardium in man in the absence of reperfusion have had only limited success (1).

The purpose of the present review is (a) to explore further the rationale supporting thrombolytic therapy in acute myocardial infarction, (b) to outline and evaluate the clinical experience with thrombolytic therapy in this setting, and (c) to identify research directions which will help better define the future role of this form of treatment in clinical practice. While emergency coronary artery bypass surgery has been performed to establish reperfusion in acute myocardial infarction (2,3), it will not be discussed.

II. Role of Coronary Thrombosis in Acute Myocardial Infarction

For 50 years after Herrick's description of coronary occlusion producing myocardial infarction, coronary thrombosis was widely accepted as the underlying cause. However, in the 1960's and early 1970's, the role of coronary artery thrombosis in infarction was questioned when pathologists described both myocardial infarction in the absence of thrombus and coronary thrombosis without recent infarction (4,5). Some authors suggested that infarction came first and thrombosis thereafter. Conflicting, inconclusive results from early clinical trials of low-dose intravenous streptokinase cast further doubt on the importance of thrombosis in myocardial infarction (6). Numerous alternate mechanisms were proposed, including (a) subintimal hemorrhage or plaque rupture without thrombosis, (b) progressive, severe, atherosclerosis, (c) coronary artery spasm, and (d) coronary embolism.

Over the past 10 years, 2 important developments lead to a resolution of the controversy over the role of coronary artery thrombosis in acute myocardial infarction. First, transmural and nontransmural infarctions were more clearly defined as separate clinical and pathologic entities, and with more advanced examination techniques, the high frequency of occlusive thrombus in individuals with *transmural* infarction was acknowledged (7-10). Second, coronary angiography during the early hours after the onset of symptoms demonstrated occlusion of the artery supplying an area of infarction in the vast majority of patients (Figure 1) (11). The thrombotic nature of these occlusions was supported by retrieval of thrombus during emergency coronary artery bypass surgery and by the characteristic angiographic appearance of retention of contrast material by an intraluminal filling defect (12). Moreover, the incidence of total occlusion decreased with time to around 50% at 12-24 hours after the onset of infarction (presumably due to spontaneous clot lysis),

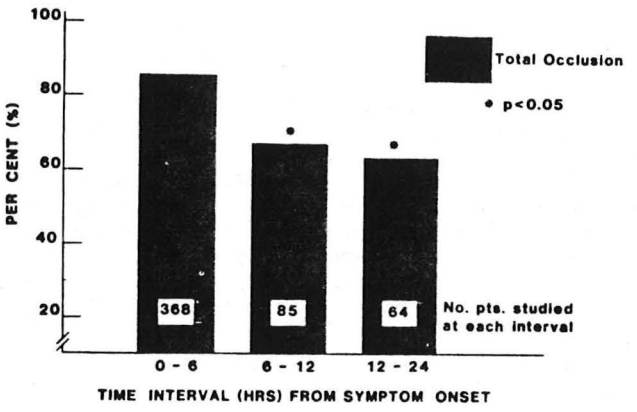

FIGURE 1 The frequency of total coronary occlusion at coronary angiography in patient groups evaluated during different time intervals from the onset of symptoms. There is a significantly lower incidence of total coronary occlusion in those studied after 6 hours. (From ref 11)

refuting the argument that thrombosis occurs as a consequence of infarction (Figure 1). More recently, numerous angiographic studies have confirmed the high incidence of coronary occlusion in acute myocardial infarction and have shown that these occluded vessels can usually be recanalized with the thrombolytic agent, streptokinase. Since intracoronary nitroglycerin rarely (<5% of cases) produces reperfusion, coronary vasospasm probably plays little role in maintaining coronary occlusion after the onset of infarction (13).

While the role of coronary thrombosis in transmural myocardial infarction is now firmly established, the acute arterial lesion *leading* to thrombosis is less well-defined. Thrombus formation almost always occurs at the site of an atherosclerotic plaque. Thrombotic coronary occlusion is probably the result of a complex interaction between (a) rupture, ulceration, or fissuring of a plaque, (b) exposure of thrombogenic lipid-rich plaque material, (c) platelet aggregation and activation, (d) release of vasoactive substances (thromboxane A2, serotonin), and (e) coronary spasm (14-17).

The role of coronary thrombosis in *nontransmural* infarction is less certain. Pathologic studies demonstrate thrombotic coronary occlusion in only 20-50% of cases (7-10). Acute angiographic findings have been reported in only a small number of patients. Mandelkorn et al (18) found total coronary occlusion in only 2 (25%) of 8 patients with acute nontransmural infarction. However, an additional 5 (63%) had partial occlusions that decreased in size after intracoronary streptokinase. Since the incidence of complete thrombotic occlusion is low and the importance of partially occluding thrombus is unknown, thrombolytic therapy has generally not been studied in patients with electrocardiographic evidence of nontransmural infarction.

III. Pharmacology of Thrombolytic Agents

Physiologic fibrinolyis is regulated by interactions between tissue plasminogen activator (originating from the vascular wall), plasminogen, fibrin, and alpha2-antiplasmin (19-21). Tissue plasminogen activator (tPA) has a weak affinity for circulating plasminogen. Within the interstices of a clot, tPA binds to fibrin; plasminogen then binds to this fibrin-tPA complex with a high affinity (22). Plasminogen is activated to plasmin within the clot and local fibrinolysis ensues. Within the thrombus, plasmin is protected from degradation by alpha2-antiplasmin. Any plasmin liberated into the circulation, however, is quickly inactivated by this enzyme.

A. Streptokinase

First observed in beta-hemolytic streptococcal infiltrates by Tillett and Garner in 1933 (23), streptokinase has no direct enzyme activity on its own. In the circulation, it combines with both free and fibrin-bound plasminogen; the streptokinase-plasminogen complex is a potent activator of plasminogen to plasmin (24). As plasminogen is activated, alpha2-antiplasmin is depleted, and free plasmin appears in the circulation. Plasmin is a serine protease which degrades fibrin, fibrinogen, and clotting factors V, VIII, and XIII. A systemic lytic state is produced and persists until the clotting factors and fibrinogen can be resynthesized.

Streptokinase is a foreign antigenic protein and low titers of antistreptokinase antibodies are ubiquitous in the general population. Resistance to the fibrinolytic effects of streptokinase may occur if high titers of antistreptokinase antibodies are present (due to prior streptokinase administration or recent streptococcal infection). Resistance to loading doses of over 1 million units has been reported (25). When resistance due to antibodies is suspected or streptokinase has been administered in the previous 6-12 months, urokinase should be used.

Since streptokinase results in the degradation of plasminogen, its own cofactor, larger doses may not produce additional fibrinolysis. There is no consistent relationship between the dose of streptokinase and fibrinolytic activity once a systemic lytic state has been achieved.

Adverse effects of streptokinase, including fever, urticaria, and flushing, were commonly noted in pulmonary embolism trials where infusions continued for many hours. With intracoronary or brief, high-dose intravenous administration, these reactions occur less commonly and premedication with aspirin or corticosteroids is no longer routinely used. With very rapid administration, vasodilation and hypotension may be produced. Anaphylaxis is rare.

B. Urokinase

Urokinase, isolated from human urine and human fetal kidney tissue cultures, differs from streptokinase in several respects (24). First, it *directly* activates plasminogen to plasmin. Second, it is nonantigenic and better tolerated than streptokinase with a lower incidence of resistance. Third, it probably depletes plasminogen less than streptokinase, although a systemic

lytic state is still produced (26). Finally, it is six to seven times more expensive than streptokinase and has, therefore, usually been reserved for patients likely to have high titers of antistreptokinase antibodies.

C. Clot-Selective Agents

Both streptokinase and urokinase convert circulating plasminogen to plasmin, producing a systemic lytic state and increasing the risk of hemorrhage. Recent efforts have been directed toward the development of "clot selective" agents which produce local fibrinolysis without systemic effects. These agents include acylated streptokinase-plasminogen complex (BRL 26921), pro-urokinase, and tissue plasminogen activator.

1. Acylated streptokinase-plasminogen complex Acylation blocks the active site of the streptokinase-plasminogen complex but permits binding of the complex to fibrin within the thrombus (27). Spontaneous deacylation then exposes the plasminogen activator site of the fibrin-bound complex and allows local rather than systemic fibrinolysis (28). In a preliminary clinical trial, intracoronary BRL 26921 achieved reperfusion in 15 (68%) of 22 patients with acute myocardial infarction in an average of 42 minutes after the start of infusion (29). A reduction of fibrinogen to below 100 mg% was seen in 8 patients. Although not strictly "clot-specific," BRL 26921 does appear to produce thrombolysis with less systemic effects than streptokinase.

2. Pro-urokinase A zymogen precursor of urokinase which has weak plasminogen activating effects, pro-urokinase is capable of binding to thrombus fibrin. Conversion to urokinase then occurs within the clot. In animal studies, intravenous pro-urokinase can successfully lyse intracoronary thrombi without reducing fibrinogen or alpha 2-antiplasmin levels (30,31). Studies in man have not been reported.

3. Tissue plasminogen activator In 1979, human tissue plasminogen activator was isolated and purified from a melanoma cell line culture (32) and was shown to produce thrombolysis in animals (32,33) and in small numbers of patients (34,35). Subsequently, the cloning and expression of the tPA gene in E. coli using recombinant DNA technology resulted in the production of recombinant tPA (r-tPA) with antigenic and thrombolytic properties indistinguishable from those of human tPA (36). The results of clinical trials assessing the efficacy of r-tPA in acute myocardial infarction are discussed in Section VII.

IV. Effects of Reperfusion in Animal Studies

A. Salvage of Myocardium

In animals, myocardial cells in the most severely ischemic subendocardium become irreversibly damaged after only 20 minutes of coronary occlusion. With longer occlusions, a "wave front" of cell death moves from the subendocardium toward the subepicardium to involve progressively more of the transmural thickness of the ischemic region (Figure 2) (37,38). Reperfusion results in salvage of reversibly ischemic cells in the subepicardial layer of the this region (39). The duration of occlusion during which meaningful salvage is still possible is variable, but in the dog and baboon, little salvage occurs

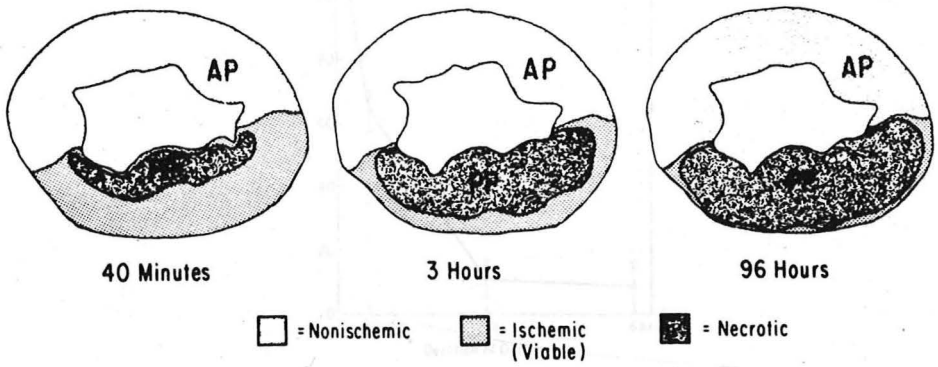

FIGURE 2 Progression of cell death with time after left circumflex coronary artery occlusion. A wave front of cell death moves from the subendocardial zone across the wall to involve progressively more of the transmural thickness of the ischemic zone. Reperfusion prior to infarct completion salvages supepicardial myocardium. AP=anterior papillary muscle; PP=posterior papillary muscle. (From ref 37)

after 3-4 hours of occlusion (Figure 3) (37,38,40,41). The rate of infarction in man is much more variable and depends upon (a) the completeness of coronary obstruction, (b) the presence of collateral circulation to the infarct region, (c) the determinants of myocardial oxygen demand, and (d) the ability of ischemic cells to utilize anaerobic glycolysis. In patients with complete coronary occlusion and no collaterals, infarction is probably complete within 3-4 hours. Those with subtotal occlusions or well-developed collaterals may have salvageable myocardium for much longer periods of time.

B. Myocardial Function and Metabolism

While timely reperfusion limits infarct size, it does not produce a prompt return of contractile function (40,42-44). Periods of ischemia as brief as 15 minutes produce no necrosis but result in marked depression of myocardial cell function for several days; full recovery of function following longer ischemic periods may require up to several weeks (Figure 4) (40,45-46). The mechanisms for this delayed return of function after reperfusion are not fully understood (44,47-49). ATP levels are rapidly depleted after coronary occlusion, and reperfusion may "wash out" precursors (adenosine, hypoxanthine, and inosine) which could be used in its resynthesis. ATP levels remain depressed for several days after temporary coronary occlusion and may partly explain the delayed return of contractile function (Figure 5) (43,47). Intracellular calcium overload produced by reperfusion may interfere with systolic and

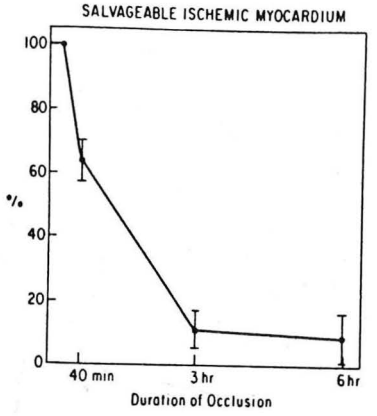

FIGURE 3 Myocardium salvaged by reperfusion, as a percentage of the ischemic bed, versus duration of occlusion. Reperfusion at 40 minutes salvaged 64% of the myocardium at risk. Little or no salvage occurred at 6 hours. (From ref 37)

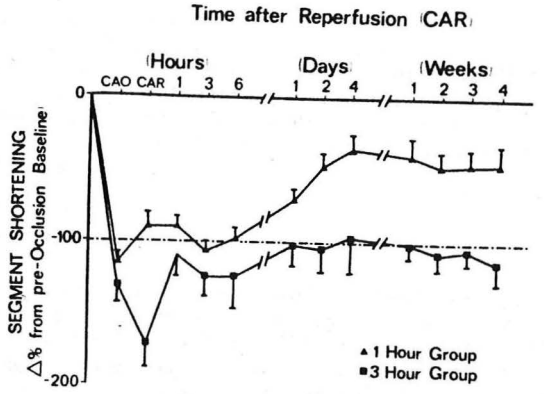

FIGURE 4 Time course of systolic segment shortening during coronary artery occlusion (CAO) and subsequent reperfusion (CAR) after 1 hour or 3 hours of occlusion in conscious baboons. Recovery of function in the 1 hour group requires several days. No recovery is seen with reperfusion after 3 hours of occlusion. (From ref 40)

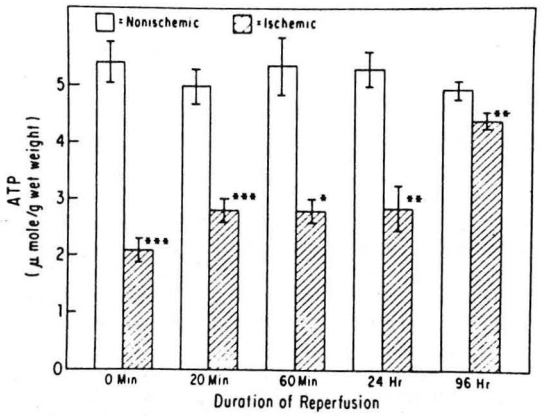

FIGURE 5 The effects of 15 minutes of ischemia with 0, 20, or 60 minutes or 24 or 96 hours of reperfusion on ATP content in ischemic and nonischemic regions. ATP levels fell by 60% after 15 minutes of ischemic and remained depressed as long as 96 hours after reperfusion. (From ref 47)

diastolic function and contribute to delayed recovery. Finally, reversible ultrastructural damage to the sarcolemma, mitochondria, and sarcomeres which might interfere with cell function can persist for several days or weeks (44,50).

The concept that ischemia "stuns" myocardium has important implications when evaluating the effects of coronary artery reperfusion in man. It must not be assumed that myocardium has not been salvaged until sufficient time has been allowed for full recovery of function in the infarct region. Accordingly, assessment of post-intervention left ventricular function should be delayed for 10-14 days, and full recovery of function may require much longer periods of time in some patients.

C. Myocardial Hemorrhage

During myocardial infarction, irreversible ischemic damage to the microvasculature occurs, so that reperfusion may rupture intramural vessel walls with subsequent myocardial hemorrhage (51). There was initial concern that this myocardial hemorrhage would increase infarct size and interfere with infarct healing (52,53). However, irreversible microvascular damage temporally follows irreversible myocardial cell injury (54). As a result, reperfusion hemorrhage is limited to areas of irreversibly damaged myocardium (55). While the rate of necrosis may be accelerated by hemorrhage (47,50,56), there is no convincing evidence that infarct size is increased (57). The effect of myocardial hemorrhage on infarct healing is uncertain (57-59). Intramyocardial hemorrhage after 4 hours of ischemia in dogs has been shown to affect the early healing process, resulting in diminished neutrophil infiltration (59). Collagen formation was not impaired. Whether tissue swelling due to hemorrhage

causes hemodynamically important increased "stiffness" of the infarct or contributes to regional depression of systolic or diastolic function is unknown.

V. Clinical Experience

Fletcher et al (60) first reported the use of intravenous streptokinase in 1959. In 1960, Bonecek and Murphy (61) administered streptokinase into the aortic root in 8 patients with acute myocardial infarction. Coronary angiography was not performed, but based on clinical and electrocardiographic evidence most patients were felt to have "benefited [sic]." After several small feasability studies, the first large-scale controlled clinical trial of long-duration late intravenous streptokinase therapy was completed in 1966 (62). By 1976, a dozen such studies had been reported (6,63). While a majority of these trials revealed a trend toward reduced mortality in patients receiving streptokinase, results were conflicting and inconclusive.

These trials were plagued by several weaknesses. Patient enrollment was allowed up to 24-72 hours after the onset of symptoms, and treatment was usually not even started until after enzymatic confirmation of infarction. As a result, most patients were treated far beyond the time period when reperfusion would significantly reduce infarct size. The mode of action of streptokinase (if any) in these studies was uncertain, as there was no documentation from coronary angiography that the dose of streptokinase used actually produced reperfusion. Other postulated mechanisms included (a) an improvement in the microcirculation, (b) a decrease in blood viscosity that favorably affected blood rheology, and (c) a reduction in afterload that decreased myocardial oxygen demands. The effect of treatment on left ventricular function was not assessed. Most of the studies had insufficient sample size to reliably detect a beneficial effect of treatment on mortality.

The largest decrease in mortality was demonstrated in the European Cooperative study completed in 1979 (64). Medium and high risk patients received placebo or intravenous streptokinase (over 24 hours) within 12 hours of the onset of symptoms. The mortality rate for the 6 month follow-up period was 15.6% in the streptokinase group and 30.6% in the control group ($p<0.01$). While bleeding complications were more frequent in the streptokinase group, only 2 were classified as major. Since coronary angiography was not performed, the reduction in mortality could not be definitely linked to reperfusion.

The "modern era" of thrombolytic therapy in acute myocardial infarction began in 1979 when Rentrop et al (65) demonstrated thrombolysis in 4 of 5 patients treated with intracoronary streptokinase. By 1981, several centers in Germany and the U.S. had confirmed the ability of intracoronary streptokinase to achieve thrombolysis in the majority of patients within the first few hours of infarction. At the same time, reports appeared showing that thrombolysis and reperfusion could also be achieved by the brief intravenous infusion of a high dose of streptokinase.

A. Patient Selection

The selection criteria for patient with acute myocardial infarction who are to receive thrombolytic therapy seek to exclude (a) patients with completed infarctions, (b) patients without intracoronary thrombi, and (c) those at increased risk of bleeding. Although the rate of infarction in man is variable and an arbitrary time limit will exclude a small number of patients who might benefit, longer time limits will expose more patients with completed infarctions to the risks of thrombolytic therapy. Based on animal studies and preliminary patient trials, little benefit can be expected after 3-5 hours of coronary occlusion. Whether the presence of continued pain identifies a subgroup with viable myocardium who might benefit from reperfusion beyond this limit is unknown.

As discussed earlier, research efforts have usually been restricted to patients with acute transmural myocardial infarction, since the incidence and importance of coronary thrombosis in those with nontransmural infarction is less well established. One millimeter or greater ST-segment elevation (presumed to be new) in at least 2 inferior, lateral, or anterior leads in a patient with at least 30 minutes of severe chest pain felt due to ischemia and unrelieved by nitroglycerin reliably identifies those who (a) have thrombotic coronary obstruction and (b) develop enzymatic and scintigraphic evidence of myocardial necrosis. While most patients with a similar clinical presentation but ST-segment depression develop evidence of infarction, these are often nontransmural (non-Q-wave) infarctions.

Since the major complication of thrombolytic therapy is bleeding, selection criteria should exclude those at increased risk of hemorrhage. With modifications, the recommendations of the National Institute of Health Consensus Development Conference on Thrombolytic Therapy (66) are listed in Table 1.

TABLE 1 Contraindications to Thrombolytic Therapy (from ref 66)

Absolute Contraindications

- Active internal bleeding
- Recent (within 2 months) cerebrovascular accident or neurosurgical procedure
- Recent (<10 days) major surgery, organ biopsy, previous puncture of noncompressible vessels
- Recent serious gastrointestinal bleeding
- Recent serious trauma, including prolonged cardiopulmonary resuscitation

Relative contraindications

- Severe arterial hypertension (>200 mm Hg systolic or >110 mm Hg diastolic)
- Recent minor trauma, including brief cardiopulmonary resuscitation
- Hemostatic defects, severe hepatic or renal disease
- Age over 65 years
- Diabetic hemorrhagic retinopathy

TABLE 2 Protocol for Intracoronary Streptokinase Administration

Prophylactic lidocaine infusion; steroids and aspirin usually not given
Systemic heparinization (100 units/kg)
Baseline coronary angiography
IC nitroglycerin 200 mcg - often omitted due to low rate of reperfusion
Ostial infusion of SK
    10,000-20,000 unit bolus (optional)
    2,000-4,000 units/min
    Use urokinase (6000-24,000 u/min) if SK therapy within 6-12 months
Duration of infusion: usually 1 hr following reperfusion or 90-120 min total
Left ventriculography, if stable
To CCU with sheaths in place and on continuous heparin infusion to maintain PTT 1.5-2 X normal. Remove sheaths in 24-36 hrs.
Prior to discharge, aspirin + dipyridamole or warfarin.

Patients with cardiogenic shock should probably not be categorically excluded since they may have much to gain from successful reperfusion. Certainly these patients are at increased risk from any procedure, including cardiac catheterization.

B. Treatment Protocol

1. Intracoronary therapy There are only minor differences in the protocols for intracoronary streptokinase administration currently used by most investigators (67). A representative protocol is outlined in Table 2. Initial attempts to disrupt the thrombus with a guidewire were not usually successful, potentially dangerous, and have been abandoned (except when coronary angioplasty is to be performed). Likewise, subselective infusion of streptokinase through a small catheter positioned within the infarct artery proximate to the clot has been advocated (68). This technique may be time consuming, is of unproven benefit, and is seldom used. Drug infusion is usually continued for 30-60 minutes after reperfusion to eliminate any residual thrombus.

Follow-up care after catheterization and drug administration is less uniform. A continuous heparin infusion to prevent rethrombosis is started either immediately after catheterization or when the activated partial thromboplastin time has returned toward twice normal and is maintained for a variable period, usually 4-10 days. Antithrombotic therapy is then continued with either (a) aspirin plus dipyridamole or (b) warfarin. There is no data to suggest which regimen is more effective or when these agents should replace heparin. In the absence of such data, many prefer aspirin and dipyridamole, since this regimen is easier to monitor and probably safer than warfarin. Continuous anti-

thrombotic coverage can be maintained by starting these agents several hours before stopping heparin.

2. Intravenous therapy Unlike the earlier low dose thrombolytic therapy trials, current research efforts with intravenous streptokinase employ the early administration of a high dose, brief duration infusion of drug. A high dose is given rapidly to saturate antistreptokinase antibodies and ensure adequate concentrations of the drug within the coronary circulation. The brief duration of infusion (20 to 60 minutes) should reduce the duration of hyperplasminemia and therefore decrease the risk of bleeding. A typical protocol is shown in Table 3. As discussed previously, the pharmacokinetics of streptokinase's actions are complex, and there is little evidence that one high-dose regimen is more effective than another (as long as a systemic lytic state is produced). Therefore, the choice of dosage is more often based on the size of the vial (750,000 units) than on pharmacokinetic principles. Since a rare patient may be resistant to even very large doses of streptokinase (usually due to antistreptokinase antibodies), a fibrinolytic effect should be documented by (a) prolongation of the prothrombin time, activated partial thromboplastin time, or thrombin time, (b) a decrease in fibrinogen, or (c) the presence of elevated fibrin degradation products. Urokinase should be used in patients with recent streptococcal infection or recent streptokinase therapy (within the previous 6-12 months) or when streptokinase resistance is encountered.

Some authorities advocate immediate heparinization after streptokinase administration to prevent early reocclusion; others suggest delaying anticoagulation for several hours (eg. when the activated partial thromboplastin time has declined toward twice normal) to reduce the risk of hemorrhage. The heparin infusion rate is adjusted to maintain the activated partial thromboplastin time at 1.5 to 2 times normal. The intricacies of monitoring the activity of fibrinolytic agents, including the effect of heparin, fibrin degradation products, and hypofibrinogenemia on laboratory studies, have recently been reviewed (19).

TABLE 3 Protocol for Intravenous Streptokinase Administration

Prophylactic lidocaine infusion
Heparin lock for blood sampling
Percutaneous femoral venous sheath if invasive procedures anticipated
Premedication with hydrocortisone (usually omitted)
Streptokinase 500,000-1,500,000 units over 30-60 minutes. Use urokinase (2 million units) if SK therapy within previous 6 months.
Careful observation for signs of reperfusion or bleeding
After completion of SK infusion, start heparin infusion (1000 units/hr) to maintain PTT at 1.5-2 times upper limit of normal. Continue heparin for 3-10 days.
Measure fibrinogen and FDP to insure fibrinolysis.
CPK levels every 4-6 hr to detect early peak
Aspirin + dipyridamole or warfarin for 3-12 months

Fibrinous pericarditis with or without symptoms is common 2-4 days after transmural myocardial infarction. Management of antithrombotic therapy in a patient who develops a pericardial rub must balance the risks of rethrombosis of the infarct artery and cardiac tamponade due to pericardial hemorrhage (which is rare in conventionally treated patients). In the recently completed Thrombolysis in Myocardial Infarction (TIMI) trial (69), heparin administration was not interrupted when an asymptomatic rub was detected. Symptomatic pericarditis was treated with aspirin, heparin was switched to a low dose subcutaneous regimen, and dipyridamole was started. Thirty of the 290 patients in this trial developed pericarditis (an unusually low percentage); none developed tamponade.

Obviously, invasive procedures should be kept to a minimum after streptokinase administration, especially when fibrinogen levels are below 100 mg%. A percutaneous venous sheath can be placed by an experienced physician prior to treatment if invasive procedures (Swan-Ganz monitoring, temporary transvenous pacing) are anticipated; this is routine at some centers. Inadvertent femoral arterial puncture is a relative contraindication to subsequent thrombolytic therapy. Blood samples should be drawn from a heparin lock to minimize the need for repeated venipuncture.

C. Complications

1. Bleeding The most frequent complication with either intravenous or intracoronary streptokinase is bleeding. It was initially hoped that intracoronary streptokinase would produce local thrombolysis without causing a systemic lytic effect. However, the total dose of streptokinase administered is typically 150,000 to 360,000 units, and a systemic effect is almost always observed. Cowley et al (70) detected a 70% or greater reduction in fibrinogen level in 22 (88%) of 25 patients treated with an average of 201,000 units of intracoronary streptokinase. Mean fibrinogen level fell from 342±80 to 87±94 mg% and remained depressed (43% of baseline) at 24 hours. The Clauss method used by these investigators to assay fibrinogen levels may have underestimated the actual fibrinogen concentration in the presence of fibrin degradation products. Plasminogen rapidly fell to 7% of baseline activity after treatment. Partial thromboplastin time was markedly prolonged (>100 sec) after infusion, returned to 2 times control at 5±2 hours and to normal at 9±4 hours. These observations have been confirmed by others (71-73), although much less marked systemic effects have been reported (74).

Despite significant fibrinolytic activity, serious bleeding is relatively uncommon and life-threatening or fatal hemorrhage is rarely reported (Table 4). The vast majority of bleeds requiring transfusions occur at the site of arterial puncture; minor bleeding and hematoma formation at that site is common. Bleeding is often more closely related to heparin therapy than to the thrombolytic agent itself, frequently occuring after the systemic lytic effects have resolved (75). Some caution is advised in extrapolating the published risk of hemorrhage to clinical practice. Since there is no consistent definition of what constituted a "minor" or "major" bleed, the exact incidence of bleeding complications in published studies is sometimes difficult to determine. In addition, it is possible that investigator bias leads to an underemphasis of bleeding risks. Alternatively, the low risk of serious

TABLE 4 Serious Bleeding Episodes after Thrombolytic Therapy

	Author (ref)	Total patients	No. Bleeds
Intracoronary	Merx (143)	204	15 (7%)
	Rentrop (74)	29	2 (7%)
	Schwarz (155)	101	6 (6%) (one fatal)
	Rogers (158)	25	1 (4%)
	Smalling (144)	136	5 (4%)
	Mathey (156)	41	0
	Anderson (71)	24	0
	Khaja (157)	20	0
	Kennedy (148)	134	7 (5%)
Intravenous	Rogers (158)	26	1 (4%)
	Neuhaus (82)	40	0
	Schroder (88)	93	0
	Spann (159)	43	0
	Anderson (160)	27	4 (15%)
	Taylor (161)	121	6 (5%)

hemorrhage may reflect careful patient selection and follow-up care by skilled, experienced clinicians in a research environment.

Although a brief intravenous infusion of streptokinase produces a greater systemic lytic effect, the actual incidence of bleeding complications is no higher than following intracoronary streptokinase since femoral arterial puncture has not been performed (Table 4). Two (1.2%) patients in the European Cooperative Trial (64) suffered nonfatal intracereberal bleeds after a 24-hour streptokinase infusion. Careful patient selection and strict avoidance of unnecessary invasive procedures will minimize the risk of hemorrhage.

Management of life-threatening hemorrhage inaccessible to direct pressure in a patient with a systemic lytic state can be exceedingly complex and should properly involve consultation with the hematologist. Heparin should be discontinued and can be reversed with protamine sulfate. Epsilon-aminocaproic acid (Amicar) inhibits the binding of plasmin to fibrin but does not prevent further activation of plasmin or the destruction by plasmin of other coagulation factors. A loading dose of 5 gm is given over 30 min, followed by a 1 gm/hr infusion. Thrombotic complications can occur when disseminated intravascular coagulation or upper genitourinary tract bleeding is present. Clotting factors, especially factor VIII and fibrinogen, should be replaced with cryoprecipitate or fresh frozen plasma. Since plasma is rich in plasminogen, it may paradoxically worsen bleeding by providing the substrate for increased plasmin production.

2. Arrhythmias Since arrhythmias occur frequently in conventionally treated patients, it is not always possible to attribute them to complications of reperfusion. In animal models, reperfusion after brief periods of coronary occlusion often produces serious ventricular arrhythmias, including ventricular fibrillation, which may be fatal. Initial concern that such refractory ventricular arrhythmias would complicate reperfusion in man has not been borne out by clinical experience. While arrhythmias are often noted at the time of reperfusion, they are almost always managed with conventional antiarrhythmics, especially lidocaine. Life-threatening recurrent ventricular tachycardia and fibrillation have been reported but are rare. The most characteristic rhythm disturbance produced by reperfusion in man is accelerated idioventricular rhythm, occurring at the time of reperfusion in up to 50% of patients in some series (76), less often in others. This rhythm is usually well tolerated rarely degenerates to rapid ventricular tachycardia, and may require no specific treatment. Overdrive suppression with atropine or atrial pacing is usually successful.

Reperfusion of the inferoposterior myocardium activates vagal afferents, causing bradycardia and hypotension (Bezold Jarisch reflex) (77,78). This usually responds to volume, atropine, and postural changes, and may rarely require temporary pacing. In other patients with inferior myocardial infarction, high-degree atrioventricular (AV) block due to AV nodal ischemia may resolve with reperfusion.

The mechanism of reperfusion ventricular arrhythmias is uncertain, but rapid changes in K^{+}, pCO_2, and intracellular Ca^{++}, and stimulation of alpha1-adrenergic receptors may play a role (79). In animal studies, the occurrence of arrhythmias with reperfusion implies the presence of viable myocardium in the infarct region; the frequency of such arrhythmias falls as the length of temporary occlusion increases. Whether reperfusion arrhythmias imply salvage of myocardium in man is unknown.

3. Cardiac catheterization Patients with acute myocardial infarction tolerate cardiac catheterization and coronary angiography surprisingly well. Serious complications directly attributed to these procedures are rare in reports from experienced laboratories. Left ventriculography usually produces transient mild hypotension and should be avoided in patients with shock. Dissection of the right coronary artery has been reported (80). Three deaths directly attributed to the catheterization procedure itself were described in 1 report: asystole after injection of a normal right coronary artery in 1 and dislodgement of a proximal left anterior descending thrombus by a guidewire with embolization into the left circumflex artery in 2 (81).

4. Recurrent myocardial ischemia After thrombolytic therapy, recurrent ischemia may be due to reinfarction from reocclusion of the infarct-related artery, infarct extension, or a myocardial oxygen supply-demand mismatch due to hemodynamically severe coronary artery disease. Theoretically, by salvaging myocardium distal to a residual stenosis, successful reperfusion might be associated with a higher incidence of post-infarction angina. This has generally not been observed by most investigators. Antianginal agents, coronary angiography, and coronary revascularization are employed in much the same way as for conventionally treated patients. Reinfarction due to rethrombosis of the infarct vessel has been successfully treated with repeat admini-

stration of a thrombolytic agent or with mechanical or surgical revascularization.

5. Other complications Hemorrhagic myocardial infarction after thrombolytic therapy has been described in postmortem specimens, but there is no convincing evidence that infarct size or eventual wound healing are adversely affected. Myocardial rupture has been reported following thrombolytic therapy (82), but appears to be less common than in conventionally treated patients, perhaps due to salvage of subepicardial myocardium. Allergic or febrile reactions to streptokinase are uncommon; anaphylaxis to either streptokinase or contrast material is rare.

D. Recanalization Rates

1. Intracoronary therapy Recanalization of totally occluded infarct-related arteries is achieved in 50-89% of patients by intracoronary streptokinase (Table 5). The differences in reperfusion rates from various centers is not readily explained by differences in technique, drug dosage, or patient

TABLE 5 Intracoronary Streptokinase - Reperfusion Rates in Patients with Total Coronary Occlusions

Author (ref)	Recanalization rate		Time from onset of pain to SK (hr)	Time to reperfusion (min)
Rogers (158)	19/25	76%	6.5	31
Rentrop (90)	32/43	74%	5.9	
Tennant (26)	20/35	57%	5.7	45
Raizner (147)	8/16	50%	5.6	
Khaja (157)	12/20	60%	5.4	
Kennedy (148)	73/108	68%	4.6	
Blunda (162)	8/13	62%	4.4	
Anderson (160)	18/21	86%	4.3	23
De Coster (102)	18/21	86%	4.1	
Anderson (71)	15/20	75%	4.0	30
Leiboff (95)	15/22	68%	4.0	44
Valentine (163)	50/85	59%	4.0	
Taylor (161)	44/63	70%	3.6	20
Cribier (109)	39/61	64%	3.6	
Ganz (108)	64/74	86%	3.4	25
Alderman (75)	11/15	73%	3.3	28
Cowley (70)	16/18	89%		
Rentrop (74)	17/20	85%		
Smalling (144)	73/100	73%		
OVERALL	**552/780**	**71%**		**avg 30 min**
Time to SK				
<4.5 hr	282/395	71%		
>4.5 hr	164/247	66%		

selection. Small sample sizes and different angiographic criteria of reperfusion are partly responsible. Overall, reperfusion occurred in 508 (71%) of 717 patients with total occlusions in 19 studies. The average time from onset of symptoms to reperfusion was 30 minutes. Recanalization rates for urokinase are similar (26,83).

Several investigators have examined the factors associated with an increased recanalization rate. Tendera and associates (84) treated 117 patients with intracoronary streptokinase or urokinase and compared the 66 reperfused and 51 nonreperfused patients. Recanalization rates were statistically higher for patients with (a) proximal location of the thrombus (74%) vs distal (38%), (b) left anterior descending thrombus (74%) vs right or left circumflex coronary thrombus (44%), and (c) collaterals absent (66%) vs collaterals present (45%). The explanation for the influence of collaterals on recanalization is unknown, but a higher pressure gradient across the thrombus in those without collaterals may encourage greater penetration of drug. In contrast to several other studies, the time from pain onset to treatment was not associated with recanalization rate (4.5±1.7 hrs for patients with opening, 4.9±1.6 hrs for those with no opening, p=NS).

Kennedy et al (80) analyzed factors associated with reperfusion rate in 1029 patients treated with intracoronary streptokinase an average of 4.0±6.9 hours after pain onset. While overall reperfusion rate was 71%, those treated within 6 hours were more likely to reperfuse (75%) than those treated beyond 6 hours (58%). Reperfusion was least likely in the 45 patients with cardiogenic shock (43%). In contrast to the report by Tendera et al (84), recanalization rate was not associated with the location of the thrombus. In another registry report of 209 patients treated with intracoronary streptokinase, the reperfusion rate was highest in those treated within 3 hours (85%) (85).

Intracoronary streptokinase nearly always causes a systemic lytic effect; indeed, the absence of such an effect is highly predictive of treatment failure. Rothbard and colleagues (72) treated 10 patients with "low dose" (average 753 u/min) and 5 with "standard dose" (average 4202 u/min) intracoronary streptokinase. Low dose patients were treated with the standard dose regimen if reperfusion was not achieved within 90 minutes. The recanalization rate was then correlated with the presence of a systemic lytic state (defined as a >10% reduction in fibrinogen level). A lytic state was produced in 5 of 10 low dose and 11/13 standard dose treatments.

Systemic lytic state?	Reperfusion	No reperfusion
No	0/7 (0%)	7/7 (100%)
Yes	12/16 (75%)	4/16 (25%)

Thus, a systemic lytic state is a frequent accompaniment of successful therapy and may even be a necessary requirement for attaining reperfusion with intracoronary streptokinase.

Since a systemic fibrinolytic effect is produced in the vast majority of both successfully and unsuccessfully treated patients, failure to achieve such an effect is an uncommon explanation for treatment failure (73). Occlusion resistant to thrombolytic therapy may be due to nonthrombotic coronary occlusion by plaque hemorrhage (which might actually be caused or worsened by

thrombolytic therapy), coronary artery dissection, or coronary embolus (86,87). Necropsy evaluation of 4 patients with unsuccessful thrombolytic therapy revealed medial dissection and intraplaque hemorrhage in 1, old, organized thrombus in 1, and intraplaque hemorrhage with fresh thrombus in 2 (87). In contrast, none of the 3 specimens from successfully reperfused patients contained dissection or intraplaque hemorrhage.

2. Intravenous therapy While it is clear that intracoronary streptokinase can quickly achieve thrombolysis in the majority of patients with acute myocardial infarction, this approach suffers from 2 major limitations. First, since cardiac catheterization must be performed, there is an inevitable delay between patient presentation and delivery of therapy. Even in the most experienced centers, this delay is 45–120 minutes. Continued myocardial necrosis during this time substantially reduces the ultimate benefit from reperfusion. Second, the majority of patients with acute myocardial infarction do not currently have immediate access to facilities capable of delivering 24 hour-a-day intracoronary therapy. Providing such facilities on a nationwide scale would place a great burden on financial and professional resources. Rapid intravenous administration of an effective thrombolytic agent would permit earlier treatment and, therefore, greater myocardial salvage by reperfusion and would be readily available to the majority of patients with acute myocardial infarction, since specialized facilities and personnel would not be necessary.

There are 8 published studies which have utilized coronary angiography at baseline and during treatment to assess the recanalization rate after intravenous streptokinase (Table 6). Overall reperfusion was achieved in 129 (42%) of 304 patients at an average of 45 minutes after the start of treatment. While this contrasts with the 71% rate for intracoronary streptokinase, the recanalization rate may be highly dependent on the time form the onset of occlusion to treatment (Figure 6) (88). In the 3 studies with a mean time to

TABLE 6 Intravenous Streptokinase – Angiographically Documented Reperfusion Rates in Patients with Total Coronary Occlusion

Author (ref)	Recanalization rate		SK dose X 10^3	Time from onset of pain to SK (hr)	Time to reperfusion (min)
Rogers (158)	8/26	31%	500–1,000	6.8	38
TIMI (69)	40/115	35%	1,500	4.8	
TIMI (164)	11/34	32%	1,500	4.5	
Blunda (162)	6/12	50%	478	4.0	54
Schroeder (88)	11/21	52%	500	3.8	
Spann (159)	21/43	49%	850–1,500	3.5	
Neuhaus (82)	24/40	60%	1,700	3.4	48
Alderman (75)	8/13	62%	725	3.4	39
OVERALL	**129/304**	**42%**			**avg 45 min**
Time to SK					
>4 hr	59/175	34%			
≤4 hr	70/129	54%			

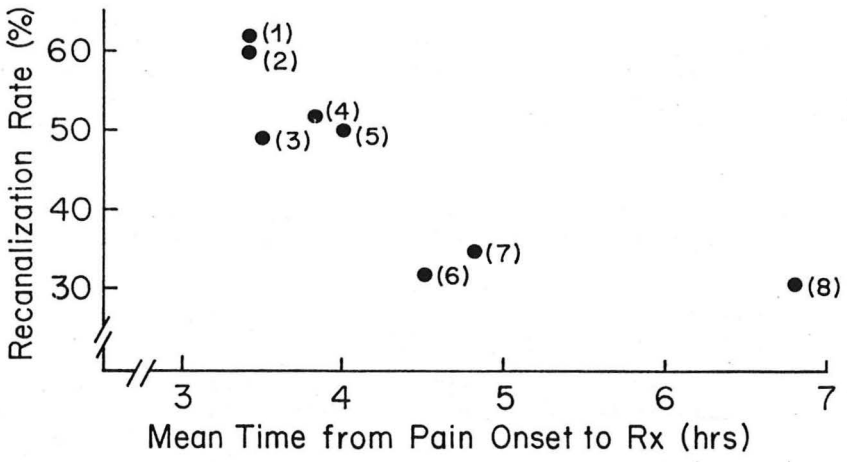

FIGURE 6 Recanalization rate with intravenous straptokinase vs mean time from pain onset to treatment for the 8 studies in Table 6. (1=ref 75, 2=ref 82, 3=ref 159, 4=ref 88, 5=ref 162, 6=ref 164, 7=ref 69, 8=ref 158)

treatment over 4 hours, reperfusion was achieved in 59 (34%) of 175 patients, whereas the 5 trials with a mean time less than or equal to 4 hours report reperfusion in 70 (54%) of 129 patients. The recanalization rate does not appear closely associated with the total streptokinase dose; a systemic lytic state was produced in essentially all patients treated in these studies. Reperfusion rates for intravenous urokinase are similar (89).

Since angiographic studies will not detect drug-induced reperfusion which occurs after the 60 to 90 minute observation period in the catheterization lab, they likely underestimate the ultimate recanalization rate of intravenous streptokinase. The primary advantage of intravenous streptokinase is the ability to administer treatment very early (within 3 hours of the onset of symptoms). Unfortunately, angiographically controlled trials can not be used to assess the reperfusion rate during this very early period, since an insufficient number of patients can be undergo catheterization and be treated within this time. Other markers have been used to determine if reperfusion has been achieved with intravenous treatment.

Delayed angiography Several investigators have performed coronary angiography after treatment to determine the patency of the infarct-related artery (Table 7). Patent vessels were found in 348 (75%) of 463 patients at angiography performed several hours to 4 weeks after treatment, which was administered much earlier (average 2.8 hours) than in the studies in Table 6. This approach likely overestimates the true drug-induced recanalization rate for 2 reasons. First, in the absence of a baseline angiogram, it is impossible to determine which patients have patent infarct vessels prior to treatment and

would, therefore, be inappropriately counted as treatment successes. A review of reports describing coronary angiography within a mean of 4 hours of pain onset reveals 12% of patients with patent vessels before any treatment (Table 8). Second, spontaneous reperfusion, even in the first 24 hours, is not uncommon in patients with acute myocardial infarction treated conventionally.

TABLE 7 Intravenous Streptokinase – Reperfusion Rates Assessed by Delayed Angiography (No Pretreatment Angiography)

Author (ref)	Recanalization rate		Time from onset of pain to SK (hr)	Time of late angiogram	Early CK peak	
Verstraete (152)	34/62	55%	2.6	Same day		
Mathey (89)	30/50	60%	1.8 (urokinase)	Same day		
Valentine (163)	42/66	64%	2.9	Same day		
Taylor (161)	99/121	82%	3.2	Within 2 days		
Ganz (92)	63/66	95%	2.2	3–7 days	75/81	93%
Anderson (160)	16/22	73%	2.8	2 weeks	23/25	92%
Olson[1]	22/26	85%	4.4	2 weeks	22/28	79%
Schroeder (88)	42/50	84%	2.9	4 weeks		
OVERALL	**348/463**	**75%**	**Avg 2.8**			

[1] abstract

TABLE 8 Angiographic Findings in Acute Transmural Infarction

Author (ref)	Time of cath (hrs)	Total occlusion		Subtotal occlusion	
Mathey (156)	<3	39/41	95%	2/41	5%
Ganz (108)	3.4	74/81	91%	7/81	9%
Anderson (71)	4.0	20/24	83%	4/24	17%
Leiboff (95)	4.0	43/55	78%	12/55	22%
De Coster (102)	4.2	36/44	82%	8/44	17%
TIMI (164)[1]	4.7	70/87	80%	17/87	20%
TIMI (Phase I) (69)	4.8	214/290	74%	76/290	26%
Khaja (157)	5.4	45/54	83%	9/54	17%
Rentrop (74)	5.6	20/29	69%	9/29	31%
Tennant (26)	5.7	102/139	73%	37/139	27%
Rentrop (90)	5.9	61/91	67%	30/91	33%
OVERALL		**724/935**	**77%**	**211/935**	**23%**
Time of cath					
≤4.0 hr				25/201	12%
>4.0 hr				186/734	25%

[1] Includes open-label tPA patients not described in ref 159

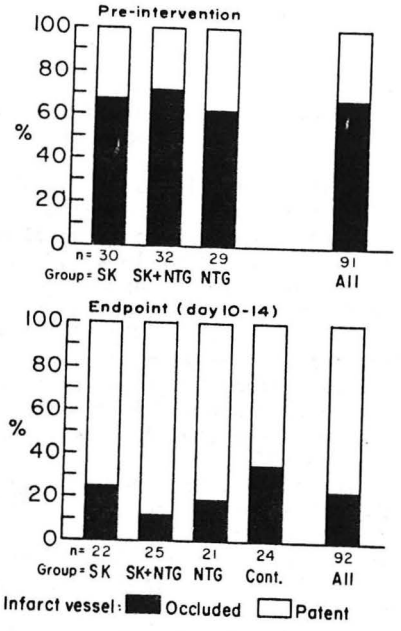

FIGURE 7 Patency rates for infarct-related coronary arteries before intervention and at day 10–14 in patients treated with intracoronary streptokinase (SK), streptokinase and nitroglycerin (SK+NTG), nitroglycerin (NTG), or conventional therapy. (From ref 90)

As shown in Table 8 and Figure 1, the incidence of patent vessels rises as the mean time from pain onset to angiography increases. By 2–4 weeks, approximately one-half of conventionally treated patients in some series will have patent infarct-related arteries (Table 9). Of 13 patients studied by Rentrop et al (90) with totally occluded vessels at initial angiography who received no thrombolytic therapy, 10 (77%) were patent 10–14 days later (Figure 7). Therefore, delayed angiography, unless performed immediately after treatment, is of limited value in determining the rate of drug-induced reperfusion.

TABLE 9 Late Patency Rate for Conventionally Treated Patients

Author (ref)	Patency rate		Time of late angiogram
De Wood (11)	38/114	33%	6–24 hr
Bertrand (165)	50/106	47%	2 weeks
Rentrop (90)	16/24	67%	2 weeks
Betriu (166)	141/259	54%	4 weeks

Same-day post-treatment angiography in 3 trials demonstrated patent infarct arteries in 106 (60%) of 178 patients treated with either intravenous streptokinase or streptokinase an average of 2.5 hours after symptom onset (Table 7).

Clinical signs of reperfusion The following clinical events may be noted at the time of reperfusion: rapid relief of chest pain, rapid resolution of ST-segment elevation; resolution of conduction disturbances, transient bradycardia and hypotension, and appearance of ventricular arrhythmias (76,77,91,92). Some authorities believe the appearance of one or more of these markers reliably indicates that reperfusion has occurred. Using clinical markers, reperfusion rates of over 90% are reported (92). Others have found these clinical events to be less sensitive and specific markers of reperfusion. In the TIMI trial (69), reperfusion (documented angiographically) was actually associated with worsening of pain in 10 patients and exacerbation of ST-segment elevation in 2. New arrhythmias appeared in only 36% of reperfused patients.

Time to peak CPK activity The most useful noninvasive marker of reperfusion has been the time to peak CPK activity. In patients without reperfusion, CPK activity usually peaks 20-25 hours after the onset of symptoms. Reperfusion produces a rapid "wash-out" of this enzyme from the infarct region (93). In experimental infarction with reperfusion 1 to 3 hours after coronary occlusion, maximal plasma CK activity is reached much earlier than with sustained coronary occlusion. Patients with acute infarction and successful recanalization with streptokinase also have earlier peak CK activity, usually within 2-8 hours after treatment and within 12-16 hours of symptom onset (Figure 8) (94-97). In an angiographically controlled trial by Alderman and associates (3), a 15 hour demarcation from the onset of pain to peak CK activity separated those with and without recanalization with 95% sensitivity and 88% specificity. However, this study contained only 28 patients; much larger numbers will be needed to test the predictive value of an early CK peak as a marker of reperfusion. Preliminary data from the TIMI trial suggests that a very early (within 4 hours of treatment) and a very late (beyond 16 hours after treatment) peak CK are highly predictive of successful and unsuccessful reperfusion, respectively. Using early peaking CK as a marker of reperfusion, rates of 65-90% have been reported (Table 7)

Unfortunately, early peaking CK activity can not distinguish between early spontaneous and drug-induced recanalization (90,98). Rentrop et al (90) found no difference in time from pain onset to peak CK in successfully reperfused patients (15.9±7.1 hours) and those with patent vessels prior to treatment (14.6±5.0 hours).

Spontaneous reperfusion can occur early enough to salvage myocardium in conventionally treated patients with acute myocardial infarction (99-101). Ong et al (101) compared changes in left ventricular function after acute myocardial infarction in 24 patients with early peaking CK levels (average 11.6±2.7 hr after pain onset) and 28 with late CK peaking (average 22.1±5.3 hr after pain). None had received thrombolytic therapy. Left ventricular ejection fraction improved from 0.38 to 0.48 ($p<0.001$) in those with an early CK peak (presumed a result of spontaneous early reperfusion) and was unchanged in the late-peaking CK group. While the actual incidence of spontaneous reperfusion may differ from that reported in this study, others have confirmed that early spontaneous reperfusion does occur and is associated with both an early peaking CK level and an improvement in ventricular function after myocardial

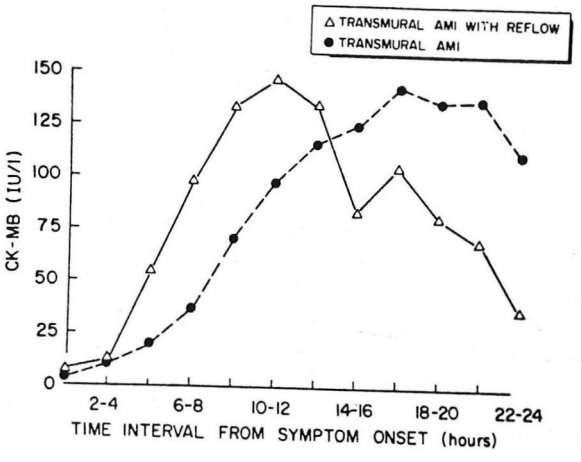

FIGURE 8 A comparison of the CK-MB release curves for conventionally treated patients and for streptokinase treated patients with reflow. Reperfusion causes a rapid increase in CK at the time of vessel opening and an earlier peak. (From ref 96)

infarction. In trials of intravenous streptokinase that employ early CK peaking to assess reperfusion, credit for any beneficial effect attributed to reperfusion must be shared by both spontaneous and drug-induced recanalization.

Thallium Scintigraphy Performed early after intravenous injection of the radionuclide, thallium-201 imaging reflects the distribution of myocardial blood flow. De Coster et al (102) evaluated the effect of reperfusion during acute myocardial infarction on pre- and post-intervention thallium-201 perfusion imaging and assessed the ability of thallium-201 to predict infarct-related artery patency in 23 patients treated with intracoronary streptokinase and 21 control patients. Planar imaging was performed acutely (before treatment), at 2-8 hours, 4 days, and 6 weeks. In the 26 reperfused patients, the thallium defect score fell from 40% to 14% at 6 weeks, whereas it remained unchanged in those who did not reperfuse.

Technetium-99m pyrophosphate imaging The delivery of technetium-99m stannous pyrophosphate (Tc-99m-PPi), a widely used infarct-avid imaging agent, into the area of infarction is dependent on flow. In the absence of reperfusion, intense uptake of Tc-99m-PPi rarely occurs earlier than 2-3 days post-infarction. Wheelan and associates (103) found a good correlation between the presence of a strongly positive (3 or 4+ uptake) Tc-99m-PPi scan performed an

average of 7.2 hours after pain onset and early peaking CK activity in 14 patients treated with intravenous streptokinase. A strongly positive acute scan identified those patients with a subsequent improvement in left ventricular function after treatment (presumably due to reperfusion). Others have attempted to detect coronary artery thrombi using indium-111-labeled platelets and technetium-99m-labeled red blood cells (104).

E. Reocclusion

A significant stenotic lesion in the infarct-related artery is present at the site of thrombosis in most patients with acute myocardial infarction. Despite anticoagulation, reocclusion of the vessel after initially successful thrombolysis occurs in 10-35% of patients prior to hospital discharge. In most instances, reocclusion is due to rethrombosis; obstruction of the vessel by intraplaque hemorrhage may occasionally be responsible. Reocclusion will have 1 of 2 consequences. First, it may be clinically silent if no viable myocardium remains in the infarct region or if an extensive collateral circulation is present. Second, it may present as reinfarction which, while confirming the salvage of myocardium by the initial intervention, negates the beneficial effects of reperfusion.

Two main factors are associated with an increased risk of reocclusion: the severity of the residual stenosis (105-107) and inadequate or interrupted anticoagulation (108). Harrison et al (105) used quantitative coronary angiography to compare the residual stenosis in patients with and without reocclusion after successful reperfusion. Seven (54%) of 13 patients with a minimal cross-sectional area less than 0.4 mm^2 had rethrombosis; none of the 11 with a minimal cross-sectional area greater than 0.4 mm^2 had rethrombosis. Similarly, 7 (50%) of 14 patients with residual lesions causing more than 90% area stenosis had rethrombosis while none of the 10 with lesions less than 90% had rethrombosis. Serruys and colleagues (107) noted an increased risk of reocclusion when greater than a 58% diameter stenosis (82% area stenosis) remained after reperfusion.

There is no consensus on the most appropriate management of a residual stenosis after successful reperfusion. Some investigators claim that the risk of reocclusion is low with aggressive anticoagulation (108). They point out that the severity of the residual lesion consistently decreases in size between the acute angiogram and hospital discharge (105,109). In the study by Harrison et al (105) cited above, an average 116% increase in cross-sectional area of the residual stenosis was observed over an 8-14 day period in 17 patients after successful streptokinase therapy. This change may be due to continued lysis of persistent thrombi, resolution of coronary spasm, or remodeling of a ruptured atherosclerotic plaque as it heals.

Others argue that the risk of reocclusion in patients with a high-grade residual stenosis (with once-proven thrombotic potential) after treatment is high enough to warrant mechanical revacsularization with percutaneous transluminal coronary angioplasty (PTCA) or surgical revascularization (106,107,110-114). The assumption is made that, by reducing the severity of the residual stenosis with PTCA, the risk of reocclusion is diminished. Little information is available on the ability of PTCA to reduce the reocclusion rate when applied in this way. PTCA, either alone or combined with streptokinase, is currently

being evaluated at some centers as a means of achieving reperfusion in patients with acute myocardial infarction. In carefully selected patients, acute recanalization can be achieved safely with a high degree of success. Residual stenosis severity is usually less than following reperfusion with streptokinase. It is clear that in carefully selected patients and in experienced hands, PTCA can be safely performed to (a) achieve reperfusion and (b) reduce the severity of residual stenosis after reperfusion with streptokinase. As a primary means of establishing reperfusion, this technique suffers from even greater limitations than intracoronary streptokinase. Its availability is restricted to patients in close proximity to specialized laboratories and experienced angiographers. As a means of reducing the risk of reocclusion after thrombolytic therapy, its efficacy is unproven. Papapietro et al (115) performed PTCA in 18 selected patients after intracoronary streptokinase; 11 had a severe residual stenosis and 7 persistent occlusion. Successful dilatation was achieved in 13 (9 with patent vessels, 4 with occluded vessels) with an average residual diameter stenosis of 27%. However, reocclusion occurred in 4 (31%) of the 13 patients prior to hospital discharge. Gold et al (116) reported the results of PTCA performed after intracoronary streptokinase in 28 patients with acute myocardial infarction (12 with high-grade residual stenosis, 16 with persistent occlusion). Reperfusion was achieved 11 of the 16 persistently occluded vessels, and residual stenosis diameter was reduced by more than 20% in 9 of the 12 patent vessels. However, early reinfarction occurred in 1 and late restenosis or reocclusion was documented in 5 (45%) of 11 patients at repeat angiography 5 months after treatment. Others report much lower reocclusion rates after acute PTCA (107,111). Since, despite anticoagulation, the risk of reocclusion in many centers appears to be high in patients with a severe residual stenosis, further studies to assess the role of PTCA as adjuvant therapy to reduce this risk seem warranted.

Most patients with high-grade residual stenosis and severe 3-vessel or left main coronary disease would be candidates for coronary artery bypass graft surgery.

F. Reperfusion and Myocardial Salvage

Reperfusion of the infarct vessel is not an end in itself, but a means of salvaging viable myocardium. What is the evidence that reperfusion salvages myocardium in man? Unfortunately, assessment of infarct size in man is hampered by the highly variable size of the territory at risk after coronary occlusion, spontaneous variability in ventricular function after infarction, and lack of a sensitive, precise technique to detect small changes in infarct size. The most dramatic but least quantifiable evidence that myocardium has been salvaged is the occurrence of clinical reinfarction after successful reperfusion. Several electrocardiographic, enzymatic, and imaging techniques have been utilized to detect myocardial salvage after thrombolytic therapy.

1. Electrocardiographic indices Blanke et al (91) evaluated the effect of reperfusion on various electrocardiographic indices of ischemia and infarction in patients with acute anterior myocardial infarction, including the magnitude of ST-segment elevation, the sum of R wave heights, and the number of Q waves in V1-V6. They observed Q wave regression and an increase in R wave height in recanalized patients compared with a retrospectively selected group of conventionally treated patients with anterior myocardial infarction, suggesting

salvage of myocardium by reperfusion. Goldberg et al (117) noted a decline in Q waves and partial regrowth of R wave amplitude in some patients after successful reperfusion. Unfortunately, these electrocardiographic techniques lack the precision required to quantitate myocardial salvage.

2. Thallium imaging Myocardial labelling with thallium-201 is dependent upon intact myocardial perfusion and uptake of the isotope by viable myocardial cells. Several investigators have reported significant reductions in the size of thallium perfusion defects in successfully reperfused patients in comparison to patients without reperfusion, suggesting salvage of viable myocardium (108,118-121).

3. Positron emission tomography Accumulation of ^{11}C-palmitate is homogeneous in normal myocardium and diminished in reversibly or irreversibly injured zones of ischemia. In animal studies, positron emission tomography can delineate restoration of myocardial uptake of ^{11}C-palmitate after reperfusion in regions of salvaged myocardium. Thus, this technique can be used to quantitatively assess areas of ischemic, viable myocardium and temporally follow the fate of these areas after various interventions. Sobel and associates (122) compared ^{11}C-palmitate accumulation in 11 patients with and 8 without reperfusion. In each of the reperfused patients, myocardial accumulation of ^{11}C-palmitate improved between the acute and delayed study, suggesting improved regional metabolism by salvaged myocardial cells. No change in tomographic images was found in the nonreperfused patients. In addition to positron emission tomography, nuclear magnetic resonance imaging and single photon emission tomography (123) will likely emerge as valuable tools for evaluating infarct size.

4. CK activity curves In addition to altering the time to peak CK activity, reperfusion results in a relatively greater release of CK for a given infarct size in comparison with nonreperfused infarctions (94,97). Thus, conventional calculations of infarct size from CK activity curves may be unreliable when early reperfusion has occurred. While demonstration of similar peak CK levels in reperfused and nonreperfused patients has been used as suggestive evidence of smaller infarctions in those reperfused, CK activity curves have not been widely employed to assess myocardial salvage with thrombolytic therapy (124,125).

G. Reperfusion and Left Ventricular Function

If reperfusion reduces mortality after myocardial infarction, it most likely does so by improving left ventricular function and preventing pump failure. The most useful techniques used to assess the effect of reperfusion on global and regional ventricular function are contrast left ventriculography, radionuclide ventriculography, and two-dimensional echocardiography. Since improvement in ventricular function may take several days, the effect of reperfusion should not be assessed until at least 10-14 days after treatment (Figure 9).

Numerous uncontrolled studies have demonstrated improvements in global and/or regional left ventricular function when reperfused patients are compared to nonreperfused patients (Figure 10). Representative findings of these comparisons are shown in Table 10. Several points will be emphasized.

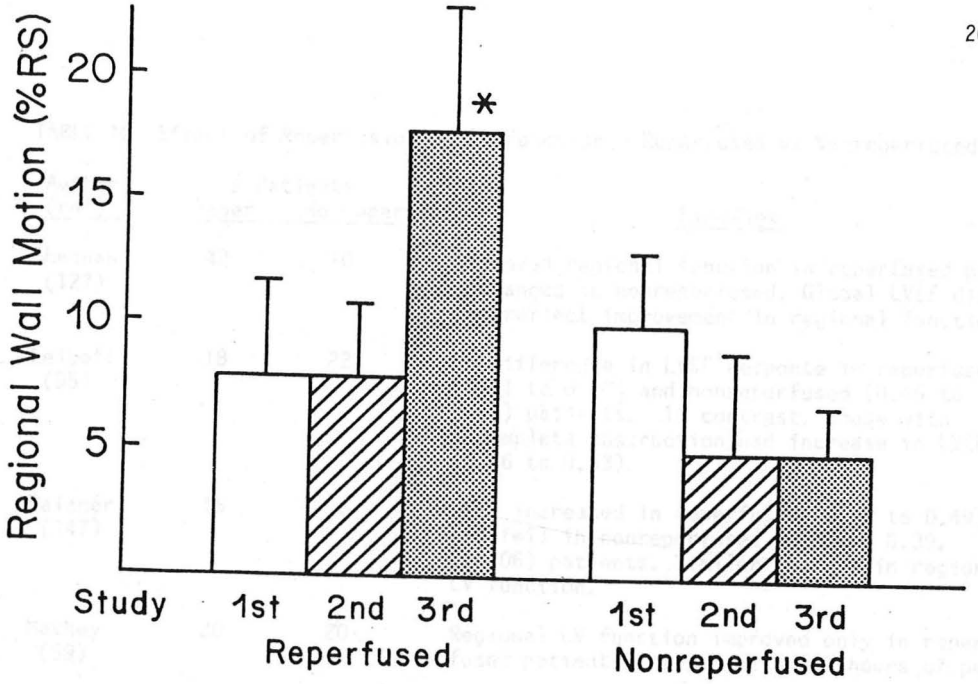

FIGURE 9 Regional wall motion in the infarct zone in patients with and without reperfusion studied acutely (1st), at 24 hours (2nd), and at hospital discharge (3rd). Regional function improved in those successfully reperfused. However, no improvement was evident at 24 hours. (From ref 126)

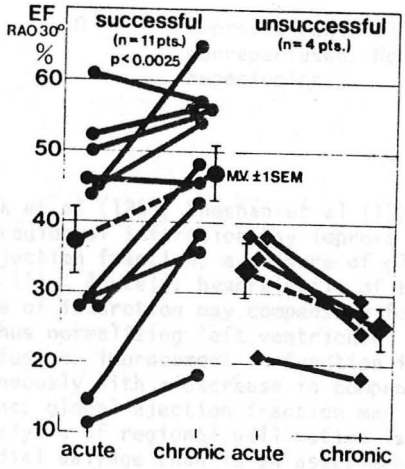

FIGURE 10 Left ventricular ejection fraction acutely and 7–21 days after intracoronary streptokinase. Ejection fraction improved in the successfully recanalized patients. (From ref 156)

TABLE 10 Effect of Reperfusion on LV Function - Reperfused vs Nonreperfused

Author (ref)	# Patients Reper	No reper	Findings
Sheehan (127)	42	10	Improved regional function in reperfused pts; unchanged in nonreperfused. Global LVEF did not reflect improvement in regional function.
Leiboff (95)	18	22	No difference in LVEF response in reperfused (0.41 to 0.40) and nonreperfused (0.46 to 0.44) patients. In contrast, those with incomplete obstruction had increase in LVEF (0.46 to 0.53).
Raizner (147)	16	6	LVEF increased in reperfused (0.42 to 0.49) and fell in nonreperfused (0.45 to 0.39, p=0.06) patients. Similar changes in regional LV function.
Mathey (89)	30	20	Regional LV function improved only in reperfused patients treated within 2 hours of pain.
Valentine (163)	62	30	Greater improvement in LVEF in reperfused (0.39 to 0.48) than nonreperfused (0.36 to 0.40) patients.
Yasuno (83)	11	10	Improved LVEF in reperfused (0.51 to 0.72) and no change in nonreperfused or reperfused with reocclusion (0.41 to 0.41).
Charuzi (167)	23	10	Improved regional wall motion in reperfused, not in nonreperfused. No improvement immediately after reperfusion.

1) As shown by Stack et al (126), Sheehan et al (127), and others (109), function in the region of infarction may improve substantially without an improvement in ejection fraction, a measure of global left ventricular function (Figure 11). Acutely, hyperkinesis of the ventricular region opposite the site of infarction may compensate for hypokinesis in the area of infarction, thus normalizing left ventricular global function. After successful reperfusion, improvement in function in the infarct region proceeds simultaneously with a decrease in compensatory hyperfunction of uninvolved regions; global ejection fraction may remain unchanged. Therefore, an analysis of regional wall motion is a more sensitive method of detecting myocardial salvage than is an assessment of global ventricular function.

2) Not surprisingly, when improvements in left ventricular ejection fraction have been demonstrated, changes are most marked in those with the lowest

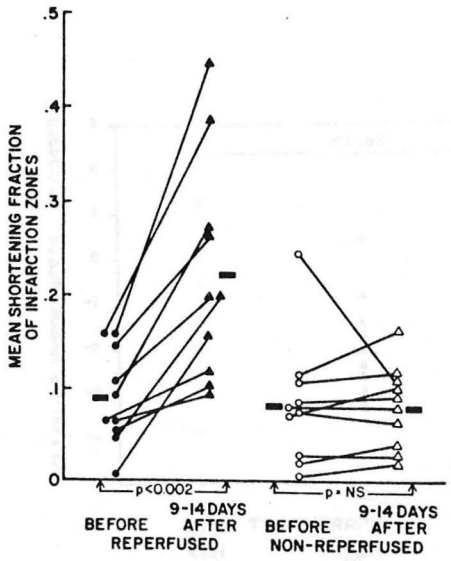

FIGURE 11 Regional function in the infarct zone before and 9–14 days after treatment with intravenous streptokinase. Regional function improved in the patients with successful reperfusion. (From ref 159)

initial values (128,129). In patients with cardiogenic shock, striking changes in function have been noted after successful reperfusion.

3) As predicted from animal studies, improvement in ventricular function is dependent upon the time delay between the onset of pain and reperfusion (129–131). In general, little or no consistent improvement in global or regional function occurs in patients reperfused beyond 3–4 hours (Figure 12). A notable exception is the report by Smalling et al (132) where improvements in ejection fraction in patients reperfused as late as 18 hours were found. The explanation for this observation is unclear. All were said to have persistent pain at the time of enrollment and this may identify a subgroup who may benefit from delayed treatment; others have been unable to demonstrate such an effect.

4) Residual flow to the infarct region (either by collaterals or flow through a subtotal occlusion) prior to treatment may significantly improve eventual recovery of ventricular function (99,129,133–136). Presumably, such residual flow prolongs the viability of ischemic myocardial cells, permitting greater salvage when reperfusion is achieved. Even in the absence of reperfusion, residual flow may permit recovery of left ventricular function (Figure 13) (98).

5) In addition to posing an increased risk of reocclusion, a high-grade residual stenosis may limit or prevent recovery of regional function after reperfusion (131,137,138). The role of mechanical or surgical revascularization

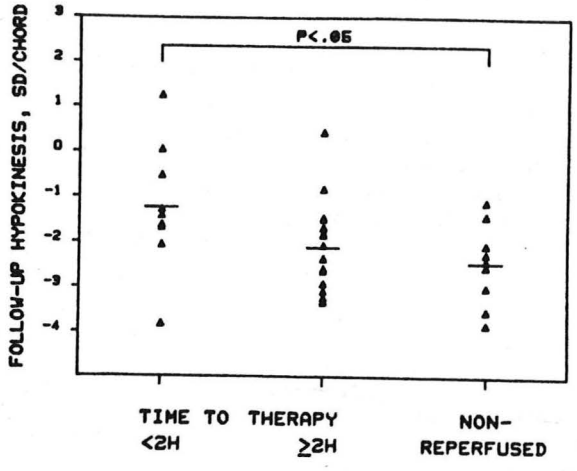

FIGURE 12 Regional wall motion at the infarct site in reperfused patients who received intravenous urokinase within 2 hours of symptom onset and after 2 hours but within 3 hours of symptom onset, and in nonreperfused patients. Negative values represent hypokinesis. (From ref 89)

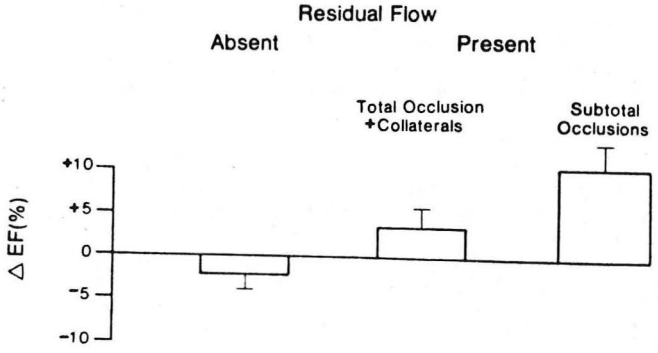

FIGURE 13 Mean changes in left ventricular ejection fraction from hospital admission to discharge in 40 patients who either received no thrombolytic (N=32) or had persistent occlusion after streptokinase (N=8). Ejection fraction improved in those with residual flow from collaterals or subtotal occlusions compared to those without residual flow ($p<0.01$). (From ref 98)

zation to maximize the beneficial effect of reperfusion in this subgroup of patients is undetermined.

6) No improvement in function is seen in those with reocclusion after initially successful reperfusion (109,138).

Right Ventricular Function The effect of reperfusion on right ventricular function in patients with right ventricular infarction complicating inferior infarction has been less well studied. Right ventricular dysfunction often spontaneously improves in conventionally treated patients. Verani et al (139) found the same degree of improvement in right ventricular function in patients without reperfusion as in those with reperfusion.

Mural Thrombus Formation Thrombolytic therapy might reduce mural thrombus formation by either a reduction in infarct size or by a direct fibrinolytic effect on the acutely formed thrombus. Since heparin itself may decrease thrombus formation after myocardial infarction, it is difficult to separate the effects of streptokinase from those of subsequent heparin therapy. Eigler et al (140) noted thrombus formation in 1 of 12 patients with anterior myocardial infarction treated with streptokinase compared with 7 of 10 nonrandomized controls who had not received anticoagulation. In contrast, Stratton et al (141) detected a left ventricular thrombus in 5 of 45 streptokinase patients and in none of 38 randomized control patients 8 weeks after infarction. All patients had received anticoagulant therapy in the hospital, and a similar number in each group continued such therapy after hospital discharge. Thus, streptokinase therapy may not decrease the incidence of mural thrombus formation over that which can be achieved by anticoagulant treatment alone.

H. Reperfusion and Mortality in Uncontrolled Trials

Several uncontrolled reports have suggested that successfully reperfused patients have a lower mortality rate than nonreperfused patients after intracoronary streptokinase. Kennedy et al (80) compared hospital mortality rates for 1029 patients entered into a registry. Overall reperfusion rate was 71%. Mortality rates were lower in reperfused than nonreperfused patients overall, and lower in reperfused patients with shock, anterior myocardial infarction, and age 60-69 years (Table 11). There was no uniform protocol for treatment or follow-up.

TABLE 11 Mortality Rates From the Society for Cardiac Angiography Report on Intracoronary Streptokinase Hospital Mortality Rates

	n	Reperfused	Not reperfused	p
Overall	1029	5.5%	14.7%	<0.0001
Age 60-69	309	6.8%	25.9%	<0.0001
Shock	44	42.1%	84.0%	<0.0001
Anterior MI	448	8.4%	21.2%	0.0002
Age <60	593	2.5%	5.2%	NS
Stable	884	3.8%	8.1%	NS
Inferior MI	424	2.9%	6.8%	NS

Other registry reports (85,142) and uncontrolled trials (128,143-145) have also described lower mortality rates in reperfused vs nonreperfused patients, especially in those with initially depressed left ventricular function.

VI. Controlled Trials

The studies discussed above demonstrate evidence of myocardial salvage and reduced mortality when successfully reperfused patients are compared with nonreperfused patients. There are obvious limitations in evaluating the efficacy of a therapy by comparing successfully and unsuccessfully treated patients. First, it is possible that patients with a good prognosis with conventional treatment are also those in whom reperfusion can most easily be achieved. For example, reperfusion may be more likely in patients who would have had spontaneous thrombolysis (and, therefore, an improvement in ventricular function) had they not been treated. While it is impossible to prove or disprove this notion from available data, it is interesting to note that reperfusion occurred in only 23 (40%) of 57 patients with cardiogenic shock in 2 series (80,109). Alternately, those most likely to reperfuse could have smaller areas of myocardium at risk than those who fail to reperfuse. While improbable, this also cannot be disproved for existing data. Second, all patients are exposed to the risk of treatment, whereas only those who reperfuse receive the benefit of treatment. By comparing successfully and unsuccessfully treated patients, adverse effects of therapy cannot be assessed. Third, salvaged myocardium supplied by a vessel with proven thrombotic potential may provide the substrate for recurrent ischemia, ventricular arrhythmias, and sudden death from reinfarction. It is not possible, therefore, to assume that treatment with thrombolytic agents is beneficial simply because timely reperfusion is beneficial.

TABLE 11 Assessment of Left Ventricular Function - Controlled, Randomized Trials of Intracoronary Streptokinase (see Table 12 for references)

Author	SK	Control	Time (hrs)	Rate of recanal.	ΔEF SK	ΔEF Control	p value
Anderson[1]	24	26	4.0	75%	+3.9	-3.0	<0.01
Leiboff[2]	20	17	4.0	68%	-2.8	-0.4	NS
Kennedy[3]	134	116	4.6	68%	+1.0	+1.0	NS
Khaja	20	20	5.4	60%	0	+1	NS
Raizner[4]	22	16	5.6	72%	+3	+3	NS
Rentrop	23	24	5.9	74%	+2.1	-1.4	NS
OVERALL	**243**	**219**	**4.8**	**69%**	**+1.2**	**+0.3**	

[1] Improvement in regional wall motion also demonstrated.
[2] ΔEF +7.3 (p=0.05) in untreated pts with subtotal occlusions.
[3] No difference in global or regional LV function between SK and control patients at 2 mos.
[4] Incomplete obstruction present initially in 45% of SK pts. Reperfusion rate was 50% (8/16) in those with complete obstruction.

TABLE 12 Assessment of Mortality - Controlled, Randomized Trials of Intracoronary Streptokinase

Author (ref)	Mean duration of F/U	Mortality rates SK	Control	p value
Anderson (71)	In-hosp	1/24	4/26	NS
Raizner (147)	In-hosp	4/29	2/35	NS
Rentrop (90)	6 mos	13/62	6/61	NS
Khaja (157)	9.6 mos	1/20	4/20	NS
Simoons[1]	10 mos	10/86	11/87	NS
Leiboff (95)	11 mos	4/22	2/18	NS
Kennedy[2] (148)	12 mos	11/134	17/116	.10
OVERALL (average time to SK 4.8 hr)		**44/377 11.6%**	**46/363 12.6%**	

[1] abstract
[2] 30 day mortality rates were 5/134 SK vs 13/116 control (p=0.02)

A. Intracoronary Streptokinase

There are currently 6 published randomized trials comparing treated and control patients after intracoronary streptokinase (Table 11, Table 12). In contrast to uncontrolled comparisons of reperfused and nonreperfused patients, the results of these randomized trials fail to consistently demonstrate a significant improvement in left ventricular function. While none have sufficient size and statistical power to accurately assess the effect of intracoronary streptokinase on mortality, a beneficial effect is not strongly suggested by the pooled results (Table 12).

Anderson et al (71) found a significant improvement in left ventricular ejection fraction and regional function in 24 treated patients compared to 26 controls. Follow-up after 1.5 years suggests sustained clinical benefit in the streptokinase treated patients (146). This remains the only one of the studies that demonstrates an improvement in ejection fraction in the treated patients. In the study by Raizner and associates (147), changes in left ventricular ejection fraction were not different in control and treated patients, but regional function in the infarct zone (measured by radionuclide ventriculography; p=0.027) improved modestly in the streptokinase treated patients. The largest of the trials, the Western Washington Trial (148-150), demonstrated a lower mortality rate in the streptokinase patients vs controls at 3 and 6 months. However, this apparent survival benefit was no longer statistically significant at 12 months, primarily due to late deaths in those patients with only partial reperfusion (Figures 14 and 15). If early reperfusion prolongs survival after acute myocardial infarction, it most likely does so by improving ventricular function and thereby decreasing death due to pump failure. Despite an apparent reduction in early mortality, no difference in either ventricular function or infarct size (by thallium scintigraphy) between the treated and control patients was found (Figure 16) (150).

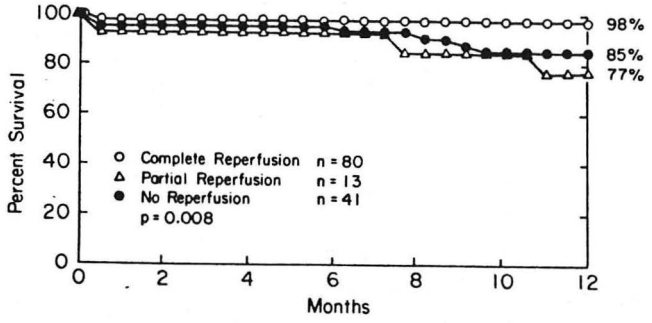

FIGURE 14 One year survival curves for the streptokinase and control groups in the Western Washington Trial. Difference in mortality which was seen at 6 months is no longer statistically significant at 1 year. (From ref 149)

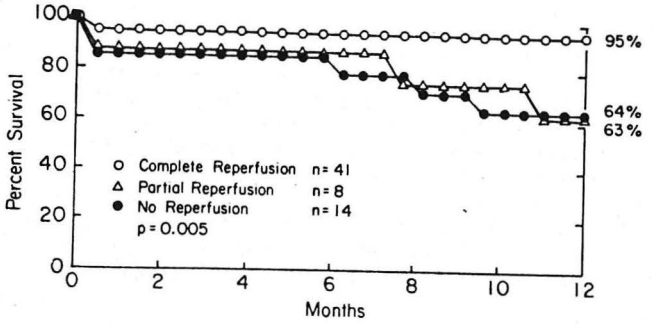

FIGURE 15 One year survival curves for the 63 patients with anterior MI in the streptokinase group, according to reperfusion status. Survival is higher in those with complete reperfusion than in those with incomplete or no reperfusion. (From ref 149)

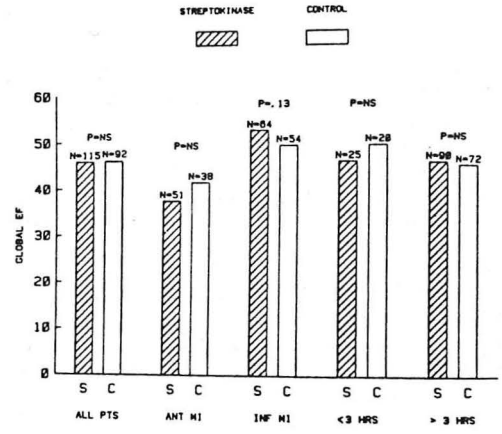

FIGURE 16 Left ventricular ejection fraction for all patients in the Western Washington Trial and for those with anterior infarction (ANT MI), and inferior infarction (INF MI), and those treated before and after 3 hours from onset of pain. There were no significant differences between streptokinase-treated and control patients in any group. (From ref 150)

If reperfusion is beneficial, why have controlled trials failed to convincingly demonstrate an improvement in left ventricular function or a reduction in mortality? Possible explanation include:

1) To late. It is likely that initiating treatment at a mean of 4.0 to 5.9 hours after the onset of infarction is too late to salvage myocardium.

2) Residual stenosis and reocclusion. As discussed earlier, reocclusion negates any beneficial effects of thrombolysis. Partial reperfusion with a high grade residual stenosis may limit recovery of function after successful reperfusion (106) and adversely affect long-term survival. In the Western Washington Trial (149), 12-month survival of patients with partial reperfusion and a high-grade residual stenosis was significantly lower than that of patients with complete reperfusion and similar to the survival rate of nonreperfused patients (Figure 15). This detrimental effect of partial reperfusion on survival was even more apparent in those with anterior myocardial infarction. In the study by Leiboff et al (95), reocclusion was documented angiographically in 5 (45%) of 11 reperfused patients who had repeat catheterization.

3) Failure to examine regional function. Leiboff et al (95) examined only global ejection fraction and, thus, may have overlooked a beneficial effect on regional function.

4) Inadequate sample size. Assuming a 10% in-hospital mortality rate in the control patients, demonstration of a 25% reduction in mortality to 7.5% would require 1500 patients in each group (power of study = 0.8). The above studies also lacked sufficient size to define subgroups of patients who benefited from treatment.

5) Unanticipated detrimental effect of either streptokinase or reperfusion, such as delayed healing or extension of the infarction from intramyocardial hemorrhage or increased arrhythmias from salvaged or hemorrhagic myocardium. There is no convincing evidence that hemorrhage into the area of infarction expands infarct size or interferes significantly with infarct healing or that ventricular arrhythmias occur more frequently in salvaged or hemorrhagic myocardium *after* the initial period of reperfusion (146).

Although not yet proven, patients most likely to benefit from thrombolytic therapy include (a) those treated early (within 3 hours), (b) high risk patients as defined by the presence of anterior myocardial infarction, previous myocardial infarction, heart failure, hypotension, age over 60 years, or shock, (c) those without reocclusion, and (d) those without a high-grade residual stenosis.

B. Intravenous Streptokinase

There are no published, randomized, controlled trials evaluating the effect of high-dose, brief-infusion intravenous streptokinase on ventricular function or mortality. Such trials are being conducted in this country and in Europe, but results are not yet available. The drug has not received Food and Drug Administration approval for intravenous use in acute myocardial infarction.

VII. New Approaches to Thrombolytic Therapy

Tissue plasminogen activator (r-tPA), currently being produced using recombinant DNA technology, has several potential advantages as a thrombolytic agent. First, it is relatively "clot-selective", producing local thrombolysis with far less systemic lytic effect than streptokinase. Second, it is nonantigenic and causes no adverse reactions with rapid intravenous infusion. Allergic reactions have not occurred with initial administration. Repeated administration should be possible without producing an antibody response. Finally, it has a very brief duration of action (151), theoretically allowing the thrombolytic effect to be quickly "turned off" if bleeding occurs or invasive procedures are required. Three recently completed controlled trials have confirmed the ability of r-tPA to achieve thrombolysis.

Phase I of the Thrombolysis in Myocardial Infarction (TIMI) trial (69) is a double-blind, randomized comparison of intravenous r-tPA and streptokinase. Two hundred and forty patients with coronary occlusion randomly received either r-tPA (80 mg over 3 hr) or streptokinase (1.5 million units over 1 hr) an average of 4.8 hours after the onset of pain. All patients had coronary angiography performed at baseline and every 15 minutes after the start of treatment for a total of 90 minutes. Reperfusion occurred in 78 (66%) of 118 r-tPA patients and 44 (36%) of 122 streptokinase patients ($p<0.001$). Mean time to reperfusion was nearly identical for the 2 drugs (50 minutes).

Bleeding complications were frequent but were limited to the arterial puncture site in the vast majority of patients, all of whom were fully anticoagulated after catheterization. There was no difference in the incidence of bleeding complications requiring transfusion in the 2 treatment groups. No adverse

effects during r-tPA administration were noted. Systemic lytic effects were produced by this dose of r-tPA, but were much less marked marked than those produced by streptokinase.

	Pre	Post	2 hr	24 hr
Fibrinogen (mg%)				
tPA	365	275	243	320
SK	371	160	157	286
Plasminogen (%)				
tPA	101	37	43	60
SK	99	15	16	42
FDP (ug/ml)				
tPA	3	89	93	26
SK	5	258	241	75

Angiographically documented reocclusion occurred in 31% of the r-tPA and 26% of the streptokinase patients with initially successful reperfusion. Thus, when administered at an average of 4.8 hours after the onset of symptoms, intravenous r-tPA is nearly twice as effective as intravenous streptokinase in opening thrombosed coronary arteries.

Similar findings were reported by the European Cooperative Study Group for Recombinant Tissue Plasminogen Activator (152). Patients in this trial were treated much sooner after the onset of symptoms (average 2.8 hr) and underwent catheterization and angiography immediately *after* treatment. Patent vessels at angiography were found in 43 (70%) of the r-tPA patients and 34 (55%) of the 62 streptokinase patients. Fibrinogen level fell to 61% of baseline in the r-tPA patients vs 12% of baseline in the streptokinase patients and fell to below 50 mg% in 3 of 60 r-tPA patients vs 54 of 62 streptokinase patients. In a randomized, placebo controlled trial, Collen and associates (153) observed angiographic reperfusion in 25 (75%) of 33 patients receiving 0.5 to 0.75 mg/kg of r-tPA intravenously. None of the patients had a fall in fibrinogen level to below 100 mg%. From these trials, it appears that *intravenous* r-tPA is approximately as effective at producing thrombolysis as intracoronary streptokinase.

VIII. Future Research Directions

Future research efforts to define the clinical value of thrombolytic therapy in acute myocardial infarction will likely emphasize the following areas:

1) Earlier treatment with intravenous clot-selective agents. Coronary angiography's role in future clinical trials will likely be limited to identifying patients at high risk of reocclusion and will be performed after treatment.

2) Attempts to reduce the rate of reocclusion. The optimal antithrombotic regimen after successful treatment must be defined. Further efforts to identify characteristics of patients at high risk of reocclusion are needed. The role of early PTCA or bypass surgery in those at high risk of reocclusion and those with only partial reperfusion will be assessed.

3) Determination of the ability of the early administration of nonthrombolytic pharmacologic agents to enhance myocardial salvage and hasten recovery of ventricular function after reperfusion. In the dog, the administration of propranolol and diltiazem prior to reperfusion causes a dramatic recovery of systolic and diastolic function in areas of ischemia compared to reperfusion alone (154).

4) Continued development of more effective clot-selective thrombolytic agents.

5) Large-scale, randomized, controlled trials to assess the impact of thrombolytic therapy on mortality and quality of life. There are few advances in medicine that so dramatically alter the natural history of a common disease process that they can be legitimately accepted into clinical practice without having efficacy proven in a randomized trial. Were such a trial to be performed, the benefit of the new treatment would quickly become apparent. It is not evident from controlled trials so far published that the value of thrombolytic therapy in acute myocardial infarction has been established. While there is substantial data from uncontrolled trials that *reperfusion* is beneficial, only from large-scale properly controlled trials that the true benefit of *thrombolytic therapy* be assessed.

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