

FEATURES

Thrombolytic therapy in patients with acute myocardial infarction

K. PETER RENTROP, M.D.

THROMBOLYTIC THERAPY in patients with acute myocardial infarction has received renewed attention since intracoronary infusion of streptokinase has been introduced into clinical practice.

Efficacy of intracoronary infusion of streptokinase. Intracoronary infusion of streptokinase results in recanalization of approximately 75% of completely obstructed infarct-related vessels^{1, 2} (table 1). Modifications of the technique, such as subselective infusion of streptokinase via small catheters, increased infusion rate, or injection of a bolus at the initiation of therapy, have not resulted in reproducibly higher recanalization rates³⁻¹² (table 1). The influence of intracoronary infusion of streptokinase on ejection fraction has been assessed in five controlled trials^{3, 4, 7, 8, 12} (table 2), but only Anderson et al.⁴ found a significant improvement in left ventricular function from the acute to the chronic stage of infarction in patients treated with streptokinase. Lack of functional improvement in the majority of trials has been attributed to a delay of more than 4 hr between onset of infarction and commencement of therapy. However, Leiboff et al.⁸ found no improvement of function in patients treated with streptokinase, although therapy was initiated within 4 hr. This negative result may be related to the relatively high reocclusion rate in Leiboff's study. The published data suggest, but do not prove, that sustained early reperfusion may be associated with improvement of left ventricular function. Additionally, reperfusion after more than 4 hr may be beneficial in some subgroups of patients, as suggested by the functional improvement associated with infusion of streptokinase after 6 hr in our trial, although this finding was not statistically significant.¹² To test these hypotheses, a much larger trial is being conducted.

Statistically significant improvement in mortality after infusion of streptokinase was reported in only one trial.⁷ The mechanism of improved survival in this study remains unclear, since there was no parallel increase in ejection fraction. Furberg¹³ pooled the survival data of eight prospective randomized trials, including the one that showed significant improvement, and calculated a mortality of 11.0% in 382 patients treated with intracoronary infusion of streptokinase compared with 12.4% in 364 control patients; this difference was not statistically significant. The influence of intracoronary infusion of streptokinase on mortality remains unknown.

Complications associated with intracoronary infusion of streptokinase. Because of the high complication rates inherent in acute myocardial infarction, it is difficult to pinpoint those complications that are the result of early intervention. The intervention-related complication rates can be assessed only by randomized trials that include a control group not subjected to angiographic examination during the acute stage of infarction. In such a trial, fatal cardiogenic shock occurred in two patients as a result of dislodgment of clot caused by manipulation of the catheter from the infarct-related left anterior descending artery to the circumflex artery.¹⁴ In two additional patients, fatal pump failure after injection of dye was attributed to the negative inotropic properties of the contrast medium. Furthermore, recanalization of the right coronary artery was frequently associated with hypotension, bradycardia, and conduction delays caused by activation of the Bezold-Jarisch reflex.

Reocclusion of coronary arteries after recanalization by intracoronary infusion of streptokinase has been associated with reinfarction and death.¹⁵ It has been suggested that patency can be maintained by anticoagulation with heparin.^{5, 10} Heparinization is associated with a risk of bleeding, however, which may be increased if infusion of streptokinase has resulted in a drop of fibrinogen concentration

From the Division of Cardiology, Mount Sinai Medical Center, New York.

Address for correspondence: Peter Rentrop, M.D., Director of Interventional Cardiology, The Mount Sinai Medical Center, One Gustav L. Levy Pl., Annenberg 8-26, New York, NY 10029.

TABLE 1

Recanalization rates of total coronary obstruction with intracoronary infusion of streptokinase in 10 studies

Study	SK dose (U/min)	Bolus ^A (U SK)	Sub- selective ^B	Recanalization rate ^C	
				n/n	%
Khaja et al. ³	5,000	15,000	—	12/20	60
Anderson et al. ⁴	5,000	—	—	15/20	75
Ganz et al. ⁵	4,000	—	Yes	17/18	94
Serruys et al. ⁶	4,000	—	Yes	30/36	83
Kennedy ⁷	4,000	—	Yes	73/108	68
Leiboff et al. ⁸	2,000–4,000	—	—	15/22	68
Mathey et al. ⁹	2,000	Plasminogen	—	39/39	77
Rentrop et al. ¹⁰	2,000	10,000	—	17/20	85
Smalling et al. ¹¹	2,000	10,000	—	73/100	73
Rentrop et al. ¹²	2,000	—	—	32/43	74
				Σ314/426	74

SK = streptokinase.

^AApplication of a bolus of streptokinase into the infarct-related vessel before infusion.^BSubselective infusion of streptokinase via special catheter into the infarct-related vessel.^CRecanalization rate documented by sequential angiography during infusion of streptokinase.

below 100 mg/dl.¹⁸ Angioplasty^{15, 16} and coronary bypass surgery¹⁰ have been performed after intracoronary infusion of streptokinase to maintain and augment flow to the reperfused myocardium.¹⁵ These procedures may be particularly beneficial in patients with more than 90% residual stenosis and a large segment of jeopardized myocardium.¹⁵ Although they can be performed with minimal risk shortly after infusion of streptokinase, the optimal timing of their use has not been established.

Intracoronary infusion of urokinase. Urokinase has been infused into infarct-related coronary arteries at rates between 2000 and 24,000 U/min, resulting in recanalization in 62% to 94% of the vessels.^{17–19} A relationship between the dosage of urokinase and recanalization rates has not been found. In a randomized study, Tennant et al.¹⁸ found that intracoronary infusions of urokinase and streptokinase were of compara-

ble efficacy in achieving recanalization. However, infusion of urokinase was associated with a significantly less marked reduction in fibrinogen concentration and significantly fewer bleeding complications.

Value and limitations of intracoronary thrombolytic therapy. As an important research tool, intracoronary infusion of thrombolytic agents has enhanced our understanding of the pathogenesis of acute myocardial infarction. In addition, it facilitates the analysis of benefits and limitations of reperfusion. In clinical practice, however, the value of this method is limited by several factors. Since the majority of hospitals are not equipped with cardiac catheterization laboratories, and the existing laboratories are usually not sufficiently staffed to perform intracoronary infusions of streptokinase at all times, substantial investments would be necessary to make this therapy available to all patients with acute myocardial infarction. Where such facilities

TABLE 2

Change in ejection fraction after intracoronary infusion of streptokinase in five controlled clinical trials

Study	IC SK (n)	Control (n)	Time to infusion (hr) ^A	Recana- lization rate (%) ^B	Reoc- clusion (%) ^C	ΔEF IC SK (%)	ΔEF control (%)	p value
Anderson et al. ⁴	24	26	4.00 ± 0.75	75	0	3.9 ± 4.6	−3.0 ± 8.4	<.001
Leiboff et al. ⁸	20	17	4.03	68	45	−2.8	−0.8	NS
Kennedy et al. ⁷	134	116	4.57 ± 2.15	68		1.0	0	NS
Khaja et al. ³	20	20	5.40 ± 1.50	60		3.0	2.0	NS
Rentrop et al. ¹²	23	24	5.90 ± 2.80	74	17	2.1 ± 1.1	−1.4 ± 9.5	NS

ΔEF = change in ejection fraction; IC SK = streptokinase group; control = control group.

^ATime interval from onset of infarction to infusion of streptokinase.^BRecanalization rate documented by sequential angiography during infusion of streptokinase.^CReocclusion rate as assessed by repeat angiography in the chronic stage of infarction.

do exist, initiation of therapy is delayed while the cardiac catheterization laboratory is prepared and baseline angiographic studies are initiated.^{20, 21}

Intravenous infusion of streptokinase. The influence of prolonged intravenous infusion of streptokinase on mortality was assessed in several controlled trials during the 1960s and 1970s.²² However, the recanalization rates associated with the dosage schedules used in these trials were not studied. After the introduction of intracoronary infusion of streptokinase, the concept of a short-term, high-dose intravenous infusion of streptokinase was developed. Pooled data of five studies in which intravenous infusion of streptokinase was preceded by baseline angiographic studies show a recanalization rate of 45% with a range of 10% to 62%²³⁻²⁷ (table 3). There is no relationship between the dose of streptokinase and recanalization rates. Several authors attempted to determine recanalization rates on the basis of indirect parameters without performing baseline angiographic studies. The most commonly used indirect parameters were patency of the infarct-related vessel at angiographic examination performed with some delay after the intervention, and an early peak of the creatine kinase level. Pooled data of five such studies show a recanalization rate of 84% with a range of 73% to 96%^{20, 21, 25, 28, 29} (table 4). These recanalization rates are much higher than those found in studies that carried out preintervention angiographic examination.

This discrepancy may be explained by two factors. First, in most studies documentation of recanalization by sequential angiographic studies is limited to approximately 1 hr. Since it is likely that recanalization can occur beyond this time frame, sequential angiographic studies probably underestimate recanalization rates. On the other hand, experimental and clinical

TABLE 3
Recanalization rates with intravenous infusion of streptokinase (preintervention angiograms)

Study	SK dose (U)	Recanalization rates ^A	
		n/n	%
Roger et al. ²³	500,000	1/10	10
Saltups et al. ²⁴	500,000	3/10	30
Schroeder et al. ²⁵	500,000	11/21	52
Alderman et al. ²⁶	725,000	8/13	62
Spann et al. ²⁷	850,000	6/13	46
Roger et al. ²³	1 million	7/16	44
Spann et al. ²⁷	1.5 million	15/31	48
		Σ51/144	45

SK = streptokinase.

^ARecanalization rates documented by sequential angiography during intravenous infusion of streptokinase.

TABLE 4
Long-term patency rates with intravenous infusion of streptokinase (preintervention angiography not done)

Study	SK dose (U)	Patency rates ^A	
		n/n	%
Ganz et al. ²⁸	750,000	65/68	96
Olson et al. ²⁹	700,000	22/26	85
Schroeder et al. ²⁵	500,000–1.5 million	42/52	84
Taylor et al. ²¹	700,000–1.3 million	99/121	82
Anderson et al. ²⁰	750,000–1.5 million	16/22	73
		Σ244/289	84

SK = streptokinase.

^APatency rates at angiography after intervention.

data suggest that the value of recanalization in salvaging myocardium decreases rapidly with time.¹ Second, preintervention angiographic studies revealed incomplete obstruction of the infarct-related vessel in 5% to 33% of the patients (table 5); these patients were excluded from the analysis of recanalization rates. Such a differentiation is not possible without the use of preintervention angiographic evaluation. Early peaking of creatine kinase levels does not reliably identify streptokinase-induced recanalization, since creatine kinase levels also peak early in patients with incomplete coronary obstruction at baseline angiographic examination.¹² Therefore, in the absence of preintervention angiograms, recanalization rates are likely to be overestimated. Complications associated with intravenous infusion of streptokinase are primarily related to bleeding. The reported incidence of bleeding with high-dose, short-term intravenous infusion of streptokinase varies between 0% and 21%.^{20, 21, 23, 25, 26, 28} This variation may be related to relatively small sample size in the studies, lack of a standard definition of complica-

TABLE 5
Incidence of incomplete obstruction of infarct-related vessel at preintervention angiography in 12 studies

Study	n/n	%
Rentrop et al. ¹²	30/91	33
Rentrop et al. ¹⁰	9/29	31
Hartzler et al. ¹⁶	12/41	29
Tennant et al. ¹⁸	37/139	27
Smalling et al. ¹¹	36/136	27
Leiboff et al. ⁸	12/55	22
Serruys et al. ¹⁴	15/83	18
Khaja et al. ³	9/54	17
Anderson et al. ⁴	4/24	17
Kennedy et al. ⁷	19/134	14
Ganz et al. ⁸	2/20	10
Mathey et al. ⁹	2/41	5
	Σ187/847	22

tions, and investigator bias. To date, the risk-benefit ratio of high-dose, short-term intravenous infusion of streptokinase has not been assessed in a large controlled trial.

Second-generation thrombolytic agents. Recently, clinical testing of acylated plasmin streptokinase and recombinant tissue-type plasminogen activator (rt-PA) has begun. These substances possess some degree of clot selectivity; that is, they can effect thrombolysis without inducing a lytic state.³⁰ More importantly, a review of angiographic studies reveals that the recanalization rates associated with intravenous application of these drugs are considerably higher than recanalization rates achieved by intravenous infusion of streptokinase and are comparable to the results reported with intracoronary infusion of streptokinase.³¹⁻³³ A trial directly comparing recanalization rates in patients treated with intravenous infusion of streptokinase and those treated with intravenous infusion of rt-PA is in progress. If the results confirm that recanalization rates are significantly higher in the rt-PA group, additional trials will be necessary to assess the efficacy of second-generation thrombolytic agents in preserving left ventricular function and reducing infarct-related mortality.

References

1. Rentrop P, Smith H, Painter L, Holt J: Changes in left ventricular ejection fraction after intracoronary thrombolytic therapy. *Circulation* **68**(suppl I): I-55, 1983
2. Kennedy JW and the Registry Committee, Society for Cardiac Angiography: Intracoronary streptokinase in acute MI: report from the society for cardiac angiography registry. *Circulation* **68**(suppl III): III-121, 1983
3. Khaja F, Walton JA, Brymer JF, Lo E, Osterberger L, O'Neill WW, Colfer HT, Weiss R, Lee T, Kurian T, Goldberg AD, Pitt B, Goldstein S: Intracoronary fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* **303**: 1304, 1983
4. Anderson JL, Marshall HW, Bray BE, Lutz JR, Frederick PR, Yanowitz FG, Datz FL, Klausner SC, Hagan AD: A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. *N Engl J Med* **308**: 1312, 1983
5. Ganz W, Buchbinder N, Marcus H, Mondkar A, Maddahi J, Charuzi Y, O'Connor L, Shell W, Fishbein M, Kass R, Miyamoto A, Swan HJC: Intracoronary thrombolysis in evolving myocardial infarction. *Am Heart J* **101**: 4, 1981
6. Serruys PW, Van Den Brand M, Hooghoudt TEH, Simmons ML, Fioretti P, Ruiter J, Fels PW, Hugenholtz PG: Coronary recanalization in acute myocardial infarction: immediate results and potential risks. *Eur Heart J* **3**: 404, 1982
7. Kennedy JW, Ritchie JL, Davis KB, Fritz JK: Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* **309**: 1477, 1983
8. Leiboff RH, Katz RJ, Wasserman AG, Bren GB, Schwartz H, Varghese PJ, Ross AM: A randomized, angiographically controlled trial of intracoronary streptokinase in acute myocardial infarction. *Am J Cardiol* **53**: 404, 1984
9. Mathey DG, Kuck KH, Tilsner V, Kribber HJ, Bleifeld W: Non-surgical coronary artery recanalization in acute transmural myocardial infarction. *Circulation* **63**: 489, 1981
10. Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K: Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. *Circulation* **63**: 307, 1981
11. Smalling RW, Fuentes F, Matthews MW, Freund GC, Hicks CH, Reduto LA, Walker WE, Sterling RP, Gould KL: Sustained improvement in left ventricular function and mortality by intracoronary streptokinase administration during evolving myocardial infarction. *Circulation* **68**: 131, 1983
12. Rentrop KP, Feit F, Blanke H, Stecy P, Schneider R, Rey M, Horowitz S, Goldman M, Karsch K, Meilman H, Cohen M, Siegel S, Sanger J, Slater J, Gorlin R, Fox A, Fagerstrom R, Calhoun WF: Effects of intracoronary streptokinase and intracoronary nitroglycerine infusion on coronary angiographic patterns and mortality in patients with acute myocardial infarction. *N Engl J Med* **311**: 1464, 1984
13. Furberg C: Clinical value of intracoronary streptokinase. *Am J Cardiol* **53**: 626, 1984
14. Serruys PW, Van Den Brand M, Hooghoudt TEH, Simoons ML, Fioretti P, Ruiter J, Fels PW, Hugenholtz PG: Coronary recanalization in acute myocardial infarction: immediate results and potential risks. *Eur Heart J* **3**: 404, 1982
15. Gold HK, Cowley MJ, Palacios IF, Vetrovec GW, Akins CW, Block PC, Leinbach RC: Combined intracoronary streptokinase infusion and coronary angioplasty during acute myocardial infarction. *Am J Cardiol* **53**: 122C, 1984
16. Hartzler GO, Rutherford BD, McConahay DR, Johnson WL, McCallister BD, Gura GM, Conn RC, Crockett JE: Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J* **106**: 965, 1983
17. Cernigliaro C, Sansa M, Campi A, Bongo AS, Rossi P: Efficacy of intracoronary urokinase in acute myocardial infarction. *Circulation* **68**(suppl III): III-407, 1983
18. Tennant SN, Dixon J, Venable TC, Page HL, Roach A, Kaiser AB, Frederiksen R, Tacogue L, Kaplan P, Babu NS, Anderson EE, Wooten E, Jennings HJS, Breinig J, Cambell WB: Intracoronary thrombolysis in patients with acute myocardial infarction: comparison of the efficacy of urokinase with streptokinase. *Circulation* **69**: 756, 1984
19. Yasuno M, Saito Y, Ishida M, Suzuki K, Endo S, Takahashi M: Effects of percutaneous transluminal coronary angioplasty: intracoronary thrombolysis with urokinase in acute myocardial infarction. *Am J Cardiol* **53**: 1217, 1984
20. Anderson JL, Marshall HW, Askins JC, Lutz JR, Sorensen SG, Menlove RL, Yanowitz FG, Hagan AD: A randomized trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction. *Circulation* **70**: 606, 1984
21. Taylor GJ, Mikell FL, Moses HW, Dove JT, Batchelder JE, Thull A, Hansen S, Wellons HA, Schneider J: Intravenous versus intracoronary streptokinase therapy for acute myocardial infarction in community hospitals. *Am J Cardiol* **54**: 256, 1984
22. Stamfer MJ, Goldhaber SZ, Yusuf S, Peto R, Hennekens CH: Effect of intravenous streptokinase on acute myocardial infarction: pooled results from randomized trials. *N Engl J Med* **307**: 1180, 1982
23. Roger WJ, Mantle JA, Hood WP, Baxley WA, Whitlow PL, Reeves RC, Soto B: Prospective randomized trial of intravenous and intracoronary streptokinase in acute myocardial infarction. *Circulation* **68**: 1051, 1983
24. Saltups A, Boxal J, Ho B: Intracoronary versus intravenous streptokinase in acute myocardial infarction. *Circulation* **68**(suppl III): III-119, 1983
25. Schroeder R, Biamino G, Von Leitner ER, Linderer T, Brueggemann T, Heitz J, Voehringer HF, Wegscheider K: Intravenous short-term infusion of streptokinase in acute myocardial infarction. *Circulation* **67**: 536, 1983
26. Alderman EL, Jutzy KR, Berte LE, Miller RG, Friedman JP, Creger WP, Eliastam M: Randomized comparison of intravenous versus intracoronary streptokinase for myocardial infarction. *Am J Cardiol* **54**: 14, 1984
27. Spann JF, Sherry S, Carabello BA, Denenberg BS, Mann RH, McCann WD, Gault JH, Gentzler RD, Belber AD, Maurer AH, Cooper EM: Coronary thrombolysis by intravenous streptokinase in acute myocardial infarction: acute and follow-up studies. *Am J Cardiol* **53**: 655, 1984
28. Ganz W, Gefit I, Shah PK, Lew AS, Rodriguez L, Weiss T, Mad-

- dahi J, Berman DS, Charuzi Y, Swan HJC: Intravenous streptokinase in evolving acute myocardial infarction. *Am J Cardiol* **53**: 1209, 1984
29. Olson HG, Lyons KP, Butman S, Pifers KM, Gardin JM: A randomized controlled trial of intravenous streptokinase in acute myocardial infarction. *Circulation* **70**(suppl II): II-155, 1984
 30. Van De Werf F, Ludbrook PA, Bergman SR, Tiefenbrunn AJ, Fox KAA, De Geest H, Verstraete M, Collen D, Sobel B: Coronary thrombolysis with tissue-type plasminogen activator in patients with evolving myocardial infarction. *N Engl J Med* **310**: 609, 1984
 31. Marder VJ, Rothbard RL, Fitzpatrick PG, Francis CW, Smith EK, Rogal GJ: Dose-response study of intravenous acylated streptokinase: plasmin complex (BRL-26921) in coronary artery thrombolysis. *Circulation* **70**(suppl II): II-29, 1984
 32. Van Rey FJ, Bonnier HJ, Michels HR, Gamal MIE, Hoffman HJ: Efficacy and safety of BRL 26921, a new fibrinolytic agent for intravenous administration in acute myocardial infarction. *Circulation* **70**(suppl II): II-330, 1984
 33. Collen D, Topol EJ, Tiefenbrunn AJ, Gold HK, Weisfeldt ML, Sobel BE, Leinbach RC, Brinker JA, Ludbrook PA, Yasuda I, Bulkley BH, Robison AK, Hutter AM Jr, Bell WR, Spadaro JJ Jr, Khaw BA, Grossbard EB: Coronary thrombolysis with recombinant human tissue-type plasminogen activator. *Circulation* **70**: 1012, 1984