

**THERAPY AND PREVENTION
THROMBOLYSIS**

Sustained improvement in left ventricular function and mortality by intracoronary streptokinase administration during evolving myocardial infarction

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ABSTRACT One hundred eighty-eight patients with acute myocardial infarction were studied prospectively from August 1980 to September 1982. One hundred thirty-six of these patients were entered into an intracoronary streptokinase study after informed consent was obtained. The remaining 52 patients, who either met exclusion criteria for the study or refused to participate, served as a control group and were treated as those in the study group except that they did not undergo emergency cardiac catheterization. Left ventricular function was determined in both groups by gated radionuclide ejection fraction (EF) on admission to the hospital, at discharge, and 6 months after discharge. With successful reperfusion up to 18 hr after onset of chest pain, mean left ventricular function in the study group improved (EF $39 \pm 13\%$ on admission and $46 \pm 12\%$ at discharge; $p < .001$). Mean EF in control patients and those not achieving reperfusion did not change from admission to discharge. Mean EF at 6 month follow-up was not significantly different than at discharge in the study group or the control group. Total cardiac mortality in the control group was 19% compared with 10% in the study group ($p = .06$, NS). When patients admitted in pulmonary edema or shock (Killip class III or IV) were excluded from both groups, total cardiac mortality in the study group was significantly lower (4%) compared with in the control group (12.5%, $p < .05$). The administration of intracoronary streptokinase during evolving myocardial infarction up to 18 hr after onset of chest pain may result in decreased mortality and sustained improvement in left ventricular function.

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STANDARD CURRENT THERAPY for acute myocardial infarction entails prevention or treatment of complications secondary to evolving myocardial necrosis. Mortality during the first 30 days after acute myocardial infarction has been reported to be between 16% and 30% in large series and no definite decrease in this rate was noted between 1960 and 1975.¹⁻⁴ Although there is no universally accepted method for reducing myocardial damage, emergency aortocoronary bypass surgery has been reported to decrease mortality^{5,6} in certain patients. Intracoronary streptokinase

has been shown to be effective in lysing intracoronary thrombus and restoring blood supply to jeopardized myocardium during evolving myocardial infarction.⁷⁻¹⁰ In reports of small series of patients, reperfusion with intracoronary streptokinase has induced improvement in left ventricular function by the time of hospital discharge.⁹⁻¹³ This report presents the first substantial data from a single center on the effects of intracoronary streptokinase therapy on mortality and left ventricular function at long-term follow-up.

Methods

Patients. We prospectively studied 188 consecutive patients with acute myocardial infarction between August 1980 and September 1982. One hundred thirty-six of these patients were entered into the streptokinase therapy protocol after informed consent was obtained. Fifty-two patients who either met exclusion criteria or refused to participate served as controls and were studied by noninvasive methods. Exclusion criteria for the protocol included (1) greater than 18 hr elapsed time between onset of chest pain and evaluation for study entry, (2) history of

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streptokinase allergy, (3) recent (within 2 months) cerebrovascular accident, (4) recent (within 2 weeks) surgery, or (5) evidence of significant valvular disease. The characteristics of the patient population are listed in table 1 and specific reasons for entry of patients into the control group are listed in table 2.

Study protocol. The diagnosis of myocardial infarction was made by a typical history of prolonged severe chest pain combined with characteristic electrocardiographic findings of injury current in two adjacent leads with reciprocal ST changes. In all patients diagnostic creatine kinase elevation evolved, with positive MB fraction determinations. The patients were stabilized in the emergency room before being transported to the cardiac catheterization laboratory. All patients received intravenous lidocaine prophylactically.

In the first 17 patients studied, radionuclide and angiographic ejection fraction determinations were made immediately before and up to 4 hr after streptokinase administration. There was no significant change in ejection fraction after cardiac catheterization, even in patients who had successful thrombolysis.^{9, 10} In the remaining patients, thallium images were obtained before coronary arteriography with the intravenous injection of 1.5 to 2 mCi of thallium 201, as described previously.¹⁰

Thallium scintigraphy should not be immediately preceded by gated radionuclide ventriculography. We felt that thallium imaging would provide useful information on the success of reperfusion and would also aid in localization of the infarct-related artery. Since there was no change in left ventricular function from hospital admission thru postcatheterization in the initial 17 patients, we felt that it was reasonable to perform ventriculography after reperfusion thallium imaging on admission of patients to the coronary care unit.

The majority of patients underwent right heart catheterization with a balloon-tipped thermodilution catheter and insertion of a temporary transvenous pacemaker. Coronary arteriography was first performed in the presumed infarct-related artery. If a total occlusion was demonstrated in this artery intracoronary nitroglycerin was administered (100 to 300 μ g into the right coronary artery; 300 to 500 μ g into the left coronary artery). If reperfusion was not achieved by nitroglycerin administration, then a 10,000 U bolus of streptokinase (250,000 U of streptokinase dissolved in 100 ml normal saline; Streptase, Hoechst-Roussel Pharmaceuticals Inc.) was followed by a 2000 U/min infusion. Coronary arteriography was repeated every 15 min to assess progress in thrombolysis. The first 60 patients in the series (group A) underwent streptokinase infusion for a total period of 60 min or less and in 25 of these patients clot perforation by a 0.032 inch guidewire (Surgimed Inc.) was attempted. Thirteen of these patients also underwent subselective strepto-

TABLE 1
Patient population

	Study group	p	Control groups
No. of patients	136	—	52
Age (yr)	55 \pm 12	< .02 ^A	62 \pm 15
Average age of patients who died	68 \pm 9 (n = 17)	NS ^A	67 \pm 10 (n = 11)
Previous MI	20	NS	11
History of CHF	6	NS	5
Anterior MI	69	NS	29
Shock or pulmonary edema on admission	11	NS	4

MI = myocardial infarction; CHF = congestive heart failure.

^ABy student's t test; all others by chi-square statistic.

TABLE 2
Reasons for patient entry into control group

Reason	n
Diagnosis of MI > 18 hr from onset of chest pain	15
Refused study	10
Age > 70 (in first 60 patients evaluated)	10
History of recent CVA	8
Recent surgery	4
Valvular disease	2
Vascular access not achieved	2
Bleeding disorder	1
Total	52

MI = myocardial infarction; CVA = cerebrovascular accident.

kinase infusion by a small perfusion catheter (American Edwards or USCI) that was inserted through the larger angiographic catheter. After reevaluation of the protocol, the subsequent 76 patients (group B) underwent infusions up to 90 min long in an attempt to increase the reperfusion rate; intracoronary guidewire manipulation was not performed in patients in this group. Two patients in group B underwent subselective streptokinase administration after 90 min of ostial streptokinase failed to produce thrombolysis. No additional benefit was achieved by subselective streptokinase administration.

At the termination of streptokinase infusion, repeat coronary arteriography was performed in the infarct-related vessel and in the remaining coronary artery. If the patients were hemodynamically stable, a biplane left ventricular cineangiogram was performed with 20 to 40 ml of sodium diatrizoate (Hypaque 76, Winthrop). After completion of the procedure the arterial sheath, the pulmonary artery catheter, and the pacing catheter were left in place for a minimum of 24 hr. Delaying removal of these catheters reduced the incidence of local bleeding and hematoma formation after streptokinase administration. After return to the coronary care unit, delayed thallium redistribution images were obtained by a method described previously and analyzed quantitatively.¹⁰ Gated radionuclide left ventricular angiograms were then performed with ^{99m}Tc-labeled red blood cells, as described previously.^{9, 10} The radionuclide ejection fraction determinations were repeated 10 days after admission and at 6 months after hospital discharge. Processing of each ventriculogram was performed by two technicians independent of the catheterization team and of each other. Discordant results were resolved by consensus. As previously noted,⁹ ejection fraction values determined by gated ventriculography agreed well ($r = .92$) with those determined angiographically. Gated radionuclide ejection fraction variability in our laboratory was $\pm 6\%$ at the 95% confidence level.

Two patients received intra-aortic counterpulsation. In one, the indication was pulmonary edema and cardiogenic shock after successful reperfusion. The second patient had cardiogenic shock before initiation of thrombolytic therapy for an inferior myocardial infarction. Both patients survived and have been discharged from the hospital. No patients in the control group received intra-aortic counterpulsation. Due to previous reports of poor results with this treatment in the setting of myocardial infarction, we felt that it should be reserved for those patients who had a good chance of successful reperfusion and who were in cardiogenic shock.

Excluding emergency cardiac catheterization, the control group and the study group were comparable in their use of parenteral nitroglycerin, β -blockers, and calcium antagonists. In both groups gated radionuclide ejection fractions were determined within 24 hr of admission to the hospital, at discharge,

and 6 months after discharge. All ejection fraction data reported were obtained by gated ventriculography. Ejection fraction and average demographic data were analyzed by two-tailed paired and nonpaired Student's *t* tests. A chi-square analysis was performed on group data, as noted in table annotations. Statistical significance was accepted at $p \leq .05$. Odds ratio calculations were performed to predict probability of survival for the study population compared with the control population.

Results

As demonstrated in figure 1, 74% of the 136 patients in the study group had sustained total occlusion of the infarct-related artery. The coronary arteries in four patients in this group were partially reperfused by intracoronary nitroglycerin and residual thrombus was further cleared by intracoronary streptokinase administration. Sixty-nine patients demonstrated reperfusion, yielding an overall reperfusion rate of 73% after intracoronary streptokinase alone. Twenty-seven patients (27%) failed to demonstrate reperfusion after either nitroglycerin or streptokinase. Thirty-six patients had a subtotal occlusion associated with acute transmural myocardial infarction. Of these, three had unequivocal coronary spasm superimposed on a fixed stenosis. The majority of those in the nonthrombotic infarct group had a severe proximal stenosis with slow antegrade flow. Of the remaining patients, one had diffuse disease with no discrete infarct-related lesion and one patient had normal coronary arteries.

Those patients with coronary occlusion who had successful thrombolysis demonstrated a significant ($p < .001$) improvement in mean left ventricular ejection fraction from $39 \pm 13\%$ to $46 \pm 12\%$ by the time they were discharged from the hospital (table 3). Patients in the control group and those with thrombolysis who failed to reperfuse had no change in mean left ventricular function from the time of admission through the time of hospital discharge.

The optimal timing for medical or surgical reperfu-

sion is immediately after total occlusion. There have been no conclusive studies to determine the maximum allowable amount of time between onset of pain and successful reperfusion. To evaluate this problem, we grouped the patients in whom reperfusion was achieved into those presenting 0 to 6 hr, 6 to 12 hr, and 12 to 18 hr from onset of pain. Each group demonstrated a significant increase in mean ejection fraction from admission to hospital discharge (figure 2), with greater increases usually occurring in those patients admitted with an abnormal ejection fraction. Fifty-eight percent of patients admitted with ejection fractions of less than 50% had significant (greater than 2 SDs of intrinsic variability) increases in ejection fraction by the time of hospital discharge.

There was a slight increase in mean left ventricular function in the control group that was not statistically significant. Several patients in the control group had an increase in ejection fraction by the time of hospital discharge, but an equal number experienced a significant fall in ejection fraction. Although the number of patients studied 12 to 18 hr after the onset of chest pain is small, none had a significant fall in ejection fraction, while 40% had a significant increase. These data suggest that some patients may benefit from reperfusion up to 18 hr after onset of chest pain.

Left ventricular function 6 months after myocardial infarction. Forty-five patients who had successful coronary reperfusion and 11 control patients have returned for follow-up radionuclide angiograms 6 months after their myocardial infarction. There was a significant increase in ejection fraction from admission through discharge in the reperfusion group. Although the follow-up ejection fraction was slightly lower than that at discharge, this difference was not significant. Also, the follow-up ejection fraction was significantly higher than that on admission ($p < .05$; table 4). The left ventricular function in the control group was not sig-

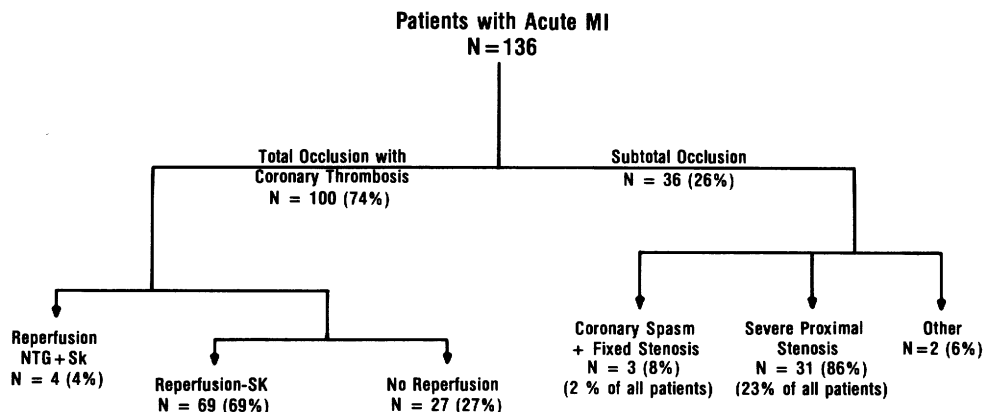


FIGURE 1. Coronary anatomic characteristics in 136 patients with acute myocardial infarction.

TABLE 3
Ejection fractions (EFs, mean \pm SD) on admission to and discharge from hospital

Group	Sample size	Admission EF (%)	p ^A	Discharge EF (%)	Δ EF
Reperfusion	65	39 \pm 13	<.001	46 \pm 12	7 \pm 8
Group A	28	42 \pm 16	<.001	51 \pm 13	9 \pm 8
Group B	37	36 \pm 9	<.001	43 \pm 10	6 \pm 7
No reperfusion	19	41 \pm 17	NS	43 \pm 18	2 \pm 5
Control	48	43 \pm 13	NS	43 \pm 13	0 \pm 5

^ABy Student's t test.

nificantly different at follow-up compared with at discharge.

Approximately 38% of all patients entering the protocol underwent coronary artery bypass surgery before their discharge from the hospital. Bypass surgery was performed in patients with significant three-vessel disease, in those with isolated left anterior descending coronary artery disease with significant return in function in the infarct area, or in those who had significant angina and were on maximal drug therapy. One might anticipate that the effect of coronary artery bypass surgery would influence return of left ventricular function and sustain ejection fraction improvement at late follow-up. In those patients in whom 6 month follow-up data were available, 17 patients had coronary artery bypass surgery and 28 were treated medically. Interestingly, the ejection fraction on admission was essentially equal and follow-up ejection fractions were also equal, with significant improvement at follow-up compared with on admission. Although the initial improve-

ment in ejection fraction was slightly but not significantly higher in the bypass surgery patients compared with the medically treated patients at hospital discharge, this enhanced improvement was not sustained through follow-up. Even in patients admitted with ejection fractions of less than 45%, bypass surgery did not appear to have a significant effect on changes in resting left ventricular function at late follow-up. One patient in the bypass group had a perioperative myocardial infarction and his data were excluded from comparisons.

Comparison of mortality rates in the study and control groups. In the 136 patients entered into the streptokinase protocol, there have been 17 deaths. One death occurred in the cardiac catheterization laboratory in a patient admitted with pulmonary edema and progressive hypotension. Eight of the 17 had sustained a previous myocardial infarction and nine were either in overt pulmonary edema (characteristic radiographic appearance, orthopnea, and pulmonary capillary wedge pressure greater than 25 mm Hg) or cardiogenic shock (blood pressure less than 80 mm Hg systolic) on admission. Admission status and other demographic characteristics of patients who died are listed in table 5.

Eleven patients in the control group died. Four of these had pulmonary edema on admission (by same criteria used in study group) and two had possibly had previous myocardial infarctions. The mean age of the control group was slightly higher than that of the study group. Other than a small difference in average age, differences between the groups were not statistically significant. The average age of those patients who died

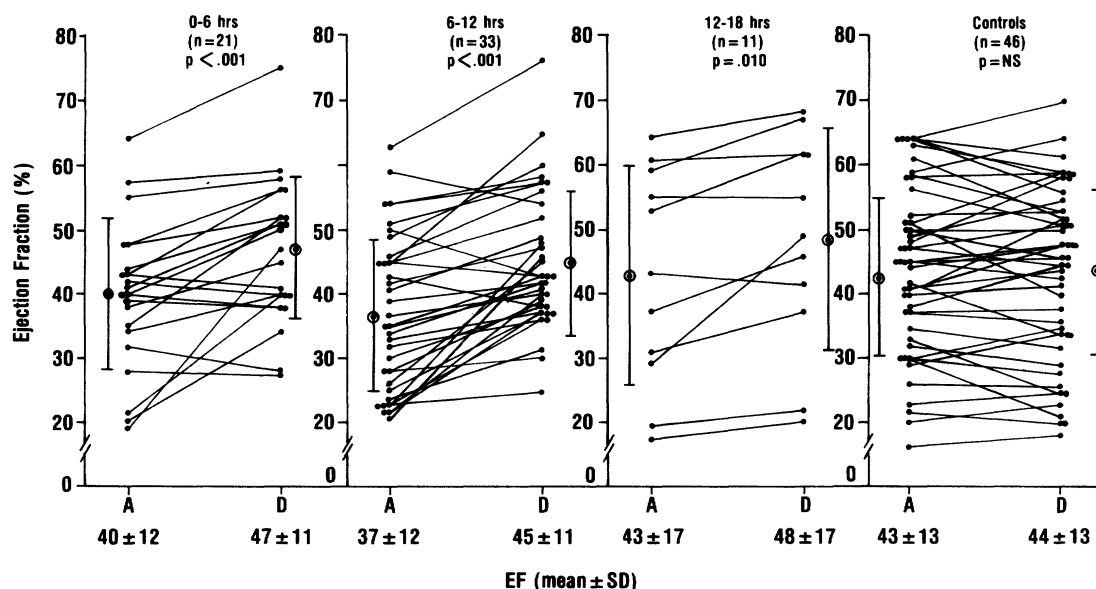


FIGURE 2. Ejection fraction on admission to the hospital (A) and at discharge (D) in patients who underwent reperfusion 0 to 6, 6 to 12, and 12 to 18 hr after onset of pain and in control patients (p by paired Student t test).

TABLE 4
Ejection fraction (EFs, mean ± SD) in patients who underwent successful coronary reperfusion 6 months after myocardial infarction

Group	Sample size	Admission		Discharge		Follow-up EF (%)
		EF (%)	p [^] <	EF (%)	p [^]	
All patients	45	39 ± 14	.001	47 ± 12	NS	45 ± 15
Medical therapy	28	38 ± 14	.001	46 ± 11	NS	45 ± 14
CAB	17	40 ± 14	.001	49 ± 13	NS	45 ± 17
Medical therapy (admit. EF < 45%)	20	31 ± 9	.001	42 ± 10	NS	41 ± 14
CAB (admit. EF < 45%)	11	32 ± 9	.001	41 ± 7	.05	37 ± 13

[^]By student's t test.

in both groups was comparable (67 to 68 years).

It is interesting to note that only five deaths occurred in those patients who had successful reperfusion and only one of these five was a cardiac death. This patient presented with an inferior myocardial infarction and had successful reperfusion of a totally occluded right coronary artery. He had residual subtotal left anterior descending coronary artery occlusion, previous anterior myocardial infarction, and 100% circumflex occlusion. Although his initial ejection fraction was 49%, he developed heart failure on day 3 and died during attempted emergency bypass surgery. Other noncardiac deaths in the study group included those from anoxic brain death secondary to prehospital cardiac arrest, pulmonary embolism 10 months after hospital discharge, sepsis after gastrointestinal surgery 3½ months after myocardial infarction, and embolic cerebrovascular accident.

One patient in group A and one in group B (see Study protocol) who had pulmonary edema on admission have survived. Patient No. 110 had pulmonary edema with an arterial partial pressure of oxygen of 44 mm Hg on hospital admission. He had sustained a large anterior myocardial infarction and had an ejection fraction of 17%. His left anterior descending coronary artery was completely occluded at its origin. The circumflex artery was severely stenosed, with a 95% proximal lesion, and the right coronary artery was completely occluded. The patient had successful reperfusion after 75 min of streptokinase infusion. After the reperfusion, a percutaneous intra-aortic balloon was inserted and he became hemodynamically stable. He underwent bypass surgery on the fifth day after myocardial infarction and is doing well at home 6 months later, with an ejection fraction of 50%.

As described above, group A consisted of the first 60 patients in the streptokinase series; they were treat-

ed with a streptokinase infusion of 2000 U/min for 60 min or less. Many of these patients were treated with intracoronary guidewire manipulation and/or subselective streptokinase infusion. Group B consisted of the subsequent 76 patients who were treated with a streptokinase infusion at 2000 U/min for up to 90 min. None of these patients underwent guidewire manipulation and only two had subselective streptokinase infusion after failure of ostial reperfusion.

On admission to the hospital there were fewer (and a smaller percentage of) control patients who were in Killip class III or IV compared with in the study group. Consequently, we examined total and cardiac mortality rates in all patients except those in cardiogenic shock or with pulmonary edema on admission. The total mortality rate in group B compared with that in control patients demonstrated a threefold increase in probability of survival, which was statistically significant (p < .03; table 6). Although there was an almost twofold increase in probability of survival in the entire study group (including patients in cardiogenic shock or pulmonary edema) when compared with control patients, this increase was not significant statistically. When the patients in shock or with pulmonary edema were excluded, the cardiac mortality rate in the streptokinase-treated group demonstrated a threefold increase in probability of survival when compared with the control group. This difference was even more striking in group B, with an almost tenfold increase in probability of survival compared with control; this difference was significant (p < .01).

The mortality rate was inversely related to the reperfusion rate. The mortality in group A (18%, associated with a reperfusion rate of 67%) was insignificantly greater than the 8% in group B (reperfusion rate of 79%).

TABLE 5
Characteristics of patients who died

	Study group		Control group	
	Total	%	Total	%
Total no. of deaths	17	100	11	100
Cardiogenic shock				
on admission	2	12	1	9
Pulmonary edema				
on admission	8	47	4	36
Anterior MI	9	53	8	73
History of previous MI	8	47	2	18
In-hospital deaths	15	88 (11)	7	67 (14)
Cardiac death				
after reperfusion	1	6 (1.4)	—	—

Values in parentheses are percentages of total patient population.

TABLE 6
Effect of streptokinase therapy on mortality rate

Group	Total mortality rate				Cardiac mortality rate				Cardiac mortality rate in class I and II			
	Total	%	Odds ratio	p ^A	Total	%	Odds ratio	p ^A	Total	%	Odds ratio	p ^A
Study group	17/136	12.5	1.88	NS	13/136	9.6	2.55	.06 (NS)	5/125	4	3.43	<.04
Group A	11/60	18.3	1.20	NS	8/60	13.3	1.55	NS	4/55	7.3	1.82	NS
Group B	6/76	7.9	3.13	<.03	5/76	6.6	3.38	<.03	1/70	1.4	9.86	<.01
Control group	11/52	21.2	—	—	10/52	19.2	—	—	6/48	12.5	—	—

Odds ratio = probability of survival compared with control.

^ABy chi-square analysis.

In order to further evaluate the effect of age on mortality in our study, we analyzed data from patients who were 65 years old or younger in both the study and control groups. In these patients (109 streptokinase patients and 28 control patients) there is no difference in age between the groups, the mean being 51 ± 9 years in both. As demonstrated by table 7, the cardiac mortality rate in the streptokinase-treated patients who were 65 years old or less was 4.6% compared with 14% in the control group; this difference did not reach statistical significance ($p = .06$). In group B, however, the mortality rate was 3.2%, which was significantly less than that in the control group (14.3%). Thus, eliminating the possible deleterious effect of age on mortality rate, there remains a significant decrease in mortality in patients treated with intracoronary streptokinase therapy as compared with controls.

Complications with intracoronary streptokinase therapy. Although four deaths were associated with intracoronary streptokinase therapy, none could be directly ascribed to it. One patient died in the catheterization laboratory while in cardiogenic shock. Two other patients died during emergency surgery after unsuccessful reperfusion. All three of the aforementioned patients had extremely poor left ventricular function and

TABLE 7
Effect of streptokinase therapy on cardiac mortality rate in patients 65 years old or younger

Group	Average age (yr) ^B	Cardiac mortality rate			
		Total	%	Odds ratio	p ^A
Study group	51 ± 9	5/109	4.6	3.47	.061 (NS)
Group A		3/46	6.5	2.39	NS
Group B		2/63	3.2	5.05	.046
Control group	51 ± 9	4/28	14.3	—	—

Odds ratio = survival compared to control.

^ABy chi-square analysis.

^BMean \pm SD.

all had had previous myocardial infarctions. One patient sustained an embolic cerebrovascular accident during catheter manipulation around the right coronary ostium. This patient had an anterior myocardial infarction with successful reperfusion of the left anterior descending coronary artery. She subsequently died after an iatrogenic cerebrovascular accident. Her death must be considered a complication of cardiac catheterization that may or may have not been exacerbated by streptokinase. No patients died as a result of blood loss in this series and bleeding complications were minimal, with only five patients requiring transfusion; these complications are listed in table 8.

Discussion

Since it has been established that coronary thrombosis is frequent in myocardial infarction, thrombolytic reperfusion, if performed early enough, should be an effective method of achieving myocardial salvage. Unfortunately, intravenous thrombolytic therapy has not been established as an efficacious method of achieving improved survival,^{14, 15} and no long-term studies have been performed to determine its effect on left ventricular function.

Our results demonstrate that intracoronary streptokinase infusion during acute myocardial infarction significantly preserves left ventricular function and improves survival compared with that in nontreated control patients, thereby suggesting significant myocardial salvage. These results are sufficiently important to warrant discussion of possible bias influencing the data.

All patients admitted to our hospital with acute myocardial infarction and who met our preestablished criteria were entered into the streptokinase protocol consecutively without clinical selection and therefore without the bias inherent in such selection. There was no significant difference between the study and control groups in incidence of anterior myocardial infarction

TABLE 8
Complications associated with intracoronary streptokinase therapy

	n	%
Bleeding complications		
Hematemesis	5	3.7
Bleeding or hematoma at cath. site	6	4.4
Bleeding at other arterial puncture site	1	0.7
Bleeding after percutaneous balloon-pump removal (patient heparinized)	2	1.5
Total bleeding complications	14	10.3
Total no. of patients requiring transfusion	5	3.7
Deaths from bleeding	0	0.0
Other complications		
Bradycardiac arrest	1	0.7
Ventricular fibrillation (during angiography)	3	2.0
Embolic CVA during catheter manipulation (subsequent late death)	1	0.7
Death in cath. lab secondary to cardiogenic shock	1	0.7
Death during emergency surgery after unsuccessful reperfusion	2	1.5
Total deaths associated with intracoronary streptokinase therapy	4	3.0

CVA = cerebrovascular accident.

or incidence of shock or pulmonary edema on admission. Although the control group mean age was slightly but significantly higher than that in the study group, the average age of patients who died in both groups was not different. Restricting comparison of cardiac mortality to patients 65 or younger eliminated possible age bias (mean age of study group = control group = 51 ± 9). In this subgroup, intracoronary streptokinase resulted in a statistically significant reduction in mortality rate in group B and in the entire study group the reduction approached significance ($p = .06$). The total control group mortality rate at up to 2 years follow-up is not excessive at 21%.

As stated earlier, mortality rate in comparable groups at 30 days after myocardial infarction ranges between 15% and 30%. For example, in the European collaborative study of intravenous streptokinase,¹⁵ the average mortality rate at 6 months was 30% in the untreated control group. A recent report of 105 patients treated for initial myocardial infarction between 1971 and 1978 found an overall in-hospital mortality rate of 13%, with patients who had an anterior myocardial infarction having a higher mortality rate (15.6%) than did those with inferior infarcts (9.1%).¹⁶ We would anticipate a slightly higher in-hospital mortality rate in our series since patients with previous myocardial infarctions were included, but the rate in our control group was 15%. It is therefore unlikely that better survival in the streptokinase group was due to

an excessive mortality rate in the control group.

The benefits of intracoronary streptokinase therapy in reducing mortality depend on achieving adequate reperfusion rates. The cardiac mortality rate for the total study group approaches statistical significance when compared with that in the control group, with an increased probability of survival greater than 2.5. The mortality rate in group B, with a higher reperfusion rate (79%), is consistently significantly less than in the control group whether one studies total mortality, cardiac mortality, or cardiac mortality in Killip class I and II patients only.

The difference in reperfusion success (67% vs 79%) and in mortality rates between group A and group B may reflect a learning curve in the use of intracoronary streptokinase for the treatment of acute myocardial infarction. We have modified our methods during the 2 years of the study in order to improve our reperfusion rates. The use of the intra-aortic balloon in patients who are hemodynamically unstable after successful reperfusion may be a further step in achieving a favorable outcome. Clot perforation with the 0.032 inch guidewire may be associated with plaque disruption and irreversible coronary occlusion. Sixteen of 25 attempts at guidewire clot perforation were successful. In nine of these, coronary reperfusion was achieved by the end of the procedure. In five patients, however, transient opening of the vessel was followed by permanent reclosure. Two patients did not demonstrate reperfusion after clot perforation. We have eliminated this technique from our therapeutic protocol because initial success in clot perforation by a guidewire often did not lead to lasting patency.

Previous reports have established that mean left ventricular function does not change in patients with evolving myocardial infarction from their admission to the hospital through discharge.^{9, 10, 17, 18} We designed our protocol to look prospectively at the effects of intracoronary streptokinase therapy on myocardial function (both at hospital discharge and follow-up) in all consecutive patients meeting admission criteria, thereby avoiding bias due to patient selection. The effectiveness of late reperfusion in relation to onset of infarction in human beings is not known. In animals, reperfusion at 2 to 3 hr after complete occlusion has been shown to result in significant return in function in border zones surrounding an area of myocardial necrosis.^{19, 20} Clearly, the earlier reperfusion is achieved the greater the possible benefits. Yet, in humans with chronic coronary stenosis, some degree of collateralization may be present that may alter the time course of necrosis. We therefore designed our protocol to accept

patients with an onset of chest pain of up to 18 hr before initiation of therapy in order to answer this question without preconceived bias. There was no significant difference in mortality between the 0 to 6 hr group and the 6 to 18 hr group. Also, statistically significant improvement in global left ventricular function was seen in each of the reperfusion subgroups (0 to 6 hr, 6 to 12 hr, and 12 to 18 hr) and no significant improvement was observed in the control group. However, not all patients who had successful reperfusion had improved global left ventricular function, even when they underwent reperfusion early after onset of chest pain. Regional wall motion changes were not examined by this study and, as reported by other investigators,^{12, 13, 21} some return of function may occur regionally but due to concomitant left ventricular dilatation the global ejection fraction may not change. Fifty-eight percent of the patients who were admitted with an ejection fraction of less than 50% and who had successful reperfusion had a significant increase in their left ventricular ejection fraction by the time of hospital discharge and it persisted for up to 6 months. The factors that determine which patients will improve with reperfusion are unknown. We suspect that only direct measurement of cellular viability by a method such as positron metabolic imaging will provide an answer to this question.

In conclusion, intracoronary streptokinase therapy during evolving myocardial infarction up to 18 hr after the onset of chest pain was associated with improved mean left ventricular performance compared with that on admission. This was true at hospital discharge and at 6 month follow-up. The improvement in function was not seen in a comparable control group or in patients in whom reperfusion failed. Cardiac mortality rate was significantly lower in the study group than in the control group when patients in cardiogenic shock or with pulmonary edema on admission were excluded from both groups. Both survival and improvement in left ventricular function appear to be related to the success rate of coronary reperfusion in the treatment of patients with acute myocardial infarction. A learning curve may exist in the successful treatment of myocardial infarction by intracoronary streptokinase administration.

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