

ORIGINAL ARTICLE

Intracoronary Streptokinase after Primary Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND

Microvascular perfusion is often impaired after primary percutaneous coronary intervention (PCI). We proposed that in situ thrombosis might contribute to poor myocardial perfusion in this setting. To test this hypothesis, we evaluated the effect of low-dose intracoronary streptokinase administered immediately after primary PCI.

METHODS

Forty-one patients undergoing primary PCI were randomly assigned to receive intracoronary streptokinase (250 kU) or no additional therapy. Two days later, cardiac catheterization was repeated, and coronary hemodynamic end points were measured with the use of a guidewire tipped with pressure and temperature sensors. In patients with anterior myocardial infarction, the deceleration time of coronary diastolic flow was measured with transthoracic echocardiography. At 6 months, angiography, echocardiography, and technetium-99m single-photon-emission computed tomography were performed.

RESULTS

Two days after PCI, all measures of microvascular function (means \pm SD) were significantly better in the streptokinase group than in the control group, including coronary flow reserve (2.01 ± 0.57 vs. 1.39 ± 0.31), the index of microvascular resistance (16.29 ± 5.06 U vs. 32.49 ± 11.04 U), the collateral-flow index (0.08 ± 0.05 vs. 0.17 ± 0.07), mean coronary wedge pressure (10.81 ± 5.46 mm Hg vs. 17.20 ± 7.93 mm Hg), systolic coronary wedge pressure (18.24 ± 6.07 mm Hg vs. 33.80 ± 11.00 mm Hg), and diastolic deceleration time (828 ± 258 msec vs. 360 ± 292 msec). The administration of intracoronary streptokinase was also associated with a significantly lower corrected Thrombolysis in Myocardial Infarction frame count (the number of cine frames required for dye to travel from the ostium of a coronary artery to a standardized distal coronary landmark) at 2 days. At 6 months, however, there was no evidence of a difference between the two study groups in left ventricular size or function.

CONCLUSIONS

In our pilot trial, the administration of low-dose intracoronary streptokinase immediately after primary PCI improved myocardial reperfusion but not long-term left ventricular size or function. These findings require clarification in a larger trial. (ClinicalTrials.gov number, NCT00302419.)

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P RIMARY PERCUTANEOUS CORONARY INTERVENTION (PCI) is an established reperfusion strategy in the treatment of acute myocardial infarction with ST-segment elevation.¹ Nevertheless, myocardial damage is not immediately terminated after the elimination of epicardial occlusion with successful primary PCI. It has been presumed that reperfusion injury and embolization of epicardial thrombus and plaque debris jeopardize tissue-level perfusion.²⁻⁴ Although thromboembolism of proximal origin may limit microvascular perfusion,^{5,6} a thrombus may also form in the microvasculature itself. This concept may help explain why recent randomized trials have failed to show a beneficial effect of distal protection devices on microvascular perfusion during primary PCI, despite effective retrieval of thrombus and plaque content from epicardial coronary arteries.^{7,8}

We proposed that the intracoronary infusion of low-dose streptokinase immediately after primary PCI might further improve tissue-level perfusion by dissolving thrombi (either formed in situ or embolic) at the microvascular level. This hypothesis was investigated prospectively in a pilot trial.

METHODS

PATIENTS

Patients who had their first ST-segment elevation and were scheduled to undergo primary PCI within 12 hours after the onset of symptoms were considered for trial enrollment. Inclusion criteria were ongoing chest pain, ST-segment elevation on electrocardiography, and occlusion of the infarct-related artery (Thrombolysis in Myocardial Infarction [TIMI] flow grade of 0 or 1) on angiography. The main exclusion criteria were the presence of the culprit lesion in a saphenous-vein graft, an additional lesion causing more than 50% narrowing distal to the culprit lesion, or a left bundle-branch block; history of prior myocardial infarction; and contraindications to streptokinase, tirofiban, aspirin, clopidogrel, or heparin. Written informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by our hospital ethics committee.

STUDY PROTOCOL

Immediately after diagnostic angiography, eligible patients were assigned to either the streptokinase

group or the control group (which received no additional therapy) according to a computer-generated random sequence. In both groups, primary PCI was performed with the use of stent implantation after balloon dilation. All patients received 300 mg of aspirin; a loading dose of 600 mg of clopidogrel; an intracoronary infusion of unfractionated heparin at a dose of 100 U per kilogram of body weight during the procedure; tirofiban as a bolus of 0.1 μ g per kilogram 3 minutes after the start of the procedure, followed by continuous infusion of tirofiban at 0.15 μ g per kilogram per minute for 12 hours; and low-molecular-weight heparin initiated 4 to 5 hours after primary PCI and continued for at least 48 hours. After PCI, coronary angiography was repeated to assess the corrected TIMI frame count,⁹ the number of cine frames required for dye to travel from the ostium of a coronary artery to a standardized distal coronary landmark, and the myocardial blush grade.¹⁰

In the streptokinase group, immediately after the postprocedure coronary angiography, 250 kU of streptokinase diluted with 20 ml of saline was infused through the guiding catheter for 3 minutes. The control group received no additional treatment. Electrocardiograms were recorded both immediately and 60 minutes after the PCI to assess the resolution of ST-segment deviation.¹¹

The femoral sheath was removed as soon as the activated partial-thromboplastin time was appropriate (first checked 4 hours after the conclusion of the PCI), and hemostasis was achieved by manual compression. During the period of hospitalization, patients were monitored carefully for bleeding at the femoral access site and other bleeding complications. Prespecified medications consisted of 100 mg of aspirin daily for an indefinite period, 75 mg of clopidogrel daily for 1 year, and the maximum tolerated doses of beta-blockers and angiotensin-converting-enzyme inhibitors if not contraindicated.

INTRACORONARY HEMODYNAMIC MEASUREMENTS AND ANGIOGRAPHIC ANALYSIS

Two days after primary PCI, all patients underwent a second cardiac catheterization for evaluation of microvascular function. Several distinct assessments were performed during this evaluation, including angiography and measurement of intracoronary hemodynamic characteristics.

For the assessment of hemodynamic characteristics, a guidewire tipped with pressure and

temperature sensors (PressureWire5 Sensor, Radi Medical Systems) was positioned distal to the stented segment of the infarct-related artery. Papaverine was used as the hyperemic agent. The transit time (in seconds) of room-temperature saline injected into a coronary artery at rest and during hyperemia was measured three times and averaged, as previously described.¹² The thermodilution-derived coronary flow reserve was calculated as the mean transit time at rest divided by the mean transit time during hyperemia.¹³ The index of microvascular resistance (in mm Hg–seconds, or units) was defined as the distal coronary pressure multiplied by the mean transit time during hyperemia, measured simultaneously.¹⁴ Subsequently, the stented segment was occluded temporarily with a short compliant balloon, and the mean and systolic coronary wedge pressures were recorded. The pressure-derived collateral-flow index was calculated as the ratio of the mean coronary wedge pressure minus the central venous pressure, measured simultaneously, and the mean aortic pressure minus the central venous pressure. For this calculation, central venous pressure was not measured directly but was estimated as 5 mm Hg, as described elsewhere.¹⁵ All coronary hemodynamic data were recorded, stored off-line, and analyzed by an independent investigator who was unaware of the group assignments.

Coronary angiography was also performed 2 days after primary PCI. The corrected TIMI frame count and myocardial blush grade were determined from the appropriate angiographic images.

NONINVASIVE ASSESSMENT OF MICROVASCULAR PERFUSION

Two days after primary PCI, the coronary flow-velocity pattern was assessed with the use of transthoracic echocardiography (as previously described¹⁶) in patients in whom the infarct-related artery was the left anterior descending coronary artery. The deceleration time of coronary diastolic flow was measured with the use of the coronary flow-velocity spectrum.¹⁷

LONG-TERM FOLLOW-UP

Echocardiography, angiography, and technetium-99m–labeled sestamibi single-photon-emission computed tomography (SPECT) were performed 6 months after primary PCI. Left ventricular end-diastolic and end-systolic volumes were measured,

and the percent changes relative to the values 2 days after PCI were calculated. Patients with 70% or more stenosis in the stented segment on angiography were excluded from the volume analysis at 6 months to avoid the confounding effect of restenosis of the infarct-related artery. TIMI frame count and myocardial blush grade were reassessed on the follow-up angiogram. Technetium-99m–labeled sestamibi SPECT was used to measure infarct size, expressed as a percentage of the total area of the myocardium,¹⁸ by a nuclear medicine specialist who was unaware of the group assignments.

STUDY END POINTS

We designated several measures as primary end points, including coronary flow reserve, index of microvascular resistance, coronary wedge pressure, collateral-flow index, and coronary diastolic deceleration time. The secondary end points included the corrected TIMI frame count, myocardial blush grade, infarct size, changes in left ventricular volume, and major adverse cardiac events such as reinfarction, revascularization, and death.

STATISTICAL ANALYSIS

Estimated mean values for each of the primary end points were obtained from the published literature. Using GraphPad InStat software, we then calculated the number of patients that would be necessary to detect a difference of 30% between the streptokinase group and the control group for each end point, with an α of 0.05, a β of 0.20, and a statistical power of 0.80. The necessary number of patients ranged from 7 to 39 patients per group, depending on the end point. Therefore, we targeted a sample of 40 patients per group. However, at a preplanned interim analysis (including approximately half the target study sample), significant absolute differences of more than 30% between the two study groups were demonstrated for most of the primary end points (excluding the coronary diastolic deceleration time, which is reported not to have a normal distribution). The decision was therefore made to terminate enrollment.

All statistical tests were performed with SPSS software, version 7.5. Group percentages were compared with the use of the chi-square test or Fisher's exact test, as appropriate. Group means for variables with normal and nonnormal distributions were compared with the use of Student's *t*-test for independent groups and the Mann-Whit-

ney U test, respectively. All analyses were repeated for the subgroup of patients with anterior myocardial infarction (in whom the infarct-related artery was the left anterior descending coronary artery). Group means were also adjusted for possible confounding factors (age; time from chest pain that has persisted for 30 minutes to balloon dilation [pain-to-balloon time]; presence or absence of diabetes, hypertension, hyperlipidemia, angina before myocardial infarction, slow flow, and side-branch embolization; smoking status; and infarct location) with the use of analysis of covariance. The difference between groups with regard to myocardial blush grade 0 or 1 was first analyzed with the use of the chi-square test and then with a logistic-regression model including age and pain-to-balloon time, in addition to the study-group variable (intracoronary streptokinase or no treatment). Two-tailed P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

STUDY PATIENTS AND ANGIOGRAPHIC OUTCOMES

Between October 2004 and March 2006, 41 patients were enrolled and randomly assigned to receive either intracoronary streptokinase (21 patients) or no additional treatment (20 patients) (Fig. 1). Baseline demographic, clinical, and angiographic characteristics are listed in Table 1. There were no significant differences between the two groups. All patients but one were male, and the mean age was 51.8 years.

The infarct-related artery was successfully opened in all patients, each of whom received at least one stent. No major bleeding or groin complications occurred. Minimal bleeding (according to the TIMI bleeding classifications⁴⁹) was observed at the femoral access site in one patient in each group and was managed with manual compression. During postprocedural assessment, a femoral pseudoaneurysm was detected in one patient in the streptokinase group and was also managed with manual compression.

ASSESSMENT OF MICROCIRCULATION

Intracoronary hemodynamic end points were evaluated at a mean (\pm SD) of 48 \pm 10 hours after primary PCI. Microvascular perfusion was significantly better in the streptokinase group than in the control group with regard to all the primary end points

(Table 2). Coronary flow reserve was significantly greater in the streptokinase group than in the control group (2.01 \pm 0.57 vs. 1.39 \pm 0.31, adjusted P=0.002). Other end points were significantly lower in the streptokinase group than in the control group: the index of microvascular resistance (16.29 \pm 5.06 U vs. 32.49 \pm 11.04 U, adjusted P<0.001), collateral-flow index (0.08 \pm 0.05 vs. 0.17 \pm 0.07, adjusted P=0.002), mean coronary wedge pressure (10.81 \pm 5.46 mm Hg vs. 17.20 \pm 7.93 mm Hg, adjusted P=0.04), and systolic coronary wedge pressure (18.24 \pm 6.07 mm Hg vs. 33.80 \pm 11.00 mm Hg, adjusted P<0.001).

The infarct-related artery was the left anterior descending coronary artery in 30 patients. In these patients, the diastolic deceleration time of the recanalized artery was significantly longer in the streptokinase group than in the control group (828 \pm 258 msec vs. 360 \pm 292 msec, adjusted P=0.001) (Table 2).

Immediately after primary PCI, there were no significant differences between the two groups with regard to corrected TIMI frame count or myocardial blush grade. However, at 2 days after PCI, the corrected TIMI frame count was significantly lower in the streptokinase group than in the control group (22.52 \pm 5.58 vs. 31.79 \pm 7.58, adjusted P=0.001). The myocardial blush grade at 2 days did not differ significantly between the two groups after multivariate adjustment (Table 2).

There was no significant difference between the streptokinase group and the control group with respect to the mean initial ST-segment elevation across all affected leads or the percent resolution of ST-segment deviation immediately after PCI. Sixty minutes after PCI, the percent resolution of ST-segment deviation was higher in the streptokinase group than in the control group, but this difference was not significant after multivariate adjustment (Table 2).

LONG-TERM RESULTS

Echocardiography, SPECT, and coronary angiography were performed 7.5 \pm 2.4 months after primary PCI for purposes of long-term reassessment (Fig. 1). Univariate analyses showed that infarct size was smaller, ventricular volumes were less, ejection fraction was higher, and myocardial perfusion was better in the streptokinase group than in the control group (Table 3). However, after multivariate analysis, only the differences between the

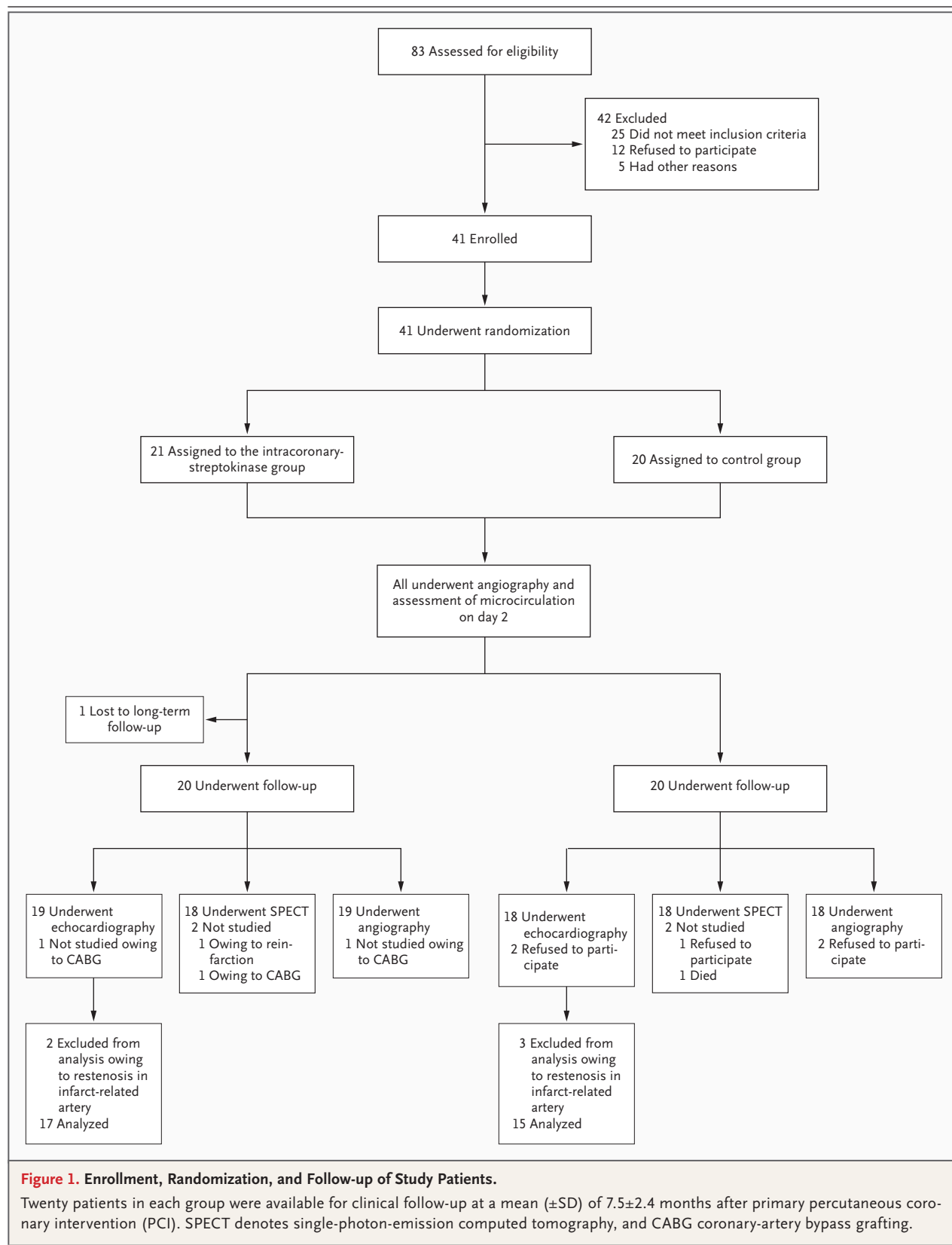


Table 1. Baseline Demographic, Clinical, and Angiographic Characteristics.*			
Characteristic	Streptokinase Group (N=21)	Control Group (N=20)	P Value
Main characteristics			
Age — yr	51.4±5.7	52.2±10.9	0.79
Male sex — no. (%)	21 (100)	19 (95)	0.98
Smoking — no. (%)	17 (81)	14 (70)	0.65
Diabetes mellitus — no. (%)	2 (10)	3 (15)	0.65
Hypertension — no. (%)	4 (19)	7 (35)	0.20
Dyslipidemia — no. (%)	12 (57)	14 (70)	0.27
History of angina before infarction — no. (%)	5 (24)	5 (25)	0.85
Infarct location — no. (%)			0.54
Anterior	14 (67)	16 (80)	
Nonanterior	7 (33)	4 (20)	
Peak troponin T concentration — ng/ml	9.1±6.5	10.4±7.6	0.61
Initial ST elevation — mm	15.6±10.5	19.0±9.7	0.18
Concomitant medication use during PCI and in the coronary care unit			
Aspirin — no. (%)	21 (100)	20 (100)	1.00
Beta-blocker — no. (%)	19 (90)	18 (90)	0.96
Low-molecular-weight heparin — no. (%)	21 (100)	20 (100)	1.00
Glycoprotein IIb/IIIa inhibitor — no. (%)	21 (100)	20 (100)	1.00
Clopidogrel — no. (%)	21 (100)	20 (100)	1.00
Statins — no. (%)	19 (90)	18 (90)	0.96
Intravenous nitroglycerin — no. (%)	16 (76)	12 (60)	0.44
ACE inhibitor — no. (%)	19 (90)	16 (80)	0.61
Angiographic characteristics			
Infarct-related coronary artery — no. (%)			
LAD	14 (67)	16 (80)	0.54
RCA	6 (29)	3 (15)	
CX	1 (5)	1 (5)	
No. of diseased vessels — no. (%)			
1	16 (76)	14 (70)	0.73
2	4 (19)	4 (20)	
3	1 (5)	2 (10)	
Baseline TIMI flow grade 0 or 1 — %	100	100	1.00
Pain-to-balloon time — min	257.7±211.8	218.8±109.8	0.93
Postprocedural results			
Slow or no reflow — no. (%)	5 (23)	2 (10)	0.41
Side-branch embolization — no. (%)	3 (14)	2 (10)	1.00
Maximal inflation pressure — atm	13.4±3.1	12.4±2.6	0.29
No. of stents	1.21±0.41	1.14±0.35	0.71
Mean residual stenosis — %	4.8±2.1	3.5±2.8	0.59
TIMI flow grades — no. (%)			
0 or 1	0	0	0.41
2	5 (24)	2 (10)	
3	16 (76)	18 (90)	
Procedural complications — no.	0	0	—

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, LAD left anterior descending coronary artery, RCA right coronary artery, CX left circumflex coronary artery, and TIMI Thrombolysis in Myocardial Infarction trial.

two groups in the corrected TIMI frame count and in the percent change in end-diastolic volume retained marginal statistical significance.

MAJOR ADVERSE CARDIAC EVENTS AND FUNCTIONAL CAPACITY AT FOLLOW-UP

In the streptokinase group, one patient underwent surgical revascularization at 2 months and one had reinfarction at 1 month. There was one case of sudden cardiac death in the control group at 4 months. Two patients in the streptokinase group and three patients in the control group underwent PCI owing to hemodynamically significant restenosis at 6 months. All other patients had a functional capacity equivalent to New York Heart Association class I at 6 months.

DISCUSSION

In our pilot trial, primary PCI immediately followed by the intracoronary administration of low-dose streptokinase was compared with standard primary PCI without the use of intracoronary streptokinase. Multiple quantitative end points including coronary flow reserve, collateral-flow index, coronary wedge pressure, and coronary diastolic deceleration time were used to evaluate microvascular integrity.²⁰⁻²² We also measured the index of microvascular resistance, which has been shown to be a useful variable for direct assessment of microcirculatory function.^{17,23} On the basis of these assessments, the use of intracoronary streptokinase was associated with better perfusion at the microvascular level.

The extent of microvascular dysfunction has been shown to be an important and independent contributor to subsequent changes in left ventricular geometry and performance.^{24,25} In our study, however, there was at best limited statistical evidence of a benefit to left ventricular size or function on the basis of long-term follow-up in the streptokinase group. The end points with marginal significance may reflect chance associations, given the number of tests performed. Since trends favoring the streptokinase group were detected, it is possible that the study was underpowered for these analyses. The trial was not originally planned to be large enough to detect differences in long-term outcome, and indeed enrollment was terminated early on the basis of the interim data on microvascular perfusion.

The precise mechanisms underlying myocardial malperfusion after the restoration of epicardial

blood flow are likely to be multifactorial. The generation of oxygen free radicals, increased myocardial-cell calcium levels, cellular and interstitial edema, endothelial dysfunction, vasoconstriction, and thromboembolism have all been proposed.^{2,26} Injury to the endothelium also promotes a procoagulant milieu. Fibrin and platelet aggregates have been found in the coronary microvasculature of patients who have died of acute myocardial infarction.²⁷ In addition to fibrin formation, red-cell and platelet aggregation also contribute to microvascular occlusion and increased resistance in the microvasculature.

It has been shown that streptokinase inhibits red-cell aggregation and reduces platelet aggregation *in vitro*.^{28,29} It has also been shown histopathologically, in an open-chest model of anterior descending artery occlusion and reperfusion, that streptokinase reduces congestion at the site of injury and results in improved perfusion of the microvasculature in severely ischemic myocardium to which blood flow has been restored.³⁰ It is therefore reasonable to assume that intracoronary streptokinase, administered immediately after primary PCI, may improve myocardial perfusion through mechanisms that cannot be invoked by distal protection devices.

We chose a 250-kU dose of streptokinase, which we anticipated would be high enough to induce fibrinolysis at the site of injury yet low enough to limit the risk of hemorrhage. At this dose, intracoronary streptokinase should have a concentration at the site of injury that is 50 times that of the standard dose of intravenous streptokinase (1.5 MU), resulting in a concentration in the systemic circulation that is 6 times less than that of the standard dose. In addition, since our protocol specified the administration of streptokinase after the infarct-related artery is opened, the drug would be expected to arrive at the target site much more quickly than with intravenous use.

Several important limitations of our study should be noted. First, because it was a pilot trial, only 41 patients were enrolled. Confirmation of the results with respect to early microvascular perfusion and clarification of the long-term effects on ventricular size and function will require a much larger trial. Second, since there is no single, uniformly accepted method for evaluating coronary microvascular perfusion, it may be argued that the measures used are not sufficiently sensitive or specific for this disease process. We had hoped to increase the reliability of our results by using mul-

Table 2. Invasive and Noninvasive Measures of Microvascular Perfusion, According to Type of Analysis.*

Measure	Univariate Analysis			Multivariate Analysis			Analysis of LAD Subgroup†				
	Streptokinase Group (N=21)	Control Group (N=20)	Mean Difference (95% CI)	P Value	Streptokinase Group (N=21)	Control Group (N=20)	mean (95% CI)	P Value	Streptokinase Group (N=14)	Control Group (N=16)	P Value
Index of microvascular resistance — U	16.29±5.06	32.49±11.04	-16.20 (-21.75 to 10.64)	<0.001	11.73 (5.53 to 17.92)	29.05 (22.17 to 35.92)		<0.001	16.18±5.50	33.54±10.70	<0.001
Coronary flow reserve	2.01±0.57	1.39±0.31	0.62 (0.35 to 0.93)	<0.001	2.29 (1.92 to 2.66)	1.66 (1.25 to 2.07)		0.002	1.81±0.52	1.38±0.32	0.01
Coronary wedge pressure — mm Hg											
Mean ±SD	10.81±5.46	17.20±7.93	-6.39 (-10.73 to -2.05)	0.004	7.98 (2.84 to 13.12)	12.54 (6.83 to 18.24)		0.04	12.07±6.21	17.78±8.11	0.04
Systolic	18.24±6.07	33.80±11.00	-15.56 (-21.27 to -9.85)	<0.001	15.17 (8.26 to 22.08)	29.46 (21.80 to 37.12)		<0.001	18.79±6.58	35.11±10.79	<0.001
Pressure-derived collateral-flow index	0.08±0.05	0.17±0.07	-0.09 (-0.13 to -0.06)	<0.001	0.08 (0.05 to 0.11)	0.17 (0.14 to 0.21)		0.002	0.09±0.06	0.17±0.07	0.002
Corrected TIMI frame count											
Immediately after primary PCI	33.65±9.45	34.44±8.26	-0.79 (-6.66 to 5.08)	0.69	30.30 (23.14 to 37.46)	29.36 (21.48 to 37.25)		0.80	35.38±9.22	35.50±8.16	0.97
2 days after primary PCI	22.52±5.58	31.79±7.58	-9.27 (-13.50 to -5.03)	<0.001	19.10 (14.16 to 24.04)	27.51 (22.03 to 32.99)		0.001	24.00±6.15	32.94±7.15	0.001
6 mo after primary PCI	21.42±4.98	27.62±6.46	-6.20 (-11.00 to -1.39)	0.01	18.88 (13.57 to 24.18)	25.89 (18.76 to 33.02)		0.02	22.63±5.55	28.91±6.14	0.04
TIMI myocardial blush grade‡											
Immediately after primary PCI				0.16				0.70			0.23
Total no. of patients	20	18							13	16	
0 or 1 — no. (%)	10 (50)	13 (72)							7 (54)	12 (75)	
2 or 3 — no. (%)	10 (50)	5 (28)							6 (46)	4 (25)	

	21	19		0.01	0.07	0.05				
2 days after primary PCI										
Total no. of patients	21	19	14	17						
0 or 1 — no. (%)	6 (29)	13 (68)	—	—	5 (36)	12 (71)				
2 or 3 — no. (%)	15 (71)	6 (32)	—	—	9 (64)	5 (29)				
6 mo after primary PCI				0.04	0.13	0.06				
Total no. of patients	12	13	8	11						
0 or 1 — no. (%)	1 (8)	6 (46)	—	—	1 (12)	6 (55)				
2 or 3 — no. (%)	11 (92)	7 (54)	—	—	7 (88)	5 (45)				
Diastolic deceleration time in the LAD artery — msec‡	828±258	360±292	468 (261 to 676)	<0.001	750 (446 to 1054)	257 (–65 to 580)	0.001	828±258	360±292	<0.001
ST-segment resolution — %										
Immediately after primary PCI	68.2±20.13	63.2±14.37	5.00 (–7.89 to 17.89)	0.42	66.75 (53.04 to 80.45)	71.36 (56.66 to 86.07)	0.45	56.4±15.22	63.75±14.96	0.32
60 min after primary PCI	67.55±22.91	51.25±24.40	16.30 (0.06 to 32.54)	0.04	77.26 (61.30 to 93.23)	71.05 (53.55 to 88.55)	0.39	55.46±18.18	48.07±24.48	0.36

* Plus-minus values are means ±SD. LAD denotes left anterior descending coronary artery, and PCI percutaneous coronary intervention.
 † The left anterior descending coronary artery (LAD) subgroup consisted of patients with anterior myocardial infarction (in whom the infarct-related artery was the LAD).
 ‡ The Thrombolysis in Myocardial Infarction (TIMI) myocardial blush grade was not available for all patients at all time points.
 § Diastolic deceleration time was measured in 14 patients in the intracoronary-streptokinase group and in 16 patients in the control group.

Table 3. Left Ventricular Function at 2 Days and 6 Months and Infarct Size at 6 Months.*

Measure	Univariate Analysis			Multivariate Analysis			
	Streptokinase Group (N = 21)	Control Group (N = 20)	Mean Difference (95% CI)	P Value	Streptokinase Group (N = 21)	Control Group (N = 20)	P Value
End-systolic volume (ml)					mean (95% CI)		
2 days after primary PCI	58.16±17.02	78.65±30.55	-20.48 (-36.38 to 4.59)	0.01	50.81 (31.25 to 66.37)	65.03 (47.76 to 82.30)	0.06
6 mo after primary PCI	50.64±18.23	83.73±39.32	-33.08 (-56.24 to 9.92)	0.004	36.08 (9.07 to 63.10)	58.68 (25.10 to 92.27)	0.07
Percent change	-13.27±25.40	12.67±30.75	-25.94 (-46.22 to -5.67)	0.01	-12.32 (-47.47 to -22.83)	15.30 (-28.40 to 59.01)	0.06
End-diastolic volume (ml)							
2 days after primary PCI	119.88±23.36	137.75±36.82	-17.86 (-37.24 to 1.51)	0.07	111.22 (88.52 to 133.91)	118.53 (93.35 to 143.71)	0.50
6 mo after primary PCI	115.70±29.67	150.13±49.28	-34.42 (-63.39 to 5.46)	0.02	92.72 (59.11 to 126.33)	118.77 (76.98 to 160.56)	0.09
Percent change	-4.60±22.01	11.90±23.50	-16.51 (-32.95 to 0.07)	0.04	-11.19 (-37.95 to 15.58)	14.97 (-18.31 to 48.24)	0.04
LVEF (%)							
2 days after primary PCI	51.52±10.76	44.51±12.40	7.00 (-0.31 to 14.33)	0.06	54.25 (46.95 to 61.55)	47.96 (39.86 to 56.06)	0.08
6 mo after primary PCI	56.18±10.69	46.19±12.21	9.99 (1.72 to 18.26)	0.02	57.68 (45.88 to 69.47)	51.56 (36.90 to 66.23)	0.24
Percent change	14.37±31.14	3.46±19.02	10.9 (-7.7 to 29.5)	0.24	5.97 (-27.32 to 39.26)	2.71 (-37.75 to 43.16)	0.82
Infarct size at 6 mo (%)	23±13.37	37.05±13.84	-14.05 (-23.27 to -4.83)	0.005	27.84 (14.35 to 41.32)	37.28 (21.57 to 52.99)	0.17

* Plus-minus values are means ±SD. Left ventricular volumes were determined with the use of echocardiography. Echocardiography data were collected 2 days after primary PCI for all patients but 6 months after primary PCI for only the 17 patients in the streptokinase group and the 15 patients in the control group with less than 70% stenosis in the stented segment on angiography, to avoid the confounding effect of restenosis of the infarct-related artery; percent changes were based on the 17 and 15 patients for whom data were available at each time point. Infarct size was determined with the use of single-photon-emission computed tomography (SPECT), which was performed in 18 patients in each of the two groups, and is expressed as a percentage of the total area of the myocardium. CI denotes confidence interval, PCI percutaneous coronary intervention, and LVEF left ventricular ejection fraction.

tiple measures. Third, although the analysis of coronary hemodynamic measurements was blinded, the measurements were made by angiographers who were aware of the group assignments, so it is not possible to rule out entirely some element of investigator bias in our findings.

Finally, although we did not observe an increase in the rate of bleeding complications in the streptokinase group, the potential risk of adding even a low dose of a thrombolytic agent to an anti-thrombotic regimen that already includes aspirin, clopidogrel, and tirofiban must be considered. In the Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) trial, the use of full-dose tenecteplase just before primary PCI was associated with an increased risk of intracranial hemorrhage.³¹ In a smaller trial of PCI facilitated with the use of abciximab, the addition of half-dose reteplase was not associated with a significant reduction in the rate of subsequent ischemic events.³² Therefore, it appears that thrombolytic

agents administered before primary PCI confer no discernible benefit at low doses and increase risk at high doses. Although the use of thrombolysis after primary PCI may have distinct effects, the implications of these related trials should be kept in mind.

In conclusion, in our pilot evaluation, primary PCI followed by the administration of low-dose intracoronary streptokinase immediately after the procedure was associated with improved microvascular perfusion, but not with long-term improvement in ventricular size or function, as compared with primary PCI alone. Confirmation of the improvement in microvascular perfusion and clarification of the long-term benefit, if any, will require a much larger trial.

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