

Limitation of Infarct Size and Preservation of Left Ventricular Function After Primary Coronary Angioplasty Compared With Intravenous Streptokinase in Acute Myocardial Infarction

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Background Early and effective flow through the infarct-related vessel is probably of paramount importance for limitation of infarct size and preservation of left ventricular function in patients with acute myocardial infarction. Primary coronary angioplasty may offer advantages in these respects compared with thrombolytic therapy. The purpose of the present study was to assess the effects on estimated enzymatic infarct size and left ventricular function in patients with acute myocardial infarction randomly assigned to undergo primary angioplasty or to receive intravenous streptokinase.

Methods and Results We evaluated 301 patients with signs of acute myocardial infarction and without contraindications for thrombolysis who presented within 6 hours after onset of symptoms or between 6 and 24 hours if there was evidence of ongoing ischemia. One hundred fifty-two patients were randomly assigned to undergo primary angioplasty, and 149 patients were assigned to receive treatment with streptokinase (1.5 million U IV). Infarct size was estimated from enzyme release. Global left ventricular ejection fraction and regional wall motion, if possible in combination with exercise testing, were evaluated by radionuclide ventriculography before discharge. Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 through the infarct-related vessel within 120 minutes after admission was achieved in 92% of all patients assigned to receive primary angioplasty therapy. Myocardial infarct size

was 23% smaller in the angioplasty group compared with patients assigned to receive streptokinase (1003 ± 784 versus 1310 ± 1198 U/L, $P = .012$). Global left ventricular ejection fraction ($50 \pm 9\%$ versus $45 \pm 11\%$, $P < .001$) and regional wall motion in the infarct-related zones ($42 \pm 14\%$ versus $34 \pm 13\%$, $P < .001$) were better in the angioplasty group, which could mainly be contributed to myocardial salvage in the infarct-related areas. The observed differences were more pronounced in patients with an anterior wall myocardial infarction, although patients with a nonanterior infarct location also showed a beneficial effect of primary coronary angioplasty on left ventricular function compared with streptokinase therapy. Furthermore, the observed differences appeared to be more pronounced in patients presenting relatively early (within 2 hours) after onset of symptoms.

Conclusions In patients with acute myocardial infarction, primary angioplasty results in a smaller infarct size and a better preserved myocardial function compared with patients randomized to receive treatment with intravenous streptokinase. This is probably due to early and optimal blood flow through the infarct-related vessel, as can be accomplished in a very high percentage of patients undergoing primary coronary angioplasty. (*Circulation*. 1994;90:753-761.)

Key Words • myocardial infarction • angioplasty • thrombolysis • left ventricle • infarcts

In patients with acute myocardial infarction, early treatment resulting in restoration of adequate blood flow through the infarct-related vessel results in limitation of infarct size, preservation of left ventricular function, and reduction in mortality.¹⁻⁸ Several large clinical trials have established that thrombolytic therapy reduces mortality, and thrombolysis is the treatment of choice in patients with acute myocardial

infarction.^{4,6-8} Recently, we demonstrated a higher patency rate of the infarct-related coronary vessels, a reduction in the severity of the residual stenotic lesions, and a lower incidence of recurrent myocardial ischemia in patients with acute myocardial infarction who underwent primary (or direct) coronary angioplasty compared with those who received intravenous streptokinase. Furthermore, global left ventricular ejection fraction, as measured with a quantitative radionuclide method, was better in the patients assigned to undergo primary angioplasty.^{9,10} After completion of this initial series of 142 patients,⁹ the randomized study was extended to a total of 301 patients to achieve greater certainty about the benefit of primary coronary angioplasty. Previous studies of percutaneous transluminal coronary angioplasty (PTCA) in acute myocardial infarction did not yield additional benefit in patients pretreated with thrombolytic agents.¹¹⁻¹⁵ This lack of

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benefit has been attributed to activation of coagulation during thrombolytic therapy but could also be related to hemorrhage in the wall of the infarct-related artery or in the infarcted myocardium.^{16,17} Primary coronary angioplasty without pretreatment with thrombolytic agents may be advantageous since these deleterious phenomena are avoided.^{9,17,18}

This report describes the results of the full cohort of 301 patients with special emphasis on infarct size as measured from enzyme release and on global and regional left ventricular function.

Methods

Patient Selection

The research protocol was approved by the institutional review board of the Weezenlanden Hospital. Enrollment began on August 20, 1990, and ended on April 26, 1993. Inclusion criteria were (1) symptoms compatible with acute myocardial infarction persisting for more than 30 minutes accompanied by an ECG with more than 0.1-mV ST-segment elevation in two or more contiguous leads; (2) all patients presenting within 6 hours after symptom onset, as well as those presenting between 6 and 24 hours if they had evidence of continuing ischemia; (3) age less than 76 years; and (4) no contraindication to thrombolytic therapy, including prior stroke or other known intracranial diseases, recent trauma or surgery, refractory hypertension, active bleeding, or prolonged cardiopulmonary resuscitation. Prior coronary artery bypass grafting, prior Q-wave or non-Q-wave infarction, and cardiogenic shock were no reasons to exclude a patient. After informed consent was obtained, patients were randomly assigned to one of the two treatment modalities using a closed envelope system.

Treatment Protocol

All patients received 300 mg aspirin IV followed by 300 mg/d PO and IV nitroglycerin in a dosage aimed at a systolic blood pressure of 110 mm Hg. Intravenous heparin was given in a bolus of 10 000 U and thereafter as a continuous infusion adjusted to maintain the activated partial thromboplastin time between two and three times the normal value for at least 2 days. Other drugs such as β -adrenergic blockers, lidocaine, or calcium antagonists were given on indication only. Patients randomized to streptokinase received 1.5 million U IV in 1 hour. Patients randomized to coronary angioplasty were immediately transported to the catheterization laboratory and underwent coronary angiography followed by immediate coronary angioplasty if indicated. Both coronary arteries were visualized, and left ventriculography was not performed. Time from admission to therapy was calculated as time from admission to the first balloon inflation or to start of the streptokinase infusion.

Enzyme Measurements and Infarct Size

Creatine kinase (CK) and lactate dehydrogenase (LDH) were determined enzymatically on a Hitachi 717 automatic analyzer according to the International Federation of Clinical Chemistry (IFCC) recommendation at 30°C.²⁰ Reference values for LDH are <320 U/L (adults) and for CK are <110 U/L (females) and <130 U/L (males). Infarct size was estimated by measurements of enzyme activities using LDH as the reference enzyme. This method is equal to estimation of infarct size from α -hydroxybutyrate dehydrogenase (HBDH) and has been described in detail.^{2,20} Cumulative enzyme release from five to seven serial measurements up to 72 hours after symptom onset (LDH Q₇₂) was calculated by the Cardiovascular Research Institute Maastricht (W.Th.H.) with blinding to all data other than hospital registration number and date of birth.

A two-compartment model was used, which has been validated in several studies on the turnover of radiolabeled plasma proteins and circulating tissue enzymes.^{2,20-22} The plasma activity of enzyme C at time t is determined by input of enzyme from the heart and elimination of enzyme determined by a fractional catabolic rate constant (FCR_{LDH}). In addition, there is extravasation of enzyme, determined by a fractional transcapillary escape rate constant (TER), and return to plasma from the extravascular pool E(t), determined by a fractional extravascular return rate constant (ERR). Cumulative release of enzyme per liter of plasma from zero time up to time t is given by:

$$(1) \quad Q(t) = C(t) + E(t) + \int_0^t \text{FCR}_{\text{LDH}} \cdot C(\tau) d\tau$$

where C(t) and E(t) are the activities still present in the intravascular and extravascular spaces and the integral term encompasses eliminated activity. A value of FCR_{LDH}=0.015 hr⁻¹ was used. The extravascular pool E(t) is determined by the time-dependent plasma activity and TER and ERR:

$$(2) \quad E(t) = \text{TER} \cdot \exp(-\text{ERR} \cdot t) \cdot \int_0^t \exp(\text{ERR} \cdot \tau) C(\tau) d\tau$$

Values of C(t) in Equations 1 and 2 were obtained by subtraction of the normal activities in plasma from the actual activities measured at time t . Individual values of these normal activities were estimated from the first sample of each patient when this sample was obtained within 3 hours after first symptoms. Otherwise, a fixed mean normal value of 175 U/L was used. Fixed values of TER=0.014 hr⁻¹ and ERR=0.018 hr⁻¹ were used.

Radionuclide Ventriculography

Left ventricular ejection fraction was measured before discharge by radionuclide ventriculography using the multiple gated equilibrium method following the labeling of red blood cells of the patient with ^{99m}Tc-pertechnetate.²³ A General Electric 300 gamma camera with a low-energy all-purpose parallel-hole collimator was used. Global ejection fraction was calculated by a General Electric Star View computer using the fully automatic PAGE program. The use of this software program protects against operator bias. The reproducibility of this method is excellent, with a mean difference (\pm SD) between first and second values of duplicate measurements of $1.2 \pm 1.1\%$.²³ The left anterior oblique projection with some degree of cranial angulation to separate the right and the left ventricle was used to analyze regional wall motion. The left ventricle was divided into five zones corresponding to the posterolateral, inferolateral, inferoapical, basoseptal, and antero-septal regions. The area involving the valve planes was excluded. Regional wall motion was calculated from maximal and minimal counts in all regions and was expressed in percentages. Infarct- and non-infarct-related segments were indicated by two investigators using the ECG site of infarction and coronary anatomy as references, without further knowledge of clinical data. A symptom-limited bicycle exercise test was performed with participants in the supine position at increments of 10 W/min, only in patients without contraindications to exercise. An exercise test indicating ischemia was defined as a test with an ST-segment depression of more than 1 mm measured 60 milliseconds after the J-point. In patients with baseline abnormalities in the ST-T wave, a depression of more than 1 mm in the ST segment was considered to indicate ischemia.

Angiography and Angioplasty Data

Data of the coronary angiography and angioplasty procedures were collected and judged by two of the investigators. Because blinding to angioplasty procedures was not possible, all angiograms were subsequently reviewed by an independent and highly experienced investigator (M.v.d.B.) who was not

TABLE 1. Baseline Characteristics and Clinical Course

	Angioplasty (n=152)	P	Streptokinase (n=149)
Age, y	59±10	.06	61±9
Male sex, n (%)	127 (84)	.59	121 (81)
Previous MI, n (%)	32 (21)	.11	21 (14)
Anterior MI, n (%)	79 (52)	.27	68 (46)
Killip class III or IV, n (%)	14 (9)	.88	12 (8)
Time from onset to admission, min (range)	195 (20 to 1440)	.43	176 (25 to 975)
Time from admission to therapy, min	64±26	...	29±16
Multivessel disease, n (%)	95 (63)	.63	88 (59)
Mortality in hospital, n (%)	3 (2)	.024	11 (7)
Recurrent MI, n (%)	2 (1)	<.001	15 (10)
Late PTCA, n (%)	3 (2)	<.001	24 (16)
Late CABG, n (%)	7 (5)	.16	14 (9)

MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass grafting.

involved in other aspects of the trial. Consensus on collateral flow, procedural success, Thrombolysis in Myocardial Infarction (TIMI) graded flow before and after the angioplasty procedure, and extent of coronary artery disease was reached in all cases. Collaterals to the infarct-related vessel were classified as proposed by Rentrop et al.²⁴

Statistical Analysis

Differences between group mean values were tested by two-tailed Student's *t* test with a separate variance estimate if the F distribution of variances was significant at the two-sided 5% level. For comparison of rates of discrete outcome variables, a conventional χ^2 test was used. Fisher's exact test was used if there was an expected cell value of less than 5. Simple linear regression analysis was used for correlation of ejection fraction and enzymatic infarct size. In our presentation of the data, continuous baseline and outcome variables are given as mean±1 SD, whereas discrete variables are given as absolute values and percentages.

Results

Baseline and Clinical Data

A total of 301 patients were included in the study: 152 patients were randomly assigned to undergo primary coronary angioplasty and 149 patients to receive intravenous streptokinase therapy. Baseline characteristics of the two groups were similar (Table 1). One hundred fifty-one patients assigned to angioplasty underwent emergency coronary angiography; one patient died before angiography could be performed. The infarct-related vessel showed TIMI grade 0 or 1 flow in 124 of the 151 patients (82%). Coronary angioplasty was performed in 140 patients. Five patients with an open or small infarct-related artery were treated conservatively. Six patients with severe multivessel disease or left main stenosis had emergency coronary artery bypass grafting after insertion of an intra-aortic counterpulsation balloon. The time between admission to start of therapy defined as the first balloon inflation was 64±26 minutes. In 4 patients, the infarct-related vessel could not be reopened. Three of these patients underwent immediate coronary artery bypass grafting; 1 was treated conservatively.

Of the 149 patients assigned to streptokinase therapy, 1 died before infusion could be started. The time from admission to start of infusion was 29±16 minutes. Sixteen patients underwent a rescue coronary angioplasty because there was clinical evidence of failed reperfusion or hemodynamic collapse. In 15 patients, this procedure was successful; 1 underwent emergency coronary artery bypass grafting and was discharged after an uneventful in-hospital stay.

Additional procedures during the in-hospital stay were infrequent in the angioplasty-assigned patients: 3 patients had an additional angioplasty procedure of a non-infarct-related vessel, and 7 underwent coronary artery bypass grafting. In the streptokinase-assigned patients, 24 underwent an angioplasty procedure, and 14 patients had coronary artery bypass grafting before discharge. The in-hospital mortality was 2% (3 patients) in the angioplasty-assigned patient group and 7% (11 patients) in the streptokinase group (*P*=.024).

Angiographic Data

Baseline angiographic data of all patients assigned to receive primary coronary angioplasty are given in Table 2. Three of the angioplasty-assigned patients (2%) had no significant coronary artery disease, 54 (36%) had one-vessel disease, and 95 (62%) had multivessel disease. Not all patients had angiography of the non-infarct-related vessel before a coronary angioplasty was done; thus, classification of collaterals to the infarct-related vessel could be assessed only in 141 patients (Table 2). Patency rates and TIMI flow rates before therapy are given for all patients undergoing angiography. The angioplasty was considered to be technically successful if there was a residual stenosis of less than 50% and a flow of TIMI grade 2 or 3 at the end of the angioplasty procedure. Primary angioplasty of the infarct-related vessel was successful in 136 patients (97%). A TIMI grade 3 flow was observed in 131 of these patients (96%) with a successful procedure. The relation between time from hospital admission to successful reperfusion is also given in Table 2. Patients who underwent immediate coronary angiography followed

TABLE 2. Angiographic Data of Patients Assigned to Receive Primary Coronary Angioplasty

	Grade	Baseline	60 min	90 min	120 min
Collaterals* (n=141)	0	85 (60%)			
	1	45 (32%)			
	2	11 (8%)			
	3	0			
TIMI† (n=151)	0	109 (72%)	56 (37%)	19 (13%)	7 (5%)‡
	1	15 (10%)	11 (7%)	3 (2%)	1 (1%)
	2	17 (11%)	7 (5%)	7 (5%)	4 (3%)
	3	10 (7%)	77 (51%)	122 (81%)	139 (92%)

*Collateral classification: grade 0, no visible filling of any collateral channels; grade 1, filling by means of collateral channels of side branches of the vessel but without any dye reaching the epicardial segment of that vessel; grade 2, partial filling via collateral channels of the epicardial segment of the vessel; and grade 3, complete filling of the vessel.

†Thrombolysis in Myocardial Infarction (TIMI) grade is flow grade through the infarct-related vessel according to the TIMI study flow classification (min indicates minutes after admission).

‡In four patients, the infarct-related vessel was opened successfully more than 120 minutes after admission.

by emergency coronary artery bypass surgery were considered to have had restoration of adequate blood flow 120 minutes after admission (3 additional patients). In 4 patients, the infarct-related vessel was opened successfully more than 120 minutes after admission.

Enzymatic Infarct Size

Values for peak creatine kinase and LDH estimated infarct size (LDH Q_{72}) are given in Table 3. Peak CK values tended to be lower in the angioplasty treated patient group, but this difference was not statistically significant. Cumulative enzyme release during the first 72 hours, with sufficient data from the sequential measurements and accurate timing of symptom onset, could be calculated in 92% of all patients, and the data are given in Table 3. For 10 patients in the angioplasty group and for 7 patients in the streptokinase group, data were insufficient for adequate analysis. Eight patients died within the first 48 hours, before serial enzyme release could be determined. Estimated infarct size using LDH Q_{72} was lower in the angioplasty-assigned patients compared with patients assigned to receive streptokinase, representing a reduction of estimated infarct size of 23% (95% confidence interval [CI], 13% to 32%). The difference of the LDH Q_{72} value between the two groups was greater in patients with anterior wall myocardial infarction than in patients with a nonanterior wall infarction.

The relation between time from onset of symptoms to reperfusion therapy and LDH Q_{72} is also shown in Table 3. In patients admitted to the hospital within 2 hours after the onset of symptoms, an even more pronounced difference was seen: LDH Q_{72} was 967 ± 730 U/L in the angioplasty group versus 1403 ± 1157 U/L in the streptokinase group ($P=.010$), representing a reduction of estimated infarct size of 31% (95% CI, 20% to 43%).

Left Ventricular Function

In 149 patients in the angioplasty group (98%) and 140 patients in the streptokinase group (94%), resting ejection fraction values were obtained. Three patients in the angioplasty-treated group and 9 patients in the streptokinase-treated group died before nuclear studies were performed. Global ejection fraction was measured in all 289 survivors, whereas regional wall motion could be obtained in 273 patients (91%). The interval between acute myocardial infarction and time of nuclear study was less in the angioplasty group than in the streptokinase group (14 ± 13 days and 17 ± 21 days, respectively; $P=.04$). In all subgroups studied, resting global ejection fraction was significantly greater in patients assigned to primary angioplasty than in patients assigned to streptokinase therapy (Table 4). This difference was mostly due to better wall motion in the infarct-related region, although a relatively small but significant difference for non-infarct-related areas was also found between the two groups. There was a clear

TABLE 3. Enzyme Measurements and Estimated Infarct Size Expressed as LDH Q_{72} ; Relation of Enzyme Measurements to Infarct Location and Interval From Onset of Symptoms to Admission

	Angioplasty (n=141)	P	Streptokinase (n=135)
Peak CK, U/L	1268 ± 1088	.37	1404 ± 1276
LDH Q_{72} , all infarcts, U/L	1003 ± 784	.012	1310 ± 1198
LDH Q_{72} , anterior MI (U/L)	1158 ± 918 (n=71)	.022	1606 ± 1264 (n=62)
LDH Q_{72} , nonanterior MI (U/L)	853 ± 580 (n=70)	.135	1060 ± 1085 (n=73)
Time from symptom onset to admission			
<2 h: LDH Q_{72} , U/L	967 ± 730 (n=81)	.01	1403 ± 1157 (n=65)
>2 h: LDH Q_{72} , U/L	1052 ± 855 (n=60)	.36	1224 ± 1237 (n=70)

TABLE 4. Global Ejection Fraction and Regional Wall Motion

	Angioplasty	P	Streptokinase
EF (all patients)	50±9 (n=149)	<.001	45±11 (n=140)
IR wall motion (all patients)	42±14	<.001	34±13
NIR wall motion (all patients)	55±11	.005	51±12
EF anterior MI	46±12	.002	39±12
EF nonanterior MI	53±9	.02	49±9
EF one-vessel disease	51±8 (n=57)	.002	46±10 (n=59)
EF multivessel disease	48±12 (n=92)	.002	43±12 (n=81)
Time from symptom onset to admission			
<2 h: EF, %	51±10 (n=83)	<.001	45±11 (n=70)
>2 h: EF, %	48±12 (n=66)	.04	44±12 (n=70)

EF indicates ejection fraction; IR, infarct-related; NIR, non-infarct-related; MI, myocardial infarction.

correlation between left ventricular ejection fraction and enzymatic infarct size in patients with a first myocardial infarction, as shown in Fig 1. Patients who had angioplasty for first nonanterior wall infarction had very well preserved left ventricular ejection fraction, and no regression line could be drawn.

One hundred twenty-three patients in the angioplasty-treated group and 118 in the streptokinase-treated group could perform an exercise test with radionuclide ventriculography before discharge. In both groups, there was a remarkably flat response of left ventricular ejection fraction during exercise with small, but significant improvement after exercise when compared with baseline (Table 5). This "pattern" was observed in patients with anterior wall infarction as well as in those with nonanterior infarctions. However, patients assigned to receive primary angioplasty therapy had less frequently significant ST-segment depression or angina during exercise than patients who received streptokinase (33 versus 49, $P=.02$). Finally, exercise tolerance of the patients assigned to angioplasty therapy was higher than of those assigned to streptokinase therapy (98 ± 30 versus 90 ± 29 W, $P=.03$).

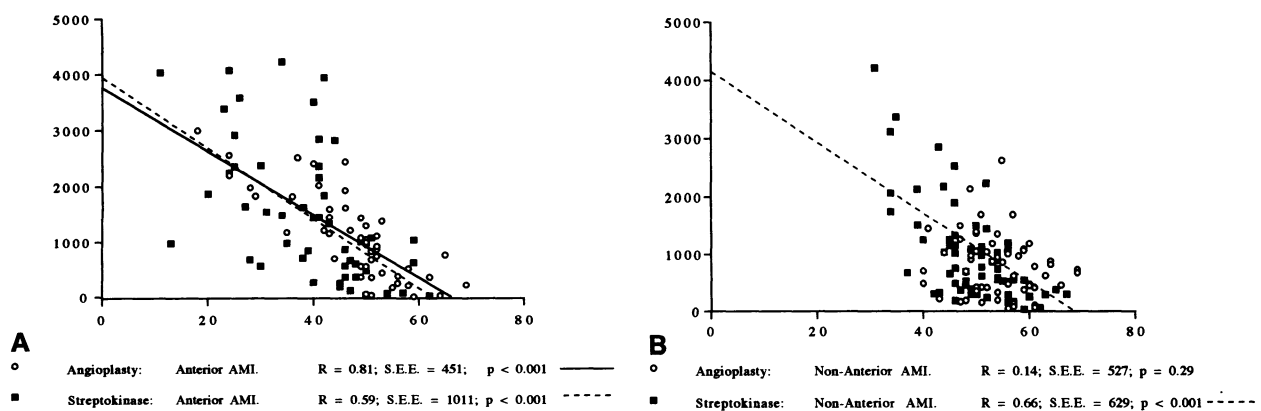
Discussion

The aim of the present study was to compare the effects of primary coronary angioplasty and thrombol-

ysis as primary reperfusion strategy. Infarct size and left ventricular function improved after primary angioplasty. The sample size was not designed to examine mortality as an end point, although in-hospital mortality in this study was significantly lower in the patients assigned to undergo primary coronary angioplasty than in those who received intravenous streptokinase (3 versus 11, $P=.024$).¹⁰ In all subgroups, a good relation was observed between the degree of reduction of infarct size and preserved left ventricular function.

Infarct Size

Due to the very slow elimination of LDH from plasma, this enzyme allows calculation of cumulative release over 72 hours from only five to seven plasma samples. Although reperfusion causes earlier enzyme release, which is also observed for LDH,²⁰ infarct size can be calculated accurately from LDH because a single measurement after 6 to 8 hours represents approximately the total release over that period. By that time, less than 10% of total release has been eliminated from plasma. It has been demonstrated that relation between global ejection fraction and LDH infarct size is maintained, regardless of whether thrombolytic therapy is given.²⁵ Similarly, in this study, regression lines relating infarct size and left ventricular function were the same



Plot showing correlation between global left ventricular ejection fraction in percent (x axis) and LDH Q_{72} (y axis) in units per liter for patients with first acute myocardial infarction (AMI) (both treatment arms). A, Anterior wall myocardial infarctions; B, nonanterior infarctions.

TABLE 5. Global Ejection Fraction at Rest, During Exercise, and After Exercise in the Two Treatment Groups

	EF at Rest, %	EF at Exercise, %	EF After Exercise, %	P*
All patients				
Primary angioplasty (n=123)	50±10	50±13	52±12	<.001
Streptokinase (n=118)	45±11	45±14	47±13	<.001
Anterior MI				
Primary angioplasty (n=64)	46±11	46±14	48±13	.05
Streptokinase (n=53)	40±11	39±14	42±14	.02
Nonanterior MI				
Primary angioplasty (n=59)	54±8	55±9	57±7	<.001
Streptokinase (n=65)	50±10	49±11	52±10	<.001

EF indicates ejection fraction; MI, myocardial infarction.

*P value for comparison of EF at rest and EF after exercise.

in patients treated with primary coronary angioplasty or streptokinase (Fig 1).

In patients assigned to angioplasty, infarct size (LDH Q_{72}) was 23% (95% CI, 13% to 32%) lower than in those assigned to receive streptokinase ($P=.012$). Half of the patients in our study presented within 2 hours after onset of symptoms. In this subgroup, the limitation of infarct size by primary angioplasty was even larger: 31%. Beyond this "time window" of 2 hours, the reduction of infarct size by primary angioplasty was smaller and did not reach the level of statistical significance. This time-related phenomenon had also been demonstrated in patients receiving thrombolysis compared with those treated with placebo.^{1,22,26}

Myocardial Salvage by Primary Coronary Angioplasty

Data from animal studies have demonstrated that myocardial salvage occurs primarily in the first 3 to 4 hours after coronary artery occlusion²⁷⁻²⁹ and therefore that very early reperfusion is important to limit infarct size. This will result in better left ventricular function and as a consequence may lead to better rate of survival.³⁰ Early complete perfusion (TIMI grade 3) of the infarct-related vessel is the key to myocardial salvage. Often, incomplete perfusion (TIMI grade 2) is also considered to represent successful therapy, but recent studies revealed that patients with grade 2 flow of the infarct-related artery have in fact indexes of myocardial infarction similar to those of patients with occluded coronary arteries (TIMI grades 0 and 1).³¹⁻³³ Primary PTCA has the potential to achieve more rapid and effective reperfusion, defined as TIMI grade 3 flow, compared with thrombolytic therapy. In fact, TIMI grade 3 flow at 90 minutes or at 3 hours was achieved in only 54% to 60% of patients who received the best available thrombolytic regimen in the GUSTO study and the TEAM-2 study.^{33,34} Rapid complete reperfusion is, in our perception, the reason for the significant additional salvage by primary angioplasty. Our study shows that in patients who undergo primary coronary angioplasty, effective restoration of blood flow through the infarct-related artery can be accomplished in 51% of patients by 60 minutes after admission, 81% by 90 minutes after admission, and 92% by 120 minutes after admission.

Left Ventricular Function

Both global and regional left ventricular function were better preserved after primary angioplasty compared with after intravenous streptokinase in the present study (Table 3). Similarly, O'Neill and coworkers³⁵ reported a more effective preservation of ventricular function in patients who underwent primary coronary angioplasty compared with those who received intracoronary streptokinase, and Erbel et al³⁶ found improved left ventricular wall motion and patency after a combined medical and mechanical approach, a finding supported by data from a subgroup of the Dutch Interuniversity trial and a report by Belenkie and coworkers.^{37,38}

In one report, primary coronary angioplasty and tissue-type plasminogen activator therapy salvaged similar amounts of myocardium, as assessed by tomographic imaging with ^{99m}Tc-sestamibi, and additional left ventricular studies at discharge and after 6 weeks failed to show a significant difference between the two patient groups. However, the time from onset of symptoms to start of therapy in this study was longer, and the percentage of anterior wall myocardial infarctions was lower (36%) than in our study population (49%).^{9,39} Furthermore, the Primary Angioplasty in Myocardial Infarction (PAMI) study¹⁸ failed to demonstrate any differences in left ventricular function, as measured with a radionuclide technique, between two groups randomized to receive coronary angioplasty or tissue plasminogen activator therapy. This contrast with our results may be caused by selection bias. These data were obtained in only 62% of patients, whereas in our study these data could be obtained in 96% of patients. Although patients in our trial were allowed to enter the study between 12 and 24 hours (these patients were not included in the PAMI trial), the mean times from symptom onset to randomization (PAMI, 189 minutes) or admission (the present study, 185 minutes) were not strikingly different. Furthermore, about half of the patients in our study presented within 2 hours after symptom onset. This may have influenced the results.

Mechanisms

In studies comparing thrombolytic therapy and placebo treatment, the differences in ejection fraction

remained small although the greatest improvement was observed in the patients with an angiographically documented patent infarct-related artery.^{40,41} Different mechanisms have to be considered to explain the remarkable differences between the two patient groups in the present study.

First, patency of the infarct-related coronary artery is established in approximately 70% to 80% of patients treated with thrombolytic therapy, whereas angioplasty results in patency rates of more than 90%.^{9,10,18,39,42}

Second, by rapid restoration of TIMI grade 3 flow and reduction of the residual stenosis in the infarct-related vessel in 92% of the patients in our study, who underwent primary angioplasty, recovery from ischemia is initiated rapidly, probably resulting in improvement of wall motion and better healing of the infarct zone. A recent study showed a close nonlinear relation between the degree of residual stenosis of the infarct-related artery and the degree of left ventricular dilation at both 6 and 12 months after the first myocardial infarction, which is also in accordance with our (in-hospital) findings.⁴³ The residual coronary artery obstruction may thus limit the flow through the infarct-related artery after successful thrombolysis and result in continuing ischemia, delayed recovery, and even ongoing necrosis of the myocardial tissue involved.^{44,45}

Third, half of our patients presented early after symptom onset and were treated rapidly, with a mean time interval from admission to first balloon inflation of 64 minutes in the angioplasty-assigned group. Several studies have shown that restoration of antegrade blood flow in the infarct-related vessel within 2 hours after symptom onset results in the highest probability of myocardial salvage.^{22,26}

Fourth, the preservation of left ventricular function after primary angioplasty compared with thrombolytic therapy may be different because of hemorrhagic extension to noninfarcted areas of myocardial tissue after thrombolytic therapy and subsequent delayed healing of myocardium. After primary angioplasty, an "anemic infarction" was seen in a small group of patients.¹⁷ However, these phenomena are speculative and need further clinical information.

Fifth, in patients with severe or diffuse three-vessel disease, enhancement of collateral flow to non-infarct-related areas of the myocardium may also contribute to improvement of left ventricular function, and the remodeling process may be reduced. The high incidence of sustained patency of the infarct-related coronary artery in the angioplasty-treated patients may therefore be an important factor in this process.⁹

Last, the avoidance of stimulation of platelet aggregation in patients without thrombolytic therapy could be responsible for the low incidence of reocclusion in patients undergoing primary angioplasty.^{46,47} However, reocclusion remains a major problem after thrombolytic therapy as it results in increased mortality and impaired left ventricular function.^{38,48,49} The reocclusion rate after initially successful thrombolytic therapy may be as high as 25% to 30%, whereas reocclusion occurs in only 3% to 15% after primary coronary angioplasty.^{9,42,46,47,50,51}

Study Limitations

This report is based on data from a single center with an experienced group of interventional cardiologists

and optimal 24-hour coverage of interventional cardiology and cardiac surgical standby. Accordingly, the results cannot necessarily be transferred to the treatment of patients with acute myocardial infarction in general practice.

It is unavoidable that measurement of infarct size and/or left ventricular function is missing for some of the patients. Still, it is unlikely that this has biased our results because the data were very consistent and measurements were complete in at least 90% of the patients. Serial enzyme measurements were not available or were insufficient for adequate analysis for some patients (8%), but most of them also were "early" nonsurvivors, and these patients are likely to have had the largest infarcts. Because only 3 patients died in the angioplasty group versus 11 patients in the streptokinase group, the observed difference in LDH Q_{72} may have been underestimated. Missing data were distributed evenly over the two groups, and imputation for missing values would have strengthened rather than weakened the differences between the two treatment groups.

Data derived from the nuclear technique used for measurement of regional wall motion may be suboptimal because limited information on certain segments of the left ventricular wall is available with the use of a single view. This radionuclide technique is based on measurements of volume and changes of volume, and it gives only an approximation of the actual regional wall motion. Delineation of the apical and inferolateral segments is especially difficult, and overlap is likely to occur in patients with anterior wall myocardial infarction. This may be the explanation for the observed differences in non-infarct-related segments between the two groups.

Evaluation of left ventricular function after myocardial infarction preferably should be done 2 to 3 weeks after the acute ischemic episode because "stunning" of the myocardium takes time to resolve.^{52,53} Delayed recovery of left ventricular function, however, may be observed much longer afterward.⁵⁴ The small difference in time (3 days) between the two groups therefore is not likely to have influenced our study results.

Finally, our observations on left ventricular function were made before or at hospital discharge. No statements about the persistence of the observed differences can be made.

Conclusions

Primary percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction results in a reduction in enzymatic infarct size and in better preserved left ventricular myocardium, especially in the infarct-related zones, compared with patients initially treated with intravenous streptokinase. This resulted in markedly improved in-hospital survival. Rapid restoration of optimal blood flow (TIMI grade 3), adequate reduction of the underlying stenosis in the infarct-related coronary vessel, and reduction of reocclusion probably are all related to the favorable results in patients with acute myocardial infarction treated with primary coronary angioplasty compared with therapy with intravenous streptokinase.

Clinical Implications

Because of the beneficial effects of primary coronary angioplasty on left ventricular myocardium, this procedure should be considered as the treatment of choice in all patients presenting with acute myocardial infarction and signs of involvement of a large amount of myocardial tissue. Primary coronary angioplasty will be particularly beneficial in patients with increased risk for intracranial bleeding or other severe bleeding during thrombolytic therapy.⁵⁵ Triage on admission should be able to identify which patients might benefit most from primary coronary angioplasty. A moderate time delay should not be a drawback to transportation of these patients to a hospital with experience and equipment for interventional cardiology, provided that transportation can be carried out safely. A study on the feasibility of such a policy will be of great importance for the optimal management of patients with acute myocardial infarction.

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