Intravenous Short-term Infusion of Streptokinase in Acute Myocardial Infarction

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SUMMARY Short-term i.v. infusion of streptokinase was performed in 93 patients within 6 hours after the onset of acute myocardial infarction. Twenty-six patients underwent angiography in the acute phase (group A) and 52 underwent angiography in the fourth week only (group B); 15 patients had no angiography. Seven patients died during the hospital stay and six suffered nonfatal reinfarctions. There were no bleeding complications.

In 11 of 21 group A patients, occluded coronary arteries were opened within 1 hour after the streptokinase infusion was started. In 84% of groups A and B, the infarct-related coronary artery was patent in the fourth week. In 75% of the patent arteries, the residual luminal diameter stenosis was less than 70%. According to serial serum CK-MB curves, recanalization was achieved mostly within 1–2 hours.

Myocardial salvage was indicated by improvement in local contraction disorders in the recanalized group A patients and by the significant relationship between infarct size and time from symptom onset to treatment in group B.

These data suggest that a high-dose, short-term, i.v. infusion of streptokinase is a safe and efficient method of restoring coronary blood flow. Expeditious initiation of i.v. streptokinase infusion is a critical determinant for early recanalization and salvage of myocardium. Patients with thrombocytically subtotal occlusion probably receive the most benefit. Evaluation of the true impact on survival and myocardial function will require controlled clinical trials.

THE MOST effective way to limit myocardial necrosis in evolving myocardial infarction may be early restoration of coronary blood flow. This concept is based on animal studies demonstrating that early revascularization can reduce the predicted extent of myocardial infarction and can favorably affect survival.

Coronary angiography within a few hours after transmural myocardial infarction in man has revealed a high incidence of coronary arteries occluded by thrombus. This finding is in accordance with the postmortem findings of occlusive thrombi in about 90% of patients dying of acute transmural myocardial infarction.

These findings were the rationale for intracoronary thrombolysis as a method of coronary artery reperfusion in patients with evolving myocardial infarction. In recent clinical studies, early reopening of the thrombocytically occluded coronary artery could be demonstrated in most patients with acute myocardial infarction. The aim of our study was to evaluate whether i.v. streptokinase in a high-dose, short-term infusion could produce similar results. Preliminary data have already been presented.

After the procedure was explained, each patient gave informed consent. The Ethical Committee of the Berlin Free University Steglitz hospital approved the study.

Methods

Patients and Treatment

Ninety-three patients with symptoms and an ECG typical of acute myocardial infarction were selected for the study. Patients with contraindications to thrombolysis and anticoagulation and those in whom treatment could not be initiated within 6 hours from the onset of chest pain were not included.

Group A

Twenty-six patients (20 male and six female; mean age 56 years, range 32–74 years) underwent angiography before and up to 3 hours after the start of the i.v. streptokinase infusion. Twenty-four hours and during the fourth week after the acute event, control angiography was performed in 25 patients. In all patients, 500,000 IU of streptokinase in 36 ml of saline were infused within 30 minutes.

Group B

Fifty-two patients (41 male and 11 female; mean age 57 years, range 27–75 years) underwent angiography only during the fourth week after myocardial infarction. In 20 of these patients, 500,000 IU of i.v. streptokinase were infused within 30 minutes; in 32 patients, 1.5 million IU of streptokinase were infused within 60 minutes.

Fifteen patients (nine male and six female; mean age 63 years, range 34–75 years) did not undergo angiography because of death, age, other contraindications or lack of consent. Three of these 15 received 500,000 IU and 12 1.5 million IU of streptokinase.

In all patients, 500 IU of heparin, 0.5 g of acetyl salicylic acid and 0.25 g of methylprednisolone were injected intravenously before the streptokinase infusion. For the next 72–96 hours, heparin was infused at a dose sufficient to maintain the partial thromboplastin time at two to four times control. The dose required ranged from 20,000 to 36,000 IU per 24 hours. Phenprocoumon treatment was initiated with 15 mg on the...
first day, 12 mg on the second day, and was continued for the next 3 weeks with the Quick prothrombin time adjusted at a range of 20%.

**CK-MB Control Group**

To compare the times between the beginning of infarct symptoms and attainment of the maximum in the CK-MB activity curve, we obtained serial serum CK-MB activity curves from 67 patients with acute transmural myocardial infarction but without streptokinase infusion. Otherwise, the patients were treated like those in group B. There were 42 men and 25 women, mean age 62 years (range 38–86 years). Twenty-nine patients had an anterior and 38 an inferior infarction.

**Angiography Protocol in the Acute Phase**

In the catheterization laboratory, a Judkins catheter was inserted with a #7F catheter sheath introducer system into the femoral artery. The coronary artery corresponding to the ECG location of the myocardial injury was visualized before and after intracoronary injection of 0.3 mg of nitroglycerin. Thereafter, 500,000 IU of i.v. streptokinase were infused within 30 minutes. At commencement of the infusion, a Dugor pigtail catheter was placed into the left ventricle and ventriculography was performed. Subsequently, selective coronary angiography of the noninfarcted coronary artery was performed and a Swan-Ganz catheter inserted percutaneously into the pulmonary artery through the right femoral vein.

If the occluded artery was not reopened 60 minutes after the i.v. streptokinase infusion was started, recanalization with a soft guide wire was attempted, followed by intracoronary infusion of streptokinase, 2000–4000 IU/min for 60 minutes.

The patient then was transferred to the coronary care unit. The Swan-Ganz catheter remained in the pulmonary artery for routine monitoring and the Dugor pigtail catheter remained in the abdominal aorta; a light-pressure bandage was placed on the femoral puncture sites. Left ventricular and coronary angiography were repeated after 24 hours; the new catheters were inserted through the introducer in the right femoral artery. The catheters were removed about 12 hours later and a tight pressure bandage was applied.

**Modes of Investigation**

In patients undergoing angiography in the acute phase, a left ventricular angiogram was performed in a 30° right anterior oblique projection before streptokinase, 24 hours later, and in the fourth week.

During the fourth week in all patients, a left ventricular angiogram in 30° right anterior oblique projection was obtained without nitroglycerin. Then, coronary angiograms were obtained in multiple projections, including two cranial angulation views. Thereafter, 0.8–1.6 mg of nitroglycerin were given sublingually and a second left ventricular angiogram was performed. This was done to establish the same conditions as in the acute phase, when all patients had also received nitroglycerin. Furthermore, it was an attempt to detect residual myocardial function.

**Quantification of Left Ventricular Wall Motion**

To eliminate observer bias in the angiographic analysis, tracings were done in a blind fashion. Films were projected by a video camera or directly displayed from a tape recorder (Sony U-Matic) to the monitor of a digital image-analysis computer (Cardio 80, Kontron Electronic Ltd.). Left ventricular cavity borders from end-diastolic and end-systolic frames were outlined within the video image by a cursor connected to a digitizer tablet and stored in the core memory. Ejection fraction was calculated by digital computation from the traced end-diastolic and end-systolic silhouettes according to the area-length method of Sandler and Dodge.17

To evaluate ventricular wall motion, the computer constructed a polar coordinate system based on the midpoints of the long axes of the ventricular silhouettes. Excluding the aortic valve plane, the computer divided the silhouettes into 48 segmental radii with equal angles. The end-diastolic and end-systolic contours were superimposed on their long axes and midpoints. The total systolic shortening of a segmental radius was calculated by the formula

\[
\frac{\% \text{ systolic shortening}}{D} = \frac{D - S}{D} \times 100,
\]

where \(D = \) length of end-diastolic segmental radius and \(S = \) length of end-systolic segmental radius.

The results were printed out as numerical data and a histogram of percent shortening of systolic segmental radii. The first five segmental radii (mitral valve area) and the last three (46–48, aortic junction) were excluded from evaluation. Figure 1 shows a hard copy computer histogram.

In group A, all segmental radii of the involved ischemic area with systolic shortening less than 26% (≤ 25%) were defined as asynergic.18 These segmental radii were counted and the average systolic shortening was calculated. The average systolic shortening of the same segmental radii was evaluated after 24 hours and in the fourth week.

In group B in the fourth week, segmental radii corresponding to the infarct-related artery with systolic shortening ≤ 25% were counted \((N_{25})\), the extent of systolic shortening was averaged as in group A \((S_{25})\), and the infarct area was calculated in area units \((U)\) by the formula \(A_{25} = (26 - S_{25}) \times N_{25}\) (fig. 1). In addition, corresponding calculations were performed of segmental radii shortening ≤ 10% for quantitative evaluation of the akinetic area.18 Patients with previous infarctions or reinfarctions after fibrinolytic treatment were excluded.

**Measurement of the Coronary Artery Lesions**

In groups A and B, the residual luminal diameter \((D)\) of the most severe stenotic area of the infarct-related coronary artery was calculated by the formula9:

\[
\% D_{\text{stenosis}} = \frac{D_{\text{stenosis}} - D_{\text{prestenosis}}}{D_{\text{prestenosis}}} \times 100.
\]
The diameter of the prestenotic as well as of the stenotic area was measured in two to five (mean 3.0 ± 0.8) cineprojections at end-diastole. The borders of the selected vessel segments were traced with a cursor and diameters were determined by digital computation. The mean diameter stenosis was computed for all measurements.

If, in patients with inferior myocardial infarction, lesions were found in the right coronary artery (RCA) as well as in the left circumflex artery (LCx), the artery with the higher graded stenosis was considered responsible for the infarction. Decisions were supported by the fact that patients in whom the LCx or one of its major branches was the infarct artery in the ECG usually showed the pattern of an inferolateral myocardial infarction.

Blood Analyses

Serial CK-MB determinations20 (CK-MB NAC akt.

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**TABLE 1.** Group A: Findings in the Infarct-related Coronary Artery

<table>
<thead>
<tr>
<th>Restoration of blood flow</th>
<th>Patients with subtotally occluded infarct artery</th>
<th>Patients with occluded infarct artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAD</td>
<td>RCA</td>
</tr>
<tr>
<td>Within 1 hour</td>
<td>3 (100%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>With additional maneuvers</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No restoration of blood flow</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: RCA = right coronary artery; LAD = left anterior descending coronary artery.
successful cases it was 1.03 hours shorter than in the 10 patients not recanalized within 60 minutes ($p < 0.05$) (fig. 3).

In four of the 10 primarily unsuccessful cases, additional maneuvers were effective. In one patient, recanalization of the LAD and immediate fast flow of contrast material through a 64% diameter stenosis was achieved by passing a soft guide wire. In two patients with occlusion of the LAD and in one patient with occlusion of the RCA, reopening occurred during a subsequent 60-minute intracoronary (intraostial) infusion of streptokinase. In six patients, reopening could not be achieved either by mechanical maneuvers or by intracoronary streptokinase. One of these patients with persisting occlusion of the LAD died from ventricular rupture 3 hours later.

In 15 of 21 patients, a totally occluded infarct artery was recanalized. The average time from symptom onset to treatment was 1.37 hours shorter than in the patients with an unsuccessful attempt at recanalization ($p < 0.05$).

The presence of collateral flow had no influence on the efficacy of the thrombolysis. Collaterals were demonstrated in three of the 15 recanalized and in two of the six nonrecanalized coronary arteries.

Angiographic studies after 24 hours and in the fourth week revealed reocclusion of the RCA in one of the 11 patients with primarily successful revascularization. In the four patients recanalized during subsequent maneuvers, the involved coronary artery remained patent. In two of the five surviving patients with unsuccessful attempts at recanalization during angiographic studies up to 3 hours, the involved coronary artery was found to be recanalized after 24 hours as well as in the fourth week.

In five patients, the initial angiography revealed only thrombotically subtotal occlusion of the coronary artery corresponding to the ECG location of myocardial injury (table 1). Two patients had sluggish flow and diminished, threadlike diameters beyond the site of obstruction and in two we observed a short-term temporary total occlusion. In all cases, a decrease in coronary obstruction was observed during i.v. streptokinase infusion and impaired coronary flow was restored. However, only one of the five patients developed no significant Q waves on the ECG. This patient also had no significant left ventricular wall motion impairment.

**Left Ventricular Function**

The individual data and mean values of the ejection fraction are shown in figure 4. Comparing the ejection fractions measured after nitroglycerin using Friedman's test, we did not find a common trend for any
After 24 hours and in the subgroup, the individual data show a wide scatter. During the acute phase before streptokinase treatment, the individual data show a wide scatter. After 24 hours and in the fourth week, the mean value increased somewhat, although in some patients the ejection fraction did not change or even deteriorated. The latter could be explained in part by a hyperkinetic contraction of noninfarcted areas in the acute phase and lack of this compensatory mechanism in the fourth week in five patients. The four patients with thrombotic subtotal occlusion (the one without significant myocardial injury is excluded) showed good improvement after lysis of the thrombus. In the five patients in whom the artery remained occluded, the ejection fraction tended to decrease from the acute phase to the fourth week.

Individual data and mean values of the segmental radii shortening ≤ 25% in the acute phase before streptokinase infusion and subsequent changes of the mean values of the same segmental radii are shown in figure 5. Examples of original printouts from the analyzing system are shown in figure 6.

Friedman’s test revealed a significant trend toward increased regional segmental shortening among patients in whom the involved coronary artery reopened (p < 0.01), which was due to improvement in the fourth week rather than in the first 24 hours (p < 0.01). Again, the best results were obtained in patients with subtotally occluded infarct arteries. Because of sample size, however, these results are not significant.

In three of the five patients in whom the infarcted artery remained occluded, there was an unexplained increase 24 hours later as compared with the acute phase. Altogether, however, segmental shortening of the infarcted areas did not change from the acute phase up to the fourth week.

The three patients with preintervention collaterals and recanalization of a totally occluded infarct artery showed improvement of ejection fraction and wall motion abnormalities. The number of patients, however, is too small to draw any conclusion.

**Group B**

Two of the 52 patients studied angiographically in the fourth week had a history of aortocoronary bypass surgery when entering the study. In both cases, in the fourth week the bypasses were open and the state of the

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**Figure 3.** Distribution of group A patients with (open) and without recanalization (hatched) of an occluded infarct artery according to the time interval from symptom onset to treatment (A) within 1 hour after beginning of streptokinase infusion; (B) including additional maneuvers.

**Figure 4.** Individual data and mean values of the ejection fraction in 24 group A patients before i.v. streptokinase infusion (acute), after 24 hours, and in the fourth week without and after nitroglycerin (NTG) sublingually.
coronary arteries unchanged compared with angiography before the acute event. All further evaluation refers only to the remaining 50 patients.

In 42 patients (84%), the involved coronary artery corresponding to the ECG location of myocardial injury was patent. Five of the eight patients with an occluded vessel had a clinically, electrocardiographically and enzymatically proved reinfarction in the primarily involved area 3–12 days after the first acute event. Thus, a primarily recanalized artery was probably reoccluded in these patients.

The average time from symptom onset to treatment in the 50 patients was 2.9 ± 1.4 hours. In the 42 patients with a patent infarct coronary artery in the fourth week, it was 1.92 hours shorter than in the three patients with an occluded infarct artery who had no reinfarction (p < 0.01). Comparison of risks between treatment beginning before or 3 hours after the onset of symptoms is given in table 2.

Left Ventricular Function

Ejection fraction and regional left ventricular wall motion abnormalities in the fourth week could be evaluated in 34 patients who had no infarction before the acute event and no reinfarctions thereafter. The time interval between onset of symptoms and beginning of treatment was 3.07 ± 1.5 hours. In table 3, mean values and standard deviations together with correlations with beginning of treatment are listed. All six variables of local contraction disorders revealed a significant correlation with the beginning of treatment after onset of symptoms, i.e., the infarct size calculated in the fourth week significantly depended on the treatment delay. Figure 7 shows this relationship for the infarct size calculated in area units (A25).

Groups A and B in the Fourth Week

Patients Without Major Myocardial Lesions

In seven of 54 patients without previous infarctions or reinfarctions, none of the segmental radii showed a systolic shortening of less than 26% (two of 20 from group A and five of 34 from group B).

In four of the five patients from group B, streptokinase infusion was initiated less than 2 hours after the onset of symptoms; in one there was a delay of 5.25 hours. All five patients had persistent ST-segment elevations before streptokinase infusion in the acute phase. Two developed only negative T waves and three also developed small but significant Q waves. The maximal CK-MB was less than 15 IU in two and 15–25 IU in three. One of the two patients of group A had a subtotal occlusion of the RCA and no significant wall motion abnormalities, although contrast runoff was delayed on the first angiogram. In the other patient, who had preintervention collaterals, a completely occluded LAD was recanalized 4 hours after onset of symptoms.

Three of the 15 patients with previous infarctions did not have new significant Q waves or an increase in the serial serum CK-MB activity curve. Treatment was initiated in these patients 0.25, 0.7 and 2.5 hours after onset of symptoms.

Thus, according to lack of significant left ventricular wall motion abnormalities in the fourth week or the absence of a significant increase in serum CK-MB, 10 of 75 patients (13%) did not develop major myocardial lesions.

Residual Infarct Artery Lesions

The residual mean diameter stenoses of the infarct-related coronary arteries in the fourth week after the acute event are shown in table 4 for the 75 patients of groups A and B. Fourteen patients had a luminal diameter stenosis of less than 55%, which equals an area stenosis of less than 80%. Thirty-three patients had a diameter stenosis of 55–69% (area stenosis of 80–90%). Sixteen patients had subtotal occlusion of the infarct-related coronary artery with a diameter stenosis of ≥ 70% (area stenosis > 90%). In 12 patients the infarct vessel was occluded. In one group A patient,
the primarily recanalized RCA was reoccluded, and in group B five of eight patients had a postintervention reinfarction.

The RCA was occluded more often than the LAD (table 5). This was not due to a higher reinfarction rate related to the RCA. There were two reinfarctions related to either vessel and one reocclusion of the RCA.

**Regional Wall Motion RAO**

**Serum CK-MB Activity Curves**

Three examples of CK-MB serial serum activity curves are shown in figure 8.

**Group A**

Table 6 is a summary of the data obtained in 25 patients of group A. One of the 26 patients of group A died before completion of the CK-MB curve. In the five patients in whom attempts to recanalize a totally occluded infarct artery were unsuccessful, the serum CK-MB activity rose about 7 hours after onset of symptoms and reached a maximum 22.9 ± 1.7 hours after onset of symptoms, or 18.15 ± 1.9 hours after treatment was started. In the 15 patients with recanalization of a totally occluded infarct vessel, the CK-MB serum curve began to rise sharply about 20–30 minutes after recanalization and reached a “washout” peak 8.1 ± 2.6 hours later (4.7 ± 12.5 hours after recanalization). The peak CK-MB was reached 9.4 ± 2.8 hours after the beginning of treatment, or 12.8 ± 2.3 hours after the onset of symptoms. The differences in these time intervals, compared with the corresponding figures in patients with remaining occlusion of the infarct artery, were highly significant (p < 0.001).

The CK-MB maximum after reopening of a totally occluded coronary artery averaged 117.1 ± 45.2 IU, which was not significantly different from the maximum CK-MB value of 86 ± 26.3 IU in the five patients in whom the infarct artery remained occluded. Patients with subtotal occlusion on the first angiogram showed premature peaks in the CK-MB serum curve like those with reopening of an occluded artery. These patients, however, had a significantly lower CK-MB maximum (mean 45.7 ± 16.1 IU, p < 0.01).

**Group B**

Six patients in whom treatment was started 1.1 ± 0.8 hours after symptom onset had no significant increase in the serum CK-MB activity curve above 15 IU. One developed a small infarction with an A_{25} of 16.5 IU.

Mean values and standard deviations for the remaining 44 patients are listed in table 7. In 36 patients with a patent infarct artery, and in five with an occluded artery who had suffered reinfarctions 3–12 days after intervention, the average peak CK-MB after beginning of treatment or after onset of symptoms was reached as early as in the 15 recanalized patients of group A (table 6). One patient with a patent infarct artery, however, showed peak CK-MB activities 19 hours after begin-

**Figure 6.** Hard copy printouts of systolic shortening of 48 segmental radii of the left ventricle. Contrast cineventriculograms are in the 30° right anterior oblique projection. From top to bottom: before streptokinase infusion (acute), after 24 hours, in the fourth week without and after nitroglycerin (NTG) sublingually. (A) Patient with thrombotic subtotal occlusion of the left anterior descending coronary artery (LAD) and lysis of the thrombus. (B) Patient with recanalization of the thrombotic occluded LAD.
ning of treatment, or 24 hours after onset of symptoms. Delayed CK-MB peaks of this order are expected in an unsuccessful attempt to reopen an occluded infarct artery, as shown in Table 6. Thus, this patient probably exhibited a late (spontaneous?) recanalization.

One of the three patients of group B with an occluded infarct artery and no postintervention reinfarction had early peaks at 7.5 and 11.5 hours, respectively. This patient had a maximum CK-MB of only 24.2 IU and the serum CK-MB activity curve showed a long plateau. In such cases, the exact time of a peak is difficult to evaluate.33

In comparison with the control group, a highly significant difference ($p < 0.001$) was observed in the time the peak CK-MB was reached after onset of symptoms (Table 7).

**CK-MB Maximum and Infarct Size**

Figure 9 shows the relationship between the infarcted areas and the CK-MB peak values in the serial serum activity curves for the 34 patients without previous infarctions or reinfarctions. Correlation coefficients for the six variables of regional left ventricular wall motion abnormalities are listed in Table 8. There is a highly significant correlation between local contraction disorders, ejection fraction and CK-MB maximum values.

**Clinical Course and Complications**

Intravenous streptokinase infusion was followed by a gradual return of ST segments and, often, by rapid development of Q waves and negative T waves. Slight

### TABLE 2. **Group B: Relationship Between Beginning of Streptokinase Infusion Within 3 Hours or Later Than 3 Hours after Onset of Symptoms and Patency of the Infarct Coronary Artery in the Fourth Week After the Acute Event**

<table>
<thead>
<tr>
<th>Infarct artery</th>
<th>≤3 hr</th>
<th>&gt;3 hr</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>patent</td>
<td>26</td>
<td>16</td>
<td>42</td>
</tr>
<tr>
<td>occluded, no reinfarction</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>19</td>
<td>45</td>
</tr>
<tr>
<td>Risk</td>
<td>0%</td>
<td>15.8%</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3. **Ejection Fraction and Six Variables of Local Contraction Disorders in 34 Patients: Mean ± so and Correlations to Time Intervals from Symptom Onset to Treatment**

<table>
<thead>
<tr>
<th>% D&lt;sub&gt;stenosis&lt;/sub&gt;</th>
<th>EF (%)</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤55%</td>
<td>64.6±12.1</td>
<td>-0.207</td>
<td>NS</td>
</tr>
<tr>
<td>(mean 42.6±10.6, range 23–51%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–69%</td>
<td>12.2±8.1</td>
<td>0.313</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(mean 61.9±3.8, range 56–68%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70%</td>
<td>14.3±8.4</td>
<td>-0.475</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(mean 74.7±4.2, range 70–82%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occluded</td>
<td>177.0±159.0</td>
<td>0.417</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(mean 74.7±4.2, range 70–82%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4.7±5.7</td>
<td>0.430</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(mean 74.7±4.2, range 70–82%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.9±5.5</td>
<td>-0.415</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(mean 74.7±4.2, range 70–82%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44.0±75.0</td>
<td>0.301</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(mean 74.7±4.2, range 70–82%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EF = ejection fraction; n = number of segmental radii; U = area units. See Methods for explanation of other abbreviations.

### TABLE 4. **Groups A and B: Residual Mean Diameter Stenosis of the Infarct-related Coronary Artery in the Fourth Week**

<table>
<thead>
<tr>
<th>% D&lt;sub&gt;stenosis&lt;/sub&gt;</th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤55%</td>
<td>6(15%)</td>
<td>2(25%)</td>
<td>6(22%)</td>
<td>14(19%)</td>
</tr>
<tr>
<td>(mean 42.6±10.6, range 23–51%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–69%</td>
<td>20(50%)</td>
<td>3(38%)</td>
<td>10(37%)</td>
<td>33(44%)</td>
</tr>
<tr>
<td>(mean 61.9±3.8, range 56–68%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70%</td>
<td>11(28%)</td>
<td>2(25%)</td>
<td>3(11%)</td>
<td>16(21%)</td>
</tr>
<tr>
<td>(mean 74.7±4.2, range 70–82%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3(8%)</td>
<td>1(12%)</td>
<td>8(30%)</td>
<td>12(16%)</td>
</tr>
</tbody>
</table>

### FIGURE 7. **Relationship between infarct size (A<sub>25</sub>) and time interval from symptom onset to treatment in 34 group B patients without previous infarction or postintervention reinfarction.**

ST-segment elevations, however, may persist for several hours. High-grade atrioventricular block in patients with inferior infarctions usually return to normal conduction within a short time. One patient developed ventricular fibrillation 20 minutes after commencement of the streptokinase infusion. Four patients had a self-terminating slow ventricular tachycardia.

Seven patients had clinical signs of cardiogenic shock on admission or shortly thereafter. They had catecholamine-dependent low blood pressure and were treated with dobutamine or dopamine, and three had an infusion of norepinephrine in addition. Three patients survived. The clinical signs of shock improved dramatically within hours.

Six of the 93 patients suffered a nonfatal reinfarction at the site of the primary injury. The clinical course of
these reinfarctions was mild and the corresponding increase in the CK-MB serum activity was small. In two of the five patients with angiography in the fourth week, the measured infarct size was large, which may indicate that very little viable myocardium survived after the first occlusion. The three other patients suffered reinfarctions, but the A25 was only 129, 172 and 182 U, respectively. One patient with unstable postinfarction angina had early bypass surgery on the twenty-fourth day and made a complete recovery.

No pyretic or allergic reactions attributable to streptokinase occurred. In a few patients, a drop in arterial blood pressure or bradycardia was observed during streptokinase infusion. Intravenous injection of 0.5–1.0 mg of atropine usually restored both.

No serious bleeding complications occurred, although serum fibrinogen concentration usually decreased below 1 g/l over a period of 24–36 hours. For technical reasons, one patient developed a somewhat larger hematoma from bleeding at the femoral puncture site. Patients who had undergone cardiovascular resuscitation with extensive external heart massage and patients who required multiple punctures before successful catheterization of the subclavian or internal jugular vein were not treated with streptokinase.

No group A patient died during the acute intervention. One patient had a blood pressure drop after the first visualization of the noninfarcted coronary artery and subsequently had ventricular fibrillation. He was defibrillated promptly and had an uneventful recovery. One patient died in hospital due to ventricular rupture 3

hours after an unsuccessful attempt to recanalize an occluded LAD, as described above. Seven of the 93 patients died during hospital follow-up, four from cardiogenic shock, two from ventricular wall ruptures, and one from reinfarction. (The last patient had severe three-vessel disease.) All deceased patients had an anterolateral infarction and five of them had had previous infarctions.

During the follow-up period of 4–25 months, four patients died. Three suffered sudden death and one had reinfarction and cardiogenic shock. Aortocoronary bypass surgery had been recommended to two patients, but both declined. Fourteen patients have had bypass surgery or transluminal angioplasty because of severe stenosis of the major arteries or chest pain unresponsive to therapy. All but six of the remaining 62 patients feel well and are remarkably free of symptoms, al-

Table 5. Groups A and B: Differences in the Occlusion Rate of the Left Anterior Descending and Right Coronary Arteries in the Fourth Week

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>RCA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent</td>
<td>37</td>
<td>19</td>
<td>56</td>
</tr>
<tr>
<td>Occluded</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>27</td>
<td>67</td>
</tr>
</tbody>
</table>

Risk 7.5% 29.6%

Chi-square = 5.75 (p < 0.05).

Abbreviations: See table 4.

Table 6. Group A: Data from Serum CK-MB Activity Curves

<table>
<thead>
<tr>
<th>Infarct-related coronary</th>
<th>No. of pts</th>
<th>Time between onset of symptoms and start of treatment (hours)</th>
<th>Time to peak CK-MB after start of treatment (hours)</th>
<th>Time to peak CK-MB after onset of symptoms (hours)</th>
<th>Maximal CK-MB (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotally occluded</td>
<td>5</td>
<td>3.3 ± 1.2 (2.0–5.2)</td>
<td>9.6 ± 3.4 (5.5–13.75)</td>
<td>12.9 ± 3.4 (9.0–16.75)</td>
<td>45.7 ± 16.1‡</td>
</tr>
<tr>
<td>Recanalized</td>
<td>15</td>
<td>3.4 ± 1.3* (1.85–6.00)</td>
<td>9.4 ± 2.8† (5.25–13.25)</td>
<td>12.8 ± 2.3† (9.5–18.0)</td>
<td>117.1 ± 45.2‡</td>
</tr>
<tr>
<td>Remained occluded</td>
<td>5</td>
<td>5.0 ± 0.7* (4.25–6.00)</td>
<td>18.15 ± 1.9† (10.0–20.75)</td>
<td>22.9 ± 1.7† (21.0–25.0)</td>
<td>86.0 ± 26.3</td>
</tr>
<tr>
<td>Sum</td>
<td>25</td>
<td>3.7 ± 1.3 (1.85–6.00)</td>
<td>10.9 ± 4.3 (5.5–20.75)</td>
<td>14.8 ± 4.7 (9.0–25.0)</td>
<td>96.6 ± 46.7</td>
</tr>
</tbody>
</table>

*p < 0.05 between recanalized and remained occluded.

†p < 0.001 between recanalized and remained occluded.

‡p < 0.01 between subtotally occluded and recanalized.
though some have severe residual stenosis of major arteries.

**Discussion**

**Restoration of Coronary Blood Flow**

Although recanalization of occluded coronary arteries by intracoronary thrombolytic agents represents a most promising new treatment for acute myocardial infarction, the necessity of intracoronary catheterization limits this therapy to a small number of patients. We have demonstrated prompt recanalization of the thrombically occluded infarct vessel by i.v. short-term, high-dose, i.v. streptokinase infusion. The success rate of about 50% in our group A patients refers to an observation time of 1 hour after the beginning of the streptokinase infusion and to a beginning of treatment 3.8 ± 1.3 hours after symptom onset on the average. Time to lyse an intracoronary clot largely depends on the age of the thrombus and, even with intracoronary streptokinase infusion, lysis may last longer than 1 hour. This may partly explain the difference between our data and the recently reported recanalization rate of 67–90% with intracoronary streptokinase infusion. Flow was restored in all of our patients who received streptokinase within 3 hours (fig. 3, table 2).

To shorten the time between onset of symptoms and thrombolytic treatment, we decided, in the beginning of 1981, not to perform angiography in the acute phase. Whenever possible, streptokinase infusion was initiated in the mobile coronary care unit or in the patient’s home. This decision was supported by the fact that early recanalization of the infarct-related coronary artery by high-dose, short-term i.v. infusion of streptokinase had been confirmed.25 Reopening of a totally occluded artery 48 ± 13 minutes after beginning a 60-minute i.v. infusion of 1.5 million IU of streptokinase in 24 of 38 patients (63%) has been reported.

**Abbreviations:** See table 3.
Benefit for Patients with Subtotal Occlusion

Objections raised against i.v. streptokinase treatment without angiography in the acute phase are based on the concern that patients who do not have complete coronary artery occlusion may not benefit from this treatment. In about 20% of patients selected in four German clinics for intracoronary application of streptokinase, only subtotal obstruction was found.22 Our findings of subtotal occlusion in five of 26 patients with evolving myocardial infarction is in keeping with these data. DeWood et al.6 observed a patent, but still highly obstructed, coronary artery in 13% of patients evaluated within 4 hours, but in 32% of patients 6–12 hours after onset of symptoms, which suggests some spontaneous recanalization after the very early hours of evolving myocardial infarction. However, a patent infarct coronary artery does not necessarily imply sufficient nutrient flow.

Our findings indicate that patients with incomplete occlusion may receive the most benefit from thrombolytic treatment because the threatening coronary thrombus is dissipated and coronary blood flow restored. Nonocclusive coronary thrombi that can progress to total occlusion and myocardial infarction have also been demonstrated in the ischemic syndromes of unstable angina or intermediate coronary syndrome.28 Neill et al.29 showed that approximately one-third of patients with intermediate coronary syndrome exhibited late total occlusion of previously highly stenotic lesions, frequently with associated myocardial infarction. In patients with unstable angina pectoris, Lawrence et al.30 showed that i.v. streptokinase infusion can prevent progression to myocardial infarction.

Serial Serum CK-MB Curves

After reperfusion of an experimentally occluded coronary artery, CK in blood rose rapidly and reached a higher peak significantly earlier than during a 24-hour occlusion.31 These experimental findings are in accordance with the changes in the serial serum CK-MB activity curves after revascularization in patients with evolving myocardial infarction (table 6). A premature appearance of myocardial enzymes and an earlier peak in the serum curve have already been demonstrated in the first clinical application of streptokinase treatment in acute myocardial infarction32 and were confirmed thereafter.15 Serial serum CK-MB activity curves with high peak values usually allow separation of patients with and without recanalization.33

The large difference in the average time intervals between the onset of symptoms and peak CK-MB in recanalized group B patients is not obscured by patients with primarily incomplete obstruction of the infarct artery. When evaluating the effect of an i.v. streptokinase infusion by serial CK-MB serum curves, we use the term “restoration of coronary blood flow.” According to what was discussed above, this expression is basically justified and is clinically meaningful.

Findings in the Fourth Week

Validation of early successful restoration of coronary blood flow based on angiography in the fourth week is weakened by the fact that acute thrombosis in the coronary artery may lyse spontaneously within a relatively brief time after the onset of infarction. However, in recent studies in patients with a history of transmural myocardial infarction, the incidence of patent infarct-related arteries after 2–8 weeks was only 20–25%.21,34 Thus, a substantial persisting recanalization does not occur at least for 1–2 months after myocardial infarction. In contrast, 84% of our patients with angiography in the fourth week showed an unimpaired runoff of the contrast material, and only 21% had a residual mean diameter stenosis of the infarct-related coronary artery of more than 70% (table 4). Taking into account that five patients have had reinfections and, therefore, probably recurrences, the recanalization rate achieved by high-dose i.v. streptokinase infusion initiated early in evolving myocardial infarction must be of the same order as with intracoronary streptokinase application.

Time Between Onset of Symptoms and Revascularization

Neuhaus et al.25 showed that lysis of an intracoronary clot lasts, on the average, 15 minutes longer than that with intracoronary streptokinase application. However, because their study was not performed in a randomized fashion, the data are not conclusive. Moreover, infusion of streptokinase not intracoronally, but in the immediate vicinity of the site of coronary occlusion, may shorten the time until reperfusion is achieved by the intracoronary approach.4 Nevertheless, the slight delay in restoration of coronary blood flow with i.v. compared with intracoronary streptokinase may not be of decisive importance, especially considering that systemic streptokinase infusion can readily be implemented by the primary care physician. If a 60-minute i.v. infusion of 1.5 million IU of streptokinase was initiated within 3 hours from symptom onset, rapid recanalization of a totally occluded infarct artery could be achieved in 73% of cases.35 These results are in keeping with the findings in our group A patients (fig. 3).

In our group B patients, the CK-MB serum curves suggest that early restoration of coronary blood flow must have been achieved in the majority of cases. To estimate without angiographic proof whether and
when restoration of coronary blood flow may have occurred, it is preferable to use the beginning of the streptokinase infusion as the point of reference. In individual cases, only a rough estimate is possible. For a group of patients, however, the mean values allow a general conclusion. There was no difference in the mean time intervals the CK-MB peaks were reached after starting of treatment in the recanalized group A patients and in those with a patent infarct artery in the fourth week in group B (tables 6 and 7). In 65% of our group B patients, the peak CK-MB appeared within 9 hours after the start of the streptokinase infusion (mean 7.5 ± 1.2 hours). This interval is even shorter than the mean interval of 8.1 ± 2.6 hours between recanalization and peak CK-MB in group A patients. Although about 20% of group B patients may have had a subtotal occlusion of the infarct artery, rapid recanalization of an occluded artery still must be assumed in the majority of cases.

Salvage of Ischemic Myocardium?

Recanalization of an infarct coronary artery does not necessarily imply benefit for the patient. From our data, no definitive conclusion can be drawn because a randomized control group is lacking. However, there is some evidence of myocardial salvage.

There was a small but significant improvement in local contraction disorders in the fourth week among patients evidencing reperfusion of occluded coronary arteries. In patients without reperfusion, regional wall motion did not change from pretreatment to the fourth week. The latter finding is in agreement with previous hemodynamic and radionuclear studies demonstrating that left ventricular performance does not change during the hospital phase of conventionally treated patients with acute myocardial infarction.

Evaluation of the infarct size in the fourth week revealed a significant relationship with the time interval from symptom onset to treatment. This finding strongly suggests that at least in the early treated patients the ultimate infarct size could be reduced. It also emphasizes the importance of expeditious initiation of streptokinase treatment, not only for achieving patency, but also for salvaging myocardium.

Ten of our patients did not develop major myocardial lesions. In their clinical presentation of evolving myocardial infarction they did not differ from those who developed significant myocardial necrosis. Thus, prevention of myocardial infarction may be possible in at least some of these patients.

In experimental animals, after reperfusion, the total amount of CK measured in the serum per gram of necrotic myocardium was nearly twice as high as without reperfusion. Thus, the infarct size cannot be calculated using the known formulas. In our patients, the infarct size in the fourth week still showed a highly significant correlation with the maximal serum CK-MB. In revascularized patients, equal infarct sizes may correlate with a higher serum CK-MB maximum value than in patients without reperfusion. Yet, in our streptokinase-treated group B, the average maximal CK-MB does not differ from that in the untreated control group. Thus, infarct size may be limited by i.v. streptokinase infusion.

Therapeutic Implications

The present study has demonstrated rapid restoration of coronary blood flow in patients with evolving myocardial infarction. Although intracoronary application may be somewhat more effective, the advantage of i.v. administration is striking. Furthermore, the shorter time required to achieve lysis by intracoronary application may be more than balanced by the earlier beginning of i.v. infusion. The optimal dosage of streptokinase and duration of i.v. infusion are not yet known. During our study, we increased the dosage to 1.5 million IU and the duration of the infusion to 60 minutes. The main reasons were that this regimen will be applied in a projected multicenter trial and that our current investigations serve as a pilot study.

Although serum fibrinogen concentration decreased markedly, there was no serious bleeding complication in our patients. However, contraindications to streptokinase, heparin and anticoagulation have to be considered. Ventricular wall rupture in two of 93 patients with acute transmural infarction is rather less than what is expected in conventionally treated patients. The occurrence of rupture very early during the course of evolving myocardial infarction, 3–4 hours after streptokinase infusion, is noteworthy. Both patients had had conventionally treated smaller infarctions in the same area 2–3 weeks before.

Considering the experience of others, we concluded that i.v. short-term infusion of streptokinase can be performed safely in patients with evolving myocardial infarction. The clinical results are encouraging. Yet, to ascertain the true impact on short- and long-term morbidity and mortality from acute myocardial infarction, a conclusive randomized trial is needed. Accordingly, a multicenter, double-blind, placebo-controlled trial with 26 German and Swiss hospitals participating was started in March 1982.

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