THERAPY AND PREVENTION
THROMBOLYSIS

The effects of the rate of intravenous infusion of streptokinase and the duration of symptoms on the time interval to reperfusion in patients with acute myocardial infarction

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ABSTRACT We studied the influence of the following variables on the time interval from initiation of an intravenous infusion of 750,000 U of streptokinase until reperfusion (reperfusion time) in 140 consecutive patients with an evolving acute myocardial infarction: (1) the rate of infusion of streptokinase, (2) the duration of chest pain before initiation of treatment, (3) patient age, (4) patient sex, (5) location of infarction, (6) history of previous myocardial infarction, and (7) pretreatment pathologic Q waves. The time of reperfusion was determined by clinical criteria that were completely concordant with the anatomic findings in all 119 patients in whom patency or occlusion of the artery of infarction was established at delayed angiography (n = 116) or at postmortem examination (n = 3). The mean reperfusion time for the 129 patients for whom data were available was 49 ± 36 min. The reperfusion time was inversely related to the rate of infusion of streptokinase (r = .41, p < .001), but this effect of infusion rate appeared to plateau at rates of greater than 500 U/kg/min. In the 64 patients receiving infusions at rates of 500 U/kg/min or less, the mean reperfusion time was 60 ± 40 min, whereas in the 58 patients receiving the drug at rates greater than 500 U/kg/min it was 35 ± 22 min (p < .001). The duration of chest pain before treatment was the only other studied variable found to influence the reperfusion time, but only at infusion rates of less than 250 U/kg/min (r = .6, p < .01). Our findings indicate that in patients with acute myocardial infarction who receive high-dose intravenous streptokinase, the time interval to reperfusion can be minimized by increasing the infusion rate up to at least 500 U/kg/min and by shortening the delay from onset of symptoms to treatment.


EARLY REPERFUSION of the artery of infarction may limit the extent of myocardial necrosis in patients with an evolving acute myocardial infarction and improve ventricular function and survival. Both experimental and clinical studies indicate that the critical determinant of the extent of myocardial necrosis and salvage is the duration of myocardial ischemia before reperfusion. In clinical practice, this ischemic period comprises (1) the time interval from the onset of infarction to the commencement of treatment, which is predominantly logistical, and (2) the time interval from commencement of treatment until reperfusion, which is predominantly a biological variable.

In this study, we investigate the potential effect of the following factors on the time interval from treatment until reperfusion by intravenous streptokinase: (1) the rate of infusion of streptokinase, (2) the duration of chest pain before initiation of treatment, (3) patient age, (4) patient sex, (5) the location of infarction, (6) the presence of electrocardiographic and/or historical evidence of a previous infarction, and (7) the presence of pretreatment, pathologic Q waves in the region of the current infarction.

Methods

Patient population. The study population consisted of 140 consecutive patients with acute myocardial infarction (107 men, 33 women) who were 62 ± 12 years old (range 32 to 86) and were included in a prospective study of intravenous streptokinase. All fulfilled the following criteria: (1) chest pain of less than 3 hr duration at the time of evaluation by the cardiology team, (2) ST segment elevation indicative of transmural ischemia, (3) persistent chest pain and electrocardiographic changes after sublingual nitroglycerin, (4) absence of contraindications to thrombolytic or anticoagulant therapy, and (5) consent from both the patient's physician and the patient.

Administration of streptokinase. A 750,000 U dose of...
streptokinase (Hoechst-Roussel) in 45 to 75 ml of normal saline was administered by infusion into a peripheral vein over a period of 3 to 78 min (mean 26 ± 16). The rate of infusion of streptokinase (U of streptokinase/kg body weight/min) could be determined in 133 of the 140 patients as the total dose of streptokinase divided by the weight of the patient and by the time interval over which the drug was administered.

One hundred and thirty-one of the 140 patients received an intravenous bolus of either 100 mg hydrocortisone or 4 mg dexamethasone before they received streptokinase. All patients were begun on a continuous infusion of heparin immediately after the infusion of streptokinase. Eight patients in whom reperfusion had not occurred by 90 min received a second infusion of 750,000 U of streptokinase at the same rate as the first infusion.

**Recognition of reperfusion.** To minimize delay in treatment, pretreatment coronary angiography was not performed and reperfusion was recognized by the following nonangiographic criteria.

**Abatement of symptoms.** Before beginning the infusion of streptokinase, the patient was asked to immediately report any change in chest pain or other symptoms.

**Decrease in ST segment elevation.** A 12-lead electrocardiogram was recorded before the infusion of streptokinase was begun and a lead with distinct ST segment elevation was continuously monitored and observed by at least one, and usually two, of the authors until either there was evidence of reperfusion or for a period of up to 4 hr in patients with no signs of reperfusion. Short recordings of the monitored lead or a 12-lead electrocardiogram were obtained at 5 to 15 min intervals during the procedure and also whenever there was a change in symptoms, a change in ST segment elevation on the monitor, or a change in cardiac rhythm.

**Cardiac enzyme washout.** Blood for determination of serum creatine kinase (CK) and CK-MB activity was drawn at 15 to 30 min intervals for the initial 2 to 4 hr and 1 to 4 hourly for the remainder of the first 24 hr after streptokinase. The CK time-activity curves were plotted and the time of an abrupt rise in CK level (CK washout) was determined.

Reperfusion was considered to have occurred when the following three events occurred in a close temporal relationship: (1) an abrupt abatement or progressive reduction of chest pain, (2) a reduction in the magnitude of ST segment elevation with its progressive decrease in sequential electrocardiograms that continued until the ST segments were isoelectric or reached a stable baseline, and (3) an abrupt and rapid rise in serum levels of CK.

In 15 patients, the chest pain had resolved before commencement of the streptokinase infusion, in two patients there was no CK data, and in six patients the onset of the abrupt and rapid rise in CK was delayed. In these 23 patients, reperfusion was considered to have occurred when there was a sustained and progressive resolution of the ST segment elevation temporally related to either an abrupt abatement or reduction in chest pain or an abrupt and rapid rise in serum CK. Because a progressive resolution of the ST segment elevation was always required as a criterion of reperfusion, the time of reperfusion was defined as the time of onset of the resolution of the ST segment elevation. The time interval to reperfusion (reperfusion time) was defined as the interval from commencement of the streptokinase infusion to the time of reperfusion.

**Coronary anatomy.** In 116 patients, coronary angiography and contrast left ventriculography were performed 4 ± 3 days (range 1 to 15) after admission and were analyzed by two angiographers who were unaware of the results of the other investigations and did not otherwise participate in the study. In three patients who died in-hospital before coronary angiography could be performed, the coronary arteries were examined at a postmortem examination.

Patency or occlusion of the artery of infarction was verified without difficulty in 115 of the 119 patients. In the remaining four patients with both a prior and current inferior infarction in whom either the right or circumflex coronary artery was occluded, determination of the artery of infarction was based on (1) angiographic evidence of an ulcerated atheromatous plaque, i.e., indistinct luminal margins and subintimal defect of the coronary artery following lysis of the clot, (2) the distribution of regional dysfunction and 201TI perfusion on sequential radionuclide studies.

**Statistical methods.** Continuous Gaussian variables are described by their mean and standard deviation. The unpaired Student t test and one-way analysis of variance were used for comparisons between two or more subgroups, respectively. Proportional differences between subgroups were compared with the use of Fisher's exact test. The relationship between continuous variables was analyzed by the unweighted linear least squares method. All analyses were performed with BMDP biostatistical programs and a two-tailed p value of <.05 was considered to indicate statistical significance.

**Results**

One hundred and thirty-four of the 140 patients had nonangiographic evidence of coronary artery reperfusion and the remaining six patients did not. Of the 119 patients with known coronary anatomy, the artery of infarction was found to be patent in all 113 patients with clinical signs of reperfusion and the artery was occluded in the six patients without clinical signs of reperfusion. The reperfusion time could be determined in 129 of the 134 patients with clinical evidence of reperfusion and was 49 ± 35 min (range 5 to 228).

**The effect of the rate of infusion of streptokinase on reperfusion time.** Figure 1 illustrates that in the 122 patients in whom both the rate of infusion of streptokinase (U/min) and the rate of intravenous streptokinase infusion (units/kg/min) could be measured, the rate of intravenous streptokinase infusion was not significantly related to the time of reperfusion.
ase and the reperfusion time were available, there was an inverse relationship between the rate of infusion of streptokinase and the time interval to reperfusion \( (r = .41, p < .001) \), which was similar for patients with anterior and those with inferior infarction. This relationship appeared to plateau at infusion rates of about 500 U/kg/min. In the 64 patients receiving infusions at rates of 500 U/kg/min or less, the mean reperfusion time was 60 ± 40 min compared with 35 ± 22 min in the 58 patients who received infusions at rates of greater than 500 U/kg/min \( (p < .001) \). Figure 1 also indicates that reperfusion time was less than 50 min in only 45% of the 64 patients who received a slower infusion rate compared with 83% of the 58 patients who received a faster infusion rate \( (p < .001) \).

Further analysis of the influence of the rate of streptokinase infusion on the reperfusion time was performed by dividing the study population into five subgroups according to the rate of intravenous infusion (table 1). In 24 patients the infusion rate was 250 U/kg/min or less (very slow group), in 39 patients it was 260 to 500 U/kg/min (slow group), in 20 patients it was 510 to 750 U/kg/min (intermediate group), in 16 patients it was 760 to 1000 U/kg/min (rapid group), and in 23 patients it was greater than 1000 U/kg/min (very rapid group). The difference in the mean reperfusion times between the very slow and slow infusion rate groups \((70 ± 49 \text{ and } 54 ± 34 \text{ min, respectively})\) was not statistically significant \( (p = .07) \), but they were both significantly longer \( (p < .01) \) than the mean reperfusion times in the intermediate \((34 ± 19 \text{ min}), \) rapid \((38 ± 23 \text{ min})\), and very rapid \((34 ± 25 \text{ min})\) infusion rate groups. There was no difference in mean reperfusion time among the latter three groups.

The effect of the duration of chest pain on reperfusion time. For the entire study population, there was no correlation between the duration of chest pain before streptokinase and reperfusion time \( (r = .13) \). To minimize the influence of the infusion rate of streptokinase, the relationship was separately analyzed in five subgroups, each including patients receiving a narrow range of infusion rates defined as the mean value ± 15% of each of the subgroups described in table 1.

The corresponding infusion rate ranges were 210 ± 30 U/kg/min (17 patients), 370 ± 50 U/kg/min (19 patients), 600 ± 90 U/kg/min (17 patients), 880 ± 130 U/kg/min (16 patients), and greater than 1450 U/kg/min (10 patients). Only in the 17 patients from the slowest infusion rate group \((180 \text{ to } 240 \text{ U/kg/min})\) was there a significant correlation \( (r = .6, p = .005) \) between the duration of chest pain and the reperfusion time (figure 2). There was no correlation, or even a trend, for any of the subgroups receiving faster infusion rates of streptokinase.

Other clinical variables (table 2). The reperfusion time was not influenced by any of the other clinical variables that were studied, including patient age, patient sex, location of infarction, the presence of electrocardiographic and/or historical evidence of a previous infarction, and the presence of pathologic Q waves in the region of the current infarction before initiation of streptokinase therapy.

Discussion

The wide range of infusion rates in this study reflects our progressive experience with intravenous streptokinase. Initially, streptokinase was administered very rapidly \((\text{in 5 to 15 min})\) to achieve a high serum concentration similar to that achieved with intracoronary administration; however, these very rapid infusion rates frequently caused hypotension,\(^2,17,19,22,23\) Subsequently, a range of slower infusion rate protocols were used in an attempt to prevent the hypotensive effect. Therefore, our total experience provided the data necessary to study the effect of varying infusion rates on reperfusion time.

Our data indicate that in patients with evolving acute myocardial infarction, the reperfusion time is inversely related to the rate of streptokinase infusion and, at slow infusion rates, is also directly related to the duration of chest pain before initiation of treatment.

Since the rate of infusion affects the serum concentration of streptokinase,\(^24,25\) our results imply that the rate of thrombolysis is a function of the serum concentration of this drug. This finding is consistent with the known direct relationships between the concentration

| TABLE 1 |
| Influence of intravenous streptokinase (IV-SK) infusion rate on time interval to reperfusion |

<table>
<thead>
<tr>
<th>Rate IV-SK (U/kg/min)</th>
<th>Very slow ((n = 24))</th>
<th>Slow ((n = 39))</th>
<th>Intermed. ((n = 20))</th>
<th>Rapid ((n = 16))</th>
<th>Very rapid ((n = 19))</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain to SK (min)</td>
<td>210 ± 30</td>
<td>370 ± 70</td>
<td>600 ± 80</td>
<td>880 ± 70</td>
<td>1700 ± 710</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td>SK to reperfusion (min)</td>
<td>135 ± 53</td>
<td>150 ± 48</td>
<td>137 ± 43</td>
<td>131 ± 55</td>
<td>130 ± 89</td>
<td>NS</td>
</tr>
</tbody>
</table>

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of streptokinase, the concentration of plasminogen activator complex,26 27 and the rate of thrombolysis.27 28 The effect of the streptokinase infusion rate on the reperfusion time appears to plateau at a rate of about 500 U/kg/min and therefore, faster infusion rates, which are more likely to produce significant hypotension, appear to have no advantage with respect to earlier reperfusion.

If one accepts that the chest pain of acute myocardial infarction commences at about the time of thrombotic occlusion of the artery of infarction, then the duration of chest pain in patients with acute infarction is an indirect approximation of age of thrombus, or at least the age of the final occlusive portion of the thrombus. Our finding that at slow infusion rates of streptokinase, the duration of chest pain was a determinant of the reperfusion time, suggests that the age of the thrombus influenced the results of thrombolytic therapy. This is in accordance with clinical studies using streptokinase in which the duration of symptoms before initiation of treatment was shown to be a determinant of both the rate of successful reperfusion16 29-31 and the rapidity of thrombolysis,29 32 and is also consistent with experimental studies showing that older thrombi are more resistant to lysis.33 34 This age-related resistance of the thrombus to lysis may be due to an increased degree of fibrin cross-linking within the thrombus,35 a decrease in plasminogen content of the thrombus due to its retraction,27 36 or thrombus growth with time.37 The finding that the age of the thrombus was a factor only in patients who received streptokinase at slow infusion rates is consistent with the experimental data reported by McDonagh et al.,38 who found the presence of fibrin cross-linking to be a determinant of the rate of thrombolysis at low concentrations of urokinase, but not at high concentrations.

The considerable scatter of our data suggests that reperfusion time after intravenous streptokinase is probably affected by other factors,39 such as the size of the thrombus independent of its age,40 serum levels of plasminogen, antiplasmins,41 42 and neutralizing anti-streptokinase antibodies,42 44 and especially access of streptokinase to the thrombus.24 45 46 The latter depends on the surface area of the thrombus exposed to the lytic agent24 and the antegrade and collateral blood flow reaching the occlusive thrombus,49 which may be especially important when the thrombus is situated distal to a tight stenosis.

A potential limitation of this study is that the determination and timing of reperfusion was based on nonangiographic criteria. However, this reperfusion syndrome, consisting of relief of chest pain, resolution of ST segment elevation, and CK washout, has a sound physiologic basis and its validity is supported by (1) experimental studies,47-49 (2) the complete concordance between the occurrence of this syndrome and the finding of patency of the artery of infarction in our study, and (3) the excellent concordance between these signs and angiographically recognized reperfusion in several intracoronary streptokinase studies.29 50-57 In the intracoronary studies of Lee, Rentrop, Mathey, and Ganz and their colleagues,29 50-52 the clinical signs of reperfusion usually occurred within minutes of the angiographic demonstration of arterial patency and in some studies, these clinical signs were used to indicate when to check the patency of the artery of infarction by angiography.50 58 59 Furthermore, these clinical signs of reperfusion have also been adopted by several other investigators using intravenous streptokinase.16 19 50 60

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>â€‰â‰¤ 60 years (n = 55)</td>
<td>50 ± 34</td>
</tr>
<tr>
<td>â€‰&gt; 60 years (n = 74)</td>
<td>49 ± 37</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male (n = 98)</td>
<td>48 ± 40</td>
</tr>
<tr>
<td>Female (n = 31)</td>
<td>50 ± 33</td>
</tr>
<tr>
<td>Location of infarction</td>
<td></td>
</tr>
<tr>
<td>Anterior (n = 58)</td>
<td>53 ± 36</td>
</tr>
<tr>
<td>Inferior (n = 71)</td>
<td>47 ± 35</td>
</tr>
<tr>
<td>Previous MI</td>
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</tr>
<tr>
<td>Yes (n = 32)</td>
<td>44 ± 27</td>
</tr>
<tr>
<td>No (n = 97)</td>
<td>51 ± 38</td>
</tr>
<tr>
<td>Pretreatment Q waves</td>
<td></td>
</tr>
<tr>
<td>Yes (n = 53)</td>
<td>55 ± 33</td>
</tr>
<tr>
<td>No (n = 68)</td>
<td>46 ± 38</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; SK = streptokinase.
The delay in the abrupt washout of CK relative to the relief of chest pain and resolution of ST segment elevation in six of our patients was similar to that observed in four patients in our intracoronary streptokinase study. In these four patients, the delay in CK washout relative to angiographic patency, as well as relief of chest pain and resolution of ST segment elevation, was associated with initially partial reperfusion and sluggish coronary flow. However, in all four patients, a rapid washout of CK occurred when the flow in the artery of infarction improved and the progression of contrast became similar to that in the other arteries.

Although our definition of reperfusion time has some inherent error, it was based on a sampling frequency of electrocardiographic recordings similar to the usual 15 min interval between coronary angiograms used in intracoronary studies. Since our definition was applied consistently throughout our study, this inaccuracy is not likely to have distorted our conclusions that the reperfusion time is affected by the streptokinase infusion rate and by the duration of chest pain before treatment.

Clinical implications. Our data indicate that in patients with acute myocardial infarction who are treated with high-dose intravenous streptokinase, the reperfusion time can be reduced by starting the infusion of streptokinase as soon as possible after the onset of symptoms and infusing streptokinase at a rate of about 500 U/kg/min, if this dose can be tolerated. Infusion of streptokinase at rates faster than 500 U/kg/min does not appear to be advantageous with respect to reperfusion time.

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