Relationship of the lytic state to successful reperfusion with standard- and low-dose intracoronary streptokinase

ROBERT L. ROTHBARD, M.D., PATRICIA G. FITZPATRICK, M.D., CHARLES W. FRANCIS, M.D., DONNA M. CATON, R.N., WILLIAM B. HOOD, JR., M.D., AND VICTOR J. MARDER, M.D.

ABSTRACT The influence of a systemic lytic state on reperfusion obtained after intracoronary streptokinase (SK) therapy has been evaluated in 15 patients with acute myocardial infarction and complete coronary occlusion. Coronary angiographic studies and measurements of blood fibrinolytic parameters were repeated at 15 min intervals during the infusion of a standard dose of SK and were compared with the results with approximately one-tenth the standard dose. Successful reperfusion was obtained in only 20% (2/10) of patients receiving the low dose, compared with a 75% to 80% success rate in patients receiving the standard dose as initial treatment (4/5) or as follow-up treatment of patients in whom low-dose therapy failed (6/8). There was a striking association between reperfusion and development of the lytic state in that all 12 treatments resulting in reperfusion also caused a lytic state and all seven treatments that failed to produce a lytic state also failed to induce reperfusion (p < .001). Among the successfully treated patients, the dose of SK that induced a lytic state was relatively constant. However, coronary arterial thrombi differed in susceptibility to treatment. Sensitive thrombi (5/12) dissolved before the lytic state occurred and at a lower SK dose than that needed to cause a lytic state; more resistant thrombi (7/12) required a longer time and a significantly larger SK dose to dissolve. These results indicate that intrinsic properties of the thrombus influence the rate and outcome of treatment and that a minimal dose of SK (about 200,000 U) is required to ensure lasting reperfusion in susceptible patients. Furthermore, a systemic lytic state is a constant accompaniment of successful therapy and may even be a necessary requirement for attaining reperfusion with intracoronary administration of SK. Circulation 71, No. 3, 562–570, 1985.

THE RATIONALE for regional thrombolytic treatment of coronary arterial thrombosis is that a high local concentration of plasminogen activator can induce maximal thrombolysis with minimal systemic effect in the blood and a low incidence of hemorrhagic complication. Implicit in this approach are the assumptions that the activator is relatively restricted to the region of the thrombus and that its concentration in the blood is below a critical threshold that would affect plasma coagulation. However, greater therapeutic efficacy and decreased risk of bleeding have not been proved by comparative trial of systemic vs regional treatment, nor has the exact dose of activator required to achieve a restricted local effect been determined by a dose-response study. Furthermore, the available studies do not clearly demonstrate superior results with local infusions.

Early studies with streptokinase (SK) have used both regional perfusions into the coronary ostia and intravenous administration in patients with acute myocardial infarction. These studies suggested efficacy of both local and systemic infusion, albeit without the benefit of angiographic documentation. The dramatic demonstration by Rentrop et al. of coronary arterial reperfusion after intracoronary administration of SK stimulated others to adopt such an approach. However, the intracoronary SK dosage was high, equivalent to that used intravenously for the treatment of deep vein thrombosis, pulmonary embolism, or peripheral arterial occlusion, suggesting that regional localization of SK may not have been accomplished in the reported successes. Although the incidence of
hemorrhagic complication was low, a drop in mean plasma fibrinogen suggests that the plasma coagulation system was deranged by a systemic SK effect, despite the intracoronary route of administration. In fact, a significant reduction in plasma fibrinogen of more than 70% has been observed in the great majority of patients treated with “low dose” regional SK infu-

sion.13, 14 Thus several questions remain unanswered regarding the comparative safety and efficacy of regional and systemic therapy. First, does regional infu-
sion by current regimens limit the fibrinolytic effect to the occluded vessel and avoid systemic fibrinogenoly-
sis? Second, if the effect is limited, can lysis of the offending thrombus still be achieved? Third, is a sys-
temic effect more than an undesirable accompaniment of treatment, or may it actually contribute to the desired thrombolytic potential of regional treatment? In the studies reported here, we have addressed these issues by correlating angiographic reperfusion with a systemic lytic state in patients with acute myocardial infarction receiving intracoronary thrombolytic ther-
apy with SK. Treatment with standard-dose SK was compared with results obtained with approximately one-tenth this dose. Angiographic and hematologic studies followed at 15 min intervals to assess vascular patency and blood fibrinolytic parameters.

Methods
Fifteen patients who presented between September 1982 and April 1983 with signs and symptoms of acute transmural myocardial infarction constituted the study population. Acute trans-
mural myocardial infarction was defined as prolonged chest pain unrelieved by nitroglycerin and with electrocardiographic evidence of persistent ST segment elevation, reciprocal ST seg-
ment depression, and minimal or no Q wave formation. Patients were excluded if the duration of symptoms was greater than 8 hr from the onset of pain to the time of therapy or if there was any contraindication to the use of thrombolytic therapy. Patients were evaluated initially in the emergency room or on the hospit-
al ward, and if the entry criteria were fulfilled, written in-
formed consent as approved by the Committee on Investigations Involving Human Subjects of the Strong Memorial Hospital was obtained before randomization.

All subjects were pretreated with 100 mg iv hydrocortisone, 50 mg iv diphenhydramine hydrochloride, and 70 to 100 mg iv lidocaine with a 2 mg/min infusion that was further titrated to control ventricular ectopy as needed. Routine cardiac catheter-
ization by the Judkins approach was performed, including left ventriculography in the 30 degree right anterior oblique projec-
tion and coronary angiography. The uninvolved coronary artery was cannulated first, then the artery that appeared to supply the infarct zone by electrocardiographic evidence. Only patients with complete coronary occlusion were admitted to the study and randomly assigned to a treatment group. Catheter ex-
changes were performed through No. 8F introducer, which was main-
tained in the femoral artery with a sidearm attachment for drawing blood and monitoring pressure during SK infusion. Once the occluded coronary artery was identified, the intracor-

onary infusion of SK (Streptase, Hoechst-Roussel Pharmaceuti-
cals, Somerset, NJ, or Kabikinase, Pharmacia, Piscataway, NJ) was begun with a Harvard pump. Subselective coronary infu-
sion catheters were not used.

Initially, patients were randomly assigned to three SK treatment groups: standard dose (20,000 U bolus and 4000 U/min infusion), low dose (about 1/10 standard), and very low dose (about 1/20 standard). Because the infusion catheters were flushed by contrast medium in performance of follow-up angiograms, the actual infusion dosages were higher than anticipated (see table 1), and the total dosages in the low-dose and very low-dose categories were not distinguishable. Therefore the two experimental groups were combined into a single low-dose treatment category (1000 or 2000 U bolus and 300 to 1200 U/min infusion) for purposes of analysis. The infusion was interrupted every 15 min or after a cardiac event, such as in-
creased ventricular ectopy or sudden bradyarrhythmia, to per-
form coronary angiographic studies. Patients assigned to stan-
dard-dose SK received 45 to 60 min of treatment (except patient 1, who received 120 min of treatment), at which time therapy was discontinued if there was no evidence of thrombolysis. Patients assigned to low-dose SK received a minimum of 45 min of therapy. To provide the potential benefit of approved throm-
bolitic therapy for all patients, those patients in whom reper-
fusion was not achieved on low-dose SK by 45 min were retreated with standard-dose SK. After the additional 45 min of standard-
dose SK, therapy was terminated if thrombolysis had not oc-
curred. In patients in whom thrombolysis was achieved, the SK infusion was continued until no further improvement was demon-
strated in the luminal diameter of the involved vessel, as assessed by coronary angiography every 15 min to a maximum treatment duration of 120 min.

Upon completion of SK administration, a bolus injection of heparin (5000 U) was given intravenously and a continuous infusion was begun, maintaining the partial thromboplastin time at approximately twice control. Lidocaine infusion was main-
tained for at least 24 hr. The introducer remained in the femoral artery to improve hemostatic control and to provide pressure monitoring for approximately 24 hr, at which time coronary angiography and ventriculography were repeated. If the pre-
viously occluded coronary artery remained patent, heparin ther-
apy was continued, replaced by warfarin after approximately 1 week. Antiplatelet agents were not routinely used. Only one patient had bleeding associated with treatment, which was lo-
calized to the femoral arterial catheterization site.

Laboratory evaluation included a baseline SK resistance test,15 fibrinogen level,16 and euglobulin lysis time,17 which was repeated every 15 min and at the termination of the SK infusion or with any clinically significant event. A systemic lytic state was considered to be present if there was a measurable decrease in fibrinogen concentration during thrombolytic treatment, tak-
en as a decrease of more than 10% from the pretreatment value. Fibrinogen polypeptide chains were analyzed after heat precipi-
tation from plasma18 and disulfide bond reduction, by elec-
trophoresis on sodium dodecyl sulfate polyacrylamide 5/14% gra-
dient gels with a sulfite-borante discontinuous buffer system.19 Gels were fixed and stained with Coomassie blue and scanned with a scanning densitometer (Quick Scan Jr., Helena Laborato-
ries, Beaumont, TX). Statistical analysis was performed with the Student distribution of significance limits or $\chi^2$ tests as appropriate.20

Results
There was no significant difference in pretreatment clinical or laboratory features (table 1) between the standard- and low-dose SK groups (mean ± SE) with
TABLE 1
Pretreatment features

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>Delay (hr)</th>
<th>Infarct location</th>
<th>Concomitant disease (%) occlusion</th>
<th>Fibrinogen concentration (mg/dl)</th>
<th>SK resistance (total units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dose</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50/M</td>
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<td>DMI</td>
<td>RCA LAD (40), CIRC (100)</td>
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<td>DMI</td>
<td>RCA None</td>
<td>430</td>
<td>30,000</td>
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<td>54/M</td>
<td>4.8</td>
<td>AMI</td>
<td>LAD None</td>
<td>410</td>
<td>--</td>
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<tr>
<td>14</td>
<td>61/M</td>
<td>2.9</td>
<td>DMI</td>
<td>CIRC LAD (60), RCA (80)</td>
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<tr>
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<td>59/F</td>
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<td>ALMI</td>
<td>LAD None</td>
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<td>6,000</td>
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<td>Low dose</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>3.3</td>
<td>DMI</td>
<td>RCA None</td>
<td>465</td>
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<tr>
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<td>DMI</td>
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<td>8.1</td>
<td>AMI</td>
<td>LAD RCA (70), MARG (60)</td>
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<td>54/M</td>
<td>3.1</td>
<td>AMI</td>
<td>LAD DIAG (90)</td>
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<td>65/M</td>
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<td>DMI</td>
<td>RCA LAD (50), CIRC (60)</td>
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<tr>
<td>13</td>
<td>43/M</td>
<td>2.5</td>
<td>DMI</td>
<td>RCA CIRC (80), MARG (95)</td>
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<td>30,000</td>
</tr>
</tbody>
</table>

DMI = diaphragmatic or inferior; AMI = anterior; ALMI = anterolateral; ASMI = anteroseptal; LAD = left anterior descending coronary artery; RCA = right coronary artery; CIRC = circumflex coronary artery; MARG = marginal; DIAG = diagonal.

regard to age (58 ± 3 vs 59 ± 2 yr), delay after onset of symptoms (4.4 ± 0.8 vs 4.0 ± 0.6 hr), fibrinogen concentration (424 ± 53 vs 335 ± 25 mg/dl), or total plasma SK resistance (24,000 ± 6000 vs 33,000 ± 3000 U), nor was there a difference in infarct location (2:3 ratio of anterior to inferior in both groups) or male preponderance (4:1 vs 10:0). The ratio of right coronary (plus circumflex) arterial occlusion to left anterior descending arterial occlusion was identical, although there was a higher incidence of concomitant coronary artery disease in the low-dose SK group (80% vs 40%). The cumulative dose of SK administered to each patient is illustrated in figure 1 and table 2. The mean standard-dose rate was approximately sixfold greater than the low-dose rate (4204 ± 178 vs 736 ± 84 U/min). Patients who experienced treatment failure at low dose, defined as no reperfusion within 45 min or reocclusion during infusion, were retreated with the standard-dose regimen. The mean dose rate for these eight patients (3570 ± 259 U/min) was similar to the initial standard-dose rate. Reperfusion was achieved in four of five patients receiving the standard dose after 46 ± 18 min, at which time 206,000 ± 80,000 U of SK had been administered. By contrast, stable reperfusion was achieved in only two (Nos. 3 and 8) of 10 patients receiving low-dose SK after an infusion time of 15 min and a mean cumulative SK dose of only 12,000 U. Three patients receiving the low dose (Nos. 2, 9, and 13) had reperfusion at 15, 30, and 36 min (mean SK dose 30,000 U) but experienced reocclusion at 60, 60, and 67 min, respectively, while the infusion continued. Six of the eight patients who received second treatments (table 2) had reperfusion after an additional mean elapsed time of 26 ± 8 min and an SK dose of 97,500 U.

The angiographic results encompassed 23 total treatments, 10 at the low dose, five initially at the standard dose, and eight follow-up standard-dose treatments of patients who did not have reperfusion with low-dose SK (table 3). Considering reocclusion as a treatment failure, successful therapy at the low dose was achieved in only 20% of patients (2/10), which compared unfavorably with the success rate of the standard dose (80% [4/5] of initial treatments and 75% [6/8] of second treatments).

The SK doses administered to the three patients who had no reperfusion and to the 12 successfully treated patients are illustrated in figure 2. There was a wide variation in SK dose at the time of the initial coronary reperfusion, ranging from a low of only 8000 U (patient 8) to over 400,000 U (patient 1). Three of the 12 patients experienced reocclusion at 45, 30, and 31 min after initial reperfusion, when the total administered SK dose was 50,000 to 60,000 U (table 2). Retreatment of these three patients at the standard SK dose for 20, 15, and 31 min achieved stable reperfusion, after
FIGURE 1. Cumulative SK dose administered to each patient during the infusion. Five patients received an initial standard SK dose and 10 received a low SK dose. The eight patients who did not have reperfusion or who had transient reperfusion on the low SK dose were retreated with the standard dose regimen, which was approximately the same as for initial standard SK treatments.

Cumulative totals of 144,000, 108,000 and 126,000 U of SK. Two other patients had successful reperfusion with less than 100,000 U of SK, of which two (Nos. 4 and 7) were receiving the standard dose at the time. Thus only two patients had stable reperfusion at a truly low dose of SK (Nos. 3 and 8), receiving 16,000 and 8000 U at the time of lysis and totals of only 64,000 and 32,000 U over the 60 min treatment interval. Except for these two patients, the total dose administered to the three patients in whom treatment failed was lower (less than 200,000 U) than for all but one of those in whom treatment succeeded. There were no other differences in any clinical or laboratory parameter between the three patients who did not have reperfusion and those who were successfully treated, specifically with regard to age, location of the myocardial infarction or coronary occlusion, initial SK resistance level, fibrinogen concentration, or delay after onset of chest pain before therapy.

Only five of the 10 low-dose SK infusions (mean total 40,000 ± 5000 U) resulted in a decreased plasma fibrinogen level, while a lytic state was produced by 11 of the 13 standard-dose treatments (table 4). All 12 successful treatments (two low dose, four initial standard dose, and six retreatment standard dose) were associated with the presence of a systemic lytic state (table 5). Of the 11 SK infusions that failed to cause reperfusion, the majority (7/11) produced no systemic lytic state. Thus the lytic state was strongly associated with coronary arterial reperfusion (p < .001).

Although all 12 successfully treated patients had a demonstrable plasma lytic state, the decrease in plasma fibrinogen concentration occurred before or just at the time of coronary arterial reperfusion in only seven cases (figure 3). Thrombolysis (reperfusion) occurred before the lytic state in five patients, suggesting SK specificity for fibrin over fibrinogen in these cases. However, plasma samples from these five patients obtained shortly after reperfusion, while the patients were still in the cardiac catheterization laboratory undergoing follow-up angiography, all showed a decrease in fibrinogen concentration indicative of a lytic state (figure 3).

Gel electrophoretic analysis of the plasma fibrinogen chains increased the sensitivity for detecting plasma degradation of circulating fibrinogen in some cases (figure 4). Patients with a markedly decreased plasma fibrinogen concentration had the expected decrease in β-γ chain ratio, reflecting the preferential cleavage of the β chain by circulating plasmin. On the assumption that a change in the fibrinogen β chain may have occurred in plasma samples that did not yet show a significant decrease in fibrinogen concentration, prererfusion samples of patients 3, 4, 7, 8, and 9 (see figure 3) were assessed. Two of the five patients showed a significant decrease in β-γ ratio of greater than 20%, although the fibrinogen concentration was unchanged. This indicated that nine rather than seven of the 12 patients had degradation of plasma fibrinogen at the time of (rather than after) reperfusion, further decreasing the possibility of significant SK specificity on the fibrin substrate. Gel analysis on prererfusion samples from patient 9 as well as from patients 4 and 8 (not shown) agreed with fibrinogen concentration results, as did all postreperfusion samples (figure 3), which showed clearly decreased β-γ ratios. Of the three patients in whom reperfusion was not achieved, two had no decrease in either fibrinogen concentration or β-γ chain ratio.

Comparisons of the SK dose that caused the lytic state or resulted in reperfusion suggested that the thrombi differed in the susceptibility to lysis, whereas plasma fibrinogen was degraded at approximately the same dose of drug in all patients. Whether the lytic
TABLE 2
Amount of SK administered during initial and second treatments in relation to reperfusion and systemic lytic state

<table>
<thead>
<tr>
<th></th>
<th>SK rate</th>
<th>Reperfusion</th>
<th>Reocclusion</th>
<th>Systemic lytic state</th>
<th>Streptokinase</th>
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<tr>
<td></td>
<td>(U/min)</td>
<td>(Yes/no)</td>
<td>Time (min)</td>
<td>(Yes/no)</td>
<td>Time (min)</td>
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<td>Patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Standard dose</td>
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<tr>
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<td>13</td>
<td>1,180</td>
<td>Yes 36</td>
<td>Yes 67</td>
<td>Yes 42,000</td>
<td>51 60,000</td>
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</table>

*Times denote the interval (min) from the start of initial treatment and SK doses are cumulative amounts at the time(s) of reperfusion and at the end of the initial or second treatment. The administered SK doses were based on direct measurements of infusion syringe volumes, while the “SK rate” for initial or second treatment was a derived value, calculated as cumulative dose divided by time of infusion.

state or reperfusion occurred first, the cumulative SK dose that produced the lytic state was similar (78,000 ± 16,000 vs 108,000 ± 33,000 U, respectively). However, the SK dose required to produce reperfusion was significantly different in the two groups. An apparently more sensitive group of thrombi, in which reperfusion occurred first, lysed at a mean SK dose of 47,000 U, which was significantly lower than the

TABLE 3
Angiographic results of 10 low-dose and 13 standard-dose intracoronary SK treatments of 15 patients

<table>
<thead>
<tr>
<th>Angiographic results</th>
<th>Initial treatment</th>
<th>Second treatment—standard dose</th>
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<td>Low dose (n = 10)</td>
<td>Standard dose (n = 5)</td>
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<td></td>
<td></td>
<td>standard dose (n = 8)</td>
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<tr>
<td>Stable reperfusion</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Reocclusion</td>
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<td>0</td>
</tr>
<tr>
<td>Failure to reperfuse</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Success rate (%)</td>
<td>20</td>
<td>80</td>
</tr>
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</table>

*Includes all eight patients who were treated unsuccessfully with low-dose SK. The six successful second treatments at standard dose occurred in the three “reocclusions” at low dose and in three of the five “failures to reperfuse” at low dose.

FIGURE 2. Cumulative doses of SK administered to 15 patients relative to the occurrence of reperfusion (lysis), rethrombosis, relysis, and total for the entire treatment interval. “Lysis” or “relysis” indicate angiographic evidence that an occluded coronary artery had reperfused. The three patients who experienced no reperfusion (open circles) include one treated with standard SK dose (No. 14) and two treated with low-dose SK followed by standard-dose SK (Nos. 5 and 6).
mean dose of 204,000 U (p < .005) at which a more resistant group lysed.

Discussion

The reperfusion success rate of SK therapy was strikingly lower with the low-dose regimen (20%), as compared to that with standard-dose intracoronary SK (80%). Retreatment of the patients in whom low-dose treatment failed (8/10) with standard-dose SK resulted in the same reperfusion rate (75%) as initial treatment with the standard dose, a success rate (table 3) that was comparable to the experience of others with this dose regimen.3-10.14.21-29 This difference could not be explained by skewing of the known pretreatment clinical or laboratory risk factors, such as the delay before treatment or unusual resistance to SK, and could be

attributed only to the lower dose regimen. One possible explanation for the high failure rate at the low dose was that an inadequate amount of activator was provided. This was unlikely in view of the fact that one-half of the treatments with the low-dose regimen (5/10) produced a lytic state (table 4). This fortuitous choice of SK dose regimen allowed for the desired correlation of the two principal end points of reperfusion and lytic state (table 5).

There was a striking positive association between reperfusion and a concomitant lytic state in that all 12 treatments that successfullly caused reperfusion also caused a lytic state, and all seven treatments that failed to cause a lytic state also failed to cause reperfusion (p < .001). Furthermore, no successful treatment occurred in the absence of a lytic state, and only four of 23 infusions that caused a lytic state failed to dissolve the thrombus. Although the reports of Cowley et al.,13 Rogers et al.,14 and de Prost et al.30 indicate a high incidence of hypofibrinogenemia after intracoronary SK administration, our data are the first to measure this effect in association with angiographic results during

![FIGURE 3. Percent decrease in plasma fibrinogen concentration in association with 12 successful SK treatments. The open portions represent changes in fibrinogen noted at or just before (mean 36 min) the time of reperfusion; the hatched portions show the fibrinogen change at or near the end of the catheterization study (mean delay after reperfusion 36 min).](image-url)
the SK infusion and to show the rapid and strict correlation of the two events.

Although the limited dose of SK was the primary reason for the absence of a lytic state, the association with failure to cause reperfusion was maintained regardless of whether standard- or low-dose SK was administered. This dose-response association with the standard SK dose was best illustrated in patients 5, 6, and 14, who experienced no reperfusion. Two of these three patients did not develop a lytic state and the total dose of SK received (mean 173,000 U) was lower than that for most of the successfully treated patients (figure 2). This suggests that a dose of approximately 200,000 U of SK may represent the necessary threshold required to induce reperfusion with regional administration. Although our observations (figure 1) suggest that initial thrombolysis usually occurs after administration of about 100,000 U, in agreement with the data of Cowley et al.,\(^{13}\) stable reperfusion requires continued infusion of more than 200,000 U (figure 2).

This effective intracoronary dose may be less than is required for intravenous use,\(^{14,31-33}\) although no prospective or randomized dose-ranging comparison has been reported. Furthermore, the experience to date in mostly uncontrolled studies suggests a lower overall response to an intravenous dose of 500,000 to 1,500,000 U (50% success) than to an intracoronary dose of 200,000 to 500,000 U (70% to 75% success).\(^{29,34}\) Our results suggest that whatever the dose, successful regional treatment is accomplished only if a significant systemic effect (decrease in plasma fibrinogen) occurs during treatment with the lytic agent (figure 3 and table 5). It is even possible that SK must enter the circulation and promote formation of the active moiety, the SK-plasminogen activator complex, to achieve reperfusion by subsequent delivery of the complex to the thrombus site. The decrease in fibrinogen would serve as a marker of circulating activator complex, and an SK perfusion that is truly limited to the regional circulation could fail to provide an adequate concentration of this complex in the blood. Thus, although there is an apparent increased effectiveness of intracoronary over intravenous SK therapy, the high correlation of reperfusion with a lytic state is most compatible with a requirement for a systemic SK effect, whether the drug is given by regional or systemic administration. This possible obligatory presence of a lytic state to ensure effective thrombolysis (reperfusion) may be less relevant for the “fibrin-specific” agents such as tissue-type plasminogen activator,\(^{35,36}\) acylated streptokinase-plasminogen derivatives,\(^{37}\) or prourokinase.\(^{38}\) Although these agents have greater potential to dissolve fibrin thrombi without degrading plasma fibrinogen, it remains to be seen whether they will work effectively in clinical situations without a detectable effect in the blood.

Analysis of the administered SK dose required to achieve reperfusion or to cause the lytic state suggests that intrinsic properties of the thrombus significantly influence the outcome of treatment. Considering only those 12 patients whose coronary arterial thrombi were dissolved (table 6), there appears to be two groups of thrombi of different susceptibility to SK therapy. Whereas the SK dose that induced a lytic state was relatively constant in all patients, the SK dose that achieved reperfusion varied. Five of 12 thrombi dis-

**FIGURE 4.** Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the plasma fibrinogen chains, analyzed after reduction and alkylation. The sensitivity of the three polypeptide chains to plasminic degradation, in decreasing order, is α, ββ, and γ. Any decrease in βγ chain ratio compared with the pretreatment sample would indicate plasmin action on the plasma fibrinogen and therefore a systemic lytic state. The values noted under the righthand gel of each pair indicates the percent change in βγ ratio compared with pretreatment values, as determined after densitometric analysis of the Coomassie blue-stained gel strips. This percent change should be compared with the percent change in clottable protein, as noted in figure 3.
solved at about the same SK dose as produced the lytic state, but the remainder (7/12) dissolved only after a significantly longer infusion time and greater SK dose than that which caused a lytic state. Thus all patients seemed alike in the dose of SK required to achieve a lytic state, but the different SK doses required to achieve reperfusion suggested that the thrombi differed in their inherent susceptibility to degradation. A subgroup of responders could be represented by the extraordinarily rapid reperfusion in patients 3 and 8, with totals of only 64,000 and 32,000 units, respectively (table 2, figure 2). These patients may correspond to the patients who undergo spontaneous thrombolysis in the first 12 hr after acute coronary occlusion, as demonstrated by the coronary angiographic data of DeWood et al. A contrasting group of thrombi would include those that do not respond to any dose of fibrinolytic agent, perhaps represented by the three nonresponders in our series.

The overall conclusions of our study are compatible with the assumption that intrinsic properties of the thrombi are of primary importance in determining response to treatment, that a minimal dose of agent is needed to achieve success in the sensitive thrombi, and that a systemic effect after intracoronary treatment is a regular accompaniment and perhaps a necessary requirement for attaining successful reperfusion. The results provide a laboratory foundation for the concept that intravenous SK administration may induce coronary reperfusion as regularly as intracoronary SK infusion.

References
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