Hemorrhage and the products of fibrinogen digestion after intracoronary administration of streptokinase

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ABSTRACT  Hemorrhage was prospectively identified in 26 of 116 consecutive patients (23%) who were receiving intracoronary streptokinase for occlusive coronary thrombi producing infarction. Bleeding was not influenced by the dose of streptokinase or the method of cardiac catheterization. Before treatment, prothrombin time and partial thromboplastin time were normal in both bleeders and non-bleeders. Fibrinogen levels measured by bioassay after streptokinase (mean ± SEM) were 62 ± 29 mg/dl in patients with major bleeding, 111 ± 26 mg/dl in patients with minor bleeding, and 109 ± 13 mg/dl in nonbleeders (p = NS). The regression slope b calculated from poststreptokinase fibrinogen time-concentration data in 71 patients was 4.7 mg/dl/hr. However, mean fibrinogen concentrations calculated at sequential 5 hr intervals revealed no net regeneration for the first 20 hr after thrombolysis. The apparent fibrinogen regeneration rate was less than normal (31 mg/kg/day) for more than 10 hr but subsequently increased to 94 ± 10 mg/kg/day by the second day. The initial apparent latency of fibrinogen regeneration paralleled the sharp rise in fibrinogen degradation products, which began to decline after 20 hr of treatment but remained elevated well into the second day. Because of their anticoagulant effects, these products may interfere with the fibrinogen assay, causing spuriously low results. Thus, whether the early delay in fibrinogen regeneration is real or simply a reflection of the effects of fibrinogen degradation products on the bioassay, it signals the time for caution in initiating systemic heparin therapy.


THE ASSOCIATION of hemorrhage with fibrinolysis was recognized well before the introduction of enzymatic thrombolytic therapy for coronary thrombosis.1–8 Various degrees of bleeding complicating streptokinase therapy have been recorded in about 15% of patients with occlusions of arteries or veins of limbs, pelvis, or trunk and in about 40% of patients treated for pulmonary embolism.9 Bleeding complications occurred in up to 18% when streptokinase was administered systemically for myocardial infarction.9–13 Some patients who have experienced severe bleeding after streptokinase therapy had undergone surgery within 8 days of treatment,1, 4, 7 while others had had some other condition likely to cause bleeding (e.g., translumbar aortography or menstruation).2–6, 8 However, in some cases severe bleeding has occurred for no obvious reason, even with relatively low doses of intracoronary streptokinase.10–15

The occurrence of complicating hemorrhage has usually been associated with plasma proteolysis and a resulting lytic state characterized by a decrease in plasminogen, shortening of the whole blood euglobulin lysis time, a decrease in plasma-clottable protein (fibrinogen), the appearance of fibrinogen and fibrin degradation products (FDP-fdp), and prolongation of the prothrombin time and thrombin time. This may contribute to the dissolution of hemostatic plugs remote from coronary arterial thrombi.16 On the other hand, we have found that the risk of hemorrhage is not a function of the success of thrombolysis or of its degree.17 This is probably true because the degree of clot dissolution does not always parallel the extent of the lytic state resulting from the systemic effects of streptokinase.18, 19 Duckert et al.20 stated that the lytic state, if severe, can contribute to hemorrhage; others have suggested that this may be caused by lysis of hemostatic plugs.21, 22

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CIRCULATION
The anticoagulant activity of FDP-fdp has long been recognized. Various fragments of FDP-fdp are known to interfere with thrombin activation, fibrin polymerization, and platelet function. An electron microscopically identifiable abnormality in clot structure has also been described, which apparently is caused by fragments of normal plasma protein that can alter the functional capacity of a fibrin clot and contribute to a hemorrhagic diathesis.

Thus the mechanisms of abnormal coagulation occurring with thrombolytic therapy are complex and as yet incompletely defined. For example, fibrinogen regeneration after streptokinase has not yet been studied. The problem is further compounded by the fact that bleeding seems more likely to occur during treatment with both streptokinase and heparin than with streptokinase alone. This may be particularly troublesome during the transition to anticoagulation therapy at the end of the infusion of streptokinase. We therefore attempted to resolve some of these issues by prospectively identifying the relationship, if any, of hemorrhage, systemic fibrinolysis, generation of FDP-fdp, and fibrinogen regeneration after intracoronary administration of streptokinase.

**Methods**

A prospective assessment of 116 consecutive patients treated with intracoronary streptokinase for acute or impending myocardial infarction was made for any evidence whatsoever of bleeding. All patients underwent a pretreatment analysis of complete blood count, platelet count, prothrombin time, partial thromboplastin time, and fibrinogen level. The criteria for patient selection and the details of therapy have been previously reported. In brief, within 5 hr of the onset of characteristic chest pain, 206,575 ± 66,849 IU (mean ± SD) of streptokinase was infused into the arteriographically identified vessel supplying the zone of infarct over 60 ± 24 min. Before arteriographic examination 5000 IU of heparin and 100 mg of hydrocortisone were administered by bolus injection. At the conclusion of the procedure, heparin was infused at an initial dose of 800 IU/hr, which was adjusted to maintain the activated clotting time at 150 sec. The arterial catheter was left in place for 24 to 48 hr until fibrinogen levels were restored to at least 100 mg/dl or more.

After the patient was returned to the cardiac care unit, any evidence of bleeding, including even minor oozing around the catheters, was prospectively recorded as a hemorrhagic complication. Major bleeding was defined as that causing death or requiring three or more units of packed red blood cells. Minor bleeding included minimal-to-negligible hematemesis, hemoptysis, or hematuria, as well as the more frequent episodes of oozing at the catheter site.

After infusion of streptokinase, serial fibrinogen levels were measured with a daily calibrated fibrometer (BBL Fibrosystem) at 4 to 6 hr intervals until estimated fibrinogen levels had reached at least 100 mg/dl; fibrinogen levels were serialized once or twice daily for an additional 2 days. Plasma samples were sufficiently diluted (1:20) and additional thrombin was added as recommended by Morse et al. to override the spurious effects of therapeutically administered heparin. From 227 such determinations obtained from 71 patients (fibrinogen study group) in whom fibrinogen data were available for analysis, a time-concentration slope was computed. To further confirm the validity of these random observations, the time-concentration slope was recomputed from 73 data points obtained from 15 of the 71 patients in whom at least four serial measurements of poststreptokinase fibrinogen levels had been made. The apparent fibrinogen regeneration rate was estimated from 107 paired sequential samples obtained from 59 patients in the fibrinogen study group. In the latter analysis, fibrinogen regeneration rates were computed by an estimation of male and female blood volumes indexed to body weight and a ratio of total extra cellular-to-intravascular fibrinogen of 1.3:1 (Takeda et al.) as follows:

\[
\text{plasma volume (ml)} = 23.7 \times \text{height (cm)} + 9.0 \times \text{weight (kg)} - 1709
\]

\[
\text{men} = 40.5 \times \text{height (cm)} + 8.4 \times \text{weight (kg)} - 4811
\]

\[
\text{fibrinogen (mg/kg)} = \frac{\text{fibrinogen (mg/kg)}}{\text{weight (kg)}}
\]

\[
\text{regeneration rate (mg/kg/day)} = \frac{F_2(\text{mg/kg}) - F_1(\text{mg/kg})}{F_1-F_2 \text{ interval (days)}}
\]

where \(F_1\) and \(F_2\) represent serial fibrinogen determinations. Values were expressed in milligrams per kilogram per day to facilitate comparisons with reported normal and abnormal fibrinogen synthesis rates.

Degradation products (FDP-fdp) were measured before and serially at 4 to 6 hr intervals after treatment by agglutination of antibody-coated latex particles with a commercial preparation (Wellcome Reagents Ltd.,*)\(^*\). Data were stored in the Wayne State University Amdahl Model V-6/470 computer, which was accessed by a Hewlett-Packard terminal (Model 9830) with Statistical Package for Social Sciences software. Regression slopes (b) of the fibrinogen time-concentration relationship were calculated from these data. Streptokinase doses, clotting factors, and catheterization techniques were compared for two subgroups of bleeders and a third group of nonbleeders by means of a one-way analysis of variance.

**Results**

**Prevalence of bleeding.** Bleeding was observed in 26 (23%) of 116 consecutive patients who were fastidiously monitored prospectively for this complication (table 1). In nonbleeders mean fibrinogen levels before and the lowest levels estimated by bioassay after streptokinase were 281 ± 11 and 110 ± 13 mg/dl compared with 302 ± 14 and 91 ± 21 mg/dl in bleeders; the decrement in the two groups was not significantly different (p = .125). Thus poststreptokinase sequelae...

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**THERAPY AND PREVENTION—THROMBOLYSIS**
TABLE 1
Prospective identification of hemorrhagic complications (see text)

<table>
<thead>
<tr>
<th>Catheterization site</th>
<th>Minor</th>
<th>Major</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ooze, hematoma)</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(hematemesis, melena)</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary (hemoptysis)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary (hematuria)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(retroperitoneal, omental)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skin (ecchymoses)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>All episodes</td>
<td>26</td>
<td>(23%)</td>
<td></td>
</tr>
<tr>
<td>Major/fatal</td>
<td>4</td>
<td>(3.5%)</td>
<td></td>
</tr>
</tbody>
</table>

did not appear to be dependent on the change in fibrinogen levels after treatment.

Most instances of bleeding (22 patients) were minor and included minimal-to-negligible hematemesis, hemoptysis, and hematuria, as well as the more frequent episodes of oozing at the catheter site. These were not influenced by the method of cardiac catheterization or by the dose of streptokinase (table 2). Sixteen of the 22 patients with minor bleeding did so on the second, third, or fourth day after the infusion of streptokinase. Blood transfusions were administered to all four patients with major bleeding and to four patients with minor bleeding.

Coagulation factors. Prothrombin time and partial thromboplastin time measured before infusion of streptokinase were the same in patients developing major and minor hemorrhage compared with those in patients who did not display evidence of bleeding (table 2). Although about 10% of the "normal" population may have deficient levels of factor XII and another small percentage of patients may have a lupuslike anticoagulant, no patient in our study demonstrated a partial thromboplastin time greater than 40 sec (our upper limit of normal) and only 15 had values in excess of 30 sec. Fibrinogen levels after streptokinase appeared to be most depressed in patients with major hemorrhage but not to a significantly different degree; individual values in this group were 20 mg/dl (patient 14), 26 mg/dl (patient 44; fatal), 60 mg/dl (patient 51), and 140 mg/dl (patient 59). Approximately half of the patients in both the groups with and without bleeding displayed poststreptokinase fibrinogen levels of less than 100 mg/dl.

A sufficient number of fibrinogen assays were performed in 71 patients to calculate a fibrinogen time-concentration slope (figure 1). These data were further analyzed by calculating the mean levels of fibrinogen measured in 5 hr cells for the first 55 hr after streptokinase administration (figure 2). Although fibrinogen levels remained above 100 mg/dl in many patients after treatment, the pooling of all data suggested an apparent latency in the restoration of fibrinogen levels lasting for at least 20 hr.

To test the accuracy of the fibrinogen time-concentration slope displayed in figure 1, which was constructed from multiple random fibrinogen levels of various numbers per patient, a second time-concentration slope was calculated from a subset of 15 patients

![FIGURE 1. Fibrinogen time-concentration relationship after streptokinase infusion. A regression slope (b) was calculated from 227 data points obtained from 71 patients.](http://circ.ahajournals.org/doi/fig/10.1161/01.C IR.0000040836.55561.69)
FIGURE 2. Mean (± SEM) fibrinogen levels calculated for each serial 5 hr interval after the intracoronary infusion of streptokinase.

in whom at least four serial levels had been measured after the infusion of streptokinase at intervals of no less than 4 and usually 6 hr (figure 3). The nearly identical slope b of 4.9 mg/dl/hr attests to the validity of figure 1. A similar apparent latency of fibrinogen regeneration was identified in these patients (figure 4). The mean rate of apparent fibrinogen regeneration was estimated from 107 paired sequential samples obtained from 59 of the 71 patients in the fibrinogen study group (figure 5). This revealed that for 10 to 15 hr after streptokinase infusion, the fibrinogen regeneration rate was apparently depressed below reported normal levels (31.3 ± 1.4 mg/kg/day).\(^3\) Thereafter the regeneration rate progressively increased to a new steady rate, more than three times normal, which lasted for at least 55 hr after streptokinase infusion. Because test data deviated so strikingly in opposite directions from normal in the early and late fibrinogen recovery period, regeneration rates were not assessed in additional normal controls; that is, reported values were accepted as a reasonable fiducial benchmark.\(^4\)

Serial levels of FDP-fdp were measured in 19 patients. These data are represented in figure 6 by a third-degree polynomial curve of midrange data points because the Thrombo-Wellcotest yields range data rather than specific levels (<10, 10 to 40, and >40 μg/ml). This shows that these degradation products (the anti-
FDP globulin used in the assay reacts primarily with the D and E fractions of the fibrinogen dimer) are most plentiful during the period when the apparent latency of fibrinogen regeneration is extant.

Discussion

Hemorrhage. The prevalence of bleeding after either systemic or selective administration of streptokinase for coronary thrombosis has ranged from 0% to 18%. 10–15 Although enzyme doses tend to be less with intracoronary instillation, hemorrhage is not necessarily less likely when administered by this route. Thus Merx et al., 13 summarizing the experience of four West German institutions, reported that 7% of their 204 patients had evidence of bleeding severe enough to require blood transfusions. Similarly, eight of our 116 patients (7%) also received transfusions.

Bleeding in our patients was neither related to a preexisting hemorrhagic diathesis nor, in contrast to other reports, to streptokinase dose. 9 Moreover, the fact that 16 of the 22 patients who displayed minor bleeding did so on the second to fourth day after treatment suggests that influences other than fibrinolysis may have been responsible. Thus the relatively short half-life of FDP-fdp (9 hr) and the rapidly spent systemic proteolytic state resulting from streptokinase (see below) suggest that anticoagulants may be the basis for bleeding.

Plasma proteolysis and the lytic state. Although Gottlob and Blümel 44 and Gross et al., 45 using autoradiographic techniques, have shown that streptokinase diffuses into blood clots in vitro over a period of several hours, the digestion of circulating fibrinogen and fibrin occurs in a matter of minutes. 9 Accordingly, clot lysis and the development of a systemic lytic state may be largely independent of each other. 16, 46, 47 Streptokinase binds to amino acids of the plasminogen chain 48 and changes the conformation of this β2-globulin 49 to form an equimolar activator complex. Once the plasminogen-activator complex has been formed it cleaves a single arginyl-valine bond from other free plasminogen molecules to form plasmin, 50–53 which is a nonspecific proteolytic enzyme with a modest preference for fibrinogen and fibrin. 54 A lytic state may promptly ensue, even though most if not all of the circulating plasmin is almost immediately neutralized by union with an α2-macroglobulin plasmin inhibitor, which forms an irreversible 55 or weakly dissociable 56 complex. Haysel and Mosesson 56 suggested that the plasmin–α2-macroglobulin complex retains some limited capacity to hydrolyze fibrinogen and chains of fibrinogen. Awareness of this continuing hydrolysis (perpetuation of the lytic state) is important in terms of the anticoagulant effects of FDP-fdp, since the half-life of the plasmin-antiplasmin complex is 12 hr. 55 The resulting intermediate (Y) and late (D and E) soluble digestion fragments of fibrinogen may both spuriously affect the assay of fibrinogen and interact with heparin to cause bleeding. 57

Anticoagulation. The patients in this study were infused with heparin at the conclusion of the cardiac catheterization. However, recommendations have recently been made that the inauguration of anticoagulant therapy be delayed for several hours, even though no data exist on poststreptokinase fibrinogen or FDP-fdp time-concentration curves. 4 On the other hand, the need for anticoagulation after streptokinase is recognized by all who use thrombolytic therapy, since the rethrombosis rate may exceed 15%. 57 Moreover, FDP-fdp may paradoxically and unpredictably produce a state of hypercoagulability during which factor VIII–like activity increases the amount of thrombin that is generated along with an increase in factor X. This may shift the balance of an unstable coagulation system toward further coagulation and extension of thrombosis. 54 Therefore, in spite of its risk, anticoagulation is essential.

Clinical implications. For several reasons, we suspect that the apparent latency of fibrinogen recovery may be an artifact reflecting the effects of FDP-fdp on the fibrinogen assay itself since the usually reported latency of fibrinogen regeneration after stimuli such as injury, trauma, or surgery is only an hour or two. 58, 58a, 58b Furthermore, the production of FDP-fdp within minutes of administration of streptokinase would be expected to result in a positive feedback

mechanism (fractions D and E) on fibrinogen synthesis. Whether or not the initial flat (20 hr) portion of the poststептонкиназе fibrinogen time-concentration curve is an artifact must await more precise methods of determining the effect of FDP-fdp on the bioassay of fibrinogen. Immunologic assays of fibrinogen and its soluble serum derivatives should shed further light on the extent and duration of fibrinolysis after streptokinase. In the meantime, a reasonable conclusion regarding the significance of the apparent latency of fibrinogen regeneration is that it reflects a sustained increase in circulating FDP-fdp. Because of their anticoagulant and antiplatelet effects, these degradation products may be troublesome in the presence of heparin therapy. Accordingly, consideration may be given to delaying the infusion of heparin until the effects of FDP-fdp have begun to dissipate.

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References


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