Thrombolytic Therapy in Acute Myocardial Infarction
Comparison of Procoagulant Effects of Streptokinase and Alteplase Regimens With Focus on the Kallikrein System and Plasmin

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Background—Thrombolytic therapy in patients with acute myocardial infarction (AMI) is hampered by procoagulant effects. In vitro studies have indicated that plasmin stimulation activates the kallikrein–contact-phase system, resulting in thrombin activation. This prospective comparative study was designed to examine the procoagulant effects of streptokinase or alteplase in AMI.

Methods and Results—Sixty-one patients with AMI received 1.5 million U of streptokinase or front-loaded alteplase (up to 100 mg) and systemic heparin. Twenty-four patients with AMI and no thrombolytic therapy and 30 control subjects were examined for comparison. Molecular markers of thrombin, plasmin activation, and coagulation activities were determined before therapy and serially for up to 10 days. Moderate thrombin (initial thrombin-antithrombin [TAT] complex 18±5 versus 4±0.3 μg/L, \(P<0.05\)) and kallikrein (up to 45±4 versus 30±1 U/L at 3 hours, \(P<0.01\)) activation occurs in patients with AMI. D-Dimers are increased (\(P<0.01\)), and plasmin is stimulated (\(P<0.01\)). Streptokinase and alteplase increase TAT to 50±17 and 51±18 μg/L at 3 hours and to 50±17 and 33±14 μg/L at 6 hours, respectively (\(P<0.01\)). Kallikrein activity is elevated (\(P<0.01\)) to 76±5 and 71±7 U/L at 3 hours and 64±6 and 47±5 U/L by streptokinase and alteplase, respectively, at 6 hours. Reductions in fibrinogen and increases in D-dimers and plasmin-antiplasmin complexes are more marked (\(P<0.05\) and 0.01) after streptokinase versus alteplase. Correlations were found among TAT, kallikrein activity, and plasmin activation (\(P<0.01\)).

Conclusions—The data indicate a more marked procoagulant action of the streptokinase regimen compared with front-loaded alteplase, thus supporting the hypothesis of a plasmin-mediated kallikrein activation with consecutive procoagulant action in vivo. (Circulation. 1998;98:2527-2533.)

Key Words: streptokinase ■ alteplase ■ infarction ■ thrombolysis ■ coagulation

In acute myocardial infarction (AMI), streptokinase and front-loaded alteplase regimens are commonly used for thrombolysis.\(^1\) Unfortunately, reperfusion is not always achieved, and the success of the therapy is limited by reocclusion.\(^2,3\) The balance between prothrombotic and thrombolytic processes can be shifted toward thrombolysis by administration of plasminogen activators; however, procoagulant effects of such drugs have been reported.\(^4-11\) These side effects are important because of a procoagulant state in acute coronary syndromes.\(^12-17\) In patients with AMI and thrombolytic therapy, markedly increased thrombin activation was associated with failure to open the occluded coronary artery and with a high reocclusion rate.\(^18\)

As one pathway of thrombin stimulation of thrombolytics, activation of the contact phase of the coagulation by plasmin has been found in vitro.\(^19\) A recent clinical study measuring indirect plasmin markers proved the activation of the kallikrein–contact-phase system after streptokinase in patients with AMI,\(^11\) but no direct data on plasmin activation are available. Another pathway of activation of the kallikrein system may be the complement cascade.\(^20\) For the more “clot-specific” thrombolytic alteplase, no comparable data on the contact phase are available.

In a prospective, randomized clinical study, we compared the usual regimen with streptokinase and front-loaded alteplase on the kallikrein–contact-phase system and on molecular plasma markers of coagulation and fibrinolysis to examine (1) whether plasmin-mediated activation of the contact phase is related to thrombin generation and (2) whether differences in extent or duration of thrombin and plasmin stimulation exist after administration of these thrombolytic regimens in AMI.

Methods

Patients and Protocol
Sixty-one patients with AMI who were eligible for thrombolytic therapy were included. All patients were referred to the intensive care unit (ICU) after evaluation of the infarct size and degree of reperfusion. Patients were randomized to receive either streptokinase or alteplase, which was subsequently followed by systemic heparin as required to achieve a target activated partial thromboplastin time (aPTT) of 1.5 to 2.0 times the control value.

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care unit for treatment of AMI. The patients fulfilled standard criteria of diagnosis of AMI: ST-segment elevation >0.1 mV in 2 limb leads or >0.2 mV in 2 chest leads, chest pain for ≥30 minutes, and start of symptoms within 8 hours before admission. Diagnosis was confirmed by serial documentation of 12-lead ECG and by serial creatine kinase level determination.

Thirty percent of the patients were on aspirin, and 3% were on ACE inhibitors. All patients received aspirin (300 mg) and systemic heparin to prolong the activated partial thromboplastin time (aPTT) to double the upper normal value (bolus of 5000 IU followed by 1000 heparin IU/h adjusted according to repeated aPTT determinations). Patients were randomized for thrombolytic therapy with streptokinase (Behring; 1.5 million U IV within 1 hour) or with recombinant tissue plasminogen activator (rtPA; Thomae) with a front-loaded and weight-adjusted regimen (up to 100 mg over 90 minutes). Randomization was done monthly for all patients admitted to the intensive care unit. Data are listed in Table 1 and indicate the absence of any significant difference between the 2 groups after randomization. Intravenous heparin was continued for 48 hours.

Blood Sampling and Measurements

Blood sampling was performed at admission and 3 hours, 6 hours, 24 hours, 2 days, 5 days, and 10 days later. The measurements were performed at all sampling time points if not otherwise indicated. The initial sampling was performed before administration of the thrombolytic drug and heparin. Except for initial samplings, the follow-up samplings were done between 7 and 8 AM to minimize diurnal variation. Details of the processing are published elsewhere.\(^\text{12}\)

Determination of the thrombin-antithrombin (TAT) complex was done with a commercially available ELISA (Behring Werke). Plasma/\(\alpha_2\)-antiplasmin (PAP) complex was measured with a sandwich immunoassay (Behring Werke).

IPA was measured with an ELISA (Chromogenix). For determination of plasminogen activator inhibitor (PAI) activity, a chromogenic substrate test (S-2403) was used (Chromogenix). To avoid interference with residual thrombolytics, PAI was not measured 3 hours after the start of drug infusion. It was also not measured at 24 hours and 10 days. d-Dimers were determined by use of a capture ELISA technique (Boehringer). Plasma kallikreinlike activity and factor XII were determined by use of the chromogenic substrate S-2302 or S-2222 (Chromogenix/Unicorn Ltd). Both tests were performed initially, at 3 and 6 hours, and at 2 and 5 days. Fibrinogen (with the method of Clauss), antithrombin III (ATIII), and aPTT were determined in the routine laboratory for clinical chemistry of our institution.

Statistical Analysis

Data are presented as mean±SE. Data were analyzed with the statistical software package JMP (SAS Institute Inc). Data that were not normally distributed were converted to a logarithmic scale before analysis. Data of patients with AMI were compared (during the first 2 days) with the control subjects and among the groups of patients with an ANOVA and Tukey-Kramer highest-significant-difference test with additional Bonferroni-Holmes adjustment for multiple comparisons. For comparison of follow-up data, a repetitive ANOVA was performed. We regarded \(P<0.05\) as significant.

Results

Coagulation

Initially, a slight activation of thrombin was observed in patients with AMI compared with control subjects (Figure 1.
and Tables 2 and 3). In most of these patients, this activation soon reached normal levels and within 2 days showed no more significance (Table 2). A similar time course of activation was found for kallikrein activity (Figure 2). During the first day, activity rose to 45.2 ± 3.8 U/L in AMI patients (P < 0.01) and returned to normal during follow-up (Figure 2 and Table 2). Factor XII was already activated at admission and remained activated during follow-up (P < 0.01; Table 2). D-Dimers were elevated in patients with AMI at admission (P < 0.01; Figure 3) and stayed increased (Table 2). D-Dimers were markedly higher after alteplase and remained activated during follow-up (P < 0.01; Table 2). Factor XII consumption was present during AMI (Table 2); Factor XII was already activated at admission in patients with AMI without thrombolytic therapy compared with control subjects (contr). D-Dimers were markedly higher after alteplase and Table 2). D-Dimers were markedly higher after alteplase and remained activated during follow-up (P < 0.01; Table 2). Factor XII was already activated at admission and remained activated during follow-up (P < 0.01; Table 2). D-Dimers were elevated in patients with AMI at admission (P < 0.01; Figure 3) and stayed increased (Table 2).

After streptokinase application, a marked and prolonged elevation of the TAT complexes was found (P < 0.01). Thrombin activation 2 days after streptokinase did not differ from that of patients without thrombolysis (Figure 1). The TAT increase after alteplase was similar to that after streptokinase, but levels 6 hours after admission were already lower after alteplase compared with streptokinase (Figure 1). TAT levels within the initial phase were correlated with PAP complexes in patients who received thrombolytic therapy (r = 0.41; P < 0.01; y = 0.61x + 2.84). During follow-up, TAT levels were moderately elevated (P < 0.05 by repetitive ANOVA) in patients with thrombolysis (Table 2).

ATIII tended to be reduced in initially in all groups of patients with AMI (P = NS) and became further reduced in all groups during follow-up without any significant difference among the patient groups (P < 0.01; Table 2).

Streptokinase increased kallikrein activity to 76.1 ± 4.8 U/L. The elevated activity persisted for 1 day (P < 0.01 versus control subjects; Figure 2). Activity was also higher as in AMI patients without thrombolytic therapy (P < 0.01; Figure 2). After alteplase, kallikrein activity rose to 71.1 ± 7.0 U/L (P < 0.01), but the increase in activity was not as prolonged as after streptokinase (P < 0.05 by repetitive ANOVA between time courses of both groups; Figure 2 and Table 2). Six hours after alteplase, the kallikrein activity was no higher than that of patients without thrombolysis (47.3 ± 4.9 versus 35.9 ± 2.7 U/L; P = NS) but was still different from that of control subjects (29.6 ± 1.3 U/L; P < 0.05; Figure 2). After 2 days, no difference in kallikrein activity between the 3 groups could be found (Figure 2). Kallikrein activity in patients who received thrombolysis was correlated to PAP levels (admission until 3 hours after thrombolysis: r = 0.60; P < 0.01; y = 2.32x − 0.45) and to TAT levels (r = 0.42; P < 0.01; y = 0.86x − 17.47). These correlations (r = 0.3 to 0.45) were also significant (as well as the correlation of TAT and PAP) if later time points and patients without thrombolysis were included.

Factor XII consumption was present during AMI (Table 2); the reductions after streptokinase (63.3 ± 8.9%) and after alteplase (68.8 ± 6.7%) were not different (P = NS for differences between groups by repetitive ANOVA).

After thrombolysis, a significant increase in D-dimer levels occurred for 2 days with streptokinase versus control subjects and patients without thrombolytic therapy (P < 0.01; Figure 3 and Table 2). D-Dimers were markedly higher after alteplase versus streptokinase after the initial 6 hours (P < 0.01). Alteplase caused a significant increase in D-dimer levels for 48 hours (Table 2), with peak values below those of the streptokinase group (P < 0.05 by repetitive ANOVA; Figure 3 and Table 2). After 6 hours, the levels did not differ from the slightly elevated levels observed in patients with AMI without thrombolytic therapy (Table 2).

**Fibrinogen and Fibrinolytic System**

In patients with AMI, initial fibrinogen levels were elevated compared with those of control subjects (P < 0.01; Table 2). After streptokinase application, fibrinogen decreased to 59 ± 9 mg/dL (P < 0.01). Fibrinogen, which recovered after 48 hours, rose further and was markedly elevated until the 10th day (Table 2). In patients with AMI and no thrombolytic therapy, fibrinogen similarly increased to values > 600 mg/dL beginning on the second day (Table 2). After alteplase, fibrinogen decreased to 208 ± 23 mg/dL (P < 0.01) at 6 hours after the start of thrombolysis and thus was not as markedly reduced as after streptokinase (P < 0.05 by repetitive ANOVA). Fibrinogen recovered after 1 day and increased further (Table 2).

PAI levels at admission did not differ significantly in patients with AMI and no thrombolytic therapy and in control subjects. At 6 and 24 hours after admission, an upward trend was observed (P < 0.05 for the whole follow-up by repetitive ANOVA). After streptokinase therapy, no significant difference from patients without thrombolytic therapy was detectable. Slightly higher PAI activity, which was statistically not different from data of other patients with AMI (Table 2), was already observed at admission in patients who received alteplase (P < 0.01 versus control subjects).

tPA mass concentration was persistently increased in AMI patients; it was twice as high as in control subjects (P < 0.01; Table 2). Streptokinase therapy did not alter these levels; 127.7 ± 32.0 ng/mL was measured after alteplase infusion (P < 0.01 versus all other groups), and the levels were equal to those of the other patients 3 hours later (Table 2).

In patients with AMI who did not receive thrombolysis (and who entered the intensive care unit later), a stimulated fibrinolysis was already present and persisted for the whole observation period (P < 0.01; Table 2). Streptokinase caused a significant increase in PAP complexes (P < 0.01; Figure 4). PAP levels remained elevated for the first 24 hours compared...
with those of patients without thrombolytic therapy (P<0.01; Figure 4 and Table 2). After alteplase, PAP complexes also increased markedly during the first day (Figure 4; P<0.01 versus patients without thrombolytic therapy) without statistical difference from the patients with streptokinase treatment (P=NS by repetitive ANOVA).

Discussion

The present prospective study compared the changes in coagulation and fibrinolysis caused by the currently used regimen with streptokinase or front-loaded alteplase. Both drugs have a procoagulant action, which was more pronounced (and longer lasting) with streptokinase. The latter regimen also tended to activate the systemic fibrinolysis more markedly compared with the more clot-specific alteplase.

Comparison of Data on Coagulation and Fibrinolysis With the Literature

In patients with AMI, a moderate hypercoagulative state is observed similar to that in unstable angina pectoris. Levels of PAI, tPA mass concentration, thrombin activation markers, fibrinogen, and other markers are changed, indicating activation because it was also found in patients

**Table 2. Markers of Coagulation and Fibrinolysis at Admission and Different Follow-Up Times in Patients With Streptokinase or Alteplase Therapy or Without Thrombolytic Therapy**

<table>
<thead>
<tr>
<th>Markers/Therapy</th>
<th>Initial</th>
<th>3 h</th>
<th>6 h</th>
<th>24 h</th>
<th>2 d</th>
<th>5 d</th>
<th>10 d</th>
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<td><strong>TAT, µg/L</strong></td>
<td></td>
<td></td>
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<tr>
<td>No lysis</td>
<td>17.8±5.4*</td>
<td>24.4±10.2</td>
<td>28.6±15.5</td>
<td>18.4±6.6</td>
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<td>49.9±17.0†</td>
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<td>9.2±2.1*</td>
<td>9.7±2.8</td>
<td>10.0±2.7</td>
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<td>12.1±2.2*</td>
<td>51.0±18.4†</td>
<td>33.1±13.5*</td>
<td>28.2±11.1*</td>
<td>19.2±7.8†</td>
<td>13.9±4.4</td>
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<td><strong>ATIII, %</strong></td>
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<td>86.6±3.1†</td>
<td>82.4±2.7†</td>
<td>78.3±3.3†</td>
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<td>84.0±3.1†</td>
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<td>86.7±3.3†</td>
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<td>92.4±3.8*</td>
<td>83.9±3.2†</td>
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<tr>
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<td>39.4±4.6</td>
<td>43.5±6.9</td>
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<td>76.0±4.8†§</td>
<td>63.6±5.8†§</td>
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<td>40.5±3.4</td>
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<td>47.3±4.9*</td>
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<td>37.4±3.3</td>
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<td>...</td>
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<td>63.3±8.9†</td>
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<td>82.7±8.2</td>
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<td>923±302</td>
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<td>794±198</td>
<td>559±121</td>
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<td>6173±1157†§</td>
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<td>5025±1216†§</td>
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<td>1245±208†‡</td>
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<tr>
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<td>447±51</td>
<td>550±68†</td>
<td>624±65†</td>
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<td>105±50†§</td>
<td>59±9†§</td>
<td>161±50§</td>
<td>334±34§</td>
<td>696±65</td>
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<tr>
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<td>227±26†</td>
<td>208±23§</td>
<td>270±25§</td>
<td>503±51</td>
<td>754±59</td>
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<td><strong>PAI, AU/mL</strong></td>
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<tr>
<td>No lysis</td>
<td>10.3±2.1</td>
<td>...</td>
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<td>...</td>
<td>15.4±2.3*</td>
<td>14.8±1.6</td>
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<td>13.0±2.2</td>
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<tr>
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<td><strong>TPA, ng/mL</strong></td>
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<td>16.4±1.8†</td>
<td>21.0±2.1†‡</td>
<td>25.1±1.7</td>
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<tr>
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<td>13.9±2.0†</td>
<td>127.7±32†§</td>
<td>34.0±3.3†§</td>
<td>31.9±4.6‡</td>
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<td><strong>PAP, µg/L</strong></td>
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<td>No lysis</td>
<td>1173±213†</td>
<td>1458±559*</td>
<td>598±96</td>
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<td>636±189</td>
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<td>10255±1443†§</td>
<td>6404±1165†§</td>
<td>803±126*</td>
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<td>1629±461</td>
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<tr>
<td>Alteplase</td>
<td>688±97</td>
<td>18426±2334†§</td>
<td>12376±2224†§</td>
<td>3300±611†§</td>
<td>644±110</td>
<td>968±112</td>
<td>1052±152</td>
</tr>
</tbody>
</table>

No lysis indicates no thrombolytic therapy; Streptokinase, streptokinase. Statistical comparison for the first 2 days with ANOVA repeated measurements and with repetitive ANOVA for total follow-up (see Methods). Mean±SEM.

*P<0.05 vs control subjects; †P<0.01 vs control subjects; ‡P<0.05 vs AMI and no thrombolytic therapy; §P<0.01 vs AMI and no thrombolytic therapy.
without thrombolytic therapy in the present study. Application of thrombolytics causes marked effects in addition to the preexisting changes.

Streptokinase infusion increases thrombin activation more than 3-fold. This increase is still detectable 6 hours after the beginning of therapy, as reported by others, whereas the later measurements of TAT complexes are at the level of those in patients with AMI but without thrombolytic therapy. The effect of streptokinase is confirmed by measuring fibrinopeptide A as a marker of thrombin action. Detection of marked activation of thrombin after streptokinase was reported to be associated with failure of lysis but not with worse clinical outcome. Elevated PAI activity after alteplase was also observed by others. Thus, PAI does not seem to be related to thrombin or to platelet activity. In contrast, other authors observed prolonged platelet activation after alteplase.

**Comparison of Both Drugs**

Comparison of thrombolytic drugs in vivo may result in very different findings compared with investigations in vitro because of dynamic changes in various activators and inhibitors. Differences in dose and mode of administration limit direct drug comparison. Only the whole thrombolytic regimen, including heparinization, can be compared. No data on the kallikrein system in relation to plasmin and thrombin activation and an increase in D-dimers. High thrombin activation markers are reported to be associated with failure of lysis but not with worse clinical outcome. Elevated PAI activity after alteplase was also observed by others. Thus, PAI does not seem to be related to thrombin or to platelet activity (β-thromboglobulin was decreased). In contrast, other authors observed prolonged platelet activation after alteplase.

**Figure 2.** Kallikrein plasma activity in patients with AMI and streptokinase, alteplase, or no thrombolytic therapy compared with control subjects (contr). Plots indicate differences in increases in plasma kallikreinlike activity in patients after thrombolytic therapy with more prolonged activation after streptokinase compared with front-loaded alteplase. *P<0.05 vs control subjects; †P<0.01 vs control subjects; ‡P<0.01 vs AMI patients without thrombolysis (mean±SEM).

**Figure 3.** D-Dimer plasma levels in patients with AMI and streptokinase, alteplase, or no thrombolytic therapy compared with control subjects (contr). After streptokinase, levels are elevated longer compared with those in patients receiving front-loaded alteplase. *P<0.05 vs control subjects; †P<0.01 vs control subjects; ‡P<0.01 vs AMI patients without thrombolysis (mean±SEM).

**Figure 4.** PAP complexes demonstrating systemic plasmin stimulation by both regimen. PAP complexes were more marked after streptokinase compared with front-loaded alteplase therapy (compared with control subjects [contr] and patients without thrombolytic therapy). *P<0.05 vs control subjects; †P<0.01 vs control subjects; ‡P<0.01 vs AMI patients without thrombolysis (mean±SEM).

**TABLE 3. Measures of Coagulation and Fibrinolysis of Control Subjects for Comparison**

<table>
<thead>
<tr>
<th>Markers</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAT, μg/L</td>
<td>3.5±0.3</td>
</tr>
<tr>
<td>ATIII, %</td>
<td>107±3</td>
</tr>
<tr>
<td>Kallikrein, U/L</td>
<td>29.6±1.3</td>
</tr>
<tr>
<td>Factor XII, %</td>
<td>104.8±4.4</td>
</tr>
<tr>
<td>D-Dimer, ng/mL</td>
<td>300±59</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>323±13</td>
</tr>
<tr>
<td>PAI, AU/mL</td>
<td>7.9±1.6</td>
</tr>
<tr>
<td>tPA, ng/mL</td>
<td>6.4±0.6</td>
</tr>
<tr>
<td>PAP, μg/mL</td>
<td>398±69</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
tion are available for comparison of the currently used streptokinase and front-loaded alteplase regimens with identical intravenous heparin. Prior studies do not provide data on the present front-loaded rtPA regimen, which is regarded as the reference in many studies. It can be supposed that the procoagulant effect measured as thrombin activation lasts longer. Similarly, the levels of α-dimers and PAP complexes are elevated for a longer time after streptokinase. Cleavage products of kininogen were detected at higher levels after streptokinase versus alteplase up to 24 hours after thrombolysis. Enhanced levels after 24 hours are probably not due to the differences in the plasma half-life of the drugs but rather to paradoxical activation by split products and to action in bound states. The local thrombolytic efficacy cannot be directly derived from systemic data, as, for example, the GUSTO I data imply a greater benefit of the alteplase regimen despite less systemically measurable plasmin activation. It may be speculated that the longer procoagulant action of the streptokinase regimen is of greater importance for coronary reocclusion or failure of reperfusion therapy compared with the less marked systemic activation of the fibrinolysis by the more clot-specific alteplase.

Mechanisms of the Procoagulant Action

Exposure of thrombin during thrombin dissolution was discussed as the source of the procoagulant activity, but quantitatively this hypothesis seems to be very unlikely as derived from clinical data. Recently, an in vitro investigation by Ewald and Eisenberg reported evidence of plasmin-induced thrombin activation via positive feedback on the kallikrein-factor XII system. They demonstrated the key role of plasmin in activation of the kallikrein-factor XII pathway in response to pharmacological thrombolysis using an in vitro test with or without a plasmin inhibitor. Their experimental findings support the present study. Plasmin-mediated bradykinin release from high-molecular-weight kininogen caused by increased kallikrein activity was also observed in vitro. Increased kallikrein activity, activated factor XII, consumption of inhibitors (including the C1-esterase inhibitor), and generation of bradykinin after streptokinase were proved in a recent study in vivo. Similarly, cleavage of kininogen and complement was found to be more marked after streptokinase. The correlations among PAP, kallikrein activity, and markers of fibrinolytic activity independent of the kallikrein-kinin system, after streptokinase versus front-loaded alteplase thrombolysis. This effect has to be seen in addition to the preexisting hypercoagulative state in AMI. Because all patients already had a systemic heparin therapy, a more effective antithrombotic supportive therapy should be developed to push the balance between coagulation and fibrinolysis toward thrombolysis. More detailed knowledge of the involved pathways, eg, the plasmin-mediated kallikrein activation, will be a prerequisite to cope with this task.

Study Strengths and Limitations

The present study was prospective and randomized but not double-blinded. Measurements were done by technicians who were not aware of the clinical data. Both intervention groups agreed very well in demographic and initial blood test data. Because a control group with AMI without specific therapy cannot be obtained for ethical reasons, we included consecutive patients with AMI who did not qualify for thrombolytic therapy. Most of the changes in coagulation and fibrinolysis are known to persist for a prolonged time with few exceptions. Therefore, the delayed admission of this kind of patients may affect only the initial blood test but not the later data.

The steady-state plasma heparin levels with our regimen were <0.5 U/mL and did not affect the measurements. After the first blood sampling, all 3 groups had an identical heparin regimen; therefore, differences among the groups cannot be attributed to heparinization. The extent of thrombin activation without heparin therapy might even be higher.

Conclusions

The results of the this study demonstrate in a prospective, randomized comparison a more marked paradoxical activation of the coagulation system, including the kallikrein system, after streptokinase versus front-loaded alteplase thrombolysis. This effect has to be seen in addition to the preexisting hypercoagulative state in AMI. Because all patients already had a systemic heparin therapy, a more effective antithrombotic supportive therapy should be developed to push the balance between coagulation and fibrinolysis toward thrombolysis. More detailed knowledge of the involved pathways, eg, the plasmin-mediated kallikrein activation, will be a prerequisite to cope with this task.

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