Plasma Levels of Plasminogen Activator Inhibitor Type 1, β-Thromboglobulin, and Fibrinopeptide A Before, During, and After Treatment of Acute Myocardial Infarction With Alteplase

By Hans J. Rapold, Vito Grimaudo, Paul J. Declerck, Egbert K.O. Kruithof, and Fedor Bachmann

Plasma levels of plasminogen activator inhibitor type-1 (PAI-1), β-thromboglobulin (βTG), and fibrinopeptide A (FPA) were followed over 24 hours in 30 patients treated with alteplase for acute myocardial infarction. Samples were taken at T 1.5h), after 120 minutes (under alteplase and heparin, T 2h), 30 minutes after thrombolytic therapy (T 3.5h), as well as 12 hours (T 12h) and 24 hours (T 24h) after baseline. PAI-1 antigen levels (55 ± 9 ng/mL at T Oh, mean ± SEM) decreased to 35 ± 5 (T 1.5h) and 40 ± 6 (T 2h) ng/mL under alteplase, before increasing to 84 ± 22 (T 3.5h), 130 ± 30 (T 12h), and 64 ± 7 (T 24h) ng/mL after therapy, P < .001. A high baseline PAI-1 activity (18 ± 3 ng/mL) decreased to 2.0 ± 0.4 (T 1.5h) and 1.7 ± 0.2 (T 2h) under alteplase and increased to 32 ± 5 (T 12h) and 19 ± 3 (T 24h) ng/mL after therapy (P < .0001). βTG levels (339 ± 105 ng/mL at T Oh) decreased to 203 ± 48 (T 2h), 154 ± 51 (T 3.5h), 187 ± 40 (T 12h), and 142 ± 32 (T 24h) ng/mL under heparin (P < .01). FPA levels (34 ± 9 ng/mL at T Oh) increased to 85 ± 15 ng/mL under alteplase alone (T 1.5h) and normalized under heparin (11 ± 4, 6 ± 2, 4 ± 2, and 3 ± 1 ng/mL at T 2h, T 3.5h, T 12h, and T 24h, respectively). A high level of FPA at T 3.5h correlated with reocclusion (33 ± 12 ng/mL, n = 4 v 2.9 ± 0.5 ng/mL, n = 21, P < .005). We conclude that plasma levels of PAI-1 antigen as well as activity markedly increase after alteplase therapy of acute myocardial infarction. The high activity of PAI-1 and decreasing βTG levels suggest that platelets do not contribute significantly to this phenomenon. The marked increase of FPA levels under recombinant tissue-type plasminogen activator alone and its normalization under heparin emphasize the important role of concomitant anticoagulation in controlling further intravascular fibrin generation under alteplase.

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P l asminog en activator inhibitor type-1 (PAI-1) is an important regulator of fibrinolytic activity in human plasma. Its synthesis by endothelial cells, hepatocytes, and fibroblasts is enhanced under conditions such as local hemostasis and in the presence of endotoxin or cytokines. It is also released, although mainly in inactive form, by platelets. PAI-1 is an acute-phase reactant protein with increasing activity after major surgery or trauma. High plasma levels of PAI have been found in conditions associated with increased thromboembolic risk, such as recurrent deep vein thrombosis, the postoperative period, pregnancy, malignant tumors, sepsis, and coronary artery disease. A predictive value of elevated PAI-1 plasma levels has been shown for reinfarction in young survivors of myocardial infarction and for postoperative deep vein thrombosis in hip surgery. Aortocoronary bypass graft occlusion has been associated with reduced fibrinolytic activity, and the circadian variation in frequency of myocardial infarction, sudden death, or stroke with the diurnal fluctuation in PAI-1 plasma levels.

Early thrombolysis has become the treatment of choice for acute myocardial infarction. Failure to recanalize or reocclusion of coronary arteries, however, remain important limits, to which an ongoing local thrombotic process, as suggested by increased fibrinopeptide A generation under alteplase, may contribute. Other reasons for a resistance to lysis and for reocclusion may be the high platelet content of arterial thrombi or an antifibrinolytic rebound phenomenon after thrombolytic therapy, as suggested by increasing PAI activity.

The purpose of this study was to measure sequential plasma levels of PAI-1, both active and complexed, in patients with acute myocardial infarction before, during, and after treatment with alteplase and to determine whether any correlation could be found between plasma PAI-1, β-thromboglobulin (βTG), and fibrinopeptide A (FPA) levels as indices of platelet activity and fibrin generation, and the occurrence of reocclusion after successful thrombolysis.

MATERIALS AND METHODS

Selection of Patients and Treatment

Thirty consecutive patients less than 65 years of age with nitroglycerin-resistant chest pain of less than 4 hours' duration, with electrocardiographic evidence of transmural ischemia, in stable hemodynamic condition, and presenting no preexisting bleeding risk (exclusion criteria according to the European Cooperative Study Group) were treated with 100 mg of intravenous alteplase (recombinant tissue-type plasminogen activator [rt-PA] provided by Boehringer Ingelheim, Basel, Switzerland) over 3 hours. Ninety minutes after starting the alteplase infusion, intravenous heparin was administered (5,000 IU as bolus, followed by 1,000 IU/h) with adjustment of subsequent doses by activated partial thromboplastin times. Oral anticoagulation was started for all patients 3 days after thrombolysis. A coronaryography and biplane left ventriculography were performed in all patients before hospital discharge. Reocclusion was defined as the combination of clear clinical and electrocardiographic signs of repertusion under rt-PA, followed by recurring chest pain and electrocardiographic evidence of transmural ischemia.

Acquisition of Plasma Samples

A luer lock 18-gauge intravenous cannula was carefully placed on the patient's left arm and used for alteplase infusion. A
contralateral cannula allowed blood sampling and heparin infusion (after the second sample). The first 5 mL of blood were withdrawn. Blood samples (10 mL) were collected (1) before alteplase and heparin (T0, baseline), (2) 90 minutes after starting the alteplase infusion, before heparin administration (T1.5h), (3) 2 hours after starting the alteplase infusion, under heparin (T2h), (4) 30 minutes after completing the alteplase infusion (T3.5h), (5) 12 hours (T12h), and (6) 24 hours (T24h) after start of treatment (samples 3 to 6 under individually adjusted heparin infusion).

Blood was collected into precooled sample tubes containing either one tenth volume of CTAD (citrate, theophylline, adenosine, dipyrindiamide; Boehringer Mannheim), supplemented with 40 µmol PPACK (D-phenyl-prolyl-arginine-chloromethylketone) or citrate (final concentration 0.01 mol/L) and trasylol (final concentration 150 KIU/mL). The blood samples were carefully mixed, immediately cooled on ice, and centrifuged at 4°C and 2,500g for 30 minutes within 1 hour after sampling. The resulting platelet-poor plasma was stored at −70°C.

Specific Assays

PAI-1 antigen (PAI-1 Ag), active PAI-1, and complexed PAI-1. PAI-1 Ag levels were determined in samples collected on citrate and trasylol using a previously described radioimmunoassay.29 The normal range of PAI-1 Ag, measured in 38 healthy volunteers at 8 AM with this assay, is 11 to 47 (median, 19) ng/mL.30 To assess the potential contribution of the physiologic diurnal fluctuation of PAI-1 Ag and PAI-1 activity levels12,26 to the observed variation of these plasma levels, each measured value was additionally corrected by deducting the corresponding normal value at that hour of the day, as previously determined in healthy individuals.26 The resulting corrected PAI-1 data, representing values in excess of normal levels at sampling time, showed the same variation after thrombolytic treatment as the uncorrected PAI-1 levels and are therefore not reported here.

PAI-1/t-PA complexes in plasma were determined as described previously.27 In brief, plasma samples were incubated for 16 hours at 4°C on microtiter plates coated with MA-15H12, a monoclonal antibody (MoAb) raised against PAI-1. PAI-1/t-PA complexes were then quantitated with a MoAb directed towards t-PA conjugated to horseradish peroxidase (62E8-HRP). Specific measurement of PAI-1 activity was performed with an immunofunctional assay, as described previously.27 Plasma samples were preincubated for 10 minutes at 37°C, either with an excess of t-PA (400 ng/mL plasma) or with an equal volume of buffer. PAI-1/t-PA complexes were determined as described above. The amount of active PAI-1 in the sample (expressed in nanograms per milliliter) was calculated as the difference between the value obtained with and the value obtained without added t-PA. Using these methods, normal values are 4 ± 3 ng/mL for PAI-1 in complex with t-PA and 13 ± 10 ng/mL for active PAI-1.27

βTG. βTG levels were measured with an enzyme-linked immunosorbent assay (ELISA) technique (Assachrome βTG; Diagnostica Stago, Asnière-sur-Seine, France) following the manufacturer's instructions (normal range, 10 to 40 ng/mL).

FPA. FPA was determined in CTAD-PPACK-inhibited plasma samples using a previously published radioimmunoassay28 with rabbit polyclonal antibodies supplied by Imco (Stockholm, Sweden), with the following modifications. Crossreacting fibrinogen was eliminated by bentonite absorption before assaying the supernatant. Free antigen was separated from bound antigen using an immobilized second goat-antirabbit antibody (Immunobeads; BioRad Laboratories, Richmond, CA). Normal FPA plasma levels from clean single venipunctures, measured previously with this assay, were 1.9 ± 0.8 ng/mL.29

All determinations were performed in blinded manner.

Statistical Analysis

Descriptive statistics (means, standard error of the mean, range, and median values) as well as correlation coefficients, differences between unpaired groups (Mann-Whitney-U test), and differences between sequential data (Friedman's test, followed by selected comparisons) were computed by means of the “stat view” program on a Macintosh SE personal computer (Apple, Sunnyvale, CA).

RESULTS

Characteristics of Patients and Clinical Results

Thirty consecutive patients, 26 males and four females (mean age, 52.9 ± 1.9 years), underwent thrombolytic therapy of an acute anterior (n = 16) or inferoposterior (n = 14) myocardial infarction with alteplase 3.1 ± 0.2 hours after onset of symptoms. Except for minor bleeding from puncture site and reperfusion-associated ventricular fibrillation in three cases, no complications occurred. New Q waves developed in all but five patients. Creatine kinase peak levels (1,821 ± 268 IU/L) were early (within 12 hours) in 23 of 30 patients. The infarct-related coronary artery was patent at angiography, 12.5 ± 1.2 days after infarction, in 24 of 30 (80%) patients. A significant (> 75%) residual stenosis was present in 17 patients. Three young males had angiographically normal coronary arteries.

Four patients, three with an occluded infarct vessel and one with a subsequently open infarct vessel, showed clear clinical signs of reperfusion followed by reocclusion: the first case with reappearance of chest pain, ST segment elevation 45 minutes after alteplase, and a late peak of creatine kinase levels at 24 hours; the second case with clinical, electrocardiographic, and enzymatic evidence of reinfarction in the same area 8 days after successful thrombolysis; the third case with recurrence of nitroglycerin-resistant chest pain 7 hours after alteplase; and the fourth case with repeated episodes of angina and ST segment elevation for 4 hours despite intravenous nitroglycerin and nifedipin. Three further patients with occluded infarct-related arteries but no clinical signs of reocclusion or ongoing ischemia were considered primary failures of thrombolytic therapy.

Plasma Levels of PAI-1, βTG, and FPA Before, During, and After Thrombolytic Therapy

Of 180 blood samples, 15 (8.3%) could not be obtained or processed without difficulty and were discarded. All parameters measured showed a significant variation of their plasma levels during the observation period of 24 hours, as summarized in Table 1 and Fig 1.

PAI-1 Ag plasma levels at baseline, ie, 3.1 ± 0.2 hours after onset of chest pain, were elevated in all but five patients to 55 ± 9 ng/mL (mean ± SEM; range, 6 to 200 ng/mL), with a median level (43 ng/mL) threefold higher than in healthy volunteers (measured at 8 AM). PAI-1 Ag levels decreased to 35 ± 5 ng/mL (median, 27 ng/mL) under alteplase alone (P < .05 at T 1.5h), without significant change after addition of heparin (T 2h). Thirty minutes after the end of the alteplase infusion a significant increase in PAI-1 levels to 84 ± 22 ng/mL (median, 55
These values decreased to nearly baseline level (64 ng/mL; median, 49 ng/mL) at T 24h. Plasma concentrations of active PAI-1 paralleled those of PAI-1 Ag (Fig 2), with elevated baseline levels (130 ± 30 ng/mL; median, 10 ng/mL, respectively, before and after heparin, P < .001), a marked increase to peak levels of 32 ng/mL at T 12h, and T 24h, respectively. For active PAI-1, the corresponding values were 23% ± 11% (P < .001), 39% ± 17% (P < .001), 400% ± 155% (P < .001), and 218% ± 84%. The circadian fluctuation of PAI-1 levels did not explain the observed variation of PAI-1 during and after thrombolytic therapy, which remained significant at approximately fivefold above normal. These levels remained unchanged under rt-PA alone (T 1.5h), but decreased significantly under heparin (94 ng/mL at T 2h) and after thrombolysis (59 ng/mL at T 3.5h, 84 ng/mL at T 12h, 59 ng/mL at T 24h, P < .05). Assuming a PAI-1 release by platelets of 1.2% of the βTG release, PAI-1 plasma levels were corrected for platelet contribution (data not shown). This correction did not alter the course of PAI-1 plasma levels.

Median plasma levels of FPA at baseline in patients with acute myocardial infarction (20 ng/mL) were 10-fold higher than our internal reference interval. FPA plasma levels remained significantly higher after thrombolytic therapy or reincreased within 24 hours in all patients with reocclusion (3 ng/mL at T 2h, 3 ng/mL at T 3.5h, 1 ng/mL at T 12h, and 1 ng/mL at 24h).

Table 1. Descriptive Statistics for Sequential Plasma Levels of PAI-1 Ag, Active PAI-1, Complexed PAI-1, βTG, and FPA in Patients With Acute Myocardial Infarction (n = 30) Treated With Alteplase

<table>
<thead>
<tr>
<th>Value</th>
<th>T 0h</th>
<th>T 1.5h</th>
<th>T 2h</th>
<th>T 3.5h</th>
<th>T 12h</th>
<th>T 24h</th>
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<tr>
<td>N Samples</td>
<td>28</td>
<td>27</td>
<td>26</td>
<td>26</td>
<td>29</td>
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<td>PAI-1 Ag (ng/mL)</td>
<td>Mean 55</td>
<td>35</td>
<td>40</td>
<td>84</td>
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<td>64</td>
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<td></td>
<td>SEM 9</td>
<td>5</td>
<td>6</td>
<td>22</td>
<td>30</td>
<td>7</td>
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<tr>
<td></td>
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<td>6-145</td>
<td>6-550</td>
<td>19-700</td>
<td>18-166</td>
</tr>
<tr>
<td></td>
<td>Median 43</td>
<td>29</td>
<td>36</td>
<td>55</td>
<td>62</td>
<td>49</td>
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<tr>
<td>PAI-1, active (ng/mL)</td>
<td>Mean 18</td>
<td>2</td>
<td>1.7</td>
<td>2.9</td>
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<td>19</td>
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<tr>
<td></td>
<td>SEM 3</td>
<td>0.4</td>
<td>0.2</td>
<td>0.7</td>
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<td>3</td>
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<td>0-14</td>
<td>2-137</td>
<td>3-65</td>
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<td></td>
<td>Median 16</td>
<td>1.3</td>
<td>1.7</td>
<td>2.4</td>
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<td>16</td>
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<td>PAI-1, complexed (ng/mL)</td>
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<td>12</td>
<td>14</td>
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<td>10</td>
</tr>
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<td></td>
<td>SEM 0.5</td>
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<td>1</td>
<td>2</td>
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<tr>
<td></td>
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<td>4-26</td>
<td>3-48</td>
<td>5-22</td>
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</tr>
<tr>
<td></td>
<td>Median 5</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td></td>
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<tr>
<td>βTG (ng/mL)</td>
<td>Mean 339</td>
<td>325</td>
<td>203</td>
<td>154</td>
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<td></td>
<td>SEM 106</td>
<td>94</td>
<td>48</td>
<td>51</td>
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<td>9-1,181</td>
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<td>94</td>
<td>59</td>
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<td>FPA (ng/mL)</td>
<td>Mean 34</td>
<td>85</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>SEM 9</td>
<td>15</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
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<tr>
<td></td>
<td>Range 1-236</td>
<td>7-301</td>
<td>0.5-97</td>
<td>0.5-61</td>
<td>0.5-66</td>
<td>0.5-23</td>
</tr>
<tr>
<td></td>
<td>Median 20</td>
<td>51</td>
<td>4</td>
<td>3</td>
<td>1</td>
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</tr>
</tbody>
</table>

P value is coefficient of significance expressing the overall difference between the values during the observation period.

ng/mL was observed (P < .05 at T 3.5h), with peak levels of 130 ± 30 ng/mL (median, 62 ng/mL) at T 12h (P < .01). These values decreased to nearly baseline level (64 ± 7 ng/mL; median, 49 ng/mL) at T 24h. Plasma concentrations of active PAI-1 paralleled those of PAI-1 Ag (Fig 2), with elevated baseline levels (130 ± 30 ng/mL; median, 10 ng/mL, respectively, before and after heparin, P < .001), a marked increase to peak levels of 32 ± 5 (median, 29) ng/mL at 12 hours (P < .001) and 19 ± 3 (median, 16) ng/mL at 24 hours. Approximately half of the PAI-1 Ag was present in active form at the peak level, as compared with one-third at baseline and 3% under alteplase. Plasma levels of complexed PAI-1 (Table 1, Fig 2) were normal at baseline (5 ± 0.5 ng/mL), increased under alteplase (11 ± 1; median, 10 ng/mL, P < .001), and remained at approximately this level throughout the observation period. With respect to each patient’s admission level (100%), PAI-1 Ag levels corresponded to 80% ± 9%, 208% ± 41% (P < .05), 281% ± 43% (P < .01), and 166% ± 21% at T 1.5h, T 3.5h, T 12h, and T 24h, respectively. For active PAI-1, the corresponding values were 23% ± 11% (P < .001), 39% ± 17% (P < .001), 400% ± 155% (P < .001), and 218% ± 84%. The circadian fluctuation of PAI-1 levels did not explain the observed variation of PAI-1 during and after thrombolytic therapy, which remained significant after correction of each measured value with a normal value according to the time of day (see Materials and Methods).

Median βTG plasma levels at baseline (181 ng/mL) were approximately fivefold above normal. These levels remained unchanged under rt-PA alone (T 1.5h), but decreased significantly under heparin (94 ng/mL at T 2h) and after thrombolysis (59 ng/mL at T 3.5h, 84 ng/mL at T 12h, 59 ng/mL at T 24h, P < .05). Assuming a PAI-1 release by platelets of 1.2% of the βTG release, PAI-1 plasma levels were corrected for platelet contribution (data not shown). This correction did not alter the course of PAI-1 plasma levels.

Median plasma levels of FPA at baseline in patients with acute myocardial infarction (20 ng/mL) were 10-fold higher than our internal reference interval. FPA plasma levels further increased in median 2.5-fold under rt-PA without heparin (51 ng/mL at T 1.5h, P < .01) before decreasing to normal values under heparin (4 ng/mL at T 2h, 3 ng/mL at T 3.5h, 1 ng/mL at T 12h, and 1 ng/mL at 24h).

PAI-1, βTG, and FPA Plasma Levels in Patient Subgroups

We compared PAI-1, βTG, and FPA levels at different time points in patients with patent infarct vessel and no clinical evidence of reocclusion (n = 23) and in patients with clinical evidence of reocclusion (n = 4), as well as in patients with (n = 27) and without (n = 3) angiographically apparent coronary artery disease after myocardial infarction. FPA plasma levels remained significantly higher after thrombolytic therapy or reincreased within 24 hours in all patients with reocclusion (33 ± 12; median, 32 ng/mL at T 3.5h) as compared with patients without reocclusion.
PLASMA PAI-1 LEVELS AFTER ALTEPLASE

PAI-1 in blood occurs either in platelets (approximately 90% of the antigen) or in plasma (approximately 10% of the antigen). Thirty percent to 60% of plasmatic PAI-1 is active, and the remaining antigen being either in latent form or complexed to t-PA. PAI-1 released from human platelets is latent to a large extent (95%). The evaluation of changes in PAI-1 levels therefore requires specific methods that quantitate antigen and activity to substantiate its likely origin.

A significant variation in plasma levels of PAI-1, active or complexed, βTG, and FPA over 24 hours could be observed in this study. PAI-1 Ag levels, initially twofold to threefold above normal level, decreased under alteplase infusion before increasing to peak levels of fourfold normal within 9 hours after termination of the drug (median values, P < .001). PAI-1 activity paralleled antigen levels with a marked increase to median levels threefold above normal after thrombolytic treatment (P < .001). βTG, initially fivefold above normal, decreased to levels approximately twofold above normal under heparin and after thrombolytic therapy (P < .01). And FPA, initially 10-fold above normal, further increased to median values 25 times above normal under rt-PA alone before decreasing to normal levels as soon as heparin was infused (P < .001).

PAI-1 may not only be an important regulator of fibrinolytic activity under physiologic conditions but also after therapeutic infusion of rt-PA. Elevated PAI-1 levels were suggested to attenuate the fibrinolytic activity of substantial amounts of residual t-PA after thrombolytic treatment with alteplase, although a marked increase in PAI activity (measured spectrophotometrically, and therefore not entirely specific for PAI-1) was observed only in 5 of 16 patients. In the present study, the significant increase in PAI-1 Ag and activity levels after alteplase therapy, as measured with specific immunologic methods, confirms these observations, identifies the increased inhibitory activity indeed as PAI-1, and adds to the hypothesis of an antifibrinolytic rebound phenomenon after thrombolytic therapy. It is tempting to speculate about a prothrombotic role of PAI-1 after thrombolytic therapy, especially because

Fig 1. Plasma levels (mean ± SEM) of PAI-1 Ag (- - -), βTG (- - -), and FPA (- - -) in patients with acute myocardial infarction (n = 30) before, during, and after treatment with alteplase and heparin. The range of normal values is marked as a grey zone.

(2.9 ± 0.5; median, 2.0 ng/mL at T 3.5h, P < .005). PAI-1 Ag levels at baseline tended to be higher in patients without angiographically detectable atheromatosus (87 ± 28; median, 110 ng/mL) than in patients with visible coronary artery disease (51 ± 9; median, 41 ng/mL, P = .16). No further difference or correlation was detected.

DISCUSSION
The aim of this study was to follow plasma PAI-1 Ag and activity levels in patients with acute myocardial infarction before, during, and after treatment with alteplase (rt-PA) and to correlate them with platelet activity and fibrin generation.

Fig 2. Plasma levels (mean ± SEM) of PAI-1 Ag (- - -), active PAI-1 (- - -), and PAI-1 in complex with t-PA (- - -) in patients with acute myocardial infarction (n = 30) before, during, and after treatment with alteplase and heparin (semilogarithmic plots).
PAI-1 concentrations in experimental thrombi occluding coronary arteries were suggested to exceed plasma concentrations by two orders of magnitude. The variation of PAI-1 levels assessed in this study remained significant when corrected for the diurnal fluctuation measured in normal individuals. Without a control group of comparable patients with early myocardial infarction but no thrombolytic treatment (an ethically problematic design for a prospective study today), one might argue that the increase in PAI-1 plasma levels observed represents an inflammatory acute-phase reaction after myocardial infarction rather than a rebound phenomenon related to thrombolytic treatment. Recent observations of acute-phase reactants, however, do not support that. Plasma levels of C-reactive protein, fibrinogen, and von Willebrand factor are not significantly different in the early phase of acute myocardial infarction and unstable angina in contrast to levels of PAI-1, t-PA, and thrombin-antithrombin III (TAT) complexes. C-reactive protein levels peak 2 days after alteplase-treated myocardial infarction, while PAI-1 levels peaked at 12 hours in the present study and decreased to pretreatment levels at 24 hours. A correlation of PAI-1 levels with the clinical or angiographic outcome of thrombolysis, as suggested earlier, could not be observed from our data. Patients with clear clinical signs of reocclusion (n = 4) did not disclose a different pattern of PAI-1 Ag or activity.

βTG plasma levels showed a distinctly different course from PAI-1 levels during and after thrombolytic treatment. The relatively low values after therapy and the lack of correlation between βTG and PAI-1 levels suggest that platelets do not contribute significantly to the increased PAI-1 levels observed early after acute myocardial infarction. The high activity of PAI-1 after thrombolytic therapy would further imply an endothelial or hepatic origin.

Increasing FPA plasma levels under alteplase before anticoagulation confirm intravascular fibrin generation under thrombolytic therapy despite successful reperfusion, as reported before for streptokinase and alteplase. This sustained thrombin activity can apparently be controlled by heparin. FPA was the only parameter measured that correlated significantly with reocclusion (P < .005 at T 3.5h).

In conclusion, this study confirms that acute myocardial infarction is associated with decreased fibrinolytic activity, increased platelet activity, and sustained fibrin generation, as evidenced by high baseline plasma levels of active PAI-1, βTG, and FPA, respectively. More importantly, levels of active PAI-1 markedly increase after thrombolytic therapy. This increase is apparently independent of physiologic diurnal fluctuations. Platelets do not contribute significantly to it, as implied by the high activity of circulating PAI-1 and by the decrease of initially high βTG levels. The early peaking of PAI-1 suggests an antifibrinolytic rebound phenomenon related to thrombolytic treatment rather than an inflammatory acute-phase reaction after acute myocardial infarction. The marked increase of FPA levels under alteplase alone and its normalization under heparin emphasizes an important role of concomitant anticoagulation in controlling further intravascular fibrin generation under alteplase. Whether a high FPA level after thrombolytic therapy indeed represents a marker of reocclusion warrants confirmation in a larger number of patients.

REFERENCES

Plasma levels of plasminogen activator inhibitor type 1, beta-thromboglobulin, and fibrinopeptide A before, during, and after treatment of acute myocardial infarction with alteplase

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