Monitoring of Fibrin Generation During Thrombolytic Therapy of Acute Myocardial Infarction With Recombinant Tissue-Type Plasminogen Activator

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Fibrinopeptide A (FPA) is a very sensitive marker of fibrin generation in vivo. Because an imbalance between thrombogenic and thrombolytic forces may be responsible for the failure to recanalize and for reocclusion of coronary arteries, such a marker could be of eminent value during thrombolytic treatment of acute myocardial infarction. Thirty-four consecutive patients with acute myocardial infarction (peak creatine kinase level, 1,869±1,543 IU/l) were treated with 100 mg recombinant tissue-type plasminogen activator (rt-PA) 3.1±1.1 hours after onset of chest pain. Angiography 12.5±6.1 days later revealed an 81% patency rate of the infarct-related vessel. FPA plasma levels (normal, 1.9±0.5 ng/ml) were 34±46 ng/ml on admission and 93±86 ng/ml (538±674% with respect to each patient’s admission level) after 90 minutes of rt-PA infusion (p<0.01). In patients without evidence of reocclusion (including three primary failures), FPA levels fell under continuous heparin infusion to 6.7±9.7 ng/ml (24±33%, p<0.01) within 30 minutes and were 3.1±2.2 ng/ml (15±15%, p<0.01), 1.6±1.1 ng/ml (8±10%, p<0.01), and 2.5±3.0 ng/ml (12±16%, p<0.01) 30 minutes, 9 hours, and 21 hours, respectively, after completion of rt-PA therapy. Five patients sustained intermittent or permanent coronary reocclusion after primary thrombolytic success. Their early postlytic FPA levels (13–51 ng/ml) remained high or increased again despite adequate anticoagulation. FPA allows the monitoring of fibrin generation during acute myocardial infarction and thrombolytic therapy. Despite successful recanalization, fibrin generation is increased under rt-PA administration before anticoagulation. Patients under anticoagulation with postlytic FPA levels less than 5 ng/ml or below their admission value seem to be at low risk of reocclusion for several days. FPA levels that are persistently high or that increase again despite adequate anticoagulation indicate ongoing fibrin generation. However, whether FPA can indeed be considered a useful marker of reocclusion remains to be confirmed in a larger population of patients with acute myocardial infarction. (Circulation 1989;79:980–989)

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levels of crosslinked fibrin degradation products have been measured during acute myocardial infarction, but being derived preferentially from degradation of circulating fibrin polymers, they are not predictive of recanalization by fibrinolytic therapy. FPA plasma levels have been recently analyzed during thrombolytic therapy of myocardial infarction with streptokinase. The marked increase of FPA levels under streptokinase therapy was interpreted as a paradoxical prothrombotic effect of the drug. Plasmin-induced fibrinogenolysis yields degradation products that include measurable fibrinopeptides. The specificity of FPA as a marker of fibrin generation must therefore be questioned in the presence of a lytic state induced by an unspecified activator of fibrinolysis.

Recombinant tissue-type plasminogen activator (rt-PA) has been recognized to be superior to intravenous streptokinase with regard to fibrin specificity and recanalization of occluded coronary arteries, but early reocclusion remains a problem. The respective roles of the drug’s short half-life, of a lacking lytic state, and of an inadequate anticoagulation or platelet inhibition for the reocclusion are so far unsettled.

We determined FPA plasma levels before, during, and after rt-PA infusion, and we examined the influence of fibrinogenolysis on FPA levels, with the hypothesis that this marker of fibrin generation may be helpful in managing patients after primary success of thrombolytic therapy.

**Methods**

**Selection of Patients for Thrombolytic Therapy**

Patients had to satisfy the following inclusion criteria to be eligible for treatment with rt-PA: age of 65 years or less, nitroglycerin-resistant chest pain of 30 minutes or longer, time lapse from onset of pain of 4 hours or less, ST segment elevation of 0.2 mV or more in at least two corresponding electrocardiographic leads without evidence of an old infarction in a different myocardial region, and signed, informed consent. Exclusion criteria were shock or pulmonary edema, uncontrollable hypertension, past or present bleeding disorder, anticoagulation therapy, arterial or subclavian venous puncture or biopsy within the previous week, surgical procedure or prolonged resuscitation within the last 2 weeks, cerebrovascular accident within the last 6 months, severe noncoronary cardiopathy with possibility of intracavitary thrombosis, other serious advanced illness, and pregnancy. The study protocol was approved by the institutional committee on ethics.

**Control Patients**

FPA plasma levels were measured in 1) healthy young volunteers receiving anticoagulation therapy (heparin, 5,000 units as a bolus followed by 1,000 units/hr i.v.) with sequential sampling during 12 hours from a luer lock 18 gauge intravenous cannula, according to the sampling protocol of patients with infarcts receiving rt-PA and heparin (n=7, group B), and 2) patients receiving anticoagulation therapy (heparin, 5,000 units as a bolus followed by 1,000 units/hr i.v.) with stable coronary artery disease, undergoing cardiac catheterization, by sequential sampling during 5 hours from a luer lock 18 gauge intravenous cannula (n=8, group C).

**Thrombolytic Treatment**

A total of 100 mg single chain rt-PA (G-11044, Genentech, South San Francisco, California), provided by Boehringer Ingelheim, was infused intravenously during 3 hours, with an initial bolus of 10 mg, followed by 50 mg during the 1st hour and 40 mg during the following 2 hours. Ninety minutes after initiation of rt-PA, an intravenous heparin infusion (1,000 units/hr) was begun after an initial bolus of 5,000 units. The heparin dose was then adjusted to keep the partial thromboplastin time 1.5–2 times above the upper normal level. Oral anticoagulation was started 3 days after thrombolysis.

**Acquisition of Plasma Samples**

A luer lock 18 gauge intravenous cannula was carefully placed on the patient’s left arm and was used for rt-PA infusion and sampling of heparin-sensitive indexes. Another intravenous cannula on the right arm allowed heparin infusion and FPA sampling. FPA samples (10 ml) were obtained 1) before rt-PA and heparin infusion, 2) 90 minutes after initiation of rt-PA infusion before heparin administration, 3) 120 minutes and 30 minutes after the initiation of rt-PA and heparin infusion, respectively, 4) 30 minutes after completion of rt-PA infusion, 5) 12 hours after initiation of rt-PA infusion, and 6) 24 hours after initiation of rt-PA infusion (samples 3–6 were obtained during continuous heparin infusion). Blood was collected into precooled sample tubes containing the following anticoagulants (for 9 ml blood): 1 ml CTAD (Boehringer Mannheim) supplemented with 200 μg (final concentration 40 μmol) N-phenyl-prolyl-arginine-chloromethylketone (PPACK) as thrombin inhibitor. The blood samples were carefully mixed, immediately cooled on ice, and centrifuged at 4°C at 2,500g during 30 minutes within 1 hour after sampling. The plasma was stored at −70°C. A record was kept on each blood sample to identify eventual difficulties. Samples obtained with difficulty or suboptimal venipuncture were discarded.

**Fibrinopeptide A Assay**

FPA was determined in our laboratory with a previously published radioimmunoassay with polyclonal antibodies supplied by Imco (Stockholm, Sweden) with the following modifications: cross-reacting fibrinogen was eliminated by bentonite absorption before using the fibrinogen-free supernatant for the radioimmunoassay. Free antigen was separated from bound antigen by use of an immobilized sec-
ond goat-anti-rabbit antibody (Immunobeads, Bio-
Rad Laboratories, Richmond, California). Previ-
ously measured levels of FPA in 15 normal
individuals had been 1.9±0.8 ng/ml. All FPA
determinations were done by an experienced lab-
oratory staff member unaware of the clinical or
angiographic result of thrombolytic therapy.

Thrombin-Increaseable Fibrinopeptide A and
Thrombin-Corrected Fibrinopeptide A

To evaluate the contribution of FPA-containing
larger peptides originating from fibrinogenolysis to
FPA levels, an aliquot of the bentonite supernatant,
nearly free of fibrinogen, was incubated with 5 IU
thrombin for 2 hours at 37°C. The difference
between FPA measurements in the bentonite super-
natant before and after thrombin incubation was
called thrombin-increaseable FPA fraction (ti-FPA).

Plasma samples of 20 normal control subjects
treated in that way resulted in a thrombin-
increaseable FPA of 19.8±9.7 ng/ml. This increase is
due to minimal amounts (~2 μg/ml) of remaining
fibrinogen in the bentonite supernatant. The addition
to control plasmas of increasing amounts (1–50 μg/
ml) of fibrinogen degradation products, obtained by
incubation of fibrinogen with urokinase for 1–5 hours,
resulted in a mean crossreactivity contribution of
these FPA-containing peptides of 20±10% compared
with FPA values measured after thrombin incubation
of the bentonite supernatant. FPA correction from
fibrinogenolytic peptides (=thrombin-corrected FPA,
tc-FPA) can be therefore obtained by subtracting
0.2×[ti-FPA–20] ng/ml from direct FPA mea-
surements in the bentonite supernatant.

Fibrinogen and Fibrin Degradation Products

Fibrinogen was determined by the chronometric
method of Clauss.39 Fibrin degradation products
were determined semiquantitatively by the latex
agglutination test with antibodies against fibrin de-
gradation products (Boehringer, Mannheim, FRG).

Noninvasive Signs of Recanalization

Sudden relief of chest pain, reperfusion arrhyth-
mias, sudden resolution of ST segment elevation,
and peaking of plasma MB-creatinine kinase in the
first two of four samples taken 8, 12, 16, and 24
hours after onset of therapy were registered as signs
but not as criteria of early recanalization, consider-
ing their limited predictive value.40,41

Cardiac Catheterization

All patients receiving treatment underwent biplane
left ventriculography and selective coronarography
between 1 and 26 days after thrombolytic therapy to
assess left ventricular damage, patency, residual
stenosis of the infarct-related vessel, and severity of
the coronary artery disease.

Statistical Analysis

A semiquantitative left ventricular salvage score
comparing regional wall motion with the extent of
myocardium at risk, differentiated 0% (0), 25% (1),
50% (2), 75% (3), and 100% (4) myocardial salvage.

Data are reported as mean±SD. Geometric mean
values are added in the tables for not normally
distributed data. Nonparametric methods were used
for further statistical analysis; paired data were
compared by the Wilcoxon's signed-rank test;
sequential data were compared by the Friedman's
and the Wilcoxon-Wilcox tests.

Results

Characteristics of Patients

Thirty men and four women (mean age, 53.2±10.1
years) fulfilling the selection criteria underwent
thrombolytic therapy of acute myocardial infarction
3.1±1.1 hours after onset of symptoms in hemody-
namically stable conditions. Electrocardiographic
evidence of anterior (n=17) or inferoposterior (n=16)
transmural ischemia was present in all patients but one (patient 32).

Clinical and Angiographic Results of
Thrombolytic Therapy

In 30 of 34 patients, thrombolytic therapy, blood
sampling, and angiographic evaluation after 12.4±6.2
(1–26) days could be completed. The pertinent
details are compiled in Table 1. The reasons for
exclusion from further analysis were absence of
infarction (patient 32), interruption of thrombolytic
therapy for intubation after recurrent ventricular
fibrillation (patient 4), refusal of angiography (patient
15), and lack of early FPA levels (patient 3) in one
case each. Except minor bleeding from puncture
sites and reperfusion-related ventricular fibrillation
in three patients, no complications occurred. Among
the clinical signs of reperfusion, a sudden relief of
chest pain was noted in 22 of 34, a resolution of ST
segment elevation in 25 of 34, and typical ventricu-
lar arrhythmias or nodal bradycardia in 15 of 34
patients. A Q wave infarction developed in all but
five patients. Plasma levels of creatine kinase peaked
early (within 12 hours after onset of therapy) in 26
of 34 patients to a mean of 1,869±1,543 IU/l. Patency
of the infarct-related coronary artery and
Thrombolysis in Myocardial Infarction trial (TIMI)
grade 3 perfusion was documented by angiography
in 24 of 31 (77.4%) patients; TIMI grade 2 perfusion
was documented in one (3.2%) patient.

Among the six patients with occluded infarct-
related arteries, three (patients 24, 27, and 29) had
no clinical signs of reocclusion or ongoing ischemia
and could be considered as primary failures of
thrombolytic therapy. Three patients with occluded
vessels had clear clinical signs of reperfusion and
reocclusion before angiography: patient 12, with
reappearance of chest pain and ST segment eleva-
tion 45 minutes after completion of rt-PA infusion.
TABLE 1. Clinical and Angiographic Results of Thrombolytic Therapy

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<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Onset of symptoms to rt-PA infusion (min)</th>
<th>Clinical reperfusion signs (pain/ST/arrhythmia)</th>
<th>Peak CK (IU/l)/time to peak (hr)</th>
<th>Angiographic patency IRV/days after thrombolysis</th>
<th>Residual stenosis IRV (%)/extent CAD</th>
<th>Score LV</th>
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Mean 53.2 ± 10.1 1,869 ± 66 min 1,543 ± 6.1 days 81 ± 29%  

rt-PA, recombinant tissue-type plasminogen activator; CK, creatine kinase (normal 0–125 IU/l); IRV, infarct-related vessel; CAD, coronary artery disease; LV, left ventricle; LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex coronary artery; Diag, diagonal branch; 1,2,3-VD, 1,2,3-vessel disease; u, unilocular; d, diffuse.  
*rt-PA infusion not terminated.  
†No angiography.  
‡TIMI grade 2 perfusion.  

and a late peak of creatine kinase levels at 24 hours; patient 18, with clinical, electrocardiographic, and enzymatic evidence of reinfarction in the same territory 8 days after successful thrombolysis; and patient 26 with reappearance of nitroglycerin-resistant chest pain 7 hours after rt-PA therapy. Two other patients with subsequently open infarct-related vessels showed impressive signs of repeated
Plasma Levels of Fibrinopeptide A at Admission, Under rt-PA, and After Heparin Treatment

Blood sampling from intravenous cannulas during 24 hours in patients treated with heparin who had acute myocardial infarction was unproblematic in 171 of 186 (92%) samples. Fifteen samples obtained with difficulty were discarded. The course of FPA plasma levels in patients undergoing thrombolysis and in controls is shown in Tables 2 and 3 and in Figure 1.

FPA plasma levels from healthy young volunteers who had received anticoagulation therapy (control group B), obtained by sequential sampling from an intravenous cannula, were normal (0.6±0.1 ng/ml after 2 hours, 1.1±1.3 ng/ml after 3.5 hours, and 0.7±0.2 ng/ml after 12 hours). The initial value (9.8±11.0 ng/ml) was elevated because of the insertion of the cannula. But, even without anticoagulation for the first 90 minutes, a further increase of FPA levels by the cannula was not observed (2.1±1.4 ng/ml after 1.5 hours). Sequential FPA levels in control patients treated with heparin who had stable coronary artery disease (group C), obtained from intravenous cannula during 5 hours preceding angiography, were only moderately elevated and remarkably stable.

Baseline FPA levels in patients with acute myocardial infarction 3.1±1.1 hours after onset of chest pain were clearly elevated to 34±46 ng/ml with marked individual variance (see Table 3). After 90 minutes (60 mg) of rt-PA infusion, but before anticoagulation, FPA levels increased in all but four patients to a mean of 93±86 ng/ml (p<0.01 compared with admission value). In patients without clinical signs of reocclusion (n=25), FPA levels fell to 6.7±9.7 ng/ml (p<0.01) 30 minutes after heparin and reached the level of control patients of 3.1±2.2 ng/ml (p<0.01) 30 minutes after completion of rt-PA therapy (20 of 22 FPA and 22 of 22 tc-FPA values <5 ng/ml). FPA mean levels were 1.6±1.1 ng/ml 12 hours after onset of successful thrombolytic therapy (25 of 25 FPA and tc-FPA values <5 ng/ml) and 2.5±3.0 ng/ml 24 hours after onset of thrombolysis (22 of 25 FPA and tc-FPA values <5 ng/ml). Among the patients without clinical signs of reocclusion, a patent infarct-related artery was documented in 22 of 25 (88%). In three patients (patients 24, 27, and 29) with occluded infarct vessels considered primary failures of thrombolysis, FPA levels fell to normal under heparin infusion.

Five patients (patients 12, 18, 26, 30, and 34) had clear clinical and electrocardiographic signs of coronary reocclusion after primary success of thrombolysis (see above). Elevated FPA plasma levels (12.8–51.0 ng/ml) were found 30 minutes after completion of rt-PA infusion under heparin treatment in all of them, despite a partial thromboplastin time two times above the normal level. In three patients, initially normalized FPA under heparin treatment rose again; in two patients, FPA elevation was still impressive after 12 and 24 hours (see Figure 1). All patients had normal plasma levels of antithrombin III, protein C, and protein S.

If one considers the relative change of FPA levels in each patient compared with the admission value (=100%), FPA levels in patients without reocclusion increased to 439±614% under rt-PA infusion, before falling to 24±33%, 15±15%, 8±10%, and 12±16% after 30 minutes, 2 hours, 10.5 hours, and 22.5 hours, respectively, of continuous anticoagulation with heparin. In patients with clinical evidence of reocclusion, the increase of FPA levels under rt-PA infusion tended to be more pronounced (954±830%). FPA exceeding admission levels (120–

### Table 2. Mean Sequential Fibrinopeptide A Levels in Patients and Control Subjects

<table>
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<tr>
<th>Treatment time (hr)</th>
<th>Group A (n=30)</th>
<th>Group B (n=7)</th>
<th>Group C (n=8)</th>
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<td>5.2±0.7/5.2</td>
</tr>
<tr>
<td>12</td>
<td>3.7±10.1/1.5</td>
<td>0.7±0.2/0.7</td>
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</tr>
<tr>
<td>24</td>
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</tr>
</tbody>
</table>

Values are mean±SD/geometric mean in ng/ml.

Group A, all patients with acute myocardial infarction undergoing thrombolytic therapy with recombinant tissue-type plasminogen activator; group B, healthy young volunteers; group C, patients with stable coronary artery disease undergoing cardiac catheterization.

*p<0.01.
418%) were measured under heparin anticoagulation in four of five patients.

No significant correlation was found between FPA values at entry or maximal FPA levels and time lapse between onset of pain and blood sampling (within 4 hours), maximal creatine kinase level, left ventricular damage, or extent of coronary artery disease, respectively.

**Thrombin-Corrected Fibrinopeptide A**

It is well known that during thrombolytic therapy not only fibrin but also fibrinogen is cleaved by plasmin. Because the α-chain of fibrinogen has plasmin cleavage sites at positions 20 and 24, fibrinogenysis could conceivably yield peptides containing the FPA sequence (α1-16) without thrombin action. In vitro experiments performed in our laboratory showed that these peptides are not removed from plasma by bentonite and therefore lead to falsely elevated FPA values when assayed with the polyclonal antibodies supplied by Imco or Mallinkrodt. To estimate the contribution of these peptides, the thrombin increasable FPA fraction was additionally measured in all plasma samples, and the thrombin corrected FPA value (tc-FPA=FPA–0.2×[ti-FPA–20] ng/ml) was calculated with the formula proposed and explained above (see “Methods”).

Thrombin correction led to thrombin-corrected FPA values that were very similar to original FPA values (see Table 3). The correction exceeded 5 ng/ml (maximum, 19 ng/ml) in only 14 of 171 (8%) samples; in three samples (1.8%), an FPA value greater than 5 ng/ml was corrected to less than 5 ng/ml. The contribution of FPA-containing fibrinogen degradation peptides, therefore, did not change the FPA course in a way of simulating ongoing thrombin action, especially not in patients with clinical evidence of reocclusion.

Mean fibrinogen plasma levels decreased from 3.1±0.7 before therapy to 1.2±0.5 g/l 30 minutes after completion of rt-PA infusion. A postlytic fibrinogen level less than 1 g/l was found in 12 of 30 (40%) patients. The mean level of fibrinogen degradation products was elevated to 319±237 μg/ml at that time.

**Discussion**

**Fibrinopeptide A Sampling**

FPA plasma levels may be spuriously elevated by suboptimal venipuncture or central catheter placement provoking local fibrin generation. To test a sampling method from an 18-gauge intravenous cannula, sequential FPA levels were measured in two control groups. The results in Table 2 indicate that 1) normal FPA values are obtained from healthy young volunteers anticoagulated during 12 hours, 2) no prolonged FPA increase is provoked by a carefully placed cannula even without anticoagulation during 1.5 hours, 3) whereas normal FPA values obtained by optimal single venipuncture are 1.9±0.5 ng/ml, unproblematic FPA sampling from heparinized intravenous cannula in patients with coronary artery disease may be considered reliable for levels greater than 5 ng/ml.

**Fibrinopeptide A in Early Hours of Acute Myocardial Infarction**

Compared with control subjects, mean plasma levels of FPA were 10–40 times higher in patients with acute myocardial infarction. Although the individual variance is remarkable, these values clearly exceed previously reported values that were measured later after onset of symptoms (6–32 hours), but these values confirm high FPA levels measured before thrombolysis with streptokinase. Fibrin generation seems to decrease within 6–12 hours after an acute coronary occlusion. No correlation could be found between FPA levels and infarct size or extent of coronary artery disease; but interestingly, FPA levels in three young patients with angiographically normal coronary arteries after acute myocardial infarction were elevated, which emphasizes the role of fibrin generation in absence of significant coronary artery disease.

FPA, rather than being a specific marker of thrombotic coronary occlusion, may also reflect fibrin generation on damaged endothelium after prolonged ischemia and left ventricular, or venous thrombosis. An extravascular origin, as
Table 3. Fibrin Generation Before, During, and After Thrombolytic Therapy With Recombinant Tissue-Type Plasminogen Activator

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<th>FPA (ng/ml)</th>
<th>tc-FPA (ng/ml)</th>
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rt-PA, recombinant tissue plasminogen activator; FPA, fibrinopeptide A; tc-FPA, thrombin corrected fibrinopeptide A.

*excl. reocclusion group (No. 12, 18, 26, 30, 34); †all patients; ‡p<0.01 compared with admission level; §§p<0.05 compared with admission level; ††p<0.01 compared with preheparin level.

shown for patients with pulmonary infarction or pleural effusion after pulmonary embolism, can be excluded, with the highest FPA levels measured very early after coronary occlusion and falling abruptly after intravenous heparin therapy.

**Fibrinopeptide A and Thrombin-Corrected Fibrinopeptide A Under rt-PA Infusion**

Plasma levels of FPA increased from the admission value in all but four patients under rt-PA infusion (p<0.01). Compared with levels measured under streptokinase infusion, the increase under rt-PA administration is much less pronounced. Therefore, the question arises of whether a crossreaction with FPA-containing peptides originating from fibrinogen degradation leads to falsely elevated FPA levels.

All control experiments performed in this study to discover and correct for any possible contribution of peptides released by plasmin from the N-terminus of fibrinogen’s α-chain (preferably α1-20 and α1-24,
containing the FPA sequence) substantiate the existence of such peptides. However, their contribution is minimal and does not falsify the course of FPA levels originating from thrombin action.

Whether this applies to thrombolysis with a less fibrin specific agent, such as streptokinase, remains to be determined. No crossreactivity was detected in the plasma of streptokinase-treated patients by separating the large fibrinogen degradation fragments with gel chromatography; crossreactivity with α1–20 or α1–24 fibrinogen fragments, however, could not be excluded.28

Thus, further fibrin generation under thrombolytic therapy must be postulated as already proposed for streptokinase28 and rt-PA.45 Thrombin activity could be sustained by endothelial damage in the ischemic territory,16 by subendothelial collagen reexposed through thrombolysis, or by procoagulant factors (e.g., thrombin) released from clots.46 The absence of a correlation between FPA and creatine kinase plasma levels or ischemic time is not in favor of the first hypothesis, and the very early FPA increase (30 minutes after streptokinase treatment)28 does not support the second one. Thrombolysis itself or the thrombolytic drug may, by yet unknown feedback mechanisms, paradoxically promote a secondary prothrombotic reaction that reestablishes a disturbed equilibrium. Streptokinase has previously activated platelets in a dose- and plasminogen-dependent manner.47 Finally, t-PA itself releases fibrinopeptides (mainly FPB) from fibrinogen, as recently shown in vitro.48 FPA, therefore, may not be a specific marker of thrombin activity. But, compared with FPA levels measured in vitro and in patients with pulmonary embolism under rt-PA and heparin treatment (mean 5.9 nM48), our FPA levels were not only higher under rt-PA treatment (93±86 ng/ml), but fell under heparin treatment (in patients without reocclusion) to levels that may indeed represent this t-PA action on fibrinogen, considering the further decrease after completion of rt-PA infusion. Thus, although rt-PA itself may induce a minor additional FPA increase, the fluctuation of FPA levels measured in our patients under rt-PA or heparin infusion or both may be interpreted as an index of intravascular thrombin activity. Moreover, no evidence exists that fibrin originating from thrombin or thrombin/t-PA activity would behave differently with regard to thrombosis.

A substantial fibrinogen depletion under rt-PA infusion was detected in most of our patients. However, although commonly used during thrombolysis, the Clauss method may give spuriously low fibrinogen values by defective fibrin polymerization in presence of high levels of fibrinogen degradation products.49,50

Postlytic Fibrinopeptide A and Reocclusion

In patients with successful rt-PA–induced reperfusion and coronary patency 11.7±6.9 days later, FPA levels fell abruptly below the admission value within 30 minutes after heparinization and did not exceed a critical level of 5 ng/ml for the next 12 (and, with a few exceptions, up to 24) hours under continued anticoagulation (see Figure 1). The same is probably true for patients without initial reperfusion. A slight FPA increase at 24 hours (with 3 of 25 values >5 ng/ml) was observed in most of the patients. These levels are distinctly lower than those observed after streptokinase and heparin infusion in previous studies,28 raising again the question of spurious elevation of FPA by fibrinogen degradation peptides.

Each one of our five patients with clinical and electrocardiographic evidence of recurrent severe ischemia after initial reperfusion had persistent high or reincreasing FPA levels 30 minutes after completion of thrombolytic therapy. This clinical observation and the subsequent results from angiography do not allow the drawing of a conclusive correlation between postlytic FPA plasma levels and the reoclusion risk at this point. But they strongly suggest a further evaluation of FPA as a reoclusion marker. Patients with postlytic FPA levels below 5 ng/ml, or below their own admission value, seem to be at low risk of reocclusion for several days after successful reperfusion. Postlytic FPA levels that do not fall below the admission value or increase again despite full anticoagulation with heparin indicate ongoing fibrin generation. These patients seem to be at risk of reocclusion and may need more intense heparin treatment or early angiography and angioplasty.

In a short communication,51 thrombin-antithrombin III–complex levels were recently postulated as a reoclusion marker after rt-PA–induced thrombolysis. This would further support our view that monitoring of circulating thrombin activity or fibrin generation could be helpful in managing patients after successful thrombolytic therapy. On the other hand, platelet aggregation has been convincingly shown to be involved in reoclusion after thrombolysis with rt-PA despite full heparinization in a canine preparation of coronary thrombosis.52 The importance of platelet aggregation preceding rethrombosis after thrombolysis has not been examined in our patients and remains an interesting question.

Conclusions

FPA allows a monitoring of intravascular fibrin generation during acute myocardial infarction and thrombolytic therapy, provided blood sampling is unproblematic. Plasmin-induced fibrinogenolytic peptides may falsely elevate FPA levels, but their contribution is of minor importance during treatment with fibrin-specific agents such as rt-PA. High FPA plasma levels substantiate important fibrin generation in the early hours of myocardial infarction. In contrast to heparin, rt-PA does not prevent further fibrin generation despite successful recanalization, as shown by a significant increase in FPA levels. Anticoagulated patients with postlytic FPA
plasma levels below 5 ng/ml or below their admission values seem to be at low risk of reocclusion for several days. Persistent high or reincreasing FPA plasma levels despite adequate anticoagulation indicate ongoing fibrin generation that may necessitate more intense anticoagulation, increased antplatelet treatment, early intervention, or both, to prevent reocclusion. However, confirmation in a larger patient group is needed before considering FPA a clinically useful marker of reocclusion after thrombolytic therapy.

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References

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