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 reканализировать и реокклюзию коронарных артерий, такого маркера можно было бы отнести к ведущей значимости во время тромболитического лечения острого миокардиального инфаркта. Тридцать четыре последовательных пациента с острым миокардиальным инфарктом (пик уровня креатинина, 1,869±1,543 IU/l) были прооперированы с помощью 100 мг рекомбинантного тканевого типа плазминоген aktivatora (тромбolyzis) 3,1±1,1 часа после начала боли в грудной клетке. Ангиография 12,5±6,1 дней позже показала 81% патентность в области инфаркта. Уровни FPA в плазме (норма, 1,9±0,5 ng/ml) составили 34±46 ng/ml на адмиссии и 93±86 ng/ml (538±674% относительно уровня при адмиссии) через 90 минут лечения тромбolytic (p<0,01). В тех случаях, когда не удалось реокклюзировать (включая три первичных), уровни FPA в плазме в течение 6,7±9,7 ng/ml (24±33%, p<0,01) в течение 30 минут и 3,1±2,2 ng/ml (15±15%, p<0,01), 1,6±1,1 ng/ml (8±10%, p<0,01), и 2,5±3,0 ng/ml (12±16%, p<0,01) 30 минут, 9 часов, и 21 часа, соответственно, после завершения лечения тромбolytic. Пяти пациентам пришлось перенести временные или постоянные реокклюзии после тромболитического успеха. Их ранние послеотеченные FPA уровни (13–51 ng/ml) оставались высокими, несмотря на адекватное антикоагулянтовое лечение. FPA позволяет мониторингу контроль за ведущей значимостью во время тромболитического лечения острого миокардиального инфаркта и тромболитического лечения. После успешного реокклюзирования, уровень FPA увеличивался после применения тромбolytic в течение 30 дней. FPA уровни, которые были высокими, или увеличивались вновь, несмотря на адекватную антикоагулянтное лечение, продолжают означать реокклюзию FPA. Однако, вопрос, может ли FPA быть адекватным ферментом реокклюзии, который был бы подтверждён в большом количестве пациентов с острым миокардиальным инфарктом. (Circulation 1989;79:980–989)
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 unspecific 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 1½–2 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 pre-cooled sample tubes containing the following anticoagulants (for 9 ml blood): 1 ml CTAD (Boehringer Mannheim) supplemented with 200 μg (final concentration 40 μmol) D-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: crossreacting 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). Previously measured levels of FPA in 15 normal individuals had been 1.9±0.8 ng/ml. All FPA determinations were done by an experienced laboratory staff member unaware of the clinical or angiographic result of thrombolytic therapy.

**Thrombin-Increasable 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 supernatant before and after thrombin incubation was called thrombin-increasable 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 measurements 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 degradation products (Boehringer, Mannheim, FRG).

**Noninvasive Signs of Recanalization**

Sudden relief of chest pain, reperfusion arrhythmias, sudden resolution of ST segment elevation, and peaking of plasma MB-creatine 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, considering their limited predictive value.

**Cardiac Catheterization**

All patients receiving treatment underwent biplane left ventriculography and selective coronaryography 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-Wilcoxon 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 hemodynamically stable conditions. Electrocardiographic evidence of anterior (n=17) or infero-posterior (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 ventricular 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 recollection 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 recollection before angiography: patient 12, with reappearance of chest pain and ST segment elevation 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>Clinical reperfusion (IU/l)/time to peak (hr)</th>
<th>Angiographic patency IRV days after thrombolysis</th>
<th>Residual stenosis IRV (%)/extent CAD</th>
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Mean ±SD 53.2 ±10.1 188 ±66 min 1,869 ±1,543 IU/l 12.5 ±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
reocclusion and reperfusion: patient 30, with recurrent episodes of angina and ST elevation during 4 hours despite nitroglycerin and nifedipine intravenous infusion and a late peak of creatine kinase levels at 24 hours; and patient 34, with recurrent chest pain, terminated by a self-limited ventricular tachycardia 4 hours after rt-PA infusion. A significant (≥75%) residual stenosis was found on 17 of 25 patent infarct-related vessels. Three young men had angiographically normal or almost normal coronary arteries.

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>
<thead>
<tr>
<th>Treatment time (hr)</th>
<th>Group A (n=30)</th>
<th>Group B (n=7)</th>
<th>Group C (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without heparin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34±46/18</td>
<td>9.8±11.0/4.9</td>
<td>—</td>
</tr>
<tr>
<td>1.5</td>
<td>93±86/63</td>
<td>2.1±1.4/1.7</td>
<td>11.9±6.1/10.9</td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11.0±20.1/4.7</td>
<td>0.6±0.1/0.6</td>
<td>4.3±2.6/3.6</td>
</tr>
<tr>
<td>3.5</td>
<td>6.1±10.0/3.3</td>
<td>1.1±1.3/0.7</td>
<td>4.2±0.5/4.2</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>5.2±0.7/5.2</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3.7±10.1/1.5</td>
<td>0.7±0.2/0.7</td>
<td>—</td>
</tr>
<tr>
<td>24</td>
<td>3.1±4.6/1.7</td>
<td>—</td>
<td>—</td>
</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, fibrinogenolysis 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 Mallinckrodt. 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.42 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,12 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 values12,15 that were measured later after onset of symptoms (6–32 hours), but these values confirm high FPA levels measured before thrombolysis with streptokinase,28 Fibrin generation seems to decrease within 6–12 hours after an acute coronary occlusion.14 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 ischemia16 and left ventricular,43 or venous44 thrombosis. An extravascular origin, as
shown for patients with pulmonary infarction or pleural effusion after pulmonary embolism,\textsuperscript{10,22} 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,\textsuperscript{29} 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.\textsuperscript{29-31}

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 α-1–20 or α-1–24 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 reocclusion risk at this point. But they strongly suggest a further evaluation of FPA as a re occlusion 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 reocclusion 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 reocclusion 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 antiplatelet 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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