Comparison of 125I-Fibrinogen Kinetics and Fibrinopeptide A in Patients With Disseminated Neoplasias

By G. Mombelli, A. Roux, A. Haeberli, and P. W. Straub

To provide more information on the pathways of fibrinogen catabolism in generalized cancer, the effect of heparin on fibrinopeptide A (fpA) and on 125I-fibrinogen kinetics was studied in 15 patients with disseminated neoplasia. Three patients had evidence of venous thrombosis and in 2 additional patients a low fibrinogen level together with increased amounts of FDP/fdp and a positive ethanol test indicated disseminated intravascular coagulation (DIC). The plasma levels of fpA were grossly elevated (4.6–20, mean 11.4 ng/ml, normal values 1.0 ± 0.45 ng/ml) in patients with thrombosis or DIC, and normal to grossly elevated (0.4–10.4, mean 6.1 ng/ml) in the other patients. Intravenous heparin bolus lowered the fpA level in 11/11 patients, and continuous heparin treatment led to an impressive suppression or complete normalization of the plasma fpA in 5/6 patients. This finding is thought to reflect heparin suppression of thrombin activity on fibrinogen. In some cases, the fpA fall after heparin bolus was slow and/or incomplete, suggesting fpA generation at sites not easily accessible to heparin or insufficient heparin dosage. The 125I-fibrinogen kinetics were characterized by a significantly shorter half-life (t½: 2.5 days), increased catabolic rate constant (μ: 0.44 days⁻¹), and increased absolute turnover (68.9 mg fibrinogen/kg/day) as compared to 4 normal subjects (t½: 4.2 days; μ: 0.26 days⁻¹; turnover 21.7 mg fibrinogen/kg/day). As estimated from the fpA generation rates, intravascular thrombin action on fibrinogen contributed only in minor part to increase the turnover of 125I-fibrinogen. In particular, the turnover was greatly accelerated in heparin-treated patients despite impressive suppression or normalization of the fpA levels in 5/6 cases.

Metastatic cancer has been associated with thromboembolic diseases, acute or chronic intravascular coagulation (DIC), or abnormal bleeding tendency.1,2 The laboratory methods used to recognize hemostatic abnormalities related to cancer include conventional clotting tests,1 the study of the fibrinogen kinetics using labeled fibrinogen,3 and the radioimmunoassay (RIA) for fibrinopeptide A (fpA).5 Together with a positive ethanol test and with elevated fibrinogen-fibrin degradation products (FDP/fdp), a decrease of fibrinogen, factors V and VIII, and platelets is commonly interpreted to indicate DIC. However, DIC is a dynamic process, and a negative balance of the clotting substrates takes place only when depletion exceeds capacity for synthesis. Even the results of kinetic studies have to be interpreted with caution in the diagnosis of DIC. In particular, an accelerated plasma decay of 125I-fibrinogen may indicate intravascular deposition of fibrin, but may also reflect extravasation of the protein into malignant effusions,6 extravascular deposition of fibrin in tumor,7 or fibrinogen degradation by enzymes other than thrombin.8 The RIA technique for measuring fpA released by thrombin action on fibrinogen has been proposed to detect fibrin deposition.9 Again, elevated plasma levels of fpA may reflect extravascular, intratumoral thrombin action,8 or fpA release by proteolytic enzymes of malignant cells rather than by thrombin.

The present study was designed to provide more information on the pathways of fibrinogen catabolism and on the significance of elevated fpA in patients with disseminated cancer. The overall changes in fibrinogen catabolism were quantified by the 125I-fibrinogen kinetics. The presence of venous thrombosis in the legs was assessed by the 125I-fibrinogen uptake test. DIC was diagnosed as decompensated intravascular coagulation and fibrinolysis.10 The significance of fpA was evaluated by testing its suppressibility by heparin. In an attempt to estimate the relative contribution of intravascular thrombin activity in increasing the fibrinogen catabolism, the results of the fpA-RIA were related to the data on 125I-fibrinogen kinetics.

Materials and Methods

Material

125I-labeled human fibrinogen (specific activity 0.1 mCi/mg, clotability 90%–95%) was obtained from the Radiochemical Center in Amersham, England. Aprotinin (Trasylol, 10,000 KIU/ml) was purchased from Bayer, Leverkusen, Germany. Liquémine Roche (Heparin 5000 U-USP/ml) and Thrombin Roche (50 NIH-U/mg) were bought from Hoffmann-La Roche, Basle, Switzerland. The hospital pharmacy supplied potassium iodide 2% and 30%, trichloracetic acid (TCA) 10%, alkaline urea (NaOH 0.2 N, urea 7.2 M), and Trasylol-oxalate mixture (sodium oxalate 0.1 M and Trasylol 2000 U/ml).

Methods

The ethanol gelation test was performed according to Godal et al.,11 and the FDP/fdp were measured in the serum by the method of...
DIC was diagnosed as a decompensated state of intravascular coagulation and fibrinolysis in the presence of hypofibrinogenemia, positive ethanol test, and increased amounts of FDP/fdp.

**125I-Fibrinogen Study**

125I-fibrinogen kinetics were studied in 15 patients with disseminated cancer and in 4 normal subjects. Patients and subjects were informed of the investigational character of the study and agreed to participate. The method has been previously published in detail. In order to block the uptake of radioiodide by the thyroid, 15 drops of potassium iodide (2%) were administered by mouth 3 times daily throughout the study, starting 3 days before administration of labeled fibrinogen. At day 0, 2 vials containing 1 mg of liophilized 125I-fibrinogen (100 μCi), were reconstituted by adding 1 ml of sterile distilled water. After mixing, an aliquot of 1.5 ml (equivalent to 150 μCi) was injected intravenously, the injected volume being determined by weight. A quantity of 0.2 ml of the residue, weighed and diluted in an alkaline solution of potassium iodide (1 ml NaOH 20% + 1 drop KI 30% + aqua dest. ad 20 ml), was used as standard. At 10 and 30 min, blood was drawn for plasma volume determination using heparinized syringes. At 10 min, and then daily for 6-10 days, 18 ml of blood for determination of radioactivity (RA) was collected into 2 ml of a Trasylol-oxalate mixture. Every 2-3 days, clottable, nonclottable protein-bound, and protein-free RA was determined as follows:

Two milliliters of plasma were diluted with 5.5 ml of NaCl 0.9%. The mixture was clotted by adding thrombin to a final concentration of 6 U of thrombin/ml and left at room temperature for 2 hr. The clot was washed in 0.9% NaCl and dissolved in alkaline urea. After RA counting, fibrinogen was determined by a biuret method. Controls, established in vitro by adding heparin to plasma in a concentration of 2 U heparin/ml, showed that the concentration of thrombin used in this procedure was able to clot all the fibrinogen despite therapeutic levels of heparin.

Three milliliters of plasma were diluted with 3 ml TCA and left at 4°C for 1 hr; the precipitate was removed by filtration.

At the end of each study, 2-ml samples of plasma, dissolved fibrin, supernatant after TCA precipitation, and of the standard were counted simultaneously for RA in a scintillation counter. The individual sample RA was then expressed as a fraction of the 10 min RA.

Urines were collected continuously throughout the period of study. At the end of each study, 5-ml samples of each daily portion were counted simultaneously with the 125I-fibrinogen standard, diluted to the same volume. The RA excreted during each 24-hr period was expressed as a fraction of the injected dose.

The plasma volume was calculated from the total injected dose and the plasma RA at 0 time, the latter being obtained by extrapolating the RA of heparinized plasma samples taken at 10 and 30 min. The intravascular fibrinogen was calculated from the mean plasma fibrinogen and the plasma volume.

**125I-Fibrinogen Uptake Test**

Legs, precordium, and thyroid were scanned with a Pitman 235 isotope localization monitor according to Atkins and Hawkins. For leg scanning, surface RA was measured at 12 positions along both extremities. The relative RA of a particular scanning position with respect to precordial RA (fourth intercostal space) was calculated each day as cpm point × 100/cpm precordium. Leg scanning was considered indicative of deep venous thrombosis if the percent RA increase at any site of the leg was elevated by 20% or more over that observed at the previous day, and if this increase persisted for more than 24 hr.

**125I-Fibrinogen Kinetics**

In control subjects and in most patients, the plasma decay of 125I-fibrinogen showed the typical biexponential curve (Fig. 1), and the experimental data could be fitted by an equation of the form

\[ x(t) = C_1 \cdot e^{-\alpha t} + C_2 \cdot e^{-\beta t} \]

where \( x(t) \) is the plasma fibrinogen, and \( \alpha \) and \( \beta \) represent the slope of the slow and rapid component of the double exponential curve respectively. The closeness of the fit of the data to the slow component of the equation was evaluated by the variance of the fit, \( \chi^2 \). The fractional catabolic rate constant was calculated as \( j = (C_1/\alpha + C_2/\beta)^{-1} \). The half-disappearance time as \( t_{1/2} = \ln 2/\alpha \). The daily fibrinogen turnover was obtained as catabolic flux from \( j \) and from the mean fibrinogen level.

The curve for the whole body activity was obtained by successively subtracting from 1 the radioactivity excreted during each day. As indicated in Fig. 1, this curve could be described by a single straight line in a semilog plot, i.e., the data could be fitted by a single exponential equation of the form

\[ 1 - u = C_1 \cdot e^{-a t} + C_2 \cdot e^{-b t} \]

Parallelism of the curves for plasma and whole body radioactivity \( (a = a_0) \) indicates equilibrium between intra- and extravascular spaces. Divergence of the curves \( (a > a_0) \) indicates disequilibrium in the ratio circulating/retained activity, which may reflect pooling of label in fibrin or leakage of 125I-fibrinogen into abnormal extravascular spaces.

**fpA**

By careful venipuncture through an 18-gauge needle, 4.5 ml of free-flowing venous blood were collected into a conical polystyrol
tube containing 500 U heparin and 500 U aprotinin, dissolved in 0.5 ml of physiologic saline. The tube was immediately inverted three times and centrifuged at 3000 rpm at 4°C for 10 min; the plasma samples were stored at −25°C. They were then dialyzed to separate fpA from plasma and assayed for the A peptide. TheRIA technique for fpA has been described in detail.25 For this study, the 24-hr incubation method was used. Using this method, the mean fpA level found in 24 normal individuals was 1.01 ± 0.45 ng/ml. The results of the fpA-RIA were not corrected for the fpA loss during the dialysis procedure (recovery about 50%). In 11 patients, plasma fpA was measured before and after intravenous administration of 2000–5000 U of heparin and in all patients repeatedly during the 125I-fibrinogen study.

**Statistical Methods**

Statistical analysis was performed using Student's t test for either paired or independent samples.

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**Table 1. Clinical Data**

<table>
<thead>
<tr>
<th>Pat. No.</th>
<th>Age</th>
<th>Sex</th>
<th>Neoplasia, Metastases</th>
<th>Clinical Data</th>
<th>Antineoplastic Treatment</th>
<th>Outcome</th>
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<tbody>
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<td>1</td>
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<td>M</td>
<td>Bronchogenic cancer, undifferentiated; lung metastases</td>
<td>Obstruction of the vena cava superior</td>
<td>—</td>
<td>Discharged</td>
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<tr>
<td>2</td>
<td>49</td>
<td>M</td>
<td>Bronchogenic cancer, oat-cell type; lung and brain metastases</td>
<td>Bronchopneumonia</td>
<td>Chemotherapy</td>
<td>Discharged</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>M</td>
<td>Bronchogenic cancer, undifferentiated; bone metastases</td>
<td>Deep venous thrombosis left leg</td>
<td>—</td>
<td>Discharged</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>M</td>
<td>Bronchogenic cancer, oat-cell type; liver metastases</td>
<td>—</td>
<td>Chemotherapy</td>
<td>Discharged</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>M</td>
<td>Adenocarcinoma of the stomach; peritoneal metastases</td>
<td>Ascites +</td>
<td>—</td>
<td>Discharged</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>F</td>
<td>Adenocarcinoma of the stomach; peritoneal metastases</td>
<td>Ascites ++</td>
<td>—</td>
<td>Discharged</td>
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<td>7</td>
<td>75</td>
<td>M</td>
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<td>—</td>
<td>Died day 5</td>
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<tr>
<td>8</td>
<td>60</td>
<td>M</td>
<td>Pancreatic adenocarcinoma; liver metastases</td>
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<td>—</td>
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<tr>
<td>9</td>
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<td>F</td>
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<td>Chemotherapy</td>
<td>Died day 13</td>
</tr>
<tr>
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<td>58</td>
<td>F</td>
<td>Breast cancer; bone-, liver-, pleura-metastases</td>
<td>Pleural effusion ++</td>
<td>Chemotherapy</td>
<td>Discharged</td>
</tr>
<tr>
<td>11</td>
<td>31</td>
<td>M</td>
<td>Testicular cancer, type teratoma embryonale; bone metastases</td>
<td>—</td>
<td>Radiotherapy</td>
<td>Discharged</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>M</td>
<td>Testicular cancer, type carcinoma embryonale; lung and retroperitoneal metastases</td>
<td>—</td>
<td>Chemotherapy</td>
<td>Discharged</td>
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<tr>
<td>13</td>
<td>68</td>
<td>F</td>
<td>Ovarian adenocarcinoma; peritoneal metastases</td>
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<td>Discharged</td>
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<td>15</td>
<td>67</td>
<td>F</td>
<td>Polymorphous sarcoma of unknown origin; liver-, lung-, spleen- and bone-metastases</td>
<td>Pleural effusion ++</td>
<td>—</td>
<td>Died day 14</td>
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</table>

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**RESULTS**

**Clinical Data**

The clinical data are summarized in Table 1. The series included 15 patients with generalized cancer. In 3 patients, the neoplastic disease was in terminal stage, and these patients died 5, 8, and 14 days after the beginning of the study. In patient no. 8, the autopsy disclosed, in addition to diffuse metastatic lesions of the liver, multiple fibrin thrombi in the renal, splenic, myocardial, and pulmonary vessels, and prominent lesions of nonbacterial thrombotic endocarditis on the mitral valve. An additional patient (no. 9) died from acute pulmonary embolism (confirmed by postmortem examination) 13 days after the beginning of the study.
Two patients (nos. 3 and 13) had clinically evident deep venous thromboses and were treated with high heparin doses (40,000–60,000 U i.v./day). Four patients without clinical signs of venous thrombosis (nos. 9, 10, 11, and 12) received prophylactic low-dose heparin (10,000–15,000 U s.c./day) from the start of the study. In patient no. 10, heparin was stopped after 5 days because of epistaxis.

Conventional Clotting Tests

The results are summarized in Table 2. In patients 4 and 8, hypofibrinogenemia, an elevated level of FDP/fdp, and a positive ethanol test indicated DIC. In the other patients with excessive amounts of FDP/fdp in plasma, the ethanol test was negative and the fibrinogen level normal or high.

125I-Fibrinogen Uptake Test

In spite of the high-dose heparin treatment, an accumulation of the tracer, corresponding to the clinical localization of the thrombosis, was found in patients 3 and 13. A positive scan was also found in a nonheparinized patient (no. 6) without clinical signs of thrombosis. In two patients (nos. 9 and 12) and one control subject (no. 2), the radiofibrinogen uptake test showed an increase of the radioactivity over the thyroid despite previous iodine blocking.

125I-Fibrinogen Kinetics

In controls, the mean clottability of 125I-fibrinogen in serially collected plasmas averaged 94%, and the non-protein-bound fraction was below 2%. In cancer patients without DIC, the mean clottability averaged 88%, the nonclottable protein-bound fraction 7%, the free fraction 5%. In the two cases of DIC (nos. 4 and 8), there was an impressive decrease of the clottable fraction of the plasma radioactivity during the study. In these two cases, the plasma decay of 125I-fibrinogen could not be described by a simple function, whereas in an additional patient (no. 7), the experimental data were not sufficient to establish a decay curve. Therefore, plasma decay curves of 125I-fibrinogen could be established in 4 control subjects and in 12 patients. In these cases, the closeness of the fit is demonstrated by values of $s^2$ ranging from 0.0003 to 0.002 in controls and 0.0008 to 0.003 in patients.

The results are summarized in Table 3. In controls, the mean fibrinogen $t_1^2$ was 4.2 days, the mean catabolic rate constant $j$ 0.26 days$^{-1}$, and the mean daily turnover 21.7 mg fibrinogen/kg/day. In cancer patients, $t_1^2$ was shortened to 2.5 days ($p<0.001$), $j$ increased to 0.44 days$^{-1}$ ($p<0.001$), and the daily turnover increased to 68.9 mg fibrinogen/kg/day ($p<0.001$). There were no major differences comparing heparin-treated and untreated patients. Moreover, the differences in $t_1^2$, $j$, and daily turnover of fibrinogen remained highly significant when the heparin-treated subgroup of patients was compared to the control group ($p<0.001$).

In the 2 cases of DIC (nos. 4 and 8), the 125I-fibrinogen kinetics were characterized by a rapid fall of the total plasma radioactivity and by an impressive decrease of the clottability of 125I in plasma (Fig. 2).

In control subjects, the curves for plasma and total body activities were parallel, as indicated by almost identical values for $a$ and $a_n$ (mean value for $a$:

<table>
<thead>
<tr>
<th>Pat. No</th>
<th>Plasma Fibrinogen (mg/ml)</th>
<th>FDP/fdp (g/ml)</th>
<th>Ethanol Test</th>
<th>125I Fibrinogen Uptake Test</th>
<th>Initial Level</th>
<th>Heparin Treatment</th>
<th>No Heparin</th>
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<td>3.2</td>
<td>&lt;2.5</td>
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<td>6.9 ± 0.4</td>
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<td>neg</td>
<td>3.4</td>
<td>6.6 ± 7.7</td>
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<td>3.2 ± 3.6</td>
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<tr>
<td>5</td>
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<td>10.4</td>
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<tr>
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<td>neg</td>
<td>18.2</td>
<td>9.5 ± 4.0</td>
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<tr>
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<td>3.8</td>
<td>10</td>
<td>neg</td>
<td>neg</td>
<td>3.8</td>
<td>0.7 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2.9</td>
<td>&lt;2.5</td>
<td>—</td>
<td>neg</td>
<td>3.2</td>
<td>1.8 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2.2</td>
<td>&lt;2.5</td>
<td>—</td>
<td>neg</td>
<td>4.3</td>
<td>1.8 ± 0.3</td>
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<tr>
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<td>—</td>
<td>pos</td>
<td>neg</td>
<td>9.9</td>
<td>2.3 ± 1.4</td>
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<td>14</td>
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<td>15</td>
<td>2.2</td>
<td>40</td>
<td>neg</td>
<td>neg</td>
<td>0.4</td>
<td>0.8 ± 0.3</td>
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</tbody>
</table>

The mean fpA values were calculated from repeated fpA measurements during the study. For the calculation of the mean, only fpA levels measured under heparin were considered in heparin-treated patients.
0.176 ± 0.01, for \( a \); 0.177 ± 0.02). In most cancer patients, the plasma radioactivity decreased more rapidly than the total body radioactivity (Figs. 1 and 2). The values of \( a \) and \( a_u \) were calculated in 6 patients (nos. 3, 9, 10, 11, 12, and 13) in whom complete urine collections were assured by indwelling urinary catheter. In these cases, the mean value for \( a \) was 0.26 ± 0.05, for \( a_u \) 0.15 ± 0.05.

**fpA**

The results of the fpA-RIA are summarized in Table 2 and Figs. 3 and 4. At the beginning of the study, the peptide A level was elevated (>2 ng/ml) in 14/15 patients (Table 2). In particular, the plasma fpA was grossly elevated in patients with positive leg scan (20.0, 12.8, and 9.9 ng/ml), whereas patients with DIC showed peptide levels of 9.4 and 4.6 ng/ml. The mean fpA level was 11.4 ng/ml in patients with documented thromboses or DIC, as compared to 6.1 ng/ml in patients with negative leg scan and without signs of intravascular coagulation (\( p > 0.05 \)).

As indicated by high values of standard deviations from the mean, impressive fluctuations of the A peptide level were observed during the period of study in some nonheparin-treated patients (Table 2). In two cases (nos. 2 and 4), the fpA fell to normal values while under chemotherapy. In patient no. 4 in particular, the progressive decline of the A peptide paralleled the normalization of the signs of DIC. In case 15, the fpA level was found to be normal on repeated measurements.

The effect of an intravenous heparin bolus on the fpA level was studied in 11 patients. The intravenous administration of 2000–5000 U heparin resulted in a significant fall of the A peptide concentration (\( p < 0.05 \) in the paired \( t \) test between preheparin and first.
postheparin fpA) (Fig. 3). However, the rate of fall varied considerably from one patient to another. The fpA reached the normal range within 15–20 min in 4 patients (no. 2, 8, 10, 14) and dropped substantially and/or rapidly in three additional cases (nos. 1, 9, 13).

In 2 patients (nos. 11 and 12), the fpA was only measured at 30 min and was found to be normal. In 2 cases (nos. 6 and 7), the fpA fall was slow, the A peptide being still elevated 30–45 min after heparin.

With the exception of case 9, continuous heparin treatment led to an impressive decrease or to a complete normalization of the A peptide (Fig. 4). In patient 3, heparin was briefly stopped to perform a mediastinoscopy: the A peptide level rose promptly and fell again after the reinstitution of the heparin treatment. In patient 9, who had shown a prompt fall of the fpA level after intravenous heparin bolus, the fpA increased again and remained elevated despite 2 × 5,000 U heparin s.c./day. The patient died a few days later from pulmonary embolism. This course suggests an occult thrombosis that could not be stopped because of too low a dose of heparin.

Assuming an fpA t½ of 5 min for calculation, the mean fpA levels measured in our patients were estimated to be the product of the intravascular thrombin proteolysis of 1–25 (mean 10) mg fibrinogen/kg/day, representing only 1%–30% (mean 13%) of the respective total fibrinogen catabolism.

**DISCUSSION**

Out data on 125I-fibrinogen kinetics in normal controls compare well with an earlier study. In cancer patients, the following characteristics were observed: (1) the plasma decay of 125I-fibrinogen was accelerated regardless of whether the patients received heparin or not; (2) the plasma level of fibrinogen didn’t reflect the altered kinetics; (3) the urinary 125I excretion was consistently delayed. Similar observations were made by other investigators. A particularly rapid plasma clearance of the label was found in the 2 patients with DIC, suggesting that fibrinogen depletion substantially contributed to lower plasma fibrinogen. In the other patients, however, shortened half-lives were compatible with normal to elevated plasma levels of fibrinogen, indicating considerably increased turnover rates of the protein. It is noteworthy, that some of these patients presented advanced metastatic involvement of the liver. The delayed 125I excretion points to the presence of slowly equilibrating compartments. These compartments might, at least in patients without thyroidal uptake of 125I reflect fibrin or fibrinogen pools, including the deposition of fibrin in thrombi and the accumulation of fibrinogen (or fibrin) in malignant effusions and tumors.

With respect to fpA levels in generalized cancer, we summarize our observations as follows: (1) plasma levels of fpA were elevated in 14/15 patients; (2) there was no consistent relationship between fpA level and 125I-fibrinogen kinetics in plasma; (3) the rapid plasma clearance of 125I-fibrinogen was only partially attributable to the intravascular action of thrombin on fibrinogen.

As in patients with thromboembolism or DIC and with tissue sepsis, elevated plasma levels of the A peptide have been reported in those with neoplastic diseases. That the latter finding must be interpreted with caution is exemplified by the fact that in our patient group some suffered from several of the aforementioned disorders, so that it remains unclear whether and to what extent the elevated fpA reflected active neoplastic disease alone. On average, the fpA levels were higher in patients with documented thromboembolism or DIC. However, very high levels were also found in some patients with negative leg scan and without signs of DIC. Because of the limited sensitivity of the 125I-fibrinogen scanning (used as a noninvasive procedure in this study), occult thromboses may have escaped detection in some cases. This methodological uncertainty is illustrated in one patient (no. 9) who died from pulmonary embolism a few days after the end of the study.

Intravenous heparin has been reported to promptly normalize the fpA level in thromboembolic diseases, indicating suppression of thrombin action on fibrinogen. In an earlier study, heparin hadn’t significantly affected the fpA levels in ambulatory cancer patients, a finding that was attributed by the authors to a fpA
generation at extravascular sites not easily accessible to heparin. In our patients, an intravenous heparin bolus lowered the fpA level in 11/11 cases, while continuous heparin treatment led to an impressive suppression or normalization of the A peptide in 5/6 cases. These findings suggest a close relationship between A peptide and active fibrin formation. In some cases, however, the fpA fall after heparin was slow and/or incomplete. This may indicate an inadequate dose of the anticoagulant or a fpA generation by enzymes other than thrombin. Alternatively, the different patterns of fpA response to heparin may reflect different degrees of overlap of intra- and extravascular clotting processes.

Conventional clotting tests indicated DIC in two patients, and in one of them this diagnosis was confirmed by the autopsy finding of disseminated microthrombi. The fpA levels of these patients were relatively low when compared to those found in cases of venous thrombosis. This finding, however, does not necessarily indicate low effective thrombin activity. In both cases, intravascular coagulation and fibrinolysis had led to a significant depletion of fibrinogen. In the presence of hypofibrinogenemia, fpA generation may be limited by low substrate concentration. Finally, we point to the fact that the rapid plasma disappearance of $^{125}$I-fibrinogen found in our patients was only partially attributable to the intravascular action of thrombin. In particular, the plasma decay of the label was greatly accelerated in 5 cases despite an impressive suppression or normalization of the fpA under continuous heparin treatment. This observation suggests alternative explanations for the rapid kinetics of $^{125}$I-fibrinogen, like (1) nonthrombin-mediated degradation and (2) intra-–extravascular redistribution. We believe that the first mechanism was operative in a patient (no. 15) who showed greatly elevated FDP/fdp but repeatedly normal fpA. The second mechanism includes the extravascular accumulation of fibrinogen or fibrin around tumors and is probably the most important determinant of the rapid $^{125}$I-fibrinogen kinetics in disseminated cancer.

In conclusion, no correlation between the plasma level of fpA—as index of thrombin action on fibrinogen—with the turnover of $^{125}$I-fibrinogen could be established in the present study. Moreover, our results indicate that mechanisms such as extravasation of fibrinogen or extravascular thrombin action are preventing the clinical use of the plasma fpA or the $^{125}$I-fibrinogen kinetics to detect intravascular coagulation or thrombus formation in patients with cancer.

REFERENCES

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Comparison of 125I-fibrinogen kinetics and fibrinopeptide A in patients with disseminated neoplasias

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