Persistent Activation of Coagulation Mechanism in Unstable Angina and Myocardial Infarction

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Background The blood coagulation system is activated in the acute phase of unstable angina and acute myocardial infarction. However, it remains unclear whether augmented function of the hemostatic mechanism serves only as a marker of the acute thrombotic episode or whether a hypercoagulable state persists for a prolonged period after clinical stabilization.

Methods and Results We prospectively measured the plasma concentrations of prothrombin fragment 1+2 (F112) and fibrinopeptide A (FPA) in consecutive patients presenting with unstable angina (n=80) or acute myocardial infarction (n=32), respectively. At 6 months, plasma determinations were repeated in patients experiencing an uneventful clinical course (unstable angina, n=57; myocardial infarction, n=23). We quantitated the plasma levels of F112 and FPA in control patients with stable angina (n=37) or healthy individuals (n=32) who were matched for age and sex. The median plasma concentrations of F112 and FPA are significantly higher in patients presenting with unstable angina (F112, 1.08 nmol/L; FPA, 2.4 nmol/L) or acute myocardial infarction (F112, 1.27 nmol/L; FPA, 3.55 nmol/L) compared with patients with stable angina (F112, 0.74 nmol/L; FPA, 1.3 nmol/L; P<.0001) or healthy individuals (F112, 0.71 nmol/L; FPA, 0.80 nmol/L; P<.0001).

Conclusions During the acute phase of unstable angina and myocardial infarction, patients exhibit increased coagulation system activity. Over the next 6 months, patients with unstable angina or myocardial infarction experiencing an uneventful clinical course manifest a persistent hypercoagulable state with minimal generation of fibrin.

Key Words coagulation • angina • infarction • prothrombin fragment 1+2 • fibrinopeptide A

In the acute phase of unstable angina and myocardial infarction, the hemostatic mechanism is known to be activated. Plasma levels of fibrinopeptide A (FPA), cross-linked fibrin, platelet factor 4, and fibrinogen-fibrin degradation products are elevated, signaling production and lysis of the intracoronary fibrin-platelet thrombus.1-4 However, it remains unclear whether increased activity of the hemostatic mechanism is only a marker of the acute thrombotic episode or whether a hypercoagulable state persists for a prolonged period after the apparent resolution of these disorders or even precedes their appearance. The relation between the postulated hypercoagulable state and acute coronary syndromes has been difficult to assess because of the absence of reliable techniques for measuring changes in blood coagulability.

The prothrombin fragment 1+2 (F112)5,6 and FPA7,8 immunoassays allow coagulation system activity to be monitored under in vivo conditions. F112 is a 31-kd polypeptide released from the amino terminal end of prothrombin during its conversion to thrombin that quantifies factor Xa activity. FPA is a 16-amino-acid peptide cleaved from the α chain of fibrinogen during its transition to fibrin that detects thrombin action. The occurrence of elevated plasma concentrations of F112, in the presence of augmented plasma levels of FPA, signifies increased production of factor Xa, which is able to generate sufficient free thrombin to initiate thrombus formation. The occurrence of elevated plasma concentrations of F112, in the presence of normal or slightly increased plasma levels of FPA, signifies enhanced production of factor Xa, which is unable to generate sufficient free thrombin to initiate thrombus formation. This observation indicates accelerated hemostatic mechanism function, which is termed a hypercoagulable state.9

In the present investigation, we prospectively measured the plasma concentrations of F112 and FPA in patients with a first episode of unstable angina or myocardial infarction and compared the results with those of control patients with stable angina or healthy individuals. We then reevaluated patients with acute coronary syndromes who exhibited an uneventful clinical course over a subsequent 6-month period to determine whether such individuals manifest a persistent abnormality in blood coagulability.
Methods

Study Population

The study population was drawn from a cohort of 137 patients with unstable angina and 50 patients with acute myocardial infarction who were younger than 70 years and were consecutively admitted between April 1990 and April 1991 to the Division of Cardiology, Ca' Granda Niguarda Hospital, Milan, Italy.

Inclusion Criteria and Patient Subgroups

Patients were prospectively assigned to diagnostic subgroups or excluded from investigation by the physician in charge of the emergency department. A log of all hospital admissions was kept during the recruitment phase. Unstable angina was defined as chest pain occurring at rest that was accompanied by transient ischemic changes on the ECG (i.e., ST-segment elevation or depression ≥1 mm 0.08 second after the J point or pseudonormalization of previously negative T waves) with serum levels of creatine kinase–MB fraction of less than twice the upper limit of normal. Acute myocardial infarction was defined as prolonged chest pain occurring at rest accompanied by ST-segment elevation evolving into pathological Q-wave or T-wave inversion confirmed by an elevation of the creatine kinase–MB fraction of more than twice the upper limit of normal. Only patients reporting the onset of symptoms within 6 hours of presentation were eligible to enter the study.

Exclusion Criteria

Patients with comorbid conditions known to alter coagulation system activity or decrease clearance of activation fragments or who were taking drugs that affect hemostatic mechanism function were deemed ineligible for the study. Among the 137 patients with unstable angina, 57 patients were excluded because they had one of the following: incorrect diagnosis (3 patients); concomitant peripheral vascular disorders or valvular heart disease (11 patients); history of cerebrovascular accident, coronary artery bypass surgery, angioplasty, or acute myocardial infarction within the preceding 6 months (21 patients); disorders of hemostasis (1 patient); malignancy (1 patient); severely limited venous access (12 patients); renal or hepatic insufficiency (7 patients); or rheumatoid arthritis (1 patient). Among 50 patients with myocardial infarction, 18 patients were excluded because of incorrect diagnosis (1 patient), difficult venous access (8 patients), peripheral vascular disease (4 patients), renal insufficiency (1 patient), valvular heart disease (2 patients), or echocardiographic evidence of intracardiac thrombus (2 patients).

Study Protocol

Screening for the study was done in the emergency department. After determination of eligibility and inclusion into the study, venous blood samples were collected for baseline biochemical and coagulation analyses, and standardized medical therapy was started immediately. Blood withdrawal was performed before any invasive procedure, including the insertion of intravenous lines. Patients with unstable angina received intravenous heparin (100-150 U/kg bolus followed by 10-20 U/kg infusion to maintain the activated partial thromboplastin time at 1.5 to 2 times control values), intravenous nitroglycerin (0.1-0.5 μg/kg per minute), and oral atenolol (50 to 100 mg/d) or metoprolol (180 to 360 mg/d), whereas patients with myocardial infarction were treated with thrombolytic agents (1.5 million U streptokinase over 60 minutes, 100 mg tissue-type plasminogen activator over 3 hours, or 30 U anistreplase over 5 minutes) in conjunction with heparin (5000-U bolus followed by 1000 U/h adjusted to maintain the activated partial thromboplastin time above 2 times control values), aspirin (325 mg/d), and β-blockers (50 to 100 mg/d atenolol). The patients were followed for the occurrence of cardiac events, defined as death, myocardial infarction, or the need for coronary revascularization. Before discharge, the patients underwent coronary angiography. In the absence of disease of the left main coronary artery, the decision to perform revascularization was made on the basis of the patient’s symptomatic response to the medical regimen and required at least one episode of angina at rest with accompanying ischemic ECG changes. While in the hospital, all patients stopped smoking, and on discharge, they were enrolled in a program to control addictive behavior that has a documented high rate of success. Long-term treatment was standardized by administering a combination of aspirin (325 mg/d), transdermal nitroglycerin (10 to 20 mg/d), atenolol (50 to 100 mg/d), diltiazem (180 to 360 mg/d), and/or nifedipine (40 to 80 mg/d). Follow-up visits were scheduled at 1, 3, and 6 months. At the 6-month visit, the patients with an uneventful clinical course underwent 24-hour Holter monitoring to detect silent ischemia, echocardiography to uncover intracardiac thrombi, and venous blood sampling for follow-up analyses. The plasma concentrations of F1+2, and FPA have been shown to represent stable parameters that are characteristic of individuals over an extended time period. To demonstrate that the above conclusion was valid during our investigation, we drew an additional blood sample between the fourth and seventh months from a randomly selected subgroup of the study population consisting of 21 patients with unstable angina and 12 patients with myocardial infarction. The patients in the randomly selected subgroup exhibited clinical and angiographic characteristics similar to those of the overall population.

Control Population

We evaluated control patients with stable angina or healthy individuals who were matched for age and sex. Patients with stable angina but no prior history or findings of myocardial infarction, unstable angina, coronary revascularization, silent ischemia, or peripheral vascular disease were selected from a pool of individuals hospitalized for elective cardiac catheterization. Stable angina was defined as a history of chest pain induced by exercise or usual daily activity lasting more than 6 months with the development of at least 1 mm of ST-segment depression during the exercise test and with significant coronary artery disease at angiography. The medical regimen of patients with stable angina included a combination of aspirin (100 to 325 mg/d), nitrates (transdermally 10 to 20 mg/d or orally 40 to 80 mg/d), atenolol (50 to 100 mg/d) or metoprolol (100 to 200 mg/d), diltiazem (180 to 360 mg/d), or verapamil (240 to 380 mg/d) or nifedipine (30 to 60 mg/d). Healthy, nonsmoking individuals were selected at random from donors to the Blood Bank of the IRCCS, Maggiore Hospital, Milan. Blood samples for biochemical and coagulation analyses were taken from patients with stable angina during hospitalization for cardiac catheterization, and specimens were collected from healthy controls during routine visits to the blood bank. In 11 patients with stable angina who were not undergoing coronary revascularization and in 12 randomly selected healthy volunteers, additional blood samples were obtained after 6 months.

Measurement of Coagulation System Activation and Variability of the Assays

Venipuncture was performedatraumatically by two specially trained investigators with 19-gauge butterfly infusion sets using a two-prong technique. After the first 4 mL of blood was discarded, samples were collected directly into refrigerated vacutainers containing an anticoagulant mixture composed of a thrombin inhibitor, EDTA, and aprotinin (purchased from Byk-Sangtec). The ratio of anticoagulant to blood used was 1:9 (v/v). Blood samples were centrifuged immediately at 2500g for 25 minutes at 4°C; the plasma was frozen on dry ice and stored at −80°C until use. All samples were analyzed without knowledge of the clinical data. The plasma concentrations of FPA were determined in duplicate by ELISA in plasma extracted twice with bentonite to remove fibrinogen (Diagnostica Stago). This tech-
nique has an intra-assay CV of about 5%. The plasma levels of F\textsubscript{1+2}, were measured by double-antibody radioimmunoassay as previously described.\textsuperscript{12} This method has a short-term interassay CV of approximately 8%. The plasma concentrations of F\textsubscript{1+2} cited for healthy individuals are lower than those reported previously.\textsuperscript{12} This is attributable to the use of an F\textsubscript{1+2} antibody population that gives uniformly lower values. In 82 healthy individuals of varying age, the correlation coefficient (r) between the F\textsubscript{1+2} concentrations obtained with the two antibody preparations is 0.90. The plasma measurements of F\textsubscript{1+2} conducted with this antibody population are quite stable over time periods of more than 3 years with an interassay CV of about 10%. All plasma determinations in this study were performed with the same antibody population. The variability of repeated measurements was assessed in 12 patients with myocardial infarction presenting for the 6-month evaluation. Plasma samples were obtained at 0, 60, 90, 120, 180, and 240 minutes. The CV for these measurements was 11% for F\textsubscript{1+2} and 40% for FPA. However, none of the normal initial values of FPA were elevated with repeated determinations, and none of the initial abnormal values of F\textsubscript{1+2} were normal with repeated determinations.

**Coronary Arteriography**

In the study population, coronary arteriography was performed at a mean of 6±5 days after enrollment except in 3 patients who died and 11 patients who refused the procedure. Selective coronary arteriography was performed at a mean of 6±5 days after enrollment except in 3 patients who died and 11 patients who refused the procedure. Selective coronary arteriography was performed in multiple views by the Sones or Judkins technique after premedication with 10 mg diazepam. Diameter narrowing of more than 50% in the coronary arteries was considered significant coronary stenosis. Patients were classified as having one-, two-, or three-vessel disease according to the number of vessels with significant coronary stenoses.

**Holter Monitoring**

Holter monitoring was performed with a Delmar Avionics Electrocardiocorder model 445 with a frequency response of 0.05 to 100 Hz, which meets the specifications of the American Heart Association. The leads showing the most obvious ECG changes during the spontaneous attacks were monitored. Leads with abnormal waves or significant ST-segment shifts were avoided, and control recordings were made in each patient in the supine, prone, standing, and sitting position. The system was calibrated before and after each placement. The tapes were analyzed at 60 times real time under continuous visual inspection, and an episode of transient ischemia was defined as ≥1 mm of ST-segment elevation or depression occurring 80 milliseconds after the J point, lasting for at least 1 minute, and separated from other episodes by at least 1 minute. When a significant ST-segment change was noted on the monitor, the episode was recorded on ECG paper at 25 mm/s.

**Informed Consent**

The study was approved by the Institutional Review Board of the Ca’ Granda Niguarda Hospital, and informed consent was obtained from all subjects. All clinical studies and informed consent procedures were also approved by the Committee on Clinical Investigations of the Beth Israel Hospital.

**Statistical Analysis**

The deviations of plasma concentrations of F\textsubscript{1+2} and FPA from a normal distribution were tested by calculating coefficients of skewness and kurtosis. Given that the plasma levels of coagulation system markers were found to be nonnormally distributed, the Kruskal-Wallis one-way ANOVA was used to test the difference between groups; subsequent pairwise comparisons were made using the Mann-Whitney U test with downward adjustment of the α level to compensate for multiple comparisons. Paired data were analyzed with the Wilcoxon signed rank test. The number of patients who exhibited plasma concentrations of F\textsubscript{1+2} and FPA above the upper normal limits was calculated by determining the 95th percentile of the distribution in the control group of healthy individuals, which was set at 1.02 nmol/L for F\textsubscript{1+2} and 2.2 nmol/L for FPA. Prevalences were compared by χ\textsuperscript{2} test. Descriptive statistics include mean or median values, when appropriate. The 99% intervals for prevalence and median values are also given.\textsuperscript{13,14} All tests presented are two-tailed. P values of <.01 were regarded as statistically significant.

**Results**

We investigated 80 patients with unstable angina and 32 patients with acute myocardial infarction. We also evaluated 37 control patients with chronic stable angina and 32 healthy individuals. Table 1 shows the clinical and angiographic characteristics of patients with acute coronary syndromes and stable angina. A higher prevalence of one-vessel disease was observed in patients with myocardial infarction compared with those with unstable angina or stable angina (P=.0009). At admission, plasma concentrations of F\textsubscript{1+2} and FPA were higher in patients with unstable angina (P<.0001) or acute myocardial infarction (P<.0001) compared with those with stable angina or healthy individuals matched for age and sex (Table 2). Patients with unstable angina and myocardial infarction exhibit a similar initial extent of elevation of the two hemostatic system markers. Plasma levels of F\textsubscript{1+2} and FPA were statistically indistinguishable in patients with stable angina compared with age- and sex-matched healthy individuals despite significant coronary artery disease and a long-term drug regimen similar to that of patients with acute coronary syndromes after hospitalization (Tables 1 and 2). Detailed stratification of the patients with regard to the number of diseased vessels revealed no statistically significant difference in the levels of hemostatic markers compared with the severity of coronary artery disease (Table 3). Detailed comparison of patients with stable angina taking particular combinations of drugs with age- and sex-matched healthy individuals showed no significant differences in the levels of hemostatic markers (data not shown).

Patients with unstable angina or myocardial infarction were followed over 6 months. According to the clinical guidelines of our institution, most of the patients with unstable angina received chronic treatment with diltiazem, whereas most of the patients with myocardial infarction were treated with β-blockers. Based on the occurrence of cardiac events over the study period, the two cohorts of patients were divided into subpopulations with either an eventful or an uneventful clinical course (Table 2). In the population with unstable angina, 2 patients developed myocardial infarction and 17 patients required coronary revascularization. In the population with acute myocardial infarction, 3 patients died, 1 patient experienced a nonfatal reinfarction, and 5 patients required coronary revascularization. The remaining patients were re-investigated at 6 months with 24-hour Holter monitoring and echocardiography. Silent myocardial ischemia was detected in 4 additional patients with unstable angina (included in the subpopulation with an eventful clinical course) and in none
with myocardial infarction, and no patients were observed to have intracardiac thrombi.

At admission, patients with unstable angina or myocardial infarction subsequently exhibiting an uneventful clinical course have plasma concentrations of F1+2 and FPA that are similar to those of patients subsequently experiencing cardiac events (Table 2). At 6 months, patients with unstable angina or myocardial infarction exhibiting an uneventful clinical course have plasma levels of F1+2 that are similar to those observed at admission (Table 2 and Figure, A). Indeed, we noted a median increase of 0.2 nmol/L (99% confidence interval [CI], −0.04 to 0.59; P=NS) in patients with unstable angina and a median decrease of 0.06 nmol/L (99% CI, −0.49 to 0.43; P=NS) in patients with myocardial infarction. However, the same two subpopulations have plasma concentrations of FPA that are significantly reduced at 6 months compared with baseline values (Table 2 and Figure, B). We observed a median decrease of 0.7 nmol/L (99% CI, −2.1 to −0.2; P<.0001) with myocardial infarction, and no patients were observed to have intracardiac thrombi.

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### Table 1. Clinical and Angiographic Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unstable Angina (n=80)</th>
<th>Myocardial Infarction (n=32)</th>
<th>Stable Angina (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±8</td>
<td>59±7</td>
<td>58±8</td>
</tr>
<tr>
<td>Male sex, no. of patients</td>
<td>72 (90%)</td>
<td>30 (94%)</td>
<td>35 (95%)</td>
</tr>
<tr>
<td>Smokers, no. of patients</td>
<td>65 (81%)</td>
<td>21 (66%)</td>
<td>25 (68%)</td>
</tr>
<tr>
<td>Hypertension, no. of patients</td>
<td>16 (20%)</td>
<td>7 (22%)</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>Diabetes mellitus, no. of patients</td>
<td>7 (9%)</td>
<td>4 (12%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>209±36</td>
<td>225±40</td>
<td>222±34</td>
</tr>
<tr>
<td>Chronic medication, no. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>76 (95%)</td>
<td>29 (91%)</td>
<td>30 (81%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>72 (90%)</td>
<td>29 (91%)</td>
<td>33 (89%)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>51 (64%)</td>
<td>4 (12%)</td>
<td>16 (43%)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>10 (12%)</td>
<td>19 (59%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Angiography, no. of vessels with &gt;50% stenosis</td>
<td>0 (9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1</td>
<td>17 (21%)</td>
<td>13 (41%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>2</td>
<td>26 (33%)</td>
<td>3 (9%)</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>3</td>
<td>26 (33%)</td>
<td>3 (9%)</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>Left main</td>
<td>2 (2%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Angiography not performed, no. of patients</td>
<td>2 (2%)</td>
<td>12 (37%)</td>
<td>6 (16%)</td>
</tr>
</tbody>
</table>

Age and cholesterol for the patients are expressed as mean±SD.

### Table 2. Plasma Concentrations of Prothrombin Fragment 1+2 and Fibrinopeptide A in Patients With Coronary Ischemic Syndromes

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Admission F1+2 nmol/L (95% CI)</th>
<th>FPA nmol/L (95% CI)</th>
<th>6 mo F1+2 nmol/L (95% CI)</th>
<th>FPA nmol/L (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina (n=80)</td>
<td>1.08 (0.90-1.23)</td>
<td>2.4* (1.7-3.9)</td>
<td>1.26 (1.07-1.46)</td>
<td>1.1† (1.0-1.5)</td>
</tr>
<tr>
<td>Eventful course (n=23)</td>
<td>1.05 (0.68-1.43)</td>
<td>1.9 (0.9-6.2)</td>
<td>1.22 (0.71-1.67)</td>
<td>1.1‡ (0.6-1.5)</td>
</tr>
<tr>
<td>Uneventful course (n=57)</td>
<td>1.07 (0.88-1.13)</td>
<td>2.9 (1.8-4.1)</td>
<td>0.9 (0.3-1.3)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (n=32)</td>
<td>1.27* (0.85-1.75)</td>
<td>3.55* (1.5-4.9)</td>
<td>0.78 (0.61-1.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Eventful course (n=9)</td>
<td>1.44 (0.34-2.58)</td>
<td>3.9 (1.4-4.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uneventful course (n=23)</td>
<td>1.29 (0.72-1.75)</td>
<td>3 (1.6-6.1)</td>
<td>1.0 (0.4-1.7)</td>
<td></td>
</tr>
<tr>
<td>Stable angina (n=37)</td>
<td>0.78 (0.59-1.01)</td>
<td>1.3 (0.8-1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double sampling (n=11)</td>
<td>0.87 (0.57-1.47)</td>
<td>0.9 (0.4-1.7)</td>
<td>0.78 (0.61-1.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Healthy controls (n=32)</td>
<td>0.71 (0.59-0.9)</td>
<td>0.80 (0.5-1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double sampling (n=12)</td>
<td>0.80 (0.3-1.01)</td>
<td>0.75 (0.4-1.21)</td>
<td>0.77 (0.42-1.02)</td>
<td>1.0 (0.4-1.7)</td>
</tr>
</tbody>
</table>

F1+2 indicates prothrombin fragment 1+2; FPA, fibrinopeptide A. Values are median values. Numbers in parentheses are 99% confidence intervals of the median.

*P<.0001 vs stable angina and healthy controls.
†P=.0003 vs admission.
‡P=.0028 vs admission.
TABLE 3. Plasma Concentrations of Prothrombin Fragment 1+2 and Fibrinopeptide A in Patients With Coronary Ischemic Syndromes According to the Number of Diseased Vessels

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Admission n</th>
<th>F1±2, nmol/L</th>
<th>FPA, nmol/L</th>
<th>6 mo n</th>
<th>F1±2, nmol/L</th>
<th>FPA, nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or one-vessel disease</td>
<td>24</td>
<td>1.07 (0.83-1.37)</td>
<td>2.7 (1.1-4.4)</td>
<td>18</td>
<td>1.27 (1.1-1.89)</td>
<td>1.4 (0.8-3.4)</td>
</tr>
<tr>
<td>Two- or three-vessel disease</td>
<td>54</td>
<td>1.12 (0.88-1.13)</td>
<td>2.6 (1.6-4.2)</td>
<td>39</td>
<td>1.26 (0.85-1.69)</td>
<td>1.1 (0.9-1.6)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or one-vessel disease</td>
<td>13</td>
<td>1.61 (0.77-2.58)</td>
<td>3.0 (1.3-4.9)</td>
<td>10</td>
<td>1.22 (0.77-1.61)</td>
<td>1.0 (0.2-1.7)</td>
</tr>
<tr>
<td>Two- or three-vessel disease</td>
<td>7</td>
<td>1.08 (0.53-1.56)</td>
<td>1.8 (0.8-19.7)</td>
<td>7</td>
<td>1.10 (0.54-3.9)</td>
<td>1.2 (0.6-1.5)</td>
</tr>
<tr>
<td>Stable angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or one-vessel disease</td>
<td>5</td>
<td>0.57* (0.46-0.84)</td>
<td>0.8† (0.7-1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two- or three-vessel disease</td>
<td>26</td>
<td>0.77* (0.62-1.03)</td>
<td>1.3† (0.8-1.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F1±2 indicates prothrombin fragment 1+2; FPA, fibrinopeptide A. n values are number of patients. Values are median values. Numbers in parentheses are 99% confidence intervals of the median or ranges for groups with fewer than 10 patients.

*P<.01 vs unstable angina and myocardial infarction.
†P<.001 vs unstable angina and myocardial infarction.

in patients with unstable angina and a median decrease of 2.1 nmol/L (99% CI, −4.7 to −0.01; P=.0037) in patients with myocardial infarction.

In a subgroup of patients with unstable angina and myocardial infarction, a second evaluation of the plasma concentrations of F1±2 and FPA was carried out between the fourth and seventh months. Plasma levels of F1±2 or FPA were similar to those observed at the 6-month evaluation (F1±2, unstable angina: median change 0.07 nmol/L, 99% CI −0.07 to 0.20, P=NS; myocardial infarction: median change 0.05 nmol/L, 99% CI −0.03 to 0.30, P=NS; FPA, unstable angina: median change 0.1 nmol/L, 99% CI −0.2 to 0.4, P=NS; myocardial infarction: median change −0.1 nmol/L, 99% CI −0.2 to 0.1, P=NS).

At 6 months, patients with stable angina or healthy blood donors have plasma levels of F1±2 or FPA that are similar to those observed during the first evaluation (Table 2). The median changes of F1±2 and FPA in patients with stable angina are −0.04 nmol/L (99% CI, −0.3 to 0.17; P=NS) and 0.1 nmol/L (99% CI, −0.1 to 0.2; P=NS), respectively. The median changes of F1±2 and FPA in healthy blood donors are 0.02 nmol/L (99% CI, −0.14 to 0.04; P=NS) and 0.1 nmol/L (99% CI, −0.14 to 0.4; P=NS), respectively (Figure).

The subpopulation with unstable angina and an uneventful clinical course includes 34 patients with abnormal plasma levels of F1±2 at admission (prevalence, 60%; 99% CI, 42 to 75) and 37 patients at 6 months (prevalence, 68%; 99% CI, 47 to 80). The subpopulation with acute myocardial infarction and an uneventful clinical course includes 15 patients with abnormal plasma concentrations of F1±2 at admission (prevalence, 65%; 99% CI, 37 to 86) and 13 patients at 6 months (prevalence, 57%; 99% CI, 30 to 80). In both subpopulations, the prevalence of elevated plasma levels of F1±2 between admission and 6 months is not significantly different. The subpopulation with unstable angina and an uneventful course includes 34 patients with abnormal plasma levels of FPA at admission (prevalence, 60%; 99% CI, 42 to 75) and 14 patients at 6 months (prevalence, 25%; 99% CI, 12 to 42). The subpopulation with myocardial infarction and an uneventful course includes 13 patients with abnormal FPA plasma levels at admission (prevalence, 57%; 99% CI, 30 to 80) and 1 patient at 6 months (prevalence, 4%; 99% CI, 1 to 31). In both subpopulations, the prevalences of elevated plasma concentrations of FPA between admission and 6 months are significantly different (P<.0001).

Discussion
We prospectively determined the extent of coagulation system activity, as measured by F1±2 and FPA assays, in a study population with unstable angina or acute myocardial infarction compared with a control population with stable angina or healthy individuals matched for age and sex. The study population was composed of consecutive patients experiencing the initial onset of unstable angina or acute myocardial infarction with appropriate clinical and laboratory findings who presented to the emergency department of a single medical center over 1 year. We prospectively excluded individuals from our study population with comorbid conditions that augment or suppress coagulation system activity or alter the metabolic behavior of F1±2 and FPA or who ingest drugs known to affect hemostatic mechanism function.10 The patients with acute coronary syndromes were followed for 6 months after discharge, which allowed individuals to be characterized as exhibiting an uneventful clinical course or experiencing additional cardiac events. The patients with an uneventful clinical course were reinvestigated to determine whether individuals with a single episode of an acute coronary syndrome but no further evidence of active vascular disease exhibit a persistent hypercoagulable state.

At admission, most patients with acute coronary syndromes have significantly elevated plasma concentrations of F1±2 and FPA, which reflect the presence of an ongoing intracoronary thrombosis. Previous investigations document elevated plasma concentrations of FPA in the majority of patients during the acute phase of these disorders,1-3 with no data available for F1±2. The normal plasma levels of FPA and F1±2 observed in the
Unstable angina

Myocardial infarction

Healthy volunteers

Plots of the plasma concentrations of prothrombin fragment 1+2 (F1+2) (A) and plasma levels of fibrinopeptide A (FPA) (B) in 57 patients with unstable angina and 23 patients with myocardial infarction at hospital admission. All patients had an uneventful clinical course, and follow-up determinations were obtained at 6 months. In 12 healthy blood donors, plasma concentrations of F1+2 and FPA were evaluated at baseline (Admission) and after 6 months. The top of the shaded area indicates the upper limit of the normal range for each measurement (95th percentile of the distribution for the control group of 32 healthy individuals matched for age and sex with the study population).

minority of patients with acute coronary syndromes could be due to the fact that intracoronary thrombosis is an intermittent process and that the above markers have relatively short half-lives (3 to 5 minutes and 90 minutes, respectively). Alternatively, a few patients with unstable angina may exhibit normal plasma concentrations of FPA and F1+2 because their symptoms may be secondary to poor coronary reserve with otherwise uncomplicated atherosclerotic plaques. In these individuals, small changes in myocardial oxygen consumption or...
dynamic coronary vasoconstriction may be responsible for episodes of angina at rest.

At 6 months, patients with acute coronary syndromes exhibiting an uneventful course manifest increased plasma concentrations of F1+2, with greatly reduced or virtually normal plasma levels of FPA. These results are consistent with prior studies that show diminished plasma levels of FPA several days after the onset of acute coronary syndromes.1516 The normalization of FPA values has been widely interpreted as demonstrating that coagulation system hyperactivity in these disorders is restricted to the time period during which the coronary thrombus is generated. However, the present investigation, using the F1+2 assay that monitors an earlier point in the coagulation cascade, reveals that abnormalities of the hemostatic mechanism persist in patients with acute coronary syndromes long after clinical stabilization and are consistent with the presence of an hypercoagulable state.9 Thus, our studies confirm results obtained in much larger clinical trials using less specific coagulation system assays, which show an association between hemostatic system abnormalities and mortality from ischemic heart disease.11

The occurrence of a persistent hypercoagulable state in patients with unstable angina or myocardial infarction appears to be independent of coronary artery atherosclerosis or drug ingestion. The stratification of patients with acute coronary syndromes with regard to the number of diseased vessels reveals no significant differences in hemostatic markers, and no such abnormality is noted in patients with stable angina with severe coronary artery disease on a similar medical regimen. We suspect that molecular abnormalities of the hemostatic mechanism–blood vessel wall are responsible for the observed hypercoagulable state. Thus, the present investigation raises the interesting issue that increased activity of the hemostatic mechanism could predate the onset of acute coronary syndromes, and this hypothesis is under examination in a large prospective trial (Northwick Park Heart Study II).1718 However, it is difficult to exclude the possibility that patients with acute coronary syndromes, compared with those with stable angina, have a considerably more extensive atherosclerotic process outside the coronary circulation or atherosclerotic changes that more readily activate the coagulation mechanism.

We have previously hypothesized that increased activity of the hemostatic system, as observed in the present investigation, might sensitize individuals to respond at a higher frequency to relatively minor prothrombotic stimuli with overt thrombotic events.9 Prior studies have provided support for this hypothesis in congenital thrombophilic states such as protein C and protein S deficiency.1920

It obviously will be critical to determine whether the presence of a hypercoagulable state in patients who exhibit acute coronary syndromes is predictive of the subsequent development of major cardiac events.

The observation that patients with acute coronary syndromes exhibit an increased basal level of activation of the coagulation system long after clinical stabilization may have important implications with regard to the pathophysiology and treatment of acute coronary syndromes. It is tempting speculate that the higher occurrence of cardiac events in patients with unstable angina21 or myocardial infarction22 compared with those with stable angina23 may be in part attributable to the persistent hypercoagulable state observed in the first two groups. Indeed, the successful efforts at secondary prevention of unstable angina and myocardial infarction with warfarin therapy2426 could be due to suppression of the persistent activation of the hemostatic mechanism. It is reasonable to propose that detection of the hypercoagulable state with the F1+2 assay could pinpoint individuals most likely to benefit from prolonged anticoagulant therapy and provide a means for determining the optimal levels of drug to administer. The amounts of oral anticoagulant needed to suppress high plasma levels of F1+2 into the normal range are likely to be significantly less than those indicated by standard monitoring approaches based on the prothrombin time that could significantly reduce bleeding complications.2728

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References

5. Lau HK, Rosenberg JS, Beeler DL, Rosenberg RD. The isolation and characterization of a specific antibody population directed against the prothrombin activation fragments F2 and prothrombin fragment 1+2. J Biol Chem. 1979;254:8751-8761.


Persistent activation of coagulation mechanism in unstable angina and myocardial infarction.
P A Merlini, K A Bauer, L Oltrona, D Ardissino, M Cattaneo, C Belli, P M Mannucci and R D Rosenberg

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