Evidence for Time-Dependent Activation of Monocytes in the Systemic Circulation in Unstable Angina But Not in Acute Myocardial Infarction or in Stable Angina

Brigitte Jude, MD; Benaissa Agraou, MD; Eugène P. McFadden, MRCPI, FESC; Sophie Susen, MD; Christophe Bauters, MD, FESC; Pascale Lepelley; Colette Vanhaesbroucke, MD; Patrick Devos; Alain Cosson, MD; Philippe Asseman, MD

Background Platelet activation plays a pivotal role in the pathogenesis of acute coronary disease. Monocytes are involved in the progression of atherosclerosis and are potent activators of blood coagulation through their ability to synthesize tissue factor (TF). The aim of this study was to compare markers of monocyte and coagulation activation in the systemic blood of patients with unstable angina, acute myocardial infarction, or stable angina.

Methods and Results We studied 26 patients with unstable angina (10±5 hours after the onset of the last episode of pain), 18 patients with acute myocardial infarction (5±4 hours after the onset of pain), and 34 patients with stable angina. We measured levels of TF expression in peripheral blood mononuclear cells (isolated by gradient centrifugation and incubated for 16 hours, with or without endotoxin stimulation), levels of plasma prothrombin fragment 1+2 (F1+2), and levels of fibrinogen in peripheral blood. In patients with unstable angina, both stimulated and unstimulated cells exhibited higher levels of TF expression than in patients with stable angina (P=.0001). In patients with acute myocardial infarction, monocyte TF activity did not differ from that in patients with stable angina. Mean levels of F1+2 and of fibrinogen did not differ significantly between groups. Only in the unstable angina group, a modest correlation was found between fibrinogen (r=.72, P=.005) and F1+2 levels (r=.54, P=.001) and the degree of monocyte TF expression. In patients with unstable angina, monocyte TF expression (both stimulated and unstimulated, assessed by biological activity and by antigen techniques) and fibrinogen levels were correlated with the time elapsed from the beginning of the most recent episode of pain (.61<r<.72, .02<P<.0001). By contrast, there was no correlation between these variables and the time from onset of pain in patients with acute myocardial infarction.

Conclusions A time-dependent activation of systemic monocytes and a time-dependent increase in fibrinogen levels occurs in unstable angina but not in myocardial infarction. These findings provide further evidence that a specific inflammatory process occurs in unstable angina. Further studies are required to determine whether monocyte activation is a cause or a consequence of plaque instability in patients with unstable angina and to clarify the interrelations between platelet and monocyte activation in these circumstances. (Circulation. 1994; 90:1662-1668.)

Key Words • monocytes • tissue factor • angina • myocardial infarction

Although platelet activation has been demonstrated to play a major role in the pathogenesis of acute coronary syndromes,1-4 the more recent demonstration that granulocyte and monocyte activation occurs in unstable angina suggests that an inflammatory reaction may also contribute to the pathophysiology of these conditions.5,6 The involvement of various cell types, including blood leukocytes, in thrombosis and inflammation has been demonstrated through recent experimental and clinical studies.7,8

In the vasculature, activated monocytes are potent activators of coagulation, through the expression of tissue factor (TF). TF is a high-affinity receptor and cofactor for factor VII/VIIa, and thus the cell surface molecule that initiates the extrinsic pathway of coagulation.9 Its expression by monocytes is regulated by various immune and inflammatory stimuli such as bacterial lipopolysaccharides (LPS), lipoproteins, tumor necrosis factor, and T-helper lymphocyte activation.8 Whether increased monocyte TF expression is specific for unstable angina or also occurs in other acute coronary syndromes remains unclear. Additionally, the exact nature of the relation between monocyte activation and the activation of the coagulation system is not well understood.

The aim of this study was to prospectively compare TF expression in blood peripheral monocytes and a marker of activation of the coagulation system, prothrombin fragments 1 and 2 (F1+2), in patients with unstable angina, patients with myocardial infarction, and patients with stable exertional angina.10,11

Methods

Patients Seventy-eight patients were studied (Table 1). All patients gave informed consent, and the protocol was approved by the hospital ethics committee. Thirty-four patients, 22 men and 12 women with a mean (±SD) age of 60±10 years (range, 41 to 80) had stable effort
TABLE 1. Clinical Parameters in the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Effort Angina</th>
<th>Unstable Angina</th>
<th>Myocardial Infarction</th>
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<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Age, y</td>
<td>60±10 (41-80)</td>
<td>60±8 (41-70)</td>
<td>66±12 (30-83)</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1.8</td>
<td>1.9</td>
<td>2</td>
</tr>
<tr>
<td>Time after onset</td>
<td>10±5 (3-20)</td>
<td>5±4 (1.5-19)</td>
<td></td>
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<td>of pain, h</td>
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Angina. Stable angina was defined as the presence of effort angina with a stable pattern over the previous 6 months with angiographically documented significant coronary artery disease. Blood sampling was performed on an out-patient basis, at least 6 months after any invasive procedure or alteration in treatment.

Twenty-six patients, 17 men and 9 women, with a mean (±SD) age of 60±8 years (range, 41 to 70) had unstable angina. Unstable angina was defined as anginal pain at rest occurring during the preceding 24 hours with transient significant ST-segment changes, without a significant increase in plasma creatine phosphokinase or its MB fraction (<1.5-fold increase). The mean time between onset of the most recent episode of pain and hospital admission was 10±5 hours (range, 3 to 20).

Eighteen patients, 12 men and 6 women, with a mean (±SD) age of 66±12 years (range, 30 to 83) were studied at the time of an acute myocardial infarction. Acute myocardial infarction was defined as the presence of typical chest pain lasting longer than 30 minutes, with the subsequent development of new Q waves and accompanied by a significant (>twofold) increase in creatine phosphokinase and in its MB fraction. The mean time between the onset of pain and hospital admission was 5±4 hours (range, 1.5 to 19).

In the patient who presented with unstable angina or with myocardial infarction, blood sampling was performed on admission, before any invasive procedure and before any treatment modification. Most patients were on long-term therapy with nitrates and/or calcium antagonists. Thirty eight patients were on aspirin therapy at the time of blood sampling: 19 in the stable angina group, 14 in the unstable angina group, and 5 in the myocardial infarction group.

In addition, 31 healthy control subjects drawn from the hospital staff were studied. There were 15 men and 16 women, with a mean (±SD) age of 37±5 years (range, 27 to 44) who had no risk factors for cardiovascular disease and who were not taking medication. This group served as a control group for the laboratory investigations.

No patient or control subject had a history of cancer, diabetes, immunologic disorders, infection, or surgical or other invasive procedure in the 6 months that preceded the study.

Laboratory Investigations

Blood Collection

Blood was drawn with minimal venous compression, under sterile conditions, in evacuated tubes containing appropriate anticoagulants; 5 mL into 1/10 vol of 3.6 mol/L trisodium citrate for factor VII, factor V and fibrinogen levels, and 20 mL into lithium heparin tubes for mononuclear cell isolation and F1+2 levels.

Isolation of Mononuclear Cells and Cell Culture

Peripheral mononuclear cells were isolated from blood by density gradient centrifugation, washed three times, and resuspended in RPMI (Roswell Park Memorial Institute medium) 1640 (Gibco) (3×10^6 cells/mL). The viability of cells was >96% (Trypan blue exclusion). Final cell suspensions contained more than 98% mononuclear cells and less than 1 platelet per 3 nucleated cells. Monocytes, identified by May Grunwald Giemsa staining comprised 14% to 24% (mean, 18%). All reagents and culture supplies used were free of endotoxin, as determined by the chromogenic limulus amebocyte lysate assay (sensitivity, 0.012 ng/mL) (Chromogenix). After cytocentrifuge slide preparations, a third of the mononuclear cells, subsequently referred to as nonincubated cells, were frozen at −70°C. The remainder were incubated for 16 hours at 37°C in a humidified 5% CO2 atmosphere, in RPMI medium without fetal calf serum supplementation, in the presence of LPS stimulation (endotoxin 055:B5, Sigma, 10 μg/mL) (subsequently referred to as cells incubated with stimulation) or in the absence of LPS stimulation (subsequently referred to as cells incubated without stimulation). At the end of the incubation period, cytocentrifuged preparations were made, and cell suspensions were frozen at −70°C. All the cells were lysed by 3x10-second sonication bursts before assays for TF.

Tissue Factor Assays

Procoagulant activity (PCA) was determined by a modified amidolytic assay derived from the method of Carson. Briefly, lysed cell suspensions (50 μL) were incubated at 37°C in a microtiter plate (2 minutes), mixed with CaCl2 0.25 mol/L (50 μL) (60-second incubation), and prothrombin concentrate complex (Biotransfusion) as a source of factor VII (50 μL, 3 U/mL). After addition of 50 μL of the chromogenic substrate S2765 (Chromogenix), the change in optical density at 410 nm was quantitated with a microplate reader. The changes in optical density were converted to units of TF activity from log-log plots of serial dilutions of a human placental thromboplastin (Behring). Arbitrarily, 1 mL of thromboplastin was assigned a value of 100 000 mU, and results were expressed as mU/10^9 monocytes. Data are expressed as mean±SD. The coefficient of variation of the assay was 6.5% to 9.2%, respectively.

The PCA was characterized as TF by evaluating its sensitiv-ity to phospholipase C (Sigma) and by a neutralization procedure, using mouse monoclonal antibody anti-TF 4508 (American Diagnostica) as follows. Diluted (10-fold) antibody (50 μL) was incubated with 50 μL diluent buffer (0.01 mol/L HEPES, 0.015 mol/L CaCl2, 0.01% Tween 20, 0.0005% poly-;brene, pH 7.3) containing diluted TF standard or lysed cell suspensions, for 30 minutes at 37°C. After addition of 100 μL pooled normal plasma, the coagulation time was recorded. The percentage of neutralization was calculated using the pure thromboplastin activity without and with antibody as 0% and 100%, respectively.

TF antigen was determined in lysed cell suspensions by a sandwich ELISA assay, using monoclonal antibody anti-TF. Briefly, TF was solubilized by incubation of lysed cells (1 mL) with 0.05 mol/L Tris/HCl, 0.1 mol/L NaCl, 0.1% Triton X-100, 0.1% BSA, pH 7.5 (60 μL) for 30 minutes at 37°C, with vortex agitation. The contents of the tube were transferred to the ELISA plate. The ELISA was performed with the IMubind Tissue Factor ELISA kit (American Diagnostica) according to the manufacturer’s recommendations. The results were expressed in pg/10^9 monocytes. The coefficient of variation of the assay was 4.5% to 6.3%.

Hemostatic Assays on Plasma Samples

Citrated blood samples were centrifuged at 3000g within 15 minutes of venipuncture and plasma was stored at −70°C until assayed. Fibrinogen levels were measured by the Claus tech- nique (Biomerieux), and factor VII and V activity by the one-time recalcification assay using human depleted plasma (Stago) and human placental thromboplastin (Behring). The assays were performed in duplicate.

F1+2 determination was performed by the ELISA method, using commercially available kits according to the manufacturer’s recommendations (Organon Teknika). Heparinized blood was immediately centrifuged at 3000g at +4°C and frozen at −70°C until assay. The assays were performed in duplicate by techni-
cians unaware of the group assignment of the samples. The intra-assay and interassay coefficients of variation were 6.2% and 8.1%, respectively.

**Statistical Analysis**

The statistical analysis was performed by the Department of Biostatistics at the University of Lille, with SAS software (version 6.09). The distribution of values for each parameter was assessed for normality with use of the Shapiro-Wilk test. Because some of the distributions were not normal and because in some cases the number of observations was <30, the statistical tests were performed on the ranked values of the variables using nonparametric statistical tests. Correlations between variables were assessed using Spearman's correlation coefficient. Group means were compared, after ANOVA (performed on the ranks) by unpaired two-tailed Student's t tests, with the Bonferroni correction for multiple comparisons. Results are expressed as mean±SD. A value of P<.05 was considered significant.

**Results**

**Baseline Characteristics**

There were no significant between-group differences in mean age or in the ratio of men to women (Table 1). The mean time from the onset of the last episode of pain to hospital admission (ie, blood sampling) in the unstable angina group (5±4 hours) was significantly shorter (P=.003) than the equivalent interval (10±5 hours) in the patients with acute myocardial infarction.

**Mononuclear Cell Tissue Factor Expression**

There was no significant difference between groups in the number of blood mononuclear cells or of monocytes. Nonincubated mononuclear cells did not have detectable PCA. Incubated mononuclear cells demonstrated procoagulant activity that was characterized as TF in all cases by phospholipase sensitivity and by neutralization (percent neutralization, 76% to 99%). The ratio between the values for TF activity, assessed with use of the biological assays and the values for TF antigen, on lysed cells, did not differ significantly between the groups. Immunocytochemical staining confirmed the monocytic origin of the TF activity (Fig 1).

The quantitative data are presented in Table 2 and Fig 2. Monocyte TF activity and levels of TF antigen did not differ significantly between patients with unstable angina and those with myocardial infarction. In contrast, patients with unstable angina showed a marked increase in monocyte TF expression after incubation with or without endotoxin stimulation, as compared with the groups with effort angina or with myocardial infarction (P=.0001). No significant difference in monocyte TF expression was found between patients who were or were not taking aspirin.

In the group with unstable angina, monocyte TF expression was positively correlated with the time from the onset of the last episode of pain (r=.64 and .61, P<.003) for cells incubated without and with endotoxin, respectively (Fig 3). In the group with myocardial infarction, no such correlation was found. As the time from onset of symptoms differed between the myocardial infarction and the unstable angina group, levels of monocyte PCA were compared between the two groups for patients admitted in the first 10 hours after the onset of pain. In these subgroups, monocyte PCA was again significantly higher in the unstable angina group than in the myocardial infarction group (P=.0001).

**Coagulation Parameters**

The levels of fibrinogen and of F1+2 are presented in Figs 4 and 5. The mean fibrinogen level was above the
Table 2. Hemostatic Parameters in the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Effort Angina</th>
<th>Unstable Angina</th>
<th>Myocardial Infarction</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>after 16-h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>incubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without LPS</td>
<td>91±135</td>
<td>691±615</td>
<td>127±108</td>
<td>65±38</td>
</tr>
<tr>
<td>(25-1000)</td>
<td>(150-2800)</td>
<td>(25-400)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPS, mU TF/10^9 monocytes</td>
<td>1067±573</td>
<td>2854±1485</td>
<td>1152±502</td>
<td>1278±727</td>
</tr>
<tr>
<td>(160-2200)</td>
<td>(1100-6400)</td>
<td>(270-2000)</td>
<td></td>
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<tr>
<td>TF activity</td>
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<td>after 16-h</td>
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<tr>
<td>incubation</td>
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<tr>
<td>with LPS</td>
<td>23±34</td>
<td>154±197</td>
<td>23.5±3.5</td>
<td>14±11</td>
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<td>(2-110)</td>
<td>(20-730)</td>
<td>(2-124)</td>
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<tr>
<td>TF antigen</td>
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<td>after 16-h</td>
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<td>incubation</td>
<td></td>
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<td></td>
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<tr>
<td>without LPS</td>
<td>249±174</td>
<td>642±300</td>
<td>440±266</td>
<td>325±196</td>
</tr>
<tr>
<td>(70-660)</td>
<td>(200-1440)</td>
<td>(120-1160)</td>
<td></td>
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<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
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<tr>
<td>g/L</td>
<td>5.3±1.51</td>
<td>6.1±1.9</td>
<td>5.9±2.2</td>
<td>3.6±0.7</td>
</tr>
<tr>
<td>(2.7-7.7)</td>
<td>(3-10)</td>
<td>(2.6-9.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V</td>
<td>137±47</td>
<td>145±28</td>
<td>133±35</td>
<td>138±34</td>
</tr>
<tr>
<td>%</td>
<td>(68-222)</td>
<td>(100-208)</td>
<td>(68-203)</td>
<td></td>
</tr>
<tr>
<td>Factor VII</td>
<td>100±148</td>
<td>112±28</td>
<td>87±33</td>
<td>110±30</td>
</tr>
<tr>
<td>%</td>
<td>(64-132)</td>
<td>(68-182)</td>
<td>(55-137)</td>
<td></td>
</tr>
<tr>
<td>F1+2, nmol/L</td>
<td>1.35±1.48</td>
<td>1.37±1.25</td>
<td>1.20±1.55</td>
<td>0.71±0.25</td>
</tr>
<tr>
<td>(0.25-6.5)</td>
<td>(0.35-6)</td>
<td>(0.3-6.7)</td>
<td></td>
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</tbody>
</table>

TF indicates tissue factor; LPS, lipopolysaccharides; and F1+2, prothrombin fragments 1 and 2.

The results of the present study are consistent with the hypothesis that a time-dependent activation of monocytes, in peripheral blood, occurs in at least some patients with unstable angina. This activation was correlated with markers of activation of the coagulation system. In contrast, these phenomena were not observed in patients with acute myocardial infarction or with stable exertional angina. As TF synthesis by monocytes is dependent on the transcriptional activity of a regulated inflammatory gene, these results provide further evidence for a role of inflammation in the pathogenesis of unstable angina.

Discussion

The results of the present study are consistent with the hypothesis that a time-dependent activation of monocytes, in peripheral blood, occurs in at least some patients with unstable angina. This activation was correlated with markers of activation of the coagulation system. In contrast, these phenomena were not observed in patients with acute myocardial infarction or with stable exertional angina. As TF synthesis by monocytes is dependent on the transcriptional activity of a regulated inflammatory gene, these results provide further evidence for a role of inflammation in the pathogenesis of unstable angina.
Fig 3. Relation between monocyte tissue factor (TF) activity and the time elapsed from the beginning of the last episode of pain in patients with unstable angina. Filled squares represent cells incubated without stimulation; the empty squares, cells incubated with stimulation. Mean values are represented by horizontal bars. There was a positive correlation between the degree of TF expression in unstimulated \( (r = .64, P < .003) \) and in stimulated \( (r = .61, P < .003) \) cells and the time elapsed from the onset of the last episode of pain.

Mechanisms of Unstable Angina

The factors responsible for the transition from stable to unstable coronary disease remain incompletely understood. It has been conclusively demonstrated that Q-wave myocardial infarction is consequent on occlusive thrombus formation in an epicardial coronary vessel.\(^{15}\) Angiographic studies suggest that such thrombi occur frequently at the site of stenoses that are not hemodynamically important. A retrospective study showed that the artery responsible for an acute myocardial infarction had a stenosis evaluated, on a preceding angiography, to be of mild (<50% stenosis) severity in two thirds of patients.\(^{16}\) It is therefore likely that disruption or fissuring of a preexisting plaque, with subsequent thrombus formation is a common mechanism of acute infarction. Willerson et al\(^{17}\) proposed that unstable coronary syndromes be regarded as a continuum with underlying pathophysiological similarities. They suggested that unstable angina is associated with limited plaque injury that does not result in occlusive thrombus formation. In contrast, severe plaque disruption may provoke more extensive thrombus formation that may result in transient or prolonged vessel closure, thus leading to non-Q-wave or Q-wave myocardial infarction.

Role of Platelets

A large body of clinical and experimental evidence supports the theory that platelet aggregation and thrombus formation play a major role in the transition from stable to unstable coronary disease. Hirsch et al\(^{1}\) demonstrated that there was a temporal relation between chest pain and increases in the transcardiac concentration of thromboxane A\(_2\). This is consistent with the hypothesis that local release of thromboxane A\(_2\) by platelets or other cells is associated with transient platelet aggregation in patients with unstable angina. These observations were confirmed and extended by Fitzgerald et al\(^2\), who showed that many patients with unstable angina have elevated urinary concentrations of a major thromboxane metabolite, 2-3 dinor-thromboxane, and that in some patients further increases in this metabolite occur after new episodes of chest pain. A subsequent study demonstrated an increase in transcardiac levels of another platelet-derived mediator, serotonin, in subsets of patients with unstable coronary disease.\(^{4}\) Additionally, patients with limiting angina were shown to have a vasoconstrictor substance in coronary sinus blood, whose vasoconstrictor effects in vitro were inhibited by a serotonin antagonist.\(^{17}\)

Clinical studies provide additional evidence for the importance of platelet aggregation in the pathogenesis of unstable angina. Aspirin, an inhibitor of cyclooxygenase, of thromboxane, and of platelet aggregation, reduces the incidence of nonfatal myocardial infarction and of sudden death in patients with unstable angina.\(^{18,19}\)

Role of Inflammation

Recent data suggest that inflammation may also play an important role in the pathophysiology of unstable angina. Berk et al\(^{20}\) showed that there was an increase in C-reactive protein in patients with “active” coronary

Fig 4. Individual values of fibrinogen in the patients studied. The mean fibrinogen levels (indicated by the horizontal bars) in all three groups were above the normal range. There was a slightly but not significantly higher mean fibrinogen level in the group with unstable angina.

Fig 5. Individual values of F1+2 in the patients studied. Mean F1+2 levels (indicated by the horizontal bars) in all three groups were above the normal range, consistent with activation of the coagulation system. There was no difference in mean F1+2 levels between the groups.

Fig 6. Relation between the degree of monocyte tissue factor (TF) activity (biological assay in unstimulated cells) and the levels of F1+2 and of fibrinogen in the patients with unstable angina. Filled squares correspond to the individual values of fibrinogen; empty squares, individual values of F1+2. There was a modest correlation between fibrinogen levels and levels of unstimulated monocyte TF activity \( (r = .55, P = .005) \) and between F1+2 levels and levels of unstimulated monocyte TF activity \( (r = .54, P = .001) \).
The mechanisms that lead to monocyte activation in the peripheral circulation in unstable angina remain unclear. Since we did not attempt to separate lymphocytes and monocytes, our results do not allow us to determine the relative contribution of lymphocyte- or monocyte-mediated mechanisms. However, because reciprocal activation of both cell types rapidly occurs by direct cell-to-cell contact or through cytokines, this distinction is unlikely to be of pathophysiological importance.

Although we did find a modest correlation between monocyte TF expression and levels of F1+2 in patients with unstable angina, we were unable to demonstrate a difference in F1+2 levels between patients with acute coronary syndromes, namely unstable angina or acute myocardial infarction, and those with stable angina. At first sight, this appears to be in contradiction with the results of many previous studies that have provided evidence for thrombin activation in unstable angina. Using FPA or thrombin-antithrombin III complexes, previous studies have demonstrated activated coagulation in patients with unstable coronary disease compared to either healthy control subjects or to patients with stable coronary disease.33,36 F1+2 levels as a marker of thrombin generation have the potential advantage of a longer half life but have been less extensively investigated in patients with coronary disease. A study that examined F1+2 levels in consecutive patients with stable angina referred for angiography showed that mean F1+2 levels were significantly higher in patients with angiographically proven atherosclerosis than in those with normal coronary angiograms.31 Another recent study investigated levels of F1+2 and of FPA in patients with unstable angina during an episode of unstable angina and six months later.32 While levels of both FPA and of F1+2 were elevated in the acute phase, 6 months later levels of FPA were within the normal range whereas there was a persistent elevation in F1+2 levels. It may be that an elevation in F1+2 levels, an index of the degree of prothrombin activation, reflects a chronic increased basal activation of the coagulation system in patients with atherosclerosis, that results in a higher level of basal thrombin generation. The presence in the blood of neutralizing substances, such as antithrombin III and protein C, that are part of the endogenous anticoagulation system means that an increase in basal thrombin formation may not necessarily result in an increase in fibrin formation. In such circumstances, markers of coagulation that mirror fibrinogen to fibrin conversion, such as FPA, would not be increased. Thus, the results of the present study which demonstrate that levels of F1+2 were above the normal range in patients with unstable angina, with myocardial infarction, or with stable angina do not contradict previous reports that demonstrated activation of the coagulation system in unstable angina. On the contrary, the present study demonstrates that activation of the coagulation system, as assessed by F1+2 levels, is demonstrable not only in patients with unstable angina but also in patients with apparently stable atherosclerosis.

Study Limitations

The design of the study did not allow us to determine whether the increase in markers of inflammation in unstable angina was a cause or a consequence of plaque instability. The increase in systemic markers of inflammation may simply be a reflection of events occurring in
the coronary circulation. However, although the clinical manifestations of unstable angina are determined by its effects at the level of the coronary circulation, the demonstration of a systemic inflammatory response in such patients supports the intriguing possibility that systemic factors may, in some circumstances, contribute to plaque instability.

Conclusions

The results of the present study suggest that a time-dependent inflammatory process occurs in at least some patients with unstable angina and demonstrate that evidence for such an inflammatory response is detectable in the systemic circulation. Further studies are needed to determine the factors that initiate and sustain leukocyte activation in unstable angina and to determine the relative contribution of platelet and leukocyte activation in the genesis of plaque instability.

Acknowledgments

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References

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