Fibrin formation and platelet aggregation in patients with severe coronary artery disease: relationship with the degree of myocardial ischemia

A. Gallino, M.D., A. Haeberli, Ph.D., H. R. Baur, M.D., and P. W. Straub, M.D.

ABSTRACT Fibrinopeptide A (FpA) concentrations in plasma and in 24 hr urine specimens as well as betathromboglobulin (BTG) in plasma were measured in 17 patients with severe angina pectoris, including both stable and unstable angina, and in 19 patients with acute myocardial infarction. Patients with unstable angina had plasma FpA and BTG levels of 5.2 ± 1.7 ng/ml and 91 ± 23 ng/ml, respectively. The corresponding concentrations of FpA in the 24 hr urine specimens were 8.2 ± 1.4 μg/24 hr. These values were similar to those measured in patients with acute myocardial infarction and higher than the corresponding levels in patients with stable angina (p < .05) and in normal control subjects (p < .01). The similarity of the platelet and coagulation findings in patients with unstable angina and in those with myocardial infarction favors the hypothesis that coronary thrombosis may play a major role in the pathogenesis of acute myocardial infarction.


CORONARY THROMBOSIS is frequently associated with acute myocardial infarction and with sudden death due to acute myocardial ischemia.1-3 Elevated plasma levels of betathromboglobulin (BTG), reflecting enhanced platelet aggregation,4 have been reported in patients with acute myocardial infarction.5-8 We have recently found, in accordance with the results of other groups, that patients with acute myocardial infarction often present high plasma levels of fibrinopeptide A (FpA), a reliable index of fibrin formation in vivo.7-13 Whether FpA is elevated in patients with coronary artery disease without acute myocardial infarction remains controversial. Two recent studies reported elevated plasma levels of BTG but normal FpA values,6,8 whereas previous reports indicated elevated FpA values in these patients.14, 15

We measured the plasma BTG and FpA levels in patients with severe coronary artery disease with stable and unstable angina pectoris and in the absence of acute myocardial infarction and compared them with the levels in patients with acute myocardial infarction. Since the course of patients with unstable angina is often complicated by acute myocardial infarction, particular attention was paid to the results in patients with unstable angina.

We also measured 24 hr urinary excretion of FpA in all patients with angina and in most of the patients with acute myocardial infarction, since urinary FpA excretion appears to be a reliable parameter for assessing the cumulative effect of thrombin action on fibrinogen.16

Methods

Patients

Patients with angina pectoris. A total of 17 patients with severe angina pectoris were admitted to the study. Criteria for admission were: (1) absence of acute myocardial infarction during the last 3 months, (2) absence of thromboembolic events or other factors predisposing to a coagulation disorder (neoplasia, severe infection, collagen disorder, glomerulonephritis), and (3) absence of anticoagulant drugs within the preceding 3 months. Nine of the 17 patients had chronic stable effort angina without rest pain, and eight had unstable angina with recent increase in frequency or severity of chest pain, frequent pain at rest, and progressive decrease in exercise tolerance during the preceding 3 months. A total of nine patients had a history of previous myocardial infarction. All patients had three-vessel disease documented by coronary angiograms obtained within 3 months before the study; seven of 17 patients had decreased ejection fractions between 40% and 60%. All patients were treated with propranolol and long- or short-acting nitrates. Patients with unstable angina also received nifedipine. No patient with stable angina complained of chest pain within 2 hr before blood sampling.

Patients with acute myocardial infarction. FpA and BTG levels were also measured on admission in a group of 19 patients with acute myocardial infarction. Criteria for admission in this group were: (1) history of typical chest pain, (2) electrocardiographic changes of Q waves and/or evolutionary ST-T changes,
(3) presence of elevated creatine kinase (CK) for 2 days, (4) absence of thromboembolic events or other diseases associated with coagulation abnormalities, and (5) absence of anticoagulant drugs within the preceding 3 months. All patients had electrocardiographic evidence of transmural myocardial infarction; nine of 19 had signs of anterior myocardial infarction, whereas the remaining 10 patients had inferior myocardial infarctions. Urinary FpA excretion in the first 24 hr after admission was also measured in 11 of 19 patients who did not receive anticoagulants during this period.

**Platelet and coagulation tests.** Blood samples were taken by careful venipuncture through an 18-gauge needle. All collections were done by the same investigator. For the BTG measurements 4.2 ml of blood was collected into Thromboteck tubes (Abbott Laboratories, Chicago), placed immediately on ice, and centrifuged within 1 hr at 2500 rpm for 60 min at 4°C. BTG was measured by radioimmunoassay. For the FpA measurement 4.5 ml blood was collected into a plastic syringe containing 500 U of heparin and 500 U of aprotinin dissolved in 0.5 ml of physiologic saline. The samples were centrifuged within 1 hr for 30 min at 2500 rpm at 4°C. The plasma was stored at −25°C. FpA levels were measured by radioimmunoassay in plasma from which fibrinogen had been absorbed by bentonite. Urine was collected over 24 hr periods from 15 normal individuals and from 28 patients. No preservatives were added. Volume and pH were recorded and the pH was adjusted to 8.5 before the assay; urine samples were tested for the presence of blood with the use of Combur 9-test-U (Boehringer, Mannheim, West Germany). Patients with more than five erythrocytes per milliliter were excluded from the study. Urine samples were stored at −25°C. FpA assay in urine samples was performed by radioimmunoassay without previous bentonite absorption or dialysis.

**Data analysis.** The measured values of FpA showed a skewness toward high values, therefore logarithmic transformation was required to obtain a normal distribution. Statistical analyses were therefore performed with the FpA data logarithmically transformed, and mean FpA levels are expressed as geometric means with standard deviations of the logarithmically transformed data. Statistical significance of changes in the same parameter was evaluated with Student's t test.

**Results**

**Clinical course.** Of the eight patients with unstable angina, three developed acute myocardial infarction within 2 days after blood collection, whereas an intracardiac thrombus was detected by angiography in one of them.

Of the nine patients with stable angina, none developed acute myocardial infarction and none had a cardiac thrombus as documented by the previously performed angiographic examination. Nine patients underwent elective aortocoronary bypass surgery and two underwent percutaneous transluminal angioplasty; six patients were treated medically.

Of the 19 patients with acute myocardial infarction, four died in the hospital (three anterior and one inferior myocardial infarction). Two-dimensional echocardiographic results showed a cardiac thrombus in only one patient with acute anterior myocardial infarction.

**FpA in plasma and in 24 hr urine specimens** (Table 1, figures 1 and 2). Plasma and 24 hr urinary levels of FpA in patients with acute myocardial infarction were 5.3 ± 1.8 ng/ml and 6.2 ± 1.9 μg/24 hr and higher than those in patients with stable angina (p < .05) and in normal control subjects (p < .01). The concentrations of FpA in plasma and in the 24 hr urine specimens of patients with unstable angina were 5.2 ± 1.7 ng/ml and 8.2 ± 1.4 μg/24 hr and were similar to those measured in patients with acute myocardial infarction but were higher than the corresponding values in patients with stable angina (p < .05) and in normal control subjects (p < .01). Six of 17 patients with angina had normal plasma and urinary concentrations of FpA. All six had chronic stable effort angina without pain at rest (figures 1 and 2), whereas no patient with unstable angina had normal FpA concentrations in plasma or in the 24 hr urine samples. The highest plasma and urinary concentration of FpA were found in the only patient with left ventricular wall thrombus documented by echocardiography. When the values of FpA in plasma and in the 24 hr urine specimens were compared, a significant correlation was found (r = .68, p < .01, n = 43).

**BTG in plasma** (figure 3). BTG in patients with acute myocardial infarction (84 ± 25 ng/ml) was higher than

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<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td><strong>Plasma and 24 hr urinary FpA and plasma BTG levels in control subjects and in different subgroups of patients</strong></td>
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*Significantly different (p < .01) when compared with control subjects.

Significantly different (p < .01) when compared with patients with stable angina pectoris.

Significantly different (p < .05) when compared with control subjects.
may have enhanced platelet aggregation and fibrin formation similar to those in patients with acute myocardial infarction. Recent studies in patients with angina pectoris also reported elevated plasma levels of BTG but normal FpA.6,8 The discrepancy between these results and our data is probably due to the more severe degree of coronary artery disease but particularly to the presence of many cases with unstable angina in our group of patients. In fact, all our patients had three-vessel disease documented by a recent angiogram.

Our plasma FpA findings were furthermore supported by the results of the FpA concentrations found in the 24 hr urine specimens, which showed a good correlation with the plasma values. Urinary FpA excretion appears to represent a valid alternative to the measurement of FpA in plasma, because it should provide a cumulative measure of the overall thrombin action on fibrinogen.16 Furthermore, urinary FpA is not influenced by technical factors like poor venipuncture. The observation that patients with unstable angina had significantly higher BTG and FpA values than those with stable angina despite a comparable extent of coronary obstructive disease suggest that the actual degree of ischemia at the time of the examination is a more important determinant of the amount of platelet activation and fibrin formation than the extent of anatomic obstruction.15 This assumption is further supported by our findings that patients with unstable angina and patients with acute myocardial infarction showed comparable BTG and FpA elevations.

Acute myocardial infarction has often been associated with coronary thrombosis1-3 and with a high rate of

![Figure 1](image1.png)

**FIGURE 1.** Plasma FpA concentrations in control subjects (□) and in patients with stable (○) and unstable angina (●), myocardial infarction (▲), and left ventricular thrombus (■) (n = 1).

that in normal control subjects (p < 0.01) but only slightly higher than that in patients with angina. The mean BTG levels of patients with unstable angina (91 ± 23 ng/ml) and acute myocardial infarction were comparable, but both were higher than the mean levels in patients with stable angina (p < 0.05). The patient with a cardiac thrombus had the highest BTG value (220 ng/ml).

**Discussion**

The elevated BTG and FpA levels in patients with unstable angina pectoris indicate that these patients

![Figure 2](image2.png)

**FIGURE 2.** Twenty-four hour urinary FpA concentrations in control subjects (□) and in patients with stable (○) and unstable angina (●), myocardial infarction (▲), and left ventricular thrombus (■).

![Figure 3](image3.png)

**FIGURE 3.** Plasma BTG concentrations in control subjects (□) and in patients with stable (○) and unstable angina (●), myocardial infarction (▲), and left ventricular thrombus (■).
fibrin formation and increased platelet aggregation in peripheral venous blood. On the other hand, unstable angina is often complicated by the occurrence of acute myocardial infarction. The finding in this study that unstable angina was associated with a comparable hypercoagulable state and a comparable increase in platelet aggregation as in acute myocardial infarction might favor the hypothesis that coronary thrombosis plays a major role in the pathogenesis of myocardial infarction. Our results are also in agreement with the 12% incidence of intracoronary thrombus in patients with unstable angina pectoris and with the recent observation that aspirin significantly reduces the incidence of myocardial infarction in such patients. Our results do not prove a causal relationship between platelet aggregation, fibrin formation, and myocardial ischemia. It may be that the coagulation disorder represents a consequence rather than a cause of myocardial ischemia. Thus ischemia may transiently affect the integrity of the endocardial and/or the coronary endothelium to an extent that would explain the activation of both platelets and coagulation.

Further studies will be necessary to clarify the relationship between myocardial ischemia and the observed activation of both platelets and the plasmatic coagulation.

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References
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