Fibrinopeptide A Is Released Into the Coronary Circulation After Coronary Spasm

Shuichi Oshima, MD, Hirofumi Yasue, MD, Hisao Ogawa, MD, Ken Okumura, MD, and Kozaburo Matsuyama, MD

To examine whether acute myocardial ischemia activates the coagulation system and platelet activation in the coronary circulation, we measured plasma levels of fibrinopeptide A and β-thromboglobulin in the coronary sinus and the aortic root simultaneously in 15 patients with coronary spastic angina before and after the left coronary spasm induced by intracoronary injection of acetylcholine and in 15 patients with stable exertional angina before and after acute myocardial ischemia induced by rapid atrial pacing. Fifteen patients with chest pain but normal coronary arteries and no coronary spasm served as controls. The coronary sinus–arterial difference of fibrinopeptide A increased markedly (p < 0.001) from 0.1 ± 0.2 to 4.3 ± 0.7 ng/ml after the anginal attacks in the coronary spastic angina group. However, fibrinopeptide A levels remained unchanged after the attacks in the stable exertional angina group and after intracoronary injection of acetylcholine in the control group. Plasma β-thromboglobulin levels remained unchanged after the attacks in both patient groups and after acetylcholine in the control group. Our data indicate that coronary spasm induces thrombin generation and may lead to thrombus formation in the coronary artery involved, but pacing-induced ischemia does not activate the coagulation system. (Circulation 1990;82:2222–2225)

Intracoronary thrombus formation has been thought to play an important role in the genesis of acute myocardial infarction.1,2 Previous reports3–5 of the effect of pacing-induced ischemia on thrombin generation or platelet activation in the coronary circulation have produced conflicting results. It is also not known whether coronary spasm can activate the coagulation system in the coronary circulation.

The purpose of the present study was to determine whether acute myocardial ischemia induced by coronary spasm or rapid atrial pacing causes thrombin generation or platelet activation in the coronary circulation. We examined the activation of the hemostatic system before and after the left coronary spasm induced by the intracoronary injection of acetylcholine6 in the patients with coronary spastic angina and before and after atrial pacing in the patients with stable exertional angina involving the left coronary artery.

Methods

Study Population

We classified 52 patients into one of three groups—coronary spastic angina group, stable exertional angina group, and control group. The coronary spastic angina group comprised 22 patients in whom spasm of the left coronary artery was induced by the intracoronary injection of acetylcholine.6 Nineteen of the 22 patients had from one to seven anginal attacks a day in the 48 hours before the catheterization, and the remaining three were free from attacks for 1–6 months. The stable exertional angina group comprised 15 patients who had typical exertional angina and 90% or greater narrowing of the left coronary artery. The control group comprised 15 patients with atypical chest pain; their coronary angiographic findings were normal. The three groups were matched for age and sex. Patients with myocardial infarction or receiving heparin, coumarin anticoagulant, or antiplatelet agents were excluded from the study. Written informed consent was obtained from each patient, and the study design was in agreement with the guidelines approved by the Kumamoto University Medical School Ethics Committee.

Procedures for Catheterization and Stress Tests

A 6F Goodale-Lubin catheter and a 8F Sones catheter were used for blood sampling from the coronary
### Table 1. Fibrinopeptide A, β-Thromboglobulin, and Lactate Data

<table>
<thead>
<tr>
<th>Assay</th>
<th>Control subjects (n=15)</th>
<th>Patients with CSA (n=15)</th>
<th>Patients with SEA (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After ACh</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>FPA (ng/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>3.2±0.4</td>
<td>NS</td>
<td>3.1±0.4</td>
</tr>
<tr>
<td>Ao</td>
<td>3.2±0.5</td>
<td>NS</td>
<td>3.2±0.4</td>
</tr>
<tr>
<td>CS–Ao</td>
<td>−0.1±0.4</td>
<td>NS</td>
<td>−0.1±0.3</td>
</tr>
<tr>
<td><strong>BTG (IU/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>37.2±2.3</td>
<td>NS</td>
<td>37.7±2.9</td>
</tr>
<tr>
<td>Ao</td>
<td>35.0±3.0</td>
<td>NS</td>
<td>37.2±3.6</td>
</tr>
<tr>
<td>CS–Ao</td>
<td>2.2±1.3</td>
<td>NS</td>
<td>0.5±2.5</td>
</tr>
<tr>
<td><strong>Lactate extraction ratio (%)</strong></td>
<td>37.9±2.8</td>
<td>NS</td>
<td>34.9±2.7</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM.

CSA, coronary spastic angina; SEA, stable exertional angina; ACh, acetylcholine; FPA, fibrinopeptide A; BTG, β-thromboglobulin; CS, coronary sinus; Ao, ascending aorta; CS–Ao, coronary sinus–arterial difference.

* † ‡ p<0.01 versus control subjects and SEA patients.
† ‡ p<0.001, † ‡ p<0.01 versus baseline.

Sinus and the aortic root, respectively, in all patients except seven with coronary spastic angina in whom the identical catheters with heparin-bonded surfaces (USCI) were used. Immediately after the insertion of the Goodale-Lubin catheter into the coronary sinus, the Sones catheter was inserted. All patients were given 5,000 units heparin at the insertion of the Sones catheter. Blood samples for fibrinopeptide A (FPA), β-thromboglobulin (BTG), and lactate were then collected from the coronary sinus and the aortic root simultaneously at the same speed.

**Acetylcholine test.** After control blood samples were obtained, acetylcholine 20–100 μg was injected into the left coronary artery to induce coronary spasm. In patients with coronary spastic angina and control patients, a coronary arteriogram was obtained when ST segment changes or chest pain appeared or 1.5 minutes after each injection. After angiograms, blood samples were taken again simultaneously from the coronary sinus and the aortic root.

**Pacing stress test.** After control blood samples were obtained, atrial pacing was commenced in patients with stable exertional angina. The tachycardia was sustained for 3 or 5 minutes while the patients experienced angina; then blood samples were collected.

Care was taken to obtain the blood sampling at the same time interval after catheter insertion in all patients because plasma FPA or BTG may increase with time after catheter insertion.

**Assays of FPA, BTG, and Lactate**

Measurements of FPA and BTG were performed by enzyme-linked immunosorbent assay as reported previously. Blood samples for plasma lactate determination were assayed by lactate oxidase method. Percent myocardial lactate extraction was calculated as the ratio of the arteriovenous difference to the arterial level.

**Statistics**

Values for FPA and BTG levels are given as mean±SEM. Logarithmic transformation was required to obtain normally distributed variables because the measured levels of these factors show a marked skewness toward high values. FPA and BTG distribution in the control subjects and the patients with coronary spastic angina and stable exertional angina were evaluated by one-way analysis of variance. Statistical analyses were performed by Student’s t tests for paired and unpaired variables. Probability levels of less than 0.05 were considered to be statistically significant.

**Results**

The plasma FPA levels at baseline in both the coronary sinus and the aortic root in the patients with coronary spastic angina were significantly higher (p<0.01) than those in the control subjects and the patients with stable exertional angina (Table 1). The plasma BTG levels at baseline were not significantly different between each of the three groups (Table 1). Percent myocardial lactate extraction markedly decreased during the attacks in the patients with coronary spastic angina and in those with stable exertional angina but remained unchanged in the control subjects (Table 1). The FPA levels in the coronary sinus increased significantly (p<0.001) after the attacks in the patients with coronary spastic angina but remained unchanged in the patients with stable exertional angina and the control subjects (Figure 1 and Table 1). A slight elevation in plasma...
BTG levels in the coronary sinus was noted during the attacks in the patients with coronary spastic angina, but this was not significant (Table 1).

The coronary sinus–arterial difference of FPA increased significantly from 0.2±0.4 to 2.5±0.8 ng/ml after the attacks in seven patients with coronary spastic angina in whom heparin-bonded catheters were used (p<0.02).

**Discussion**

It is now established that intracoronary thrombosis plays an important role in the pathogenesis of acute myocardial infarction.1,2 Coronary spasm is also known to play an important role in the production of acute myocardial infarction in some patients.11,12 However, it is not yet clear whether coronary spasm results in intracoronary thrombus formation. FPA is a small peptide released from fibrinogen by the specific action of thrombin and is a marker of thrombosis.13

In the present study, the coronary sinus–arterial difference of plasma FPA levels increased after the spasm of the left coronary artery in all of the patients with coronary spastic angina except one. This indicates that coronary spasm induces thrombin generation in the coronary artery involved. On the other hand, the release of FPA in the coronary circulation was not observed after pacing-induced ischemia in the patients with stable exertional angina. Thus, coronary spasm activates the coagulation system in the coronary circulation and may lead to thrombus formation and ultimately to acute myocardial infarction in some patients. On the other hand, pacing-induced ischemia in the patients with stable exertional angina does not cause fibrin formation in blood-draining ischemic myocardial segment. Therefore, in the patients with stable exertional angina, the exercise-induced ischemia is less likely to lead to thrombus formation and ultimately to acute myocardial infarction.

Plasma FPA levels at baseline were higher in the patients with coronary spastic angina than in the patients with stable exertional angina and in the control subjects, probably because coronary spasm occurs often in the early morning and this study was done in the morning.9

In the previous study,9 FPA levels were high systemically after the attack. In the present study, however, systemic levels are not elevated yet the coronary sinus levels are high. This discrepancy is probably due to heparin given at the insertion of the Sones catheter. Heparin, an inhibitor of thrombin activation, is known to suppress the elevation of systemic plasma levels of FPA.

BTG is a specific indicator of platelet activation in vivo.14 Plasma BTG levels did not increase during the attack in the patients with coronary spastic angina in the present study. The reason for the discrepancy between the levels of FPA and those of BTG during
the attacks cannot be readily explained; it may be due to the difference in the sensitivity of fibrinogen and platelets to thrombin action or the difference rates of clearance of these substances. On the other hand, the release of FPA and BTG in the coronary circulation was not observed after pacing-induced ischemia in the patients with stable exertional angina and after acetylcholine injection in the control subjects.

It is known that fibrin forms and platelets adhere and are activated on the inner and outer surfaces of all known cardiac catheters. Thus, local fibrin formation and platelet release on the catheter surfaces causes the measurements made on blood drawn through the catheters to be elevated artifically. Because of this technical difficulty, we obtained blood samples using the catheters of the same quality and the same size and by the same technique. The mean time intervals from catheter insertion to blood sampling were similar in all of the three patient groups. Moreover, heparin-bonded catheters were used to reduce fibrin formation in the catheters7 in seven patients with coronary spastic angina, and the coronary sinus–arterial difference of FPA levels increased significantly after the attacks. We addressed the difference of plasma FPA levels between the coronary sinus and the aortic root before and after the attacks, not the absolute levels of plasma FPA levels in this study. Thus, the measurements of the coronary sinus–arterial difference of FPA and BTG provide information on directional changes in transcardiac thrombin generation and platelet activation.16 For these reasons, we think that the increased coronary sinus–arterial difference in plasma FPA levels after the attack in the patients with coronary spastic angina indicates thrombin generation in the coronary artery involved in spasm.

References


Key Words • fibrinopeptide A • β-thromboglobulin • coronary spasm • thrombus formation
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