FIBRINOPEPTIDE A (FPA) LEVELS IN ATRIAL FIBRILLATION AND THE EFFECTS OF HEPARIN ADMINISTRATION

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It has been reported that a patient with atrial fibrillation (AF) is in the hypercoagulable state and that this state results in a high incidence of systemic thromboembolisms. In this paper, we have investigated plasma fibrinopeptide A (FPA) levels and the effects of subcutaneous administration of heparin on these levels in patients with AF.

Forty-five patients with hypertension (HT) or mitral stenosis (MS) were classified into four groups according to whether they had AF complications; i.e., HT with normal sinus rhythm (NSR), HT with AF, MS with NSR and MS with AF. Patients with AF demonstrated significantly higher plasma FPA levels and lower plasma antithrombin III (AT III) activities than those with NSR.

When low dose heparin was administered to patients with AF, plasma FPA levels were decreased to the near normal range, accompanied by an increase in heparin-AT III complex activity and heparin concentration 0.5–1.0 h after injection. These levels were maintained for 5 h.

From these results it was concluded that patients with AF were in the hypercoagulable state and that the measurement of plasma FPA levels provided a possibility to detect the underlying activation of blood coagulation.

It is well known that thromboembolism is a major and serious complication in patients with valvular heart disease and that the incidence of systemic emboli increases with the development of atrial fibrillation (AF). However, there have been few conventional laboratory tests to detect the hypercoagulable state and to monitor the effect of anticoagulant therapies. Recently, new sensitive parameters for assessing the activation of the coagulation pathway have been established. For example the level of fibrinopeptide A (FPA), which is a product split off from fibrinogen. In this paper, we have investigated plasma FPA levels in patients with AF and the effects of subcutaneous administration of heparin on these levels.

MATERIALS AND METHODS

The subjects were 45 patients with hypertension (HT) or mitral stenosis (MS), classified into four groups according to whether they had AF complications (Table I): namely HT with normal sinus rhythm (HT-NSR, n = 24); HT with AF (HT-AF, n = 10); MS with NSR (MS-NSR, n = 8); and MS with AF (MS-AF, n = 3). All these patients had not undergone operations recently, neither had they had anticoagulant

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TABLE 1 SUBJECTS

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<th>No.</th>
<th>Sex</th>
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<td>M : F</td>
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<tr>
<td>HT</td>
<td>NSR</td>
<td>24</td>
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<td>AF</td>
<td>10</td>
<td>8 : 2</td>
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<td>58.4 ± 10.6</td>
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<tr>
<td></td>
<td>NSR</td>
<td>8</td>
<td>3 : 5</td>
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<tr>
<td></td>
<td>AF</td>
<td>3</td>
<td>1 : 2</td>
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HT = Hypertension; MS = Mitral stenosis

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Fig. 1. Relationship between plasma AT III activity and various cardiovascular diseases. **; p < 0.01, ***; p < 0.001

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Fig. 2. Relationship between AT III activity and heart rate.

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Fig. 3. Effect of AF on fibrinopeptide A level in patients with hypertension.

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therapies or thromboembolisms. All the patients with MS were normotensive. Patients with hepatic or renal dysfunction were excluded from the study. Blood sampling was carried out using the two syringe technique without venous occlusion. The coagulation and fibrinolytic parameters examined were: prothrombin time ratio (PT ratio); activated partial thromboplastin time ratio (aPTT ratio); fibrinogen (Fbg, turbidimetric assay); antithrombin III (AT III, amidolytic assay); plasminogen (Plg, amidolytic assay); α2-plasmin inhibitor (α2-PI, amidolytic assay); α2 macrogloubulin (α2-M, immune defusion); and FPA (RIA).

Six patients with AF were given 5,000 U of heparin subcutaneously and the effects on several parameters were evaluated. Blood was drawn before and 0.5, 1.0, 3.0 and 5.0 h after the injection of heparin, and in each sample the plasma levels of heparin-AT III complex (Anti-thrombin-amidolytic assay), heparin concentration (Anti Xa-amidolytic assay) and FPA (RIA) were assayed.

RESULTS

1) Coagulation and fibrinolytic state in the patients with AF

Plasma AT III activities were significantly decreased in patients with AF-HT compared to those with NSR-HT (Fig. 1). Patients with NSR-MS showed lower plasma AT III activities compared to those with NSR-HT. The relationship between heart rate (HR) and AT III activity was compared in subjects with HT only.

There was no significant correlation between the plasma AT III activities and HR (Fig. 2). As

Fibrinopeptide A in atrial fibrillation and effects of heparin

Fig. 4. Effect of AF on coagulation and fibrinolytic parameters in patients with hypertension. *; p < 0.05

Fig. 5. Effect of AF on coagulation and fibrinolytic parameters in patients with hypertension.

Fig. 6. Effect of heparin administration on heparin concentration (Hep.), heparin-AT III complex (Hep-AT III) and fibrinopeptide A (FPA). Each point denotes the mean value for six separate determinations.

for the other coagulation and fibrinolytic parameters, higher plasma FPA levels (Fig. 3) were detected in patients with AF (22.20 ± 11.49 ng/ml) compared to those with NSR (0.98 ± 0.47 ng/ml). Lower plasma Plg levels were observed in patients with AF compared with those with NSR (Fig. 4). However, significant differences in parameters such as PT ratio, aPTT ratio, Fbg and α2-M were not observed (Fig. 5).

2) Effect of subcutaneous heparin administration
At 0.5 and 1.0 h after the injection, the plasma levels of heparin-AT III complex and heparin concentration increased to 0.04 ± 0.01 and 0.15 ± 0.10 U respectively, and plasma FPA levels (37.03 ± 21.05 ng/ml) were markedly decreased to near normal levels (3.65 ± 1.91 ng/ml). These anticoagulant effects were maintained over 5 h (Fig. 6).

DISCUSSION
It is well known that patients with rheumatic mitral valve diseases have at least a 20% chance of having clinically detectable systemic emboli during the course of their diseases and that the incidence of systemic emboli increases dramatically with the development of AF. Therefore, it is very important to predict low-grade activation of blood coagulation and to prevent the development of thromboembolic incidence in patients with AF. One of the reasons for the high incidence of thromboembolism in AF is thought to be endogenous hemostatic activation induced by valvular heart diseases themselves, because patients with MS showed lower plasma AT III activities than those with HT. However, it has been reported that the risk of systemic emboli appears to correlate poorly with left atrial size and mitral valve area. In the present study, plasma AT III activities were significantly lower in patients with HT-AF than those with HT-NSR. AT III is one of the major physiological inhibitors of blood coagulation and decreased levels of AT III are suspected to be a predictor of a hypercoagulable state. These results suggest that hypercoagulability can be amplified by AF complications.

The presence of fibrinopeptide A is considered to be an indirect but highly sensitive indicator for increased generation of thrombin because of its short half life. From this point of view, higher plasma FPA levels in AF patients suggest the hypercoagulable state in AF, and also lower plasma Plg levels may be the result of accelerated secondary fibrinolysis.

When heparin was administered to patients with AF, higher plasma FPA levels decreased to the normal range, concomitantly with increased plasma levels of heparin-AT III complex and
heparin concentration, 0.5 and 1.0 h after the injection. The immediate decrease in plasma FPA levels was considered to result from inhibited FPA generation based on the inactivation of thrombin by heparin-AT III complex.

From these results, it is concluded that the measurement of plasma FPA levels is beneficial for the detection of endogenous activation of blood coagulation and therapeutic effectiveness of anticoagulant agents in patients with AF.

CONCLUSION

Endogenous hemostatic activation was observed in the patients with AF and it was detectable by the measurement of plasma FPA levels.

The hypercoagulable state in patients with AF was proved to be dissolved by subcutaneous administration of low dose heparin.

REFERENCES


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