

Coagulation Activity is Increased in the Left Atria of Patients With Paroxysmal Atrial Fibrillation During the Non-Paroxysmal Period

— Comparison With Chronic Atrial Fibrillation —

Hirohiko Motoki, MD; Takeshi Tomita, MD; Kazunori Aizawa, MD;
Hiroki Kasai, MD; Atsushi Izawa, MD; Setsuo Kumazaki, MD;
Hiroshi Tsutsui, MD; Jun Koyama, MD; Uichi Ikeda, MD

Background: Evaluation of plasma markers of thrombin activity (thrombin-antithrombin III complex: TAT), active fibrinolysis (plasmin- α 2-plasmin inhibitor complex: PIC), and platelet activity (platelet factor 4: PF4) is useful for identifying patients with various cardiovascular disorders who are at high risk of thromboembolism. In this study, these markers were investigated in the left atria (LA) of patients with paroxysmal atrial fibrillation (pAF) in the non-paroxysmal period.

Methods and Results: Patients with pAF (n=10) and chronic AF (cAF) (n=10) were enrolled. TAT, PIC, and PF4 levels were determined in blood samples obtained from the LA of AF patients before radiofrequency catheter ablation. TAT levels were high in both pAF and cAF patients. PF4 levels were slightly elevated in both groups, but there was no significant difference between the groups. On the other hand, PIC levels in both groups were almost within normal limits, again with no significant difference between groups.

Conclusions: Coagulation activity is elevated in the LA of patients with pAF, even in the non-paroxysmal period, so these patients are at high risk of thromboembolism and anticoagulant therapy is indicated. (Circ J 2009; 73: 1403–1407)

Key Words: Coagulation; Left atrium; Paroxysmal atrial fibrillation

Atrial fibrillation (AF) is now widely recognized as a risk factor for thromboembolism, but the pathogenesis of thrombus formation remains unclear. Previous reports have suggested that loss of effective atrial contraction because of AF is associated with thrombogenesis. Microthrombi are most likely to form in the left atrial (LA) appendage.^{1,2} In contrast, intravascular thrombotic events in patients without AF are generally associated with abnormalities of vascular endothelial function and/or the coagulation system.

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It is well known that in patients with non-valvular AF, the risk of ischemic stroke increases by 3- to 4-fold³ and anticoagulant therapy reduces this risk by two-thirds.⁴ Administration of anticoagulant therapy is generally thought to be necessary as a preventive measure for patients at high risk of thromboembolism, but warfarin use in AF has not increased

recently, indicating inadequate implementation of this highly effective therapy.⁵

Previous studies have demonstrated increased activation of platelets and the coagulation system in the peripheral venous blood in patients with chronic AF (cAF).^{6–9} In patients with paroxysmal AF (pAF), AF itself enhances platelet aggregation and coagulation, and these processes are influenced by the duration of AF.¹⁰ Interestingly, however, ischemic stroke occurs in patients with pAF, even during sinus rhythm.¹¹ The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study revealed that ischemic stroke was not a rare occurrence in patients not under anticoagulation therapy who were assigned to the sinus rhythm control group; a substantial number of the subjects in that group had pAF during the study period. Those results indicate that anticoagulation therapy is important not only for cAF patients but also for those with pAF.¹²

Recently introduced molecular markers with a high sensitivity for platelet activity and thrombotic and fibrinolytic status have enabled the evaluation of these parameters in patients with valvular heart disease, cardiomyopathy, congenital heart disease and AF.^{9,13–16} Risk stratification using coagulation or fibrinolytic markers would be useful for preventing thrombosis in patients with AF,¹⁷ and some studies have evaluated the levels of coagulation markers in the peripheral blood of patients with pAF during a paroxysm.^{10,18,19} However, few studies have evaluated the risk of thromboembolism in the non-paroxysmal period (eg, during sinus rhythm) in patients with pAF. Furthermore, no studies

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Department of Cardiovascular Medicine, Shinshu University Graduate School of Medicine, Matsumoto, Japan

Mailing address: Takeshi Tomita, MD, Department of Cardiovascular Medicine, Shinshu University Graduate School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. E-mail: ttomita@shinshu-u.ac.jp

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Table 1. Baseline Characteristics of Paroxysmal AF and Chronic AF Patients

	Paroxysmal AF (n=10)	Chronic AF (n=10)	P value
Age (years)	57±11	61±6	NS
Male patients (%)	70	80	NS
Diabetes (%)	0	20	NS
Hypertension (%)	20	60	NS
Dyslipidemia (%)	40	70	NS
Medications			
ACEI/ARB (%)	10	40	NS
β -blocker (%)	40	40	NS
Statin (%)	20	20	NS

Data are mean values±standard deviation.

AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker.

Table 2. Echocardiographic Parameters and BNP Levels in Paroxysmal AF and Chronic AF Patients

	Paroxysmal AF (n=10)	Chronic AF (n=10)	P value
IVS (mm)	12±3	12±4	NS
PW (mm)	9±2	12±3	NS
LVDd (mm)	46±5	47±6	NS
LVDs (mm)	28±5	30±6	NS
FS (%)	37±9	42±11	NS
LAd (mm)	41±4	48±2*	<0.01
BNP (pg/ml)	63.0±43.9	208.1±212.0	NS

Data are mean values±standard deviation.

*P<0.01 vs paroxysmal AF.

BNP, brain natriuretic peptide; IVS, intraventricular septal thickness; PW, posterior wall thickness; LVDd, left ventricular dimension in diastole; LVDs, left ventricular dimension in systole; FS, fractional shortening; LAd, left atrial dimension. Other abbreviation see in Table 1.

have evaluated LA thrombotic activity in those patients. In the present study, we evaluated coagulation and platelet activity in the LA during sinus rhythm in patients with pAF.

Methods

Twenty patients who had been treated at our university hospital between April 2005 and November 2006 were enrolled and allocated to 2 groups: 10 patients with pAF in the non-paroxysmal period (pAF group), and 10 patients with cAF (cAF group). Patients in both groups underwent catheter ablation for pulmonary vein isolation. PAF was defined as episodes of AF lasting ≥ 10 complexes documented on at least 2 occasions. CAF was defined as AF documented electrocardiographically on at least 2 occasions at least 6 weeks apart that took place either at a general practitioner's office, a hospital, or an outpatient clinic review. Diabetes mellitus was defined according to the World Health Organization criteria.²⁰ Patients were considered hypertensive if they had systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or if they were under antihypertensive therapy. Patients were defined as having hypercholesterolemia if they had a total cholesterol level ≥ 220 mg/dl or if they were receiving lipid-lowering agents.

M-mode, 2D, and Doppler transthoracic echocardiography were performed for all subjects. The dimensions of the LA and the left ventricle (LV) in systole and diastole were

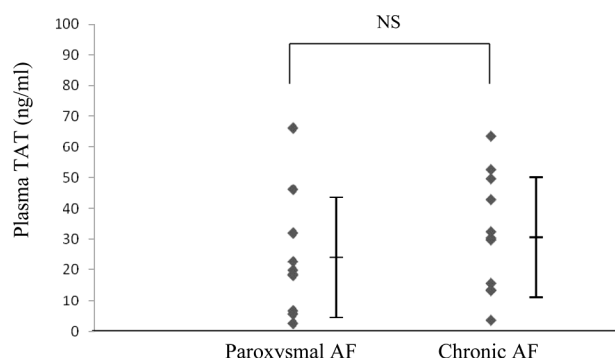


Figure 1. Thrombin–antithrombin III complex (TAT) concentration in blood collected from the left atrium and ventricle. High levels of TAT were measured in the left atria of patients with paroxysmal atrial fibrillation (AF) and chronic AF. There was no significant difference between the 2 groups. Values are means±SD.

measured by M-mode echocardiography. LV fractional shortening was determined using the standard M-mode method and defined as (LVDd–LVDs)/LVDd, where LVDd and LVDs are the LV dimensions at diastole and systole, respectively. In both the pAF and cAF groups, absence of thrombi in the heart chambers, including the LA appendage, was confirmed by transesophageal echocardiography prior to catheter ablation.

In all patients, oral anticoagulant therapy was discontinued 5 days prior to catheter ablation, and unfractionated heparin was administered continuously until 6 h before the procedure. During this period, all patients underwent ambulatory ECG monitoring to evaluate the frequency of pAF by analyzing the heart rhythm retrospectively. Blood samples were obtained from the LA. A catheter was inserted into the inguinal vein and through the inferior vena cava into the right atrium. A sheath was inserted from the right atrium into the LA using the Brockenbrough procedure via a trans-septal approach. Blood samples were immediately obtained from the LA and the coagulation activity was examined. A preliminary study revealed no difference in the levels of biochemical markers among samples obtained from the right atrium before and after the Brockenbrough procedure.

The intracardiac blood samples from patients in the 2 study groups were examined to determine the plasma levels of thrombin–antithrombin III complex (TAT), plasmin- α 2-plasmin inhibitor complex (PIC), and platelet factor 4 (PF4). The levels of these markers were assessed using enzyme-linked immunosorbent assay kits (Behringwerke, Marburg, Germany; Teijin, Tokyo, Japan; Diagnostica Stago, Asnières, France, respectively). Our study was approved by the institutional ethics committee and written informed consent was given by all study participants before participating in this study.

The results are expressed as the mean level±the standard deviation. Student's t-test was used for the evaluation of significance, and P values <0.05 were considered significant.

Results

No significant differences were observed between the 2 groups with regard to the risk factors for thromboembolism, including age, sex, diabetes, hypertension, and hypercholesterolemia (Table 1). No patients were administered antiplatelet agents, and no differences were noted in the

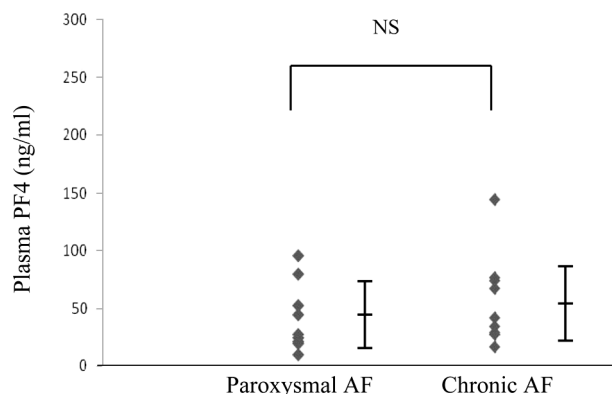


Figure 2. Plasma platelet factor 4 (PF4) levels in the left atrium and ventricle. High levels of PF4 were measured in the left atria of patients with paroxysmal atrial fibrillation (AF) and chronic AF. No significant difference between the groups was observed in platelet activity, which was evaluated on the basis of PF4 levels. Values are means \pm SD.

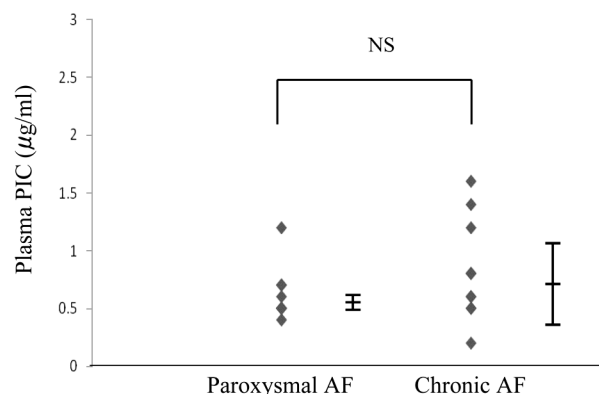


Figure 3. Plasmin- α 2-plasmin inhibitor complex (PIC) levels in the left atrium and ventricle. PIC levels in both paroxysmal atrial fibrillation (AF) and chronic AF patients were almost within normal limits, and no significant difference was observed between the groups. Values are means \pm SD.

administered doses of β -blockers, angiotensin-converting enzyme inhibitors or statins.

No significant differences were observed between the 2 groups with respect to the LV dimensions at diastole and systole (**Table 2**). The LA dimension was significantly larger in the cAF group (48 ± 2 mm) than in the pAF group (41 ± 4 mm) ($P < 0.01$). The serum levels of B-type natriuretic peptide (BNP) did not differ significantly between the 2 groups (cAF: 208.1 ± 212.0 pg/ml, pAF: 63.0 ± 43.9 pg/ml). Ambulatory ECG monitoring revealed that none of the pAF patient had AF in the 5 days before the procedure.

Figure 1 shows the plasma levels of TAT, which were high in both AF groups, with mean values above the upper limit of normal (3 ng/ml), but no significant difference between the 2 groups. Thus, despite measurement during the non-paroxysmal period, coagulation activity was increased in the LA in both pAF and cAF patients.

PF4 levels were also increased, with mean values in both the pAF and cAF groups higher than the upper limit of normal (20 ng/ml). There was no significant difference between patient groups (**Figure 2**).

Figure 3 shows that PIC levels, measured as an index of fibrinolytic activity, were almost within normal limits (0.8 μ g/ml). Again, there was no significant difference between the 2 groups.

Discussion

To the best of our knowledge, the present study is the first to report hypercoagulability in the LA of pAF patients during sinus rhythm. Our findings indicate that coagulation activity, which was estimated on the basis of TAT levels, was increased in the LA of both pAF and cAF patients, possibly leading to an increase in the risk of thromboembolism in patients with either condition. An increase in coagulation activity appears to be one of the major mechanisms underlying thrombogenesis, and there is now a consensus regarding the administration of anticoagulants for patients at risk. The present study also demonstrated that platelet activity increased slightly in the LA of pAF and cAF patients, even when measured during the non-paroxysmal period.

Previous studies have reported that patients with pAF have increased coagulation activity following paroxysm initiation, and that this is influenced by the duration of

AF.^{10,18,19} Yamaji et al speculated that the development of hypercoagulability is related to enlargement of the left atrium,¹⁹ which results in the secretion of atrionatriuretic hormone and increased hematocrit. Iga et al hypothesized that a sudden loss of the atrial booster function causes stagnation of blood in both atria and activates the coagulation system.¹⁸ However, those previous studies were conducted using peripheral blood samples and the samples were obtained during the paroxysmal period, and it was therefore unclear whether the LA plays a role in the hypercoagulability in patients with pAF during the non-paroxysmal period.

In this study, we found that there was increased coagulation activity in LA blood samples in all pAF patients who were in the non-paroxysmal period. With regard to anticoagulation therapy, Mant et al reported that warfarin is more effective than antiplatelet agents for the prevention of cerebral apoplexy in patients with AF.²¹ Our results indicate that in patients with pAF, even if they are in the non-paroxysmal period, there is hypercoagulability in the LA, which may play a significant role in thrombogenesis, with platelet activity implicated to a lesser extent.

The underlying mechanism of the observed increase in LA coagulation activity must be discussed. Several previous experimental reports have demonstrated that AF causes atrial endothelial dysfunction,²² which is manifested by decreased expressions of endothelial nitric oxide synthase, tissue factor pathway inhibitor, and thrombomodulin in the LA, as well as increased expression of plasminogen inhibitor-1, all of which leads to an imbalance in the local coagulation system on the internal surface of the atrium.^{23,24} Furthermore, one of the proposed mechanisms underlying this endothelial dysfunction is oxidative stress induced in the LA by AF.^{25,26} This hypothesis is supported by a recently published report that indicated that angiotensin II receptor blockers could partially prevent atrial endothelial dysfunction and the occurrence of AF.^{27,28} Apparently, intravascular thrombotic events in patients without AF are generally associated with abnormalities in vascular endothelial functioning and/or the coagulation system. In patients with pAF, endothelial dysfunction may also play an important role in thrombogenesis in the LA.

Clinical Implications

Our results demonstrate that the coagulation activity in the

LA was increased in pAF patients, even when they were in the non-paroxysmal period, while the increase in the platelet activity was not so remarkable, suggesting that anticoagulation therapy, rather than antiplatelet therapy, is recommended for these patients. There may be another mechanism underlying thrombogenesis in patients with pAF that differs from the stasis of blood in the LA because of fibrillation of the atrial wall.

Study Limitations

First, we cannot completely rule out the effect of puncturing the atrial septum on coagulation activity in the atria; needle perforation of the septum and catheter dilation of the septal puncture could cause the raw edges of the septal perforation to be exposed to atrial blood, although that is unlikely according to previous studies.^{13,29} For example, Roger et al²⁹ used the same methodology, the Brockenbrough procedure, to evaluate LA coagulation activity in patients with mitral stenosis. In their report, they discuss the effects of the procedure on coagulation activity in the LA and conclude that the increased level of LA prothrombin fragment 1+2 observed within the mitral stenosis group as a whole was not related to the valvuloplasty procedure. Second, the possibility of anticoagulants affecting fibrinolytic activity should be considered with regards to the PIC levels measured in the present study. Previous studies showed that fibrinolytic activity and platelet function were enhanced in AF patients as compared with those without AF.^{30,31} Patients with pAF had intermediate levels of D-dimer compared to cAF patients and healthy subjects.³² When thrombi were produced via enhanced coagulation activity in the cardiovascular system, fibrinolytic activity would have been enhanced in vivo. Thus, pretreatment with warfarin could lower the fibrinolytic activity in our patients. Third, we monitored the incidence of AF in patients with pAF at an outpatient clinic using ambulatory ECG. None of the patients in the pAF group developed AF during the 5 days of hospitalization in this study. Because asymptomatic pAF episodes are more common than symptomatic pAF episodes,³³ it is difficult to define the frequency and the exact duration of AF in the pAF patients. Fourth, we evaluated coagulation activity only in the LA. Finally, the number of patients in this study was small, and we did not measure coagulation activity in the LA of normal subjects, so further studies with more subjects are necessary. Nevertheless, high plasma TAT levels were measured in pAF and cAF patients, suggesting an increased risk of thromboembolism.

Conclusion

In patients with pAF, even when they are in the non-paroxysmal period, there is hypercoagulability in the LA, which suggest that patients with pAF are at high risk for developing cerebral thromboembolism even during sinus rhythm and therefore, anticoagulation therapy is indicated.

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