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Atrial Fibrillation Activates Platelets and Coagulation in a Time-Dependent Manner: A Study in Patients With Paroxysmal Atrial Fibrillation

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Objectives. **To determine whether atrial fibrillation (AF) alone affects the fibrinocoagulation system, we examined the relation between fibrinocoagulation activity and duration of AF in patients with paroxysmal AF (PAF).**

Background. **Patients with chronic AF are at higher risk for stroke and a hypercoagulative state. It is not clear whether this hypercoagulative state is attributable to AF alone or to the underlying disease. There are no reports on the fibrinocoagulation properties in PAF.**

Methods. **Fibrinocoagulation variables in 21 patients with PAF were measured during AF and 7 days after recovery of sinus rhythm. There were positive correlations between the duration of AF and beta-thromboglobulin, platelet factor 4, thrombin-antithrombin III complex and fibrinogen. These variables increased significantly 12 h after the occurrence of PAF; thus, patients were classified into two groups according to the duration of PAF: PAF-I group (<12 h, n = 10), PAF-II group (≥12 h, n = 11). Nine age-matched, healthy subjects formed the control group.**

Results. **Levels of beta-thromboglobulin and platelet factor 4 were significantly higher ($p < 0.001$) by two-way repeated measures analysis of variance (ANOVA), and thrombin-antithrombin III complex and fibrinogen levels tended to be but were not significantly higher ($p = 0.06$, ANOVA), in the PAF-II group than in the PAF-I group. There were no significant differences between groups in activated partial thromboplastin time, D-dimer or plasmin inhibitor complex.**

Conclusions. **These results indicate that AF itself enhances platelet aggregation and coagulation, which are influenced by the duration of AF. The acceleration of platelet activity and coagulability occurred 12 h after the occurrence of AF.**

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It is well known that the coagulative state in patients with chronic atrial fibrillation (CAF) is higher than that in patients with normal sinus rhythm (1–6) and that the incidence of thromboembolism is also significantly higher in these patients (7–12). Therefore, CAF is an important risk factor of cerebral embolism. In addition, some investigators have reported that (13–15) paroxysmal atrial fibrillation (PAF) might also be a risk factor for stroke. However, to our knowledge there are no reports of a change in coagulative state in patients with PAF. In patients with CAF, the hypercoagulative state was compared with that in patients without atrial fibrillation (AF) (1–6). Thus, it is not clear whether this hypercoagulative state in AF is attributable to AF alone or to the disease that underlies AF.

We previously reported (16) that PAF did not affect the coagulation system within an average of 6 h after onset of PAF. However, it is possible that a longer duration of PAF accelerates the coagulation system. Therefore, we examined the changes in coagulative variables in patients with PAF to determine whether the duration of PAF affects the coagulative system.

Methods

Subjects. The study group included 21 patients with PAF (15 men, 6 women; mean [±SD] age 59.1 ± 9.5 years, range 43 to 77). Patients with valvular disease, ischemic heart disease, hyperlipidemia, diabetes mellitus, dilated cardiomyopathy and sick sinus syndrome, or those with a past history of cerebral infarction or heart failure, were eliminated from the study. Two patients with high levels of platelet activity, as determined previously, were also excluded from the study because silent cerebral infarction was found during a follow-up examination with magnetic resonance imaging or computed tomography of the head. The details of the 21 subjects are shown in Table 1 (nonvalvular lone PAF in 15, hypertensive heart disease in 2, hypertrophic cardiomyopathy in 3, Wolff-Parkinson-White syndrome in 1. On the basis of exercise electrocardiographic tolerance test results, exercise tolerance thallium myocardial scintigrams and echocardiography, all 21 patients were determined to have lone PAF. The patients were treated with various antiarrhythmic agents, such as disopyramide, procain-

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Abbreviations and Acronyms

AF = atrial fibrillation
ANOVA = analysis of variance
CAF = chronic atrial fibrillation
PAF = paroxysmal atrial fibrillation

amide, propafenone, verapamil, quinidine, pilcicainide and digoxin, alone or in combination, but were not given anticoagulants. Nine age-matched healthy subjects without heart disease formed the control group (eight men, one woman). Written informed consent was obtained from all patients before the study. The study protocol was in agreement with the guidelines approved by the ethics committee at our institution.

Blood sampling and assay. Blood samples were taken during the paroxysmal period of PAF (PAF period), and antiarrhythmic agents were administered intravenously or orally to defibrillate and to suppress PAF. Seven days after recovery of normal sinus rhythm (non-PAF period), blood samples were again taken under the same conditions. Blood specimens in the control group were taken in the fasting state. The blood samples were taken from the cubital vein with the double-syringe method, using a 21-gauge needle and a 25-ml syringe (Nipro Co.). These specimens were distributed within 2 min, gently mixed by inverting the vials and immediately chilled in an ice bath, followed by centrifuging at 3,000 *g* for 10 min at −4°C. The serum was immediately frozen at below −30°C and stored for 2 days before analysis. Prothrombin time, activated partial thromboplastin time, thrombin-antithrombin III complex levels and fibrinogen levels were estimated as indexes of the coagulation system. D-Dimer and plasmin inhibitor complex levels were examined for the fibrinolytic system, and beta-thromboglobulin and platelet factor 4 levels were used to estimate platelet activity. Peripheral blood cell count, including hemoglobin and hematocrit, was also evaluated. Prothrombin time was measured by the one-step method of Quick (17) (Thromboplastin C Kit, Baxter Dade), and activated partial thromboplastin time was evaluated with the ellagic-acid activation method (Data-Fi APTT, American Dade). Thrombin-antithrombin III complex, beta-thromboglobulin and platelet-factor 4 were measured by the enzyme-linked immunosorbent assay method (18,19) (Enzygnost TAT kit, Boehringberke, Asserachrom beta-thromboglobulin and platelet factor 4, Boehringer-Mannheim). Levels of D-dimer and plasmin inhibitor complex were determined using the EIA method (20,21) (D-dimer: LPIA-ACE, Baxter; plasmin inhibitor complex: Teijin alpha$_2$-plasmin inhibitor complex, EIA-B). Fibrinogen was measured with the thrombin method (Fibrinogen a-BMY, Boehringer-Mannheim).

Statistical analysis. Clinical variables are expressed mean value ± SD. The effects of the duration from the onset of PAF on platelets and coagulation were analyzed by two-way repeated measures analysis of variance (ANOVA) (Abacus Concepts, Inc., Statview 4.02J). Intergroup differences were analyzed by a paired *t* test, and differences between patients and control subjects were analyzed by an unpaired *t* test for independent samples and separate variances. When the variances between each group differed considerably, we used a nonparametric test (Mann-Whitney *U* test or Wilcoxon signed rank test). Correlation between variables was evaluated using the Pearson correlation coefficient. The Fisher exact probability test and receiver operating characteristic analysis were used to evaluate the point at which the coagulation variables began

Table 1. Patient Characteristics

PAF-I Group					PAF-II Group					Control Group	
Pt No./ Gender	Age (yr)	Time (min)	Underlying Disease	Medication	Pt No./ Gender	Age (yr)	Time (min)	Underlying Disease	Medication	Pt No./ Gender	Age (yr)
1/M	56	180	Lone PAF	DP, PA	1/M	60	1,110	HCM	DP, PA, PRF	1/M	63
2/M	53	585	HCM	DP	2/F	49	1,140	WPW	DP	2/M	51
3/F	77	420	HHD	DP	3/M	49	1,440	Lone PAF	DP	3/M	43
4/M	53	275	Lone PAF	DP, PA	4/M	43	960	Lone PAF	DP	4/M	63
5/M	63	140	Lone PAF	DP, PA, VER	5/M	66	780	HHD	DP, PA, QUN	5/M	42
6/M	61	450	Lone PAF	DP	6/F	56	900	HCM	DP	6/M	66
7/M	48	190	Lone PAF	DP, PA	7/M	56	960	Lone PAF	DP, PLC	7/M	70
8/M	67	80	Lone PAF	DP, PA, PRF	8/M	58	880	Lone PAF	DP, PRF, VER	8/M	72
9/M	49	680	Lone PAF	DP	9/M	71	780	Lone PAF	DP, PLC	9/F	56
10/F	77	345	Lone PAF	DP, PA	10/F	69	1,000	Lone PAF	DIG, DP		
11/F	61	480	Lone PAF	DP							
Mean	57.7	348			Mean	60.5	995			Mean	58.4
±SD	±9.1	±193			±SD	±10.0	±197			±SD	±11.4

DIG = digoxin; DP = disopyramide; F = female; HCM = hypertrophic cardiomyopathy; HHD = hypertensive heart disease; M = male; PA = procainamide; PAF = paroxysmal atrial fibrillation; PAF-I = time from onset of paroxysmal atrial fibrillation ≤12 h; PAF-II = time from onset of paroxysmal atrial fibrillation >12 h; PLC = pilsicainide; PRF = propafenone; QUN = quinidine; VER = verapamil; Time = sampling time from onset of paroxysmal atrial fibrillation; WPW = Wolff-Parkinson-White syndrome.

Table 2. Fibrinocoagulation Variables During Paroxysmal and Nonparoxysmal Atrial Fibrillation Periods in 21 Patients and 9 Control Subjects

	PAF Period (A)	Non-PAF Period (B)	Control (C)	p Value A vs. B	p Value A vs. C
Hct (%)	46.0 ± 3.96	43.4 ± 3.58	42.8 ± 3.19	<0.001	<0.05
Hb (g/dl)	15.3 ± 1.41	14.4 ± 1.34	13.8 ± 1.13	<0.0001	<0.05
PT (s)	11.2 ± 1.22	10.9 ± 1.40	11.8 ± 0.54	NS	NS
aPTT (s)	31.6 ± 3.37	30.7 ± 2.97	30.3 ± 2.56	NS	NS
TAT (μg/liter)	6.68 ± 5.11	4.21 ± 3.67	3.11 ± 1.86	<0.05	<0.05
Fbg (mg/dl)	262.2 ± 65.4	257.8 ± 56.2	225.7 ± 37.5	NS	NS
D-dimer (ng/ml)	141.7 ± 208.6	127.7 ± 207.0	67.2 ± 31.7	NS	NS
PIC (μg/ml)	0.86 ± 0.44	0.90 ± 0.43	1.02 ± 0.31	NS	NS
Beta-TG (ng/ml)	38.0 ± 27.3	29.1 ± 21.2	22.8 ± 7.85	<0.05	0.10
PF4 (ng/ml)	16.4 ± 18.2	10.3 ± 11.1	3.37 ± 2.26	<0.05	<0.05

*Seven days after recovery of sinus rhythm. Data presented are mean value ± SD. aPTT = activated prothrombin time; Fbg = fibrinogen; Hb = hemoglobin; Hct = hematocrit; PAF = paroxysmal atrial fibrillation; PF4 = platelet factor 4; PIC = plasmin inhibitor complex; PT = prothrombin time; TG = thromboglobulin.

to increase significantly from the onset of PAF. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Table 2 shows the values obtained during the PAF and non-PAF periods in the PAF and control groups. Hematocrit, hemoglobin, thrombin-antithrombin III complex and platelet factor 4 values during the PAF period were significantly higher than those during the non-PAF period and in the control group. Levels of the beta-thromboglobulin during the PAF period were also significantly higher than those during the non-PAF period but did not differ from those in the control group ($p = 0.10$). These results showed that AF itself increased hemoconcentration and enhanced platelet aggregation and coagulation. When we investigated the relation between the duration of PAF and these fibrinocoagulation variables, there were positive correlations between the duration of PAF and the values of platelet factor 4, beta-thromboglobulin, fibrinogen and thrombin-antithrombin III complex in all 21 patients (Fig. 1 to 4). Statistical analysis revealed that the values of beta-thromboglobulin and platelet factor 4 began to increase significantly 12 h after the onset of PAF. On the basis of these results, the 21 patients were classified into two groups: PAF-I group (blood specimens collected ≥12 h of the onset of PAF) and PAF-II group (blood specimens collected >12 h of onset of PAF) (Table 3). To clarify the effect of the duration of PAF on platelet activity and coagulation, the data were then reanalyzed between the PAF and non-PAF periods in PAF-I and PAF-II group patients by two-way repeated measures ANOVA. Hematocrit and hemoglobin values measured during the PAF period were significantly higher than those during the non-PAF period in both group PAF-I and PAF-II and tended to be higher than those in control group (Table 3).

Beta-thromboglobulin and platelet factor 4 values measured during the PAF period in the PAF-II group were significantly higher than those in the PAF-I group ($p < 0.001$, ANOVA) (Fig. 5 and 6). Thrombin-antithrombin III complex and fibrinogen values during the PAF period in the PAF-II

Figure 1. Correlation between platelet factor 4 and time from onset of PAF. Positive correlation was demonstrated between duration of PAF and platelet factor 4 levels and began to increase significantly at 12 h after the onset of PAF.

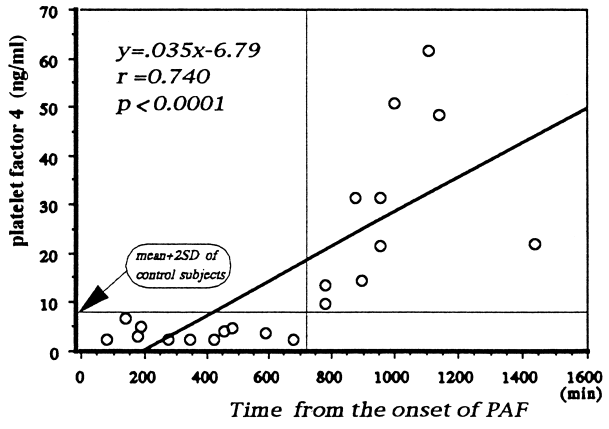
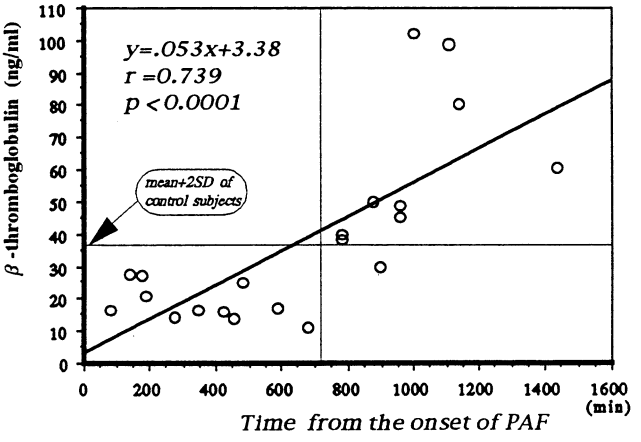


Figure 2. Correlation between beta-thromboglobulin and time from onset of PAF. Positive correlation was demonstrated between duration of PAF and beta-thromboglobulin levels and began to increase significantly at 12 h after the onset of PAF.



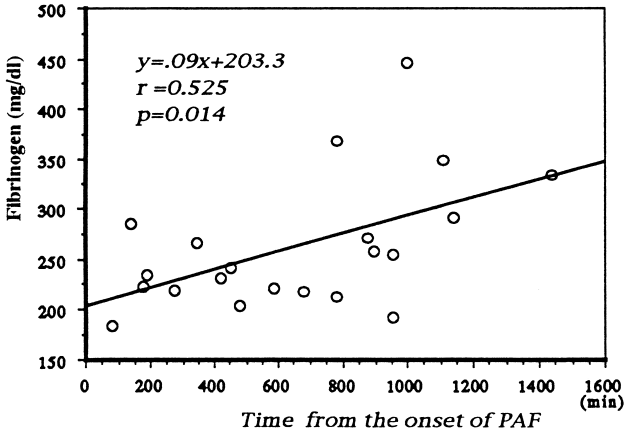


Figure 3. Correlation between fibrinogen and time from onset of PAF. Fibrinogen levels and duration of PAF demonstrated positive correlation.

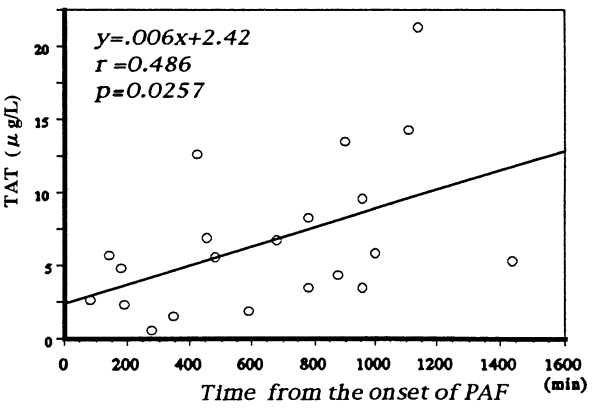


Figure 4. Correlation between thrombin-antithrombin III complex (TAT) and time from onset of PAF. Thrombin-antithrombin III complex levels and duration of PAF demonstrated positive correlation.

group tended to be higher than those in the PAF-I group but were not significantly higher (p = 0.06, ANOVA) (Fig. 7 and 8). These results indicate that the duration of PAF influences platelet activity and coagulability. Furthermore, beta-thromboglobulin and platelet factor 4 values during the non-PAF period in the PAF-II group were significantly higher than those in the control group. Prothrombin time during the PAF period in the PAF-II group was shortened compared with that in the control group (Fig. 9); however, activated partial thromboplastin time and D-dimer and plasmin inhibitor complex values did not differ significantly between groups.

Discussion

According to the Cerebral Embolism Task Force (7), cerebral embolism induced by heart disease occurs in 6% to 23% of all patients with a cerebral infarction, whereas 45% are caused by nonvalvular AF, indicating the importance of nonvalvular AF for the risk of stroke. According to the Framingham Study (8), the incidence of stroke in patients with AF without rheumatic heart disease is five times higher than that in patients without AF. Furthermore, if AF is present with rheumatic heart disease, the incidence of stroke becomes 17 times higher than that without AF. Moreover, in a report on the incidence of stroke in patients with PAF, Petersen and Gotfredsen (13) reported that of 426 patients with PAF, 33% developed CAF and that the incidence of stroke tended to be higher in the first year after this development. According to Takahashi et al. (14), the incidence of stroke was 6.4% over a 10-year follow-up period in patients with PAF, whereas Kuramoto et al. (15) reported the incidence of stroke to be about 32% of that in patients with CAF (15). These findings suggest that although PAF might be a risk factor for stroke, it might not be as great a risk factor as CAF. Three mechanisms for the development of stroke in patients with AF have been proposed (22–24): 1) reduction of cerebral blood flow; 2) hemoconcentration; and 3) activation of the coagulation system. With regard to reduction of cerebral blood flow, Lavy et al. (24) reported that in patients with AF, cerebral blood flow was reduced by 5.5% to 17.5% compared with that in patients with normal sinus rhythm. As for hemoconcentration during PAF (25), it could be that secretion of vasopressin is suppressed by left atrial distention (26), and secretion of atrial

Table 3. Comparison of Fibrinocoagulation Variables Between PAF-I and PAF-II Groups and Control Subjects

	PAF-I Group (n = 11)		PAF-II Group (n = 10)		Control Group (n = 9)
	PAF Period	Non-PAF Period	PAF Period	Non-PAF Period	
Hct (%)	45.9 ± 3.91*	43.6 ± 2.90	46.0 ± 4.23*	44.0 ± 3.72	42.8 ± 3.19
Hb (g/dl)	15.3 ± 1.34†	14.2 ± 1.02	15.2 ± 1.56†	14.5 ± 1.66	13.8 ± 1.13
PT (s)	12.0 ± 0.77	11.7 ± 1.11	10.3 ± 0.98‡	10.0 ± 1.20‡	11.8 ± 0.54
aPTT (s)	32.6 ± 2.37	30.7 ± 2.67	30.4 ± 4.01	30.6 ± 3.43	30.3 ± 2.56
TAT (μg/liter)	4.62 ± 3.44	3.37 ± 2.18	8.94 ± 5.82‡§	5.12 ± 4.78	3.11 ± 1.86
Fbg (mg/dl)	229.9 ± 28.0	246.1 ± 39.8	297.8 ± 77.2†§	270.7 ± 69.9	225.7 ± 37.5
D-dimer (ng/ml)	70.2 ± 43.0	90.6 ± 79.3	220.4 ± 285.5	168.6 ± 291.0	67.2 ± 31.7
PIC (μg/ml)	0.71 ± 0.42	0.74 ± 0.31	1.02 ± 0.42	1.07 ± 0.49	1.02 ± 0.31
Beta-TG (ng/ml)	18.7 ± 5.66	17.9 ± 6.18	59.3 ± 25.7‖¶	41.5 ± 25.2†	22.8 ± 7.85
PF4 (ng/ml)	3.54 ± 1.45	3.44 ± 1.70	30.5 ± 17.7‖¶	17.8 ± 12.2‡	3.37 ± 2.26

*p = 0.07, †p < 0.05, ‡p < 0.01, ¶p < 0.001 versus Control Group. §p = 0.06, ‖p < 0.001 versus paroxysmal atrial fibrillation (PAF) period in PAF-I group (by analysis of variance). Data presented are mean value ± SD. Abbreviations as in Tables 1 and 2.

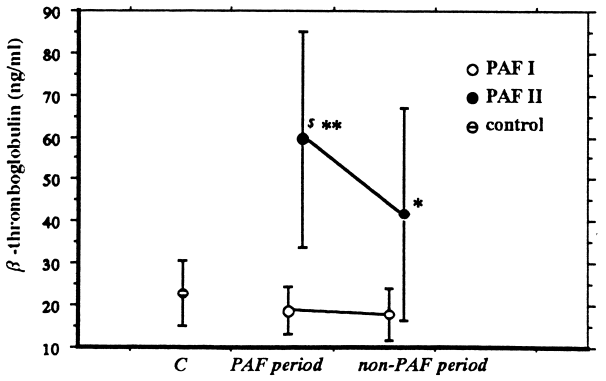


Figure 5. Comparisons of beta-thromboglobulin between PAF and non-PAF periods in the PAF groups and control subjects (C). non-PAF period = 7 days after return to sinus rhythm; PAF I = blood samples collected ≤12 h of onset of PAF; PAF II = blood samples collected >12 h of onset of PAF. *$p < 0.05$, **$p < 0.001$ versus control group. $$p < 0.001$ (ANOVA) versus PAF-I group during PAF period.

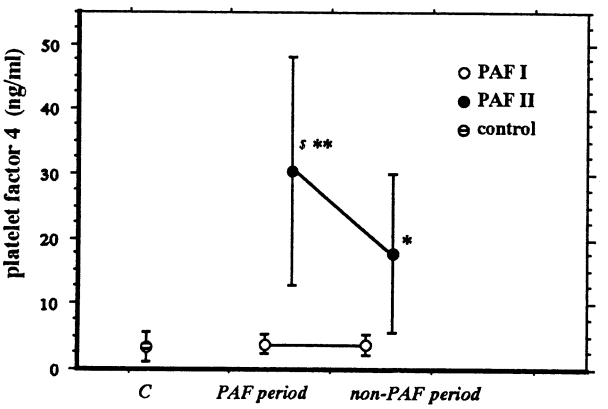


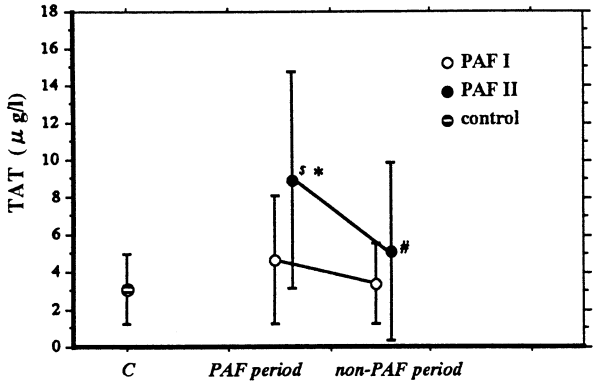
Figure 6. Comparisons of platelet factor 4 between PAF and non-PAF periods in the PAF groups and control subjects. Abbreviations and p values as in Figure 5.

natriuretic peptide is increased (27,28). In addition, the findings of several studies that examined activation of the coagulation system indicated increased levels of thrombin-antithrombin III complex and D-dimer and decreased levels of protein C (29); increased levels of fibrinogen, D-dimer, beta-thromboglobulin and platelet factor 4 (1,3,4); and increased levels of prothrombin fragment F1+2, thrombin-antithrombin III complex (6) and fibrinopeptide A (12).

However, these investigations were performed only in patients with CAF, with patients without AF as the control group. Thus, it is not clear whether these coagulation abnormalities are attributable to AF alone or to the pathologic state that underlies AF. To clarify this issue, we examined the same patients during AF and at recovery of normal sinus rhythm. Hence, we investigated the dynamics of fibrininocoagulation in the paroxysmal and nonparoxysmal states in patients with PAF. According to our previous study (16), hemoconcentration only was observed within 6 h of the onset of AF, with no evidence of hypercoagulation. However, in one patient a hypercoagulative state maintained the AF for ~20 h. Thus, we hypothesized that the duration of AF might be related to hypercoagulability. During the PAF period in the PAF-II group, beta-thromboglobulin and platelet factor 4 levels were significantly higher than those in the PAF-I group, and thrombin-antithrombin III complex and fibrinogen levels tended to be higher. Furthermore, even at 7 days after recovery of normal sinus rhythm, a significant increase in beta-thromboglobulin and platelet factor 4 levels and a reduction in prothrombin time were observed in the PAF-II group compared with these variables in the control group. Thrombin-antithrombin III complex and fibrinogen levels also tended to increase. In addition, a positive correlation was found between the duration of PAF and beta-thromboglobulin, platelet factor 4, thrombin-antithrombin III complex and fibrinogen levels. These findings indicate that acceleration of platelet activity and hypercoagulability developed 12 h (16 h on average) after the onset of PAF and were prolonged for 1 week after the recovery of normal sinus rhythm.

Acceleration of platelet activity and hypercoagulability during PAF. The development of accelerated platelet activity and hypercoagulability appears to be related to 1) irregular atrial wall motion, which causes abnormal atrial blood flow and injury to the endothelium; and 2) platelet aggregation and frequent collision of platelets, which leads to acceleration of platelet activity (30,31). Furthermore, tissue factors that are released from subendothelial tissue at the location of the endothelial injury bind to tissue factors in the presence of platelet-factor 3 to form thrombin and fibrinogen (32). This event accelerates the extrinsic coagulation cascade, resulting in the shortening of prothrombin time. The hemoconcentration that developed during AF was induced by increased secretion of atrial natriuretic peptide and decreased secretion of vasopressin (25). The increased hematocrit induced by hemoconcentration influences the acceleration of platelet thrombus formation, together with a hydrodynamic change in shear flow (30,31). This might be one reason for the acceleration of

Figure 7. Comparisons of thrombin-antithrombin III complex (TAT) between PAF and non-PAF periods in the PAF groups and control subjects. Other abbreviations as in Figure 5. *$p < 0.01$, #$p = 0.14$ versus control group. $$p = 0.06$ (ANOVA) versus PAF-I group during PAF period.



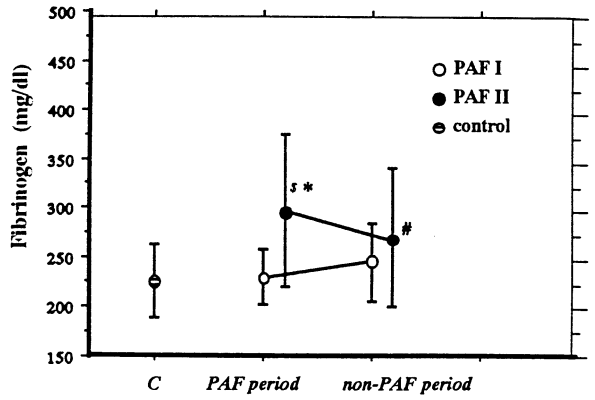


Figure 8. Comparisons of fibrinogen between PAF and non-PAF periods in the PAF groups and control subjects. Abbreviations as in Figure 5. *p < 0.05, #p = 0.09 versus control group. $p = 0.06 (ANOVA) versus PAF-I group during PAF period.

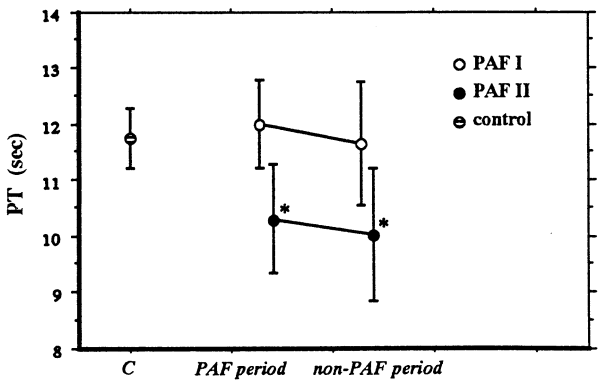
platelet activity observed in the present study. Therefore, platelet activity is increased ~12 h after the onset of PAF, aiding the formation of thrombosis. Thus, as shown in Stroke Prevention in Atrial Fibrillation trials I and II (33,34), administration of antiplatelet drugs is important to prevent the occurrence of stroke induced by AF.

Lone AF and thrombotic tendency. Lone AF has been considered a benign, low risk factor for stroke (35). A retrospective study of patients with lone AF from the Mayo Clinic (36) found that only 1.3% of patients with lone AF had a stroke during the 15-year follow-up period. Gajewski et al. (37) reported that the overall prognosis of patients with chronic AF is worse than that of patients with lone AF. Chronic AF increased mortality seven- to eightfold compared with that in control subjects with sinus rhythm, whereas paroxysmal AF increased mortality no more than twofold (37). However, evidence from the Framingham Study (38) has suggested otherwise. The risk of stroke during the 30 years of follow-up in ~5,000 subjects was 28% in patients with lone AF and 7% in control subjects without AF (38). In the present study, AF itself enhances platelet aggregation and coagulation, especially if the duration of AF was >12 h, with or without underlying disease. This finding suggests that even lone AF increases the risk of stroke if the duration of AF is >12 h.

Study limitations. The PAF-II group demonstrated considerable elevation in thrombin-antithrombin III complex, fibrinogen, D-dimer, beta-thromboglobulin and platelet factor 4 levels, even in the AF-free period. Therefore, we believe that AF >12 h in duration might cause a relatively long-term change in platelet activation and coagulation; however, we did not measure these variables a later time point to determine when they returned to normal levels or whether the fibrinolytic system was accelerated and fibrinocoagulative equilibrium was reached. Although the antiarrhythmic drugs differed in each patient with regard to type and amount, we did not examine platelet function and coagulation, which may have been affected by these agents. Therefore, further studies should address these issues.

Clinical implications. According to our results, acceleration of platelet activity and the hypercoagulative state occurred at least 12 h (16 h on average) after the onset of PAF. Thus, defibrillation should be performed within 12 h of the onset of AF, and anticoagulant therapy, including suppression of platelet activity, is required when AF continues for >12 h.

Figure 9. Comparisons of prothrombin time (PT) between PAF and non-PAF periods in the PAF groups and control subjects. *p < 0.01 versus control group.



References

1. Kumagai K, Fukunami M, Ohmori M, Kitabatake A, Kamada T, Hori N. Increased intra-cardiovascular clotting in patients with chronic atrial fibrillation. J Am Coll Cardiol 1990;16:377–80.
2. Uno M, Tsuji H, Sawada S, Toyoda T, Nakagawa M. Fibrino-peptide A (FPA) level in atrial fibrillation and effect of heparin administration. Jpn Circ J 1988;52:9–12.
3. Gustafsson C, Blomback M, Britton M, Hamsten A, Svensson J. Coagulation factors and the increased risk of stroke in non-valvular atrial fibrillation. Stroke 1990;21:47–51.
4. Shah AB, Beamer N, Caull BM. Enhanced in vivo platelet activation in subtypes of ischemic stroke. Stroke 1985;16:643–7.
5. Yamaguchi K, Furui H, Taniguchi N, Sotobata I. Plasma β-thromboglobulin and platelet factor 4 concentrations in patients with atrial fibrillation. Jpn Heart J 1986;27:481–7.
6. Asakura H, Hifumi S, Jokaji H, et al. Prothrombin fragment F1+2 and thrombin-antithrombin III complex are useful remarkers of the hypercoagulable state in atrial fibrillation. Blood Coagul Fibrinolysis 1992;3:469–73.
7. Cerebral Embolism Task Force. Cardiogenic brain embolism. Arch Neurol 1986;43:71–84.
8. William BK, Robert DA, Daniel DS. Epidemiologic-features of chronic atrial fibrillation. N Engl J Med 1982;306:1018–22.
9. Wolf PA, Dawber TR, Emerson T Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. Neurology 1978;28:973–7.
10. Sherman DG, Goldman L, Whiting RR, Jurgessen K, Kaste M, Easton JD. Thrombo-embolism in patients with atrial fibrillation. Arch Neurol 1984;41:708–10.
11. Hinton RC, Kistler JP, Fallon JT. Influence of etiology of atrial fibrillation on incidence of systemic embolism. Am J Cardiol 1977;40:509–13.
12. Britton M, Gustaffson C. Non-rheumatic atrial fibrillation as a risk factor for stroke. Stroke 1985;16:182–8.
13. Petersen P, Godtfredsen J. Embolic complication in paroxysmal atrial fibrillation. Stroke 1986;17:622–6.
14. Takahashi N, Seki A, Imataka K, Fujii J. Clinical features of paroxysmal atrial fibrillation: an observation of 94 patients. Jpn Circ J 1981;22:143–9.
15. Kuramoto K, Matsushita S, Yamanouchi H. Atrial fibrillation as a cause of myocardial and cerebral infarctions. Jpn Circ J 1984;48:67–74.
16. Sohara H, Miyahara K. Effect of atrial fibrillation on the fibrino coagulation

system: study in patients with paroxysmal atrial fibrillation. Jpn Circ J 1994;58:821–6.
17. Quick AJ. The clinical application of the liippuric acid and the prothrombin tests. Am J Clin Pathol 1940;10:222–33.
18. Pelzer H, Schwarz A, Heimburger N. Determination of human thrombin-antithrombin III complex in plasma with an enzyme-linked immunosorbent assay. Thromb Haemostasis 1988;59:101–6.
19. Amiral J, Trebaol JF, Adam A. ELISA evaluation of β-thromboglobulin and platelet factor 4. Thromb Haemostasis 1986;44 Suppl 6:376–82.
20. Rylatt DB, Blake AS, Cottis LE, Massingham DA, Fletcher WA. An immunoassay for human D-dimer using monoclonal antibodies. Thromb Res 1983;31:767–78.
21. Mimuro J, Koike Y, Sumi Y, Aoki N. Monoclonal antibodies to discrete regions in α_2-plasmin inhibitor. Blood 1987;69:446–53.
22. Friedman H, O'Connor J, Kottmeier S, Shaughnessy E, McGuinn R. The effects of atrial fibrillation on regional blood flow in the awake dog. Can J Cardiol 1987;3:240–5.
23. Petersen P, Kastrup J, Videbak R, Boysen G. Cerebral blood flow before and after cardioversion of atrial fibrillation. J Cereb Blood Flow Metab 1989;9: 422–5.
24. Lavy S, Stern S, Melamed E, Cooper G, Keren A, Levy P. Effect of chronic atrial fibrillation on regional cerebral blood flow. Stroke 1980;11:35–8.
25. Chanepa-Anson R, Williams M, Marshall JM, Lightman S, Sutton R. Mechanism of polyuria and natriuresis in atrioventricular nodal tachycardia. BMJ 1984;289:866–8.
26. Boykin J, Cadnapaphorncha P, McDonald KM, Schrier R. Mechanism of diuretic response associated with atrial fibrillation. Am J Physiol 1975;229: 1486–91.
27. Imataka K, Nakaoka H, Kitahara Y, Fujii J, Ishibashi M, Yamaji T. Blood hematocrit changes during paroxysmal atrial fibrillation. Am J Cardiol 1987;59:172–3.
28. Schiffrin EL, Gutkawska J, Kuchel O, Gantin M, Genest J. Plasma concentration of atrial natriuretic factor in a patient with paroxysmal atrial tachycardia. N Engl J Med 1985;312:1196–7.
29. Yamazaki M. Alterations of hemostatic markers in cardioembolic stroke and atherothrombotic stroke [in Japanese]. Jpn J Stroke 1991;13:385–93.
30. Baumgartner HR. The role of blood flow in platelet adhesion fibrin deposition and formation of mural thrombi. Microvasc Res 1973;5:167–79.
31. Turitto VT, Weiss HJ. Red blood cells: their role in thrombosis formation. Science 1980;207:541–43.
32. Mustard JF, Kinlough-Rathbone RL, Packham MA. Recent status of research in the pathogenesis of thrombosis. Thromb Diath Haemorrh Suppl 1974;59:157–88.
33. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation study: final results. Circulation 1991;84:527–39.
34. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in AF II study. Lancet 1994;343:687–91.
35. Close JB, Evance DW, Bailey SM. Persistent lone atrial fibrillation: its prognosis after clinical diagnosis. J R Coll Gen Pract 1979;29:547–9.
36. Kopecky SL, Gersh BJ, McGoon MD. The natural history of lone atrial fibrillation: a population-based study over three decades. N Engl J Med 1987;317:669–74.
37. Gajewski J, Singer RB. Mortality in an insured population with atrial fibrillation. JAMA 1981;245:1540–4.
38. Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation: 30 year follow-up in the Framingham Study. JAMA 1985;254:3449–53.