Prolonged Activation of Hemostatic Markers Following Conversion of Atrial Flutter to Sinus Rhythm

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Background It remains controversial whether prophylactic anticoagulation for embolism is required in patients with atrial flutter (AFL) prior to and following cardioversion as in patients with atrial fibrillation. To evaluate the potential prothrombotic state following cardioversion of AFL, concentrations of hemostatic markers were determined before and after conversion to sinus rhythm (SR).

Methods and Results In 12 patients (mean age 68 years) with AFL who underwent transesophageal echocardiography in the plasma concentrations of markers for platelet activity (platelet factor 4 (PF4) and α -thromboglobulin (α -TG)), thrombotic status (thrombin-antithrombin III complex (TAT) and prothrombin fragments 1 and 2 (F1+2)) and fibrinolytic status (D-dimer and plasmin-2-plasmin inhibitor complex (PIC)) were determined during AFL, and 3 days and 7 days after restoration of SR. Left atrial appendage (LAA) blood flow velocity was lower immediately after than before restoration of SR (29 ± 11 vs 41 ± 23 cm/s, $p < 0.05$). Three patients developed left atrial spontaneous echo contrast immediately after restoration of SR. Although the concentrations of the markers of platelet activity did not change after restoration of SR, those of TAT and PIC increased 7 days after restoration of SR as compared with during AFL ($p < 0.05$).

Conclusions AFL patients have a potential risk for thromboembolism after restoration of SR and therefore anticoagulation might be required in selected patients. (Circ J 2004; 68: 1041–1044)

Key Words: Atrial flutter; Atrial stunning; Hemostatic markers; Thromboembolism

Atrial fibrillation (AF) is a common arrhythmia and the transient left atrial dysfunction that occurs after cardioversion is associated with the formation of atrial thrombi.¹ In contrast, atrial flutter (AFL) has been traditionally considered a low risk for thromboembolism because of the more organized mechanical atrial contractions in this specific arrhythmia.^{2,3} However, studies of the effects of cardioversion on thrombogenesis in patients with AFL are few and often conflicting. Some have suggested a generally low risk for thromboembolism following cardioversion of AFL, and reported that the incidence of embolism after cardioversion of AFL was less than that following cardioversion of AF.⁴ Recovery from dysfunction to normal function by the left atrial appendage (LAA) after cardioversion may be more rapid in patients with AFL than in those with AF.⁵ On the other hand, it has been reported that the incidence of embolism after cardioversion of AFL is similar to that after cardioversion of AF,⁶ and that underlying heart disease is associated with the risk of thromboembolism after cardioversion of AFL.⁷

Elevated concentrations of the biochemical markers of coagulation and fibrinolytic activity has been well demonstrated in patients with AF,^{8,9} and this could reflect states of hypercoagulability and thrombogenesis in the left atrium (LA) and LAA. Our previous study indicated that plasma

levels of hemostatic markers in patients with AFL were similar to those in patients with sinus rhythm and lower than those in patients with AF,¹⁰ but to our knowledge, the serial changes in hemostatic markers after cardioversion of AFL have not been studied thoroughly yet. We therefore investigated whether there is a potential hypercoagulable or prothrombotic state in patients with AFL after restoration of sinus rhythm (SR) by measuring the plasma concentrations of biochemical hemostatic markers.

Methods

Study Patients

The study population consisted of 12 consecutive patients (9 men, 3 women; mean age, 68 ± 10 years) who underwent transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and determination of the concentrations of hemostatic markers at the Toyama Medical and Pharmaceutical University Hospital. The diagnosis of AFL was made from a 12-lead electrocardiogram (ECG) using the standard criteria,¹¹ and patients with AFL lasting > 7 days (10 days to 24 months, mean 6.7 ± 8.7 months) were enrolled in this study. Nine patients had common AFL and 3 had uncommon AFL at the time of the study. Seven (58%) patients had had more than 1 episode of documented paroxysmal AF previously. Patients with organic heart disease were not included. Baseline clinical characteristics including hypertension, diabetes mellitus, hyperlipidemia and embolic cerebrovascular events were determined from the medical record and routine laboratory data (Table 1). The use of oral antiplatelet or anticoagulant agents at the time of the echocardiographic studies was carefully determined. Patients with systemic illness, such as renal, hepatic,

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Table 1 Baseline Clinical Variables in Patients With AFL (n=12)

Age (years)	68±10
M/F	9/3
AF	7 (58%)
Warfarin	8 (67%)
PT-INR	1.5±0.7 (n=8)
Antiplatelet therapy	6 (56%)
Prior embolic event	1 (8%)
Hypertension	2 (17%)
Diabetes mellitus	1 (8%)
Hyperlipidemia	2 (17%)

Values are mean ±SD or number (%) of patients.

AFL, atrial flutter; AF, atrial fibrillation; PT-INR, prothrombin time-international normalized ratio.

Table 2 Serial Changes in the Echocardiographic Variables Before and After Restoration of Sinus Rhythm

	Before	After restoration of sinus rhythm		
		Within 24 h	3 days	7 days
LAD (mm)	35±8	35±5	36±6	33±6
LVDd (mm)	44±6	45±5	47±5*	47±6*
LVEF (%)	60±9	59±15	61±9	63±12
A wave (cm/s)	—	27±12	37±10†	50±12†

Values are mean ±SD.

* $p<0.05$ vs before, † $p<0.05$ vs within 24 h.

LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; A wave, mitral A wave velocity.

inflammatory, or neoplastic disease that could influence hemostatic markers, were not included in this study. Informed consent was obtained from all patients.

Echocardiography

All patients underwent TTE and TEE studies as in our previous study.^{10,12} Briefly, TTE was performed with a 2.5- or 3.75-MHz phased-array transducer connected to an ultrasound system (SSH-140A; Toshiba, Tokyo, Japan). The left atrial dimension (LAD), left ventricular end-diastolic dimension (LVDd) and left ventricular ejection fraction (LVEF) were determined from the M-mode images.¹³ To determine the serial changes in echocardiographic findings, TTE was conducted during AFL, and within 24 h, at 3 days and at 7 days after restoration of SR. The serial changes in LA function following AFL termination was assessed by pulsed Doppler interrogation of mitral inflow at the level of the mitral valve leaflet tips and A wave peak velocity. The mitral A wave velocities were averaged over 3 cardiac cycles.

TEE was performed with a 5-MHz multiplane transducer before and within 24 h of cardioversion of AFL. Each patient underwent the examination while fasting, without any premedication except for topical anesthesia of the hypopharynx with lidocaine spray. Multiple standard tomographic planes were imaged and peak LAA flow velocity (LAAPV), the presence of LA thrombi and the severity of the LA spontaneous echo contrast (LASEC) were determined.^{10,12} LASEC was diagnosed as the presence of dynamic smoke-like echoes within the LA or LAA with a characteristic swirling motion that was distinct from white noise artifact. The severity of LASEC was defined by the criteria of Fatkin et al.¹⁴ The presence of LA thrombi and SEC was determined by 2 independent observers and any discrepancy was resolved by a third observer's opinion.

Table 3 Time Course of the Plasma Concentrations of Hemostatic Markers

	Before	After restoration of sinus rhythm		p value*
		3 days	7 days	
-TG (<50 ng/ml)	71±103	46±21	47±27	
PF4 (<20 ng/ml)	31±67	17±13	12±7	
TAT (<3.0 ng/ml)	4.2±4.5	5.2±4.5	7.3±4.9	0.01
F1+2 (<1.4 nmol/L)	0.6±0.2	0.7±0.2	0.7±0.3	0.06
PIC (<0.8 µg/ml)	0.9±0.3	1.2±0.5	1.5±0.9	0.01
D-dimer (<1.0 µg/ml)	0.6±0.7	1.1±1.4	1.3±1.4	0.06

Values are mean ±SD. Figs in parentheses are normal values.

* vs before.

-TG, -thromboglobulin; PF4, platelet factor 4; TAT, thrombin-antithrombin III complex; F1+2, prothrombin fragment 1+2; PIC, plasmin-2 plasmin inhibitor complex.

Determination of Hemostatic Markers

The following hemostatic markers were determined: platelet factor 4 (PF4) and -thromboglobulin (-TG) levels as indices of platelet activation; thrombin-antithrombin III complex (TAT) and prothrombin fragments 1 and 2 (F1+2) as markers of thrombin activity; and D-dimer and plasmin-2-plasmin inhibitor complex (PIC) as indices of active fibrinolysis. Blood samples for determination of these hemostatic markers were obtained from all patients using the 2-syringe technique. An international normalized ratio of the prothrombin time (PT-INR) was also measured at each blood sample. The preparation of the blood samples and determination of the hemostatic markers were performed as in our previous studies.^{10,12,15} The hemostatic markers were determined during AFL, and 3 and 7 days after restoration of SR. All patients underwent continuous ECG monitoring during the procedure. The ECG verified the cardiac rhythm in each patient at the time of blood sampling.

Statistical Analysis

Data are presented as the mean value ±SD. Intergroup differences for continuous variables were evaluated by analysis of variance (ANOVA) for repeated measures followed by the post hoc Bonferroni test. For paired data, differences were analyzed using paired t-test and, for nonparametric data, using Fisher's exact test (Stat View, version 5.0; SAS; Cary, NC, USA). A p-value <0.05 was considered significant.

Results

Patient Characteristics

Baseline clinical characteristics are summarized in Table 1. One patient had a prior history of embolism and 8 patients were taking oral anticoagulant medication (PT-INR=1.5±0.7). Five patients were administered antiarrhythmic drugs (sotalol in 1, cibenzoline in 4) and 3 patients required treatment to control ventricular responses during AFL (calcium-channel blocker in 1; -blockers in 2). Eleven patients underwent radiofrequency ablation and the remaining 1 patient underwent pharmacological cardioversion. Dosage of warfarin was kept unchanged throughout the study period in each patient.

Echocardiographic Variables

The TTE variables are shown in Table 2. No patient had

a LVEF <40% (mean $60\pm 9\%$) or dense LASEC (grade 4) during AFL. LAA thrombus was observed in the 1 patient (8%) who had had a prior embolism. LAAPV was significantly decreased from 41 ± 23 cm/s during AFL to 29 ± 11 cm/s after restoration of SR ($p<0.05$) and LASEC became more dense 24h after restoration of SR in 3 patients (25%). Mitral A wave velocity and LVDd were gradually increased after restoration of SR, but there were no significant changes in LAD and LVEF.

Hemostatic Markers

Plasma concentrations of the hemostatic markers are summarized in Table 3. The TAT and PIC concentrations were significantly higher at 7 days after restoration of SR than during AFL: 9 patients (75%) had an abnormal TAT concentration (≥ 3.0 ng/ml) and all patients had abnormal PIC concentrations (≥ 0.8 μ g/ml) at 7 days after cardioversion. F1+2 and D-dimer also tended to increase at 7 days after restoration of SR, but the difference was of borderline significance ($p=0.06$ for both). Four patients had elevated D-dimer concentrations (≥ 1.0 μ g/ml), but none of the patients had elevated F1+2 concentrations (≥ 1.4 nmol/L) after restoration of SR. Beta-TG and PF4 did not show any significant changes after cardioversion. The patient's age affected the concentration of F1+2 at 7 days after cardioversion (ie, 0.5 ± 0.2 nmol/L in the younger patients ($n=4$, <65 years old) vs 0.8 ± 0.3 nmol/L in the elderly patients ($n=8$, ≥ 65 years old, $p=0.03$)). However, age did not affect the concentrations of the other hemostatic markers post-cardioversion.

Discussion

The major findings of the present study are as follows. First, mitral A wave velocity improved progressively after restoration of SR, although LAAPV was decreased and LASEC became more dense immediately after cardioversion, suggesting atrial stunning. Second, activation of coagulation and fibrinolysis occurred after conversion of AFL to SR and lasted at least for 1 week, although the level of activation was modest. These results suggest that patients with AFL can be in a prothrombotic state for at least 1 week after restoration of SR, even though atrial function improves progressively during this period of time.

Atrial Stunning in Patients With AFL

Grimm et al⁵ used TEE to investigate atrial function before and immediately after DC cardioversion of AF and AFL. Immediately after cardioversion, LAAPV was significantly decreased from the baseline value before cardioversion (42 ± 19 to 27 ± 18 cm/s), and new or increased SEC was found in 4 of the 19 patients with AFL. Those results are consistent with our present findings. After conversion of AFL to SR, there would be progressive disappearance of atrial stunning. Sparks et al showed peak A-wave velocities of the late diastolic filling period increasing from 13.4 ± 11.2 to 49.8 ± 10.3 cm/s at 3 weeks after radiofrequency ablation of chronic AFL, and recovery of LAA mechanical function was seen in all 15 patients by 3 weeks.¹⁶ Other investigators have used TEE to determine the serial changes in LA function and reported that LAA velocity gradually increased to the normal range by 2 weeks after ablation of AFL and that the mean mitral A-wave velocity was significantly greater at 7 days than immediately after AFL termination (from 26 to 51 cm/s).¹⁷ Our results are consistent with that finding.

Taking all the findings together, it appears that LA function is depressed immediately after conversion of AFL to SR and there are signs of atrial stunning, but there is gradual recovery within 1 or 2 weeks.

Hemostatic Markers During Atrial Stunning in Patients With AFL

The duration of anticoagulation required after cardioversion of AFL would be shorter than that required for AF because LAA function returns to normal more rapidly after cardioversion of AFL than for AF.^{5,17} We demonstrated that patients with AFL are generally not in a prothrombotic state as compared with AF,¹⁰ although other investigators have demonstrated a similar incidence of embolism after cardioversion of AFL to that of AF.⁶

It has been reported that the concentrations of hemostatic markers are increased after conversion of AF to SR.^{18,19} Our present study showed that the concentrations of the hemostatic markers for coagulation and fibrinolysis were increased after termination of AFL and remained elevated at 7 days after restoration of SR, although the mean mitral A-wave velocity, an index of mechanical function of the LA, had increased to the normal level. This suggested a modest activation of coagulation and fibrinolysis after restoration of SR, and it would disappear more slowly than the atrial stunning after termination of AFL. The atrial remodeling that occurs in AFL may account for the prolonged activation of these hemostatic markers after cardioversion; previous studies have shown that atrial endothelial damage could influence the prothrombotic state in AF,²⁰ so the duration of AFL, the patient's age and other factors also might affect the extent of atrial remodeling and thus the concentrations of hemostatic markers. Indeed, advanced age (≥ 65 years old) did affect the post-cardioversion concentrations of F1+2 in the present study.

Study Limitations

The present study is limited for several reasons. First, antithrombotic therapy might bias the results: 8 patients who had undergone anticoagulation therapy were included in this study. Although the mean INR was below the levels recommended in the guidelines,²¹ the concentrations of hemostatic markers, especially those for coagulation and fibrinolysis, might have been underestimated in those patients. Second, we evaluated hemostatic markers for 7 days after restoration of SR, but LAA function may take up to 3 weeks to recover to normal following ablation of AFL.¹⁷ Long term follow-up of the hemostatic markers is needed. Third, the number of patients with AFL who underwent TEE and serial determination of hemostatic markers was not large enough to draw a definite conclusion. Also, the method of terminating AFL (ie, antiarrhythmic drugs vs catheter ablation) could affect the mechanical function of the LA and the concentrations of hemostatic markers. This issue could not be analyzed because of the small number of patients. Lastly, 7 patients (58%) had the complication of AF in addition to AFL. Although all patients had AFL at the time of the baseline echocardiographic studies and conversion to SR, AF would have affected the mechanical function of the LA and the concentrations of hemostatic markers after restoration of SR in these patients. However, the serial changes in these variables did not differ between patients with AF and those without AF.

Although limited for these reasons, the present study indicates that impaired LAA function (ie, atrial stunning)

would activate coagulation immediately after restoration of SR in patients with AFL. Atrial mechanical function will recover progressively, but coagulation and fibrinolysis are still activated 1 week after termination of AFL. The levels of coagulation and fibrinolysis activity are only modestly increased, if present, so anticoagulation might be required for some selected patients and the duration of anticoagulation therapy after restoration of SR should be individualized according to the echocardiographic data and the concentrations of the markers post-cardioversion.

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References

1. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation-evidence for 'atrial stunning' as a mechanism of thromboembolic complications. *J Am Coll Cardiol* 1994; **23**: 307–316.
2. Narumiya T, Sakamaki T, Sato Y, Kanmatsuse K. Relationship between left atrial appendage function and left atrial thrombus in patients with nonvalvular chronic atrial fibrillation and atrial flutter. *Circ J* 2003; **67**: 68–72.
3. Santiago D, Warshofsky M, Li Mandri G, Di Tullio M, Coromilas J, Reiffel J, et al. Left atrial appendage function and thrombus formation in atrial fibrillation-flutter: A transesophageal echocardiographic study. *J Am Coll Cardiol* 1994; **24**: 159–164.
4. Arnold AZ, Mick MJ, Mazurek RP, Loop FD, Trohman RG. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or flutter. *J Am Coll Cardiol* 1992; **19**: 851–855.
5. Grimm RA, Stewart WJ, Arheart K, Thomas JD, Klein AL. Left atrial appendage 'stunning' after electrical cardioversion of atrial flutter: An attenuated response compared with atrial fibrillation as the mechanism for lower susceptibility to thromboembolic events. *J Am Coll Cardiol* 1997; **29**: 582–589.
6. Gallagher MM, Hennessy BJ, Edvardsson N, Hart CM, Shannon MS, Obel OA, et al. Embolic complications of direct current cardioversion of atrial arrhythmias: Association with low intensity of anticoagulation at the time of cardioversion. *J Am Coll Cardiol* 2002; **40**: 926–933.
7. Mehta D, Brauca L. Thromboembolism following cardioversion of 'common' atrial flutter: Risk factor and limitations of transesophageal echocardiography. *Chest* 1996; **110**: 1001–1003.
8. Lip GYH, Lip PL, Zarifis J, Watson RD, Bareford D, Lowe GD, et al. Fibrin d-dimer and -thromboglobulin as markers of thrombogenesis and platelet activation in atrial fibrillation: Effects of introducing ultra-low-dose warfarin and aspirin. *Circulation* 1996; **94**: 425–431.
9. Heppell RM, Berkin KE, McLenachan JM, Davies JA. Haemostatic and haemodynamic abnormalities associated with left atrial thrombosis in non-rheumatic atrial fibrillation. *Heart* 1997; **77**: 407–411.
10. Sakurai K, Hirai T, Nakagawa K, Kameyama T, Nozawa T, Asanoi H, et al. Left atrial appendage function and abnormal hypercoagulability in patients with atrial flutter. *Chest* 2003; **124**: 1670–1674.
11. Waldo AL, MacLean WAH, Karp RB, Kouchoukos NT, James TN. Entrainment and interruption of atrial flutter with atrial pacing: Studies in man following open heart surgery. *Circulation* 1977; **56**: 737–745.
12. Nakagawa K, Hirai T, Shinokawa N, Uchiyama Y, Kameyama T, Takashima S, et al. Relation of fibrillatory wave amplitude with hemostatic abnormality and left atrial appendage dysfunction in patients with chronic nonrheumatic atrial fibrillation. *Jpn Circ J* 2001; **65**: 375–380.
13. Henry WL, DeMaria A, Gramiak R, King DL, Kisslo JA, Popp RL, et al. Report of the American Society of Echocardiography committee on nomenclature and standards in two-dimensional echocardiography. *Circulation* 1980; **62**: 212–217.
14. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol* 1994; **23**: 961–969.
15. Nakagawa K, Hirai T, Shinokawa N, Takashima S, Nozawa T, Asanoi H, et al. Aortic spontaneous echocardiographic contrast and hemostatic markers in patients with nonrheumatic atrial fibrillation. *Chest* 2002; **121**: 500–505.
16. Sparks PB, Jayaprakash S, Vohra JK, Mond HG, Yapanis AG, Grigg LE, et al. Left atrial 'stunning' following radiofrequency catheter ablation of chronic atrial flutter. *J Am Coll Cardiol* 1998; **32**: 468–475.
17. Takami M, Suzuki M, Sugi K, Ikeda T. Time course for resolution of left atrial appendage stunning after catheter ablation of chronic atrial flutter. *J Am Coll Cardiol* 2003; **41**: 2207–2211.
18. Oltrona L, Broccolino M, Mriolini PA, Spinola A, Pezzano A, Mannucci PM. Activation of the hemostatic mechanism after pharmacological cardioversion of acute nonvalvular atrial fibrillation. *Circulation* 1997; **95**: 2003–2006.
19. Giansante C, Fiotti N, Miccio M, Altamura N, Salvi R, Guarnieri G. Coagulation indicators in patients with paroxysmal atrial fibrillation: Effects of electric and pharmacologic cardioversion. *Am Heart J* 2000; **140**: 423–429.
20. Kumagai K, Fukuchi M, Ohta J, Baba S, Oda K, Akimoto H, et al. Expression of the von Willebrand factor in atrial endocardium is increased in atrial fibrillation depending on the extent of structural remodeling. *Circ J* 2004; **68**: 321–327.
21. ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation: Executive summary. *Circulation* 2001; **104**: 2118–2150.