Relation of Fibrillatory Wave Amplitude With Hemostatic Abnormality and Left Atrial Appendage Dysfunction in Patients With Chronic Nonrheumatic Atrial Fibrillation

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Large left atrium (LA) and LA appendage (LAA) dysfunction are known to relate to cardiogenic thromboembolism, so the present study investigated the relation of the atrial fibrillatory wave (F wave) amplitude to hemostatic markers and LAA function. Transthoracic and transesophageal echocardiographic studies were performed in 82 consecutive patients with chronic, nonrheumatic atrial fibrillation (AF). Patients were divided into 2 groups according to F wave amplitude in lead V₁ on the 12-lead ECG: coarse AF (the greatest amplitude of F wave ≥ 1 mm, n=44) and fine AF (<1 mm, n=38). Plasma levels of thrombin-antithrombin III complex, D-dimer, platelet factor 4 and α -thromboglobulin were determined. Compared with patients with coarse AF, those with fine AF had lower LAA peak flow velocity (p<0.05) and higher prevalence of embolic cerebral infarction (50% vs 27%, p<0.05). Platelet activity did not differ between the 2 groups; however, plasma levels of thrombin-antithrombin III complex and D-dimer were significantly higher in patients with fine AF than in those with coarse AF (p<0.05). Multiple logistic regression analysis showed that fine AF was independently associated with cerebral embolism. Therefore, the presence of fine F wave in V₁ would be a useful marker of LAA dysfunction and hypercoagulability, and indicate a risk for cerebral embolism in patients with chronic, nonrheumatic AF. (*Jpn Circ J* 2001; 65: 375–380)

Key Words: Fibrillatory wave; Hemostatic markers; Thromboembolism

Elevation of the biochemical markers of platelet activity, coagulability and fibrinolytic activity has been recently demonstrated in patients with atrial fibrillation (AF)^{1–4} which is indicative of hypercoagulability and thrombogenesis and therefore an increased risk for embolism in patients with AF. The electrocardiographic fibrillatory wave (F wave) in AF reflects the size of the left atrium (LA), and the structural integrity and electrophysiological state of the atria.^{5–7} Recent studies have correlated rapid, repetitive and irregular emptying and filling Doppler flow patterns of the LA appendage (LAA) with atrial electrical activity in patients with AF.^{8,9} Therefore, the amplitude of the F wave on the ECG, which varies from coarse to flat-line, might reflect the LAA function in such patients.^{9,10} In particular, coarse F waves might reflect more organized atrial activity, whereas fine F waves might indicate more disorganized atrial activity with structural damage leading to a potential risk of embolism, although this relationship between F wave amplitude and prothrombotic status in patients with AF has yet to be conclusively determined.^{10,11} Low blood flow velocity in the LAA and spontaneous echo contrast on transesophageal echocardiography reflect blood stasis, and both have been frequently identified in patients

with AF who suffered from embolism.^{12–17} We therefore investigated the relationship of F wave amplitude with transesophageal echocardiography findings and hemostatic variables, in conjunction with cardiogenic embolic events, in patients with chronic, nonrheumatic AF.

Methods

Study Patients

Eighty-two consecutive patients (61 men, 21 women; mean age, 66.8 $\pm$ 1.2 years) with chronic, nonrheumatic AF, who were referred for evaluation of potential embolic risk or possible embolic source of a recent stroke, were enrolled. Chronic AF was defined as AF that had been documented by ECG and had existed for 6 months or more. The underlying cause of AF included ischemic heart disease (n=16), hypertension (n=15), hypertrophic cardiomyopathy (n=8), dilated cardiomyopathy (n=8), sick sinus syndrome (n=6), chronic lung disease (n=3), hyperthyroidism (n=2), mitral valve prolapse (n=2), and miscellaneous causes (n=4). No apparent underlying cause was identified in the remaining 18 patients. Baseline clinical characteristics, including smoking habit, diabetes mellitus and hyperlipidemia, were investigated from medical records and routine laboratory data. The use of oral antiplatelet or anticoagulant agents at the time of echocardiographic studies was carefully determined.

Echocardiography

All patients underwent transthoracic and transesophageal echocardiographic studies after giving informed consent.

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Transthoracic echocardiography was performed with a 2.5- or 3.75-MHz phased-array transducer connected to an ultrasound system (SSH-140A, Toshiba Corp, Tokyo, Japan). The LA dimension, left ventricular end-diastolic and end-systolic dimensions, and left ventricular ejection fraction were evaluated by M-mode echocardiogram according to the standards of the American Society of Echocardiography.¹⁸ Transesophageal echocardiography was performed with a 5-MHz multiplane transducer connected to the same ultrasound system. Each patient was studied in the fasting state without any premedication except for topical anesthesia of the hypopharynx with lidocaine spray.

Multiple standard tomographic planes were imaged. Subsequently, LAA peak flow velocity, presence of LA thrombus and severity of LA spontaneous echocardiographic contrast were evaluated. The presence of LA thrombus and LA spontaneous echocardiographic contrast was determined by 2 independent observers. Any difference in the determination was resolved by a third observer's opinion.

Evaluation of Left Atrial Spontaneous Echo Contrast and Left Atrial Appendage Flow

LA spontaneous echocardiographic contrast was diagnosed in the presence of dynamic smoke-like echos within the LA or LAA with a characteristic swirling motion that was distinct from white noise artifact. The severity of LA spontaneous echocardiographic contrast was defined by the criteria of Fatkin et al;¹⁶ that is, it was graded from 0 to 4+ according to the following criteria: 0 = none (absence of echogenicity), 1+ = mild (minimal echogenicity detectable only transiently during the cardiac cycle with optimal gain settings), 2+ = mild to moderate (transient spontaneous echo contrast without increased gain settings and more dense pattern than 1+), 3+ = moderate (dense swirling pattern during the entire cardiac cycle), and 4+ = severe (intense echodensity and very slow swirling patterns in the LAA, usually with similar density in the main cavity). LA appendage velocity profiles were obtained by pulsed wave Doppler interrogation at the orifice of the appendage. Peak outflow velocity signals within each R-R interval were averaged over a minimum of 6 cardiac cycles.

Left Atrial Appendage Size

The LAA was viewed from the basal short axis to determine its entire length and width.¹⁹ The maximum area of the LAA was measured with a trackball tracing the endocardial borders of the triangular extension of the LA cavity, and the area was calculated by planimetry. The length of the LAA was measured from the limbus of the upper left pulmonary vein to the apex of the LAA, and the width of the LAA orifice was calculated as the shortest line drawn from the limbus of the upper left pulmonary vein to the aorta.

Electrocardiogram

A standard 12-lead ECG was recorded within 48 h of the echocardiographic studies and all ECGs were recorded for 12 s at a conventional speed (25 mm/s) and a sensitivity (1 mV/10 mm). The ECGs were classified into coarse or fine AF according to the method of Peter et al.²⁰ F wave amplitude was measured from the upper edge of the peak to that of the trough in lead V₁ and was expressed in millimeters. Coarse AF was defined as any F waves with an amplitude equivalent to 1 mm, and fine AF as F waves less than 1 mm in amplitude. Artifactual influences on the baseline and T or U waves were carefully excluded and all classifications

were performed by 2 independent observers.

Blood Sample Measurement

Hemostatic variables were determined in 61 patients (31 patients with coarse F wave and 30 patients with fine F wave): (i) platelet factor 4 and α -thromboglobulin levels as indices of platelet activation, (ii) thrombin-antithrombin III complex as a marker of thrombin activity, and (iii) D-dimer as an index of active fibrinolysis. The blood sample was obtained using the 2-syringe technique at the time of the echocardiographic study. The initial 2–3 ml of blood was discarded and the subsequent samples were collected in a sequential manner directly into syringes containing the appropriate anticoagulant mixture and processed immediately. The anticoagulant mixtures for α -thromboglobulin and platelet factor 4 contained theophylline, adenosine, dipyridamole and sodium citrate. The mixtures of the samples for α -thromboglobulin, platelet factor 4 and anticoagulants were centrifuged at 3,000 rpm for 30 min at 4°C. For the samples for thrombin-antithrombin III complex and D-dimer, 0.2 ml of the anticoagulant trisodium citrate was added to 1.8 ml of blood and centrifugation was carried out within 2 h at 3,000 rpm for 10 min at 4°C. The supernatant plasma was separated immediately and frozen rapidly at –20°C for 24 h and subsequently stored at –80°C until assayed. Beta-thromboglobulin, platelet factor 4 and thrombin-antithrombin III complex levels were determined with enzyme immunoassay (EIA) kits and the D-dimer level with enzyme-linked immunosorbent assay (ELISA) kits (Behring Werke AG, Marburg, Germany).

Brain Computed Tomography and Magnetic Resonance Imaging

In all patients, either brain computed tomography (n=27) or magnetic resonance imaging (n=55) was performed to determine the presence of cardioembolic cerebral infarction. Cerebral embolism was diagnosed by a neurologist without any knowledge of the patient's data including F wave size. Cortical infarction was regarded as embolism, but perforating infarction (ie, infarction found in the territory of deep perforators) was excluded because this specific infarction was more likely caused by thrombosis.²¹

Statistical Analysis

Results are presented as mean $\pm$ SE. Unpaired Student's t test and Mann-Whitney 2-sample rank test were used to compare the continuous variables and nonparametric distributions, respectively. The difference in proportions between the 2 groups was tested using chi-squared test. Multivariate logistic regression analysis was performed to identify independent risk factors of prior cerebral embolism using SPSS 8.0J (Chicago, IL, USA). Explanatory variables included age, gender, hypertension, diabetes mellitus, hyperlipidemia and F wave amplitude (coarse or fine). The dependent variables were symptomatic and asymptomatic cerebral embolism. The results of the multivariate analysis are expressed as odds ratios (OR) for the comparison of risk between the 10% and 90% percentiles (with 95% confidence intervals). A p value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

The coarse AF group comprised 44 patients with the greatest F wave size of 2.3 ± 0.2 mm, and the fine AF group

Table 1 Baseline Clinical Characteristics of the 2 Groups

	Coarse AF (n=44)	Fine AF (n=38)	p value
Male/female	32/12	29/9	NS
Age (years)	64.0±1.8	70.2±1.6	<0.01
Patients ≥70 years old	15 (34%)	20 (52%)	0.09
Duration of AF (years)	5.1±1.4	6.1±1.2	NS
Hypertension	19 (43%)	14 (37%)	NS
Diabetes mellitus	7 (16%)	12 (32%)	NS
Smoking habit	24 (55%)	22 (58%)	NS
Antiplatelet	20 (45%)	16 (42%)	NS
Anticoagulation	23 (55%)	22 (58%)	NS
PT-INR	1.3±0.1	1.4±0.1	NS
Cerebral embolism	12 (27%)	19 (50%)	<0.05

Values presented as mean±SE or number (%) of patients. AF, atrial fibrillation; PT-INR, prothrombin time-international normalized ratio; NS, not significant.

Table 2 Transthoracic Echocardiographic Variables

	Coarse AF (n=44)	Fine AF (n=38)	p value
Left atrial dimension (mm)	44.2±1.3	45.5±1.5	NS
Left ventricular dimension			
End-diastole (mm)	50.8±1.2	53.5±1.5	NS
End-systole (mm)	35.5±1.4	38.8±2.0	NS
Left ventricular ejection fraction (%)	57.4±2.0	53.9±2.9	NS

Values presented are mean±SE. AF, atrial fibrillation; NS, not significant.

Table 3 Transesophageal Echocardiographic Variables

	Coarse AF (n=44)	Fine AF (n=38)	p value
LAA peak velocity (cm/s)	31.5±2.3	23.0±1.9	<0.01
LA spontaneous echo contrast	1.4±0.2	1.5±0.2	NS
LA thrombus	3 (7%)	4 (11%)	NS
LAA dimensions			
Orifice width (mm)	28.6±4.8	26.5±1.6	NS
Length (mm)	47.1±1.6	54.5±2.3	<0.01
Area (cm ²)	7.1±0.4	9.6±1.6	<0.01

Values presented as mean±SE or number (%) of patients. AF, atrial fibrillation; LAA, left atrial appendage; LA, left atrium; NS, not significant.

Table 4 Hemostatic Variables

	Coarse AF (n=31)	Fine AF (n=30)	p value
-TG (ng/ml)	76.4±8.1	92.6±11.1	NS
PF4 (ng/ml)	19.4±3.5	25.7±5.3	NS
TAT (ng/ml)	4.6±0.6	10.9±2.6	<0.05
D-dimer (ng/ml)	127.4±15.3	233.1±35.6	<0.05

Values presented as mean±SE. AF, atrial fibrillation; -TG, -thromboglobulin; PF4, platelet factor 4; TAT, thrombin-antithrombin III complex; NS, not significant.

comprised 38 patients with the greatest F wave size of 0.7±0.1 mm. The baseline clinical characteristics in the 2 patient groups are shown in Table 1. Patients with fine AF were older and tended to include more patients aged over 70 years as compared with those with coarse AF. No significant differences were found between the groups for the other clinical variables except for prevalence of cerebral embolism, both symptomatic and asymptomatic, which was significantly higher in patients with fine AF than in those with coarse AF (Table 1). Thirty-one patients (70%) from the coarse AF group and 24 (63%) from the fine AF

underwent brain magnetic resonance imaging.

Transthoracic Echocardiographic M-Mode Measurements

There were no significant differences in LA dimension, left ventricular end-diastolic and end-systolic dimensions, and left ventricular ejection fraction between the 2 groups (Table 2).

Transesophageal Echocardiographic Measurements (Table 3)

The LAA peak velocity was significantly reduced in

Table 5 Multiple Logistic Analysis of Clinical Variables Related to Cerebral Embolism

	Odds ratio	95% CI	p value
Age	0.91	0.32–2.57	0.87
Sex	1.04	0.33–3.30	0.94
Hypertension	2.19	0.82–5.88	0.12
Diabetes mellitus	1.03	0.33–3.25	0.96
Hyperlipidemia	0.91	0.27–3.06	0.88
Fine F wave	3.33	1.22–9.08	0.02

F wave, fibrillatory wave.

patients with fine AF ($p < 0.01$), but no significant differences were found in the severity of LA spontaneous echocardiographic contrast and prevalence of LA thrombus formation between the 2 groups. The area and length of the LAA were significantly larger ($p < 0.01$) and longer ($p < 0.01$), respectively, in patients with fine AF than in those with coarse AF.

Plasma Levels of Hemostatic Markers (Table 4)

Thrombin–antithrombin III complex and D-dimer were significantly higher in patients with fine AF than in those with coarse AF (both $p < 0.05$). There were no significant differences in platelet factor 4 or α -thromboglobulin between the 2 groups.

Risk for Cerebral Embolism

Multiple logistic regression analysis revealed that fine F wave was an independent clinical risk of cerebral embolism (Table 5).

Discussion

The present study revealed major new findings that are quite different from those reported previously by Li et al.¹⁰ First, the LAA was larger and its peak velocity was lower in patients with fine F wave than in those with coarse F wave, although the grade of spontaneous echocardiographic contrast and prevalence of LA thrombi did not differ between the 2 groups. Second, coagulability and fibrinolytic activity were increased in patients with fine F wave compared with those with coarse F wave, although no significant difference was found in platelet activity between the 2 groups. Finally, the prevalence of prior cerebral embolism was higher in patients with fine F wave.

LA Size and Embolism

Moss indicated that large atria are more likely to embolize than small atria²² and this has been confirmed by other investigators.^{23–26} A large, prospective study, SPAF-I, also found that LA enlargement determined from transthoracic echocardiography related to a high risk for cerebral thromboembolism,²⁶ but a relationship between stroke and enlarged LA was not shown by other investigators.^{17,27} In fact, pooled data from 3 prospective studies, BAATAF, SPAF-I and SPINAF, revealed that LA size determined by transthoracic echocardiography was not an independent risk.²⁸ As previously discussed, the lack of an association between LA size and the risk of stroke may be due, at least in part, to an underestimation of LA size when obtained by M-mode echocardiography.²⁹

In the present study, although the LA dimensions by transthoracic echocardiography did not differ between patients with fine F wave and coarse F wave, the LAA was larger in patients with fine F wave, who had a lower LAA

velocity and higher prevalence of cerebral embolism. This suggests that LAA size and function should be evaluated by transesophageal echocardiography, as well as with Doppler technique, for the risk stratification of patients with AF.

Implication of F Wave Size

The etiology of the coarse and fine F wave patterns in patients with AF is controversial. There are reports of an association between coarse F wave and hypertrophy or enlargement of the LA,^{5,6,30,31} but others do not support a relationship between F wave amplitude and LA size,^{11,32,33} and indeed the present study did not find a significant difference in the LA size between patients with coarse and fine AF.

The factors affecting F wave size should be considered: (1) atrial hypertrophy or enlargement;^{5,6,30,31} (2) degeneration of atrial myocytes resulting from underlying cardiac disease;^{5,6,33} (3) atrial fibrosis associated with aging;^{34,35} and (4) sustained AF.³⁶ In particular, previous studies have shown that LA enlargement was positively³⁶ and F wave size negatively^{34,35} related with sustained AF in patients with chronic AF. Fine F wave may be associated with atrial fibrosis and more non-uniform atrial excitement, thereby reflecting a reduction in LA contractility. In the present study, patients with fine F waves were older than those with coarse F wave. Although increased age is reported to be associated with an increase in embolic events in patients with fine F waves,³⁷ in the present study's analysis, age did not emerge as a risk for embolism.

The SPAF investigators did not find a correlation between F wave amplitude and LAA function in patients with nonrheumatic AF,¹¹ although Li et al reported that F wave size was related to LAA function in Asian people with nonrheumatic AF,¹⁰ which is totally different from our results and may be explained by differences in the duration of AF and the use of anticoagulation between the 2 studies because other clinical characteristics, such as age, gender and underlying heart diseases, did not differ.

Hemostatic Abnormalities and LAA Function

It is well established that the plasma levels of hemostatic markers are increased in patients with AF compared with those in sinus rhythm,^{1–4} and in some patients with AF, platelet activity as well as coagulability is also enhanced; for example, in AF patients with longer duration of paroxysm,³ those with thrombi in the LAA³⁹ and those showing a LAA peak velocity less than 40 cm/s.⁴⁰ In the present study, patients with fine F waves had reduced LAA peak velocity and increased coagulation activity, but not enhancement of platelet function, which might lead to an increased prevalence of cerebral embolism.

It is also established that anticoagulation with warfarin effectively reduces D-dimer,^{2,26} as well as embolic events.⁴¹

in patients with AF. Although this treatment was given in 55% of the present patients, the prevalence and intensity of anticoagulation, as expressed by the international normalized ratio of the prothrombin time, did not differ between the coarse and fine F wave groups. Therefore, antithrombotic treatment did not modify the present results.

Study Limitations

First, the definition of F wave size was arbitrary, although we used the common criteria for differentiating coarse from fine F waves.²⁰ There could be day-to-day variation of F wave size, but we determined F wave size from the ECG recorded within 48 h of transesophageal echocardiography. Second, because of the retrospective nature of the present study, F wave size, LAA function, and hemostatic variables could not be determined at the time of the embolic events. Third, the number of patients enrolled was relatively small compared with previous studies.^{12,28} In addition, the hemostatic variables were determined in approximately 75% of the study patients and therefore our conclusion on the relation of F wave size to thrombogenicity and transesophageal echocardiographic findings is limited. A prospective follow-up study with a large number of patients is required to clarify the relationship between F wave size and cerebrovascular events.

Although limited, the present study does suggest that patients with a fine F wave have a larger, dysfunctional LAA and abnormal hemostatic markers, and are at risk for cerebral embolism. Intensive anticoagulant treatment should be considered for patients with fine F waves.

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