

Echocardiographic and Hematological Variables as a Risk Factor for Stroke in Chronic Nonvalvular Atrial Fibrillation

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Abstract

The relationship between echocardiographic variables and the incidence of ischemic stroke in patients with atrial fibrillation was investigated by transthoracic and transesophageal echocardiography in 67 patients with chronic nonvalvular atrial fibrillation. Hematologic variables were also measured simultaneously, including plasma levels of D-dimer and thrombin-antithrombin III complex in these patients.

There was a prior history of ischemic stroke in 13 patients (stroke group), but not in the other 54 patients (nonstroke group). There were no significant differences in age, sex, left ventricular ejection fraction, left ventricular end-diastolic diameter, left atrial diameter or hematologic parameters between the groups. The left atrial appendage emptying flow velocity was lower in the stroke group than in the nonstroke group (21 ± 5 vs 32 ± 3 cm/sec, $p < 0.05$), and the incidence of left atrial spontaneous echo contrast was significantly higher in the stroke group than in the nonstroke group (69% vs 26%, $p < 0.01$). There was no significant difference in the incidence of left atrial thrombi between the groups (23% vs 12%).

These findings suggest that transesophageal echocardiographic variables are correlated with the risk of ischemic stroke in patients with chronic nonvalvular atrial fibrillation.

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Key Words

Atrial fibrillation, Echocardiography (transesophageal), Risk factor (arrhythmia-related), Stroke

INTRODUCTION

Atrial fibrillation in the absence of rheumatic valvular disease is associated with an increased risk of ischemic stroke¹⁻⁴). Anticoagulation with warfarin reduces the incidence of stroke in patients with nonrheumatic atrial fibrillation⁵⁻⁷), but it is associated with an increased risk of serious hemorrhage, which is an important clinical consideration because atrial fibrillation is common, especially in the elderly. Thus, criteria to identify patients sub-

ject to an increased risk of stroke are needed.

Recent studies have suggested that transesophageal echocardiography (TEE) is superior to transthoracic echocardiography (TTE) for the detection of atrial thrombus, and that spontaneous echo contrast is related to the incidence of stroke rather than thrombi in patients with nonrheumatic atrial fibrillation⁸⁻¹⁰). Coagulation-fibrinolysis abnormalities, for example thrombin-antithrombin III complex and D-dimer, have been useful for the early diagnosis and management of disseminated

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intravascular coagulation or thromboembolic disease¹¹), and also occur frequently in patients with atrial fibrillation¹²).

However, these variables have been evaluated separately, and which is more useful for managing patients with nonvalvular atrial fibrillation is still unclear. This study investigated the clinical significance of echocardiographic and hematological variables in patients with nonvalvular atrial fibrillation by performing TEE, TTE, and measurement of hematologic variables simultaneously in 67 patients nonvalvular disease.

METHODS

Study patients

We studied 67 consecutive patients, 42 men and 25 women aged 43 to 84 years (mean 68 years) with chronic nonvalvular atrial fibrillation being diagnosed between July 1993 and March 1995. Chronic nonvalvular atrial fibrillation was defined as evidence of atrial fibrillation by conventional electrocardiography on two occasions separated by at least 1 month. Patients with mitral stenosis, prosthetic heart valves, cardiomyopathy, prior and acute myocardial infarction and those receiving warfarin were excluded.

The stroke group consisted of 13 patients with a previous history of ischemic cerebrovascular stroke (mean period from stroke onset: 24.5 months) and the nonstroke group consisted of 54 patients without old ischemic cerebrovascular stroke. Patients were classified into the two groups based on previous histologic and neurologic features and the findings of brain computed tomography. The stroke group patients were diagnosed as having chronic nonvalvular atrial fibrillation when they were admitted to the hospital with ischemic cerebrovascular stroke. We excluded patients who had a history of stroke but did not have echocardiographic evidence of atrial fibrillation, and who had known esophageal disease or were unable to tolerate transesophageal study. None were receiving anticoagulant therapy. Although 22 patients were receiving antithrombotic therapy, there were no differences in the proportion of patients receiving antithrombotic therapy between the groups.

Echocardiography

TTE was performed on the same day as TEE. Standard parasternal views were obtained using a Toshiba ultrasound system (model SSH-160A,

Selected abbreviations and acronyms

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

Toshiba, Tokyo) with a 2.5 MHz phased-array transducer. We evaluated the left atrial dimension and the left ventricular ejection fraction by TTE.

Color Doppler TEE was performed after informed consent was obtained from the patient using a biplane transesophageal 5MHz transducer that interfaced with the ultrasound system. TEE parameters included the presence of left atrial appendage thrombus¹³, left atrial spontaneous echo contrast^{14,15}, systolic peak velocity of the left pulmonary vein and emptying and filling peak velocities of the left atrial appendage, which were evaluated by two independent observers. The pulmonary venous flow and left atrial appendage flow velocities were obtained using pulsed Doppler at the lowest possible filter setting (5 or 10 cm/sec). The pulmonary venous flow velocity was measured with the sample volume placed in the left upper pulmonary vein ≥ 5 mm from the origin of the pulmonary vein into the left atrium. The sample volume was placed in the left atrial appendage, just below the basis of the appendage, to measure the left atrial appendage flow velocity¹⁰. Measurements of flow velocities were recorded on a strip chart recorder at 50 and 100 mm/sec. The mean systolic velocities of the left pulmonary vein flow and the peak emptying and filling velocities of the left atrial appendage flow were obtained during 10 cardiac cycles.

Hematologic variables

The antecubital vein was punctured to obtain blood samples on the same day as the echocardiographic studies. Erythrocytes and platelets were measured using electrical impedance methods (Coulter stks analyzer, Nikken, Tokyo). Blood samples for the measurement of D-dimer were collected into tubes containing 2,000 U of heparin and 4,000 KIU of aprotinin. The tubes were centrifuged at 2,000 g for 15 min, and plasma was stored at -20°C until assayed. Plasma levels of D-dimer and thrombin-antithrombin III complex were measured by enzyme-linked immunosorbent assays^{16,17} using the LPIA-200 kit (Iatron, Tokyo) for D-dimer and the Enzygnost kit (Behring Werke, Marburg, Germany) for thrombin-antithrombin III

Table 1 Clinical and hematologic data

	Stroke group	Nonstroke group
Number of patients	13	54
Age (yr)	70±5	67±10
Sex (male/female)	10/3	32/22
Hypertension (%)	6 (46)	15 (28)
Hematocrit (%)	42.6±3.3	40.4±4.8
Platelet (10 ⁴ /μl)	19.8±4.5	20.0±4.8
D-dimer (μg/ml)	1.1±0.4	1.5±0.7
TAT(ng/ml)	1.6±0.3	2.0±0.3

TAT=thrombin-antithrombin III complex.

complex.

Statistical analysis

Values are mean ± SE. Student's unpaired *t*-tests were used to compare differences in patient age, echocardiographic and hematologic variables between groups. The χ^2 test was used to compare differences in the incidence of left atrial spontaneous echo contrast and hypertension. Fisher exact tests, when necessary, were used to compare the relationship between patient sex and the prevalence of left atrial thrombus. A level of $p < 0.05$ was accepted as statistically significant.

RESULTS

Clinical characteristics and hematologic variables

Baseline clinical characteristics were similar in both groups (Table 1). Hypertension tended to be more common in the stroke group. There were no significant differences in the hematocrit (42.6 ± 3.3% vs 40.4 ± 4.8%), the platelet count (19.8 ± 4.5 vs 20.0 ± 4.8 × 10⁴/μl), or the levels of D-dimer (1.1 ± 0.4 vs 1.5 ± 0.7 μg/ml) and thrombin-antithrombin III complex (1.6 ± 0.3 vs 2.0 ± 0.3 ng/ml) between the groups.

Transthoracic echocardiography and transesophageal echocardiography variables

There was no difference in the left atrial diameter or the left ventricular ejection fraction between the groups (Table 2).

The left atrial appendage emptying peak velocity was significantly lower in the stroke group, and the left atrial appendage filling and left pulmonary vein systolic peak velocities tended to be lower in the

Table 2 Transthoracic echocardiography and transesophageal echocardiography variables

	Stroke group	Nonstroke group
LA diameter (mm)	39 ± 5	39 ± 8
LV ejection fraction (%)	64 ± 10	65 ± 7
LAA peak flow (cm/sec)		
Emptying	21 ± 5*	32 ± 3
Filling	21 ± 6	29 ± 3
PV peak flow (cm/sec)	37 ± 5	47 ± 4
LA spontaneous echo contrast (%)	9/13 (69)**	14/54 (26)
LA thrombus (%)	3/13 (23)	7/54 (13)

* $p < 0.05$ vs nonstroke group, ** $p < 0.01$ vs nonstroke group. LA = left atrial; LV = left ventricular; LAA = left atrial appendage; PV = pulmonary vein.

nonstroke group. The incidence of left atrial spontaneous echo contrast detected by TEE was significantly higher in the stroke group, but there was no significant difference in the incidence of left atrial thrombus between the two groups. Left atrial thrombi were observed in three patients of the stroke group (23%) by TEE; two thrombi were located in the left atrial appendage and one in the left atrial cavity. Seven thrombi were observed in seven of the nonstroke group patients (13%); five thrombi were located in the left atrial appendage and two in the left atrial cavity. In patients with left atrial thrombi, the levels of D-dimer and thrombin-antithrombin III complex were significantly increased in both groups compared with patients without thrombi. However, there was no significant difference in the levels of D-dimer and thrombin-antithrombin III complex between the patients with and without spontaneous echo contrast.

DISCUSSION

There were no differences in the incidence of hypertension, or left atrial diameter and left ventricular ejection fraction between patients with and without a prior history of stroke in the patients with chronic nonvalvular atrial fibrillation in the present study, although hypertension is considered one of the most important risk factors for stroke in patients with nonvalvular atrial fibrillation¹⁸. It is possible that we failed to detect a significant association between hypertension and stroke because of the small number of patients studied. The incidence of left atrial spontaneous echo contrast was signifi-

cantly higher and the left atrial appendage emptying peak velocity was significantly lower in the stroke group. These findings suggest that left atrial spontaneous echo contrast and decreased left atrial appendage emptying peak velocity may be stronger predictors of stroke than hypertension, the left atrial diameter and the left ventricular ejection fraction. Previous studies have shown that spontaneous echo contrast is closely associated with thromboembolism in patients with rheumatic mitral valve disease, nonrheumatic atrial fibrillation or mitral valve replacement^{10,14,19}.

Spontaneous echo contrast

Spontaneous echo contrast is associated with reduced blood flow velocity, blood coagulation-fibrinolytic disorders^{13,20} and blood viscosity disorders²¹. The mechanism is unclear, but may involve increased ultrasonic backscatter after aggregation of the cellular components of blood at low shear rates¹⁴. TEE, which allows high-resolution imaging via an ultrasonic transducer inserted into the esophagus, visualizes erythrocytes as a swirling pattern of smoke-like fluid. In the present study, the left atrial appendage emptying peak velocity was significantly lower in the stroke group, in which the incidence of spontaneous echo contrast was high, suggesting that the reduced blood flow velocity in the left atrium was related to the presence of spontaneous echo contrast.

The presence of left atrial thrombi is a risk factor for stroke in patients with atrial fibrillation^{22,23}. There was no difference in the incidence of left atrial thrombi between patients with and without a history of stroke in the present study. Although no statistical significance was achieved due to the relatively small population, it is possible that microthrombi were not detected, even by TEE. The incidence of left atrial thrombus is not associated with systemic embolism in patients with nonrheumatic atrial fibrillation¹⁰. These observations suggest that stroke may not be related to the presence of left atrial thrombi in patients with chronic nonvalvular atrial fibrillation.

Hematologic variables

Coagulation-fibrinolysis abnormalities, endothe-

lial injury, circulatory abnormalities due to increased left atrial diameter, and hypercoagulability all contribute to the development of cardiac thrombi²⁴. Left atrial spontaneous echo contrast in nonvalvular patients with atrial fibrillation is related to hematocrit, fibrinogen concentration and left atrial dimension, and the hypercoagulation state contributes to thromboembolism²⁵. In the present study, there were no significant differences in the left atrial diameter, hematocrit, platelet count, or levels of thrombin-antithrombin III complex and D-dimer between the two groups. The mean interval from the onset of stroke in the stroke group was 24.5 months, so the hematologic data in the present study may not reflect the patients' hematologic status before and soon after the occurrence of stroke, although coagulation-fibrinolysis abnormalities are present at all stages in the subacute and chronic phases after stroke²⁶. We did not withdraw blood samples from the left atrium directly, and this may have caused insignificant differences in hematologic variables between the two groups, in addition to the small number of patients studied, although measurements of thrombin-antithrombin III complex and D-dimer have indicated the state of hypercoagulation as the mechanism of systemic thrombi²⁷. Despite the small number of patients, we could demonstrate that the measurement of left atrial appendage flow and detection of spontaneous echo contrast by TEE were related to a selective high risk of stroke in chronic nonvalvular atrial fibrillation, indicating that the presence of left atrial spontaneous echo contrast correlates strongly with the hypercoagulation state in left atrium.

CONCLUSIONS

The present study showed that the use of TEE to measure left atrial appendage flow and detect spontaneous echo contrast was helpful to identify patients with chronic nonvalvular atrial fibrillation with a high risk of stroke. Patients with chronic atrial fibrillation with decreased left atrial appendage emptying peak velocities appear to be the best candidates for anticoagulant treatment. Prospective studies on a large scale are needed to confirm our findings.

要 約

非弁膜症性慢性心房細動患者における脳梗塞発症危険因子：
心エコー図および血液学的検討宇随 弘泰 李 鍾大 清水 寛正 杉山太枝子
中野 顯 浜田 敏彦 上田 孝典

慢性心房細動患者における脳梗塞発症に及ぼす因子について検討する目的で、非弁膜症性慢性心房細動患者67例を対象とし、経胸壁心エコー図法にて左心房径計測、経食道心エコー図法にて左房内血栓、もやもやエコーの有無を検索し、左心耳流入速度、左肺静脈左房内流入速度を計測した。同時期にヘマトクリット、血小板、トロロンビン・アンチトロロンビンⅢ、D-dimer値を測定し、対象を症候性脳梗塞の既往の有無により2群に分け、各計測因子を比較検討した。

脳梗塞の既往のある有症候性群は13例(19.4%)あり、既往のない無症候性群(54例)との間に年齢、性別、左心房径、左室駆出率、左室拡張期径、血液学検査所見に有意差をみなかった。左心耳流出速度は 21 ± 5 vs 32 ± 3 cm/sec ($p < 0.05$)、左心房内もやもやエコーの頻度は有症候性群において13例中9例(69%)で、無症候性群54例中14例(26%)より有意に高頻度であった($p < 0.01$)。心房内血栓は各群それぞれ3例(23%)、7例(13%)で、有意差を認めなかった。

脳梗塞発症群でもやもやエコーの存在が有意に多く、左心耳血流が低下していることが示され、左心房における血流の鬱滞が脳梗塞発症に関与することが示唆された。

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