Effect of Low-Intensity Warfarin Therapy on Left Atrial Thrombus Resolution in Patients With Nonvalvular Atrial Fibrillation

— A Transesophageal Echocardiographic Study —

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The presence of left atrial thrombus (LAT) is associated with an increased risk of embolic stroke. However, it has yet to be established definitively whether low-intensity warfarin therapy (INR: 1.5–2.0) can prevent LAT formation in patients with nonvalvular atrial fibrillation (NVAF). The present study analyzed the clinical and transesophageal echocardiography (TEE) features of 123 such patients to identify risk factors for LAT formation and the efficacy of prophylactic low-intensity warfarin therapy. Left atrial thrombi were found in 35 patients (28%) in whom systemic hypertension (49% vs 23%; $p<0.01$) and ischemic heart disease (17% vs 3%; $p<0.01$) were more frequent. Left ventricular ejection fraction ($54\pm14\%$ vs $60\pm11\%$; $p<0.05$), left ventricular end-diastolic dimension (51 ± 7 mm vs 48 ± 5 mm; $p<0.05$), spontaneous echo contrast (2.2 ± 0.7 vs 1.4 ± 0.9 ; $p<0.01$), left atrial diameter (50 ± 6 mm vs 43 ± 7 mm; $p<0.01$), left atrial appendage blood velocity (22.3 ± 8.7 cm/s vs 37.2 ± 21.5 cm/s; $p<0.01$) and the incidence of left ventricular hypertrophy (37% vs 15%; $p<0.01$) were also significantly different between the groups. Fourteen patients received continuous warfarin therapy (target INR: 1.5–2.0) and on the follow-up TEE study the left atrial thrombus resolved in 10 (71%). There were no thromboembolic events or major hemorrhagic complications in these patients, so it was concluded that low-intensity warfarin therapy is efficacious in treating LAT formation in patients with NVAF. (*Jpn Circ J* 2001; 65: 271–274)

Key Words: Atrial fibrillation; Left atrial thrombus; Low-intensity warfarin therapy; Transesophageal echocardiography

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, the incidence of which increases with age,^{1,2} as does the percentage of strokes attributable to AF. The increased incidence of stroke associated with AF is presumed to be caused by cardiogenic embolism originating from left atrial thrombus (LAT).^{3–5} A number of factors are believed to be responsible for left atrial thrombus formation and clinical and transthoracic echocardiographic abnormalities have been identified that stratify embolic stroke risk.^{6,7}

Transesophageal echocardiography (TEE) has a high sensitivity for the detection of LAT.^{8–11} Left atrial spontaneous echo contrast is frequently identified when using TEE in patients with AF^{12–15} and is believed to reflect blood stasis and, therefore, to predict thrombus formation.¹⁶ It is also associated with an increased thromboembolic risk in patients with AF.¹⁷ Although several studies have demonstrated the presence of LAT in patients with AF,^{18–20} its prevalence and clinical significance in the setting of AF are not known.

Several randomized clinical trials have shown that in patients with AF, warfarin therapy decreases the risk of stroke, but there are 2 problems with full-dose conventional warfarin therapy; namely, inconvenience and safety. In Japanese elderly patients, the frequency of severe bleeding complications in the conventional-intensity group (target international normalized ratio (INR): 2.2–3.5) is significantly higher than that in the low-intensity group (target INR: 1.5–2.1);²³ and the efficacy of low-intensity warfarin therapy alone is poorly defined.

The aims of this study were to determine the incidence of LAT formation in patients with nonvalvular AF (NVAF), to understand the risk factors associated with LAT formation, and to examine the effect of low-intensity warfarin therapy (INR: 1.5–2.0) in decreasing the incidence of LAT formation in Japanese patients with NVAF.

Methods

Study Population

Between July 1995 and March 1999, a total of 123 patients with chronic NVAF underwent TEE. Chronic AF was defined as AF persisting more than 30 days as documented by serial electrocardiography. The group included 97 men and 26 women with a mean age of 65 years (range, 31–86). The underlying etiologies of AF were systemic hypertension (n=37), heart failure (n=22), ischemic heart disease (n=9), hyperthyroidism (n=4), and diabetes mellitus

(Received June 28, 2000; revised manuscript received December 15, 2000; accepted December 21, 2000)

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Table 1 Clinical Characteristics in Patients With and Without Left Atrial Thrombus (LAT)

	LAT		<i>p</i> value
	Present (n=35)	Absent (n=88)	
Age (years)	66±8	64±11	0.1913
Gender (M/F)	27/8	70/18	0.7684
Hypertension	17 (49%)	20 (23%)	0.0028
Diabetes mellitus	3 (9%)	7 (8%)	0.8725
Heart failure	9 (26%)	13 (15%)	0.1278
Ischemic heart disease	6 (17%)	3 (3%)	0.0068
Hyperthyroidism	0 (0%)	4 (5%)	0.2062

Data are presented as the mean value±SD or number of patients.

Table 2 Echocardiographic Parameters in Patients With and Without Left Atrial Thrombus (LAT)

	LAT		<i>p</i> value
	Present (n=35)	Absent (n=88)	
Age (years)	66±8	64±11	0.1913
Gender (M/F)	27/8	70/18	0.7684
LAD (mm)	50±6	43±7	0.0004
Spontaneous echo contrast	2.2±0.7	1.4±0.9	0.0001
Left atrial appendage flow (cm/s)	22.3±8.7	37.2±21.5	0.0002
LVEDD (mm)	51±7	48±5	0.0226
LVEF (%)	54±14	60±11	0.0376
LVH	13 (37%)	13 (15%)	0.0014

Data are presented as the mean value±SD or number of patients. LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

(n=10). Forty patients (33%) had no identifiable cause for AF and were considered to have lone AF. At the time of the initial TEE study, no patient had received warfarin or antiplatelet agents.

Echocardiography

All the echocardiographic studies were performed using both the transthoracic and transesophageal approaches. Transthoracic studies were performed with an ultrasound system (Aloka SSD-2200) equipped with a 2.5 or 3.5 MHz phased transducer. Multiple standard views were obtained in all patients. M-mode echocardiographic measurements were obtained according to the American Society of Echocardiography recommendations²¹ and the left ventricular ejection fraction (LVEF) was calculated using the method of Teichholz et al²². Five consecutive beats were averaged for all M-mode measurements. Left ventricular hypertrophy was considered present if the thickness of both septal and posterior walls was more than 11 mm. Transesophageal echocardiography was performed using a 5.0 MHz multiplane imaging transducer (UST-5280S-5). All patients fasted for at least 4 h beforehand; topical pharyngeal anesthesia was administered before the insertion of the transesophageal probe and the procedure was tolerated well by all of the patients without any complications.

Left atrial thrombus was diagnosed by the presence of a well-circumscribed echogenic mass in the left atrial cavity or appendage. Particular care was taken to differentiate thrombus from pectinate muscles in the left atrial appendage. Pulsed wave Doppler ultrasound was used to estimate peak antegrade (emptying) velocity of blood flow in the left atrial appendage. Left atrial spontaneous echo contrast was defined as the presence of a dynamic cloud of amorphous echoes swirling slowly in the atrial cavity. Left atrial spontaneous echo contrast was graded as mild (1), moderate (2) or severe (3). When echo contrast was absent with standard

gain and compression settings, the settings were systematically increased to increase the sensitivity of detection. However, efforts were taken to avoid noise artifact. Subsequently, optimal gain and compression settings were determined empirically and used throughout the examination. The presence or absence of left atrial spontaneous echo contrast and thrombus was determined by 2 independent observers. When discrepancies occurred, the video tape was reviewed until a consensus was reached.

Protocol for Follow-up Studies

After the initial TEE study, patients who were found to have a LAT were encouraged to undergo follow-up TEE studies and they received warfarin therapy during the follow-up period. To evaluate the effect of warfarin therapy on the resolution of the LAT, the maximum cross-sectional area of the LAT was measured from the TEE images. The patients receiving warfarin were examined every 1 month and the dosage was adjusted to maintain an INR of 1.5–2.0. Because the goal of this study was to understand the effect of low-intensity warfarin therapy, the end point was any change in the LAT on the follow-up TEE studies.

Statistical Analysis

Results are expressed as the mean±SD unless otherwise indicated. Continuous variables were compared with unpaired or paired Student's *t* test when appropriate. Categorical variables were compared using a chi-square test with Yate's correction. A *p* value <0.05 was considered statistically significant.

Results

Left Atrial Thrombus

Thirty-five LAT were found in 35 of the 123 patients (28%) by TEE. The clinical characteristics of the patients

Table 3 Clinical and Echocardiographic Characteristics of the 14 Patients who Maintained the Target INR

	LAT		<i>p</i> value
	Resolution (n=10)	No change (n= 4)	
Age (years)	64±7	73±6	0.0552
Gender (M/F)	8/2	2/2	0.2617
Hypertension	5	3	0.3932
Ischemic heart disease	3	1	0.8516
LVEDD (mm)	52±8	51±13	0.9390
LVEF (%)	56±10	55±10	0.8587
LVH	4	2	0.7782
LAD (mm)	52±5	49±8	0.3079
Spontaneous echo contrast	2.3±0.7	2.3±1.0	0.9128
Left atrial appendage flow (cm/s)	21.7±6.2	23.8±9.6	0.6426
INR	1.58±0.14	1.70±0.28	0.3634
2.01–2.10 (n)	0	1	
1.50–2.00 (n)	9	3	
1.40–1.49 (n)	1	0	

Data are presented as the mean value±SD or number of patients. LAT, left atrial thrombus; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LAD, left atrial dimension; INR, international normalized ratio.

Fig 1. (A) Transesophageal echocardiography shows the thrombus in the left atrial appendage (LAA) of a patient with nonvalvular atrial fibrillation. (B) After beginning warfarin therapy, the thrombus has resolved.

with and without LAT are summarized in Table 1. Systemic hypertension (49% vs 23%; $p<0.01$) and ischemic heart disease (17% vs 3%; $p<0.01$) were more prevalent in patients with LAT. The prevalence of heart failure, hyperthyroidism, and diabetes mellitus were similar in the 2 groups. The echocardiographic parameters of patients with and without LAT are summarized in Table 2. The left ventricular ejection fraction was significantly lower in patients with LAT ($54\pm14\%$ vs $60\pm11\%$; $p<0.05$). Spontaneous echo contrast was present in more patients with LAT (2.2 ± 0.7 vs 1.4 ± 0.9 ; $p<0.01$). Left atrial diameter (50 ± 9 mm vs 43 ± 7 mm; $p<0.01$), blood velocity within the left atrial appendage (22.3 ± 8.7 cm/s vs 37.2 ± 21.5 cm/s; $p<0.01$), left ventricular end-diastolic dimension (51 ± 7 mm vs 48 ± 5 mm; $p<0.05$), and left ventricular hypertrophy (33% vs 13%; $p<0.01$) also differed significantly between the 2 groups.

Effect of Low-Intensity Warfarin Therapy on LAT Resolution

The follow-up period in 17 patients with LAT ranged from 1 to 18 months (mean, 7 months). All 17 patients had a follow-up TEE study. During the study period, warfarin was continuously administered and the target INR maintained in 14 patients. The clinical and echocardiographic characteristics of these 14 patients are summarized in Table 3. We observed resolution of the LAT in 10 patients (71%) (Fig 1): complete thrombus resolution in 7 patients (50%) and partial resolution in 3 patients (21%). Patients without resolution of the LAT tended to be older, but the difference was not statistically significant. Other clinical and echocardiographic characteristics of patients with reso-

lution of the LAT and those without resolution were similar. There were no thromboembolic events or major hemorrhagic complications in the patients receiving warfarin during the follow-up period.

Discussion

Patients with AF have a 5-fold greater risk of systemic embolization compared with those without AF³ and it is believed that the increased incidence of thromboembolism is mainly because of thrombus formation in the left atrium^{4,5}

Thrombus Formation

In the present study, TEE found a LAT in 28% of patients with NVAf, a prevalence that is similar to that in the study by Brown et al¹⁸ who observed LAT in 27% of patients with nonrheumatic AF. In the preliminary report of the ELAT study,¹⁹ LAT were detected in 12 of 276 (4%) patients with chronic or intermittent AF without a history of embolic events. In contrast, our study excluded patients with intermittent AF.

It is important to identify the subgroup of patients who are likely to have TEE-detectable LAT based on their clinical data and transthoracic echocardiographic scans. Left atrial spontaneous echo contrast was observed in almost all of the patients with LAT and although the pathogenesis of spontaneous echo contrast remains controversial, it is usually observed under conditions that favor blood stasis in the left atrium. Spontaneous echo contrast is likely a precursor of LAT formation in the setting of AF. An enlarged left atrium is also associated with the presence of LAT in patients with AF. In keeping with the results of Brown et

al,¹⁸ patients with LAT in the present study had a significantly lower left ventricular ejection fraction than those without thrombus. Left ventricular hypertrophy was also associated with the presence of LAT. These findings suggest that reduced left ventricular contractility and relaxation impede left ventricular inflow and may predispose to thrombus formation as well as blood stasis in the left atrium.

Therapy

During the study period, warfarin was continuously administered and the target INR was achieved in 14 patients. Resolution of the LAT occurred in 71% of these patients. It is already known that anticoagulation with warfarin is an effective thromboprophylaxis in patients with AF²⁴ but the results of SPAF-II suggest that the risk of intracranial hemorrhage increases with a high INR (INR: 2.5–4.0). This potential risk may bias physicians against the use of anticoagulation in patients in whom compliance and therapeutic monitoring are problematic. The SPAF-III trial was terminated before the planned endpoint because anticoagulation with adjusted-dose warfarin (INR: 2–3) was found to be superior for the prevention of primary events than the fixed-dose combination of low-intensity warfarin therapy (INR: 1.2–1.5) and aspirin.²⁵ Therefore, efforts are being directed toward finding better and safer methods of providing thromboprophylaxis for such patients. Aspirin and simple, ultra-low-intensity warfarin therapy or low-intensity warfarin therapy regimens are being evaluated as alternatives to conventional full-dose warfarin.

Previous studies have identified the ability of warfarin therapy to reduce the risk of stroke. According to our study, it seems that low-intensity warfarin therapy (INR: 1.5–2.0) not only prevents the occurrence of ischemic stroke and major bleeding events, but also reduces the size of intracardiac thrombus, and is an important factor to consider when treating elderly patients who are at risk of hemorrhagic complications.

References

1. Wolf PA, Abbott RD, Kannel WB: Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991; **22**: 983–988
2. Aronow WS: Correlation of arrhythmias and conduction defects on the resting electrocardiogram with new cardiac events in 1153 elderly patients. *Am J Noninvasive Cardiol* 1991; **5**: 88–90
3. Wolf PA, Dawber TR, Thomas HE, Kannel WB: Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham Study. *Neurology* 1978; **28**: 973–977
4. Halperin JL, Hart RG: Atrial fibrillation and stroke: New ideas, persisting dilemmas. *Stroke* 1998; **19**: 937–941
5. Hinton RC, Kistler JP, Fallon JT, Friedlich AL, Fisher CM: Inference of etiology of atrial fibrillation on incidence of systemic embolism. *Am J Cardiol* 1977; **40**: 509–513
6. Stroke Prevention in Atrial Fibrillation Investigators: Predictors of thromboembolism in atrial fibrillation. I. Clinical features of patients at risk. *Ann Intern Med* 1992; **116**: 1–5
7. Stroke Prevention in Atrial Fibrillation Investigators: Predictors of thromboembolism in atrial fibrillation. II. Echocardiographic features of patients at risk. *Ann Intern Med* 1992; **116**: 6–12
8. Aschenberg W, Schluter M, Kremer P, Schroder E, Siglow V, Bleifeld W: Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. *J Am Coll Cardiol* 1986; **7**: 163–166
9. Pearson AC, Nagelhout D, Castello R, Gomez CR, Labovitz AJ: Atrial septal aneurysm and stroke: A transesophageal echocardiographic study. *J Am Coll Cardiol* 1991; **18**: 1223–1229
10. Hausmann D, Mugge A, Becht I, Daniel WG: Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. *Am J Cardiol* 1992; **70**: 668–672
11. Castello R, Pearson AC, Labovitz AJ: Prevalence and clinical implications of atrial spontaneous echo contrast in patients undergoing transesophageal echocardiography. *Am J Cardiol* 1990; **65**: 1149–1153
12. Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF: Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *J Am Coll Cardiol* 1994; **24**: 755–762
13. Tsai LM, Chen JH, Fang CJ, Lin LJ, Kwan CM: Clinical implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *Am J Cardiol* 1992; **70**: 327–331
14. Tsai LM, Chen JH, Lin LJ, Yang YJ: Role of transesophageal echocardiography in detecting left atrial thrombus and spontaneous echo contrast in patients with mitral valve disease or non-rheumatic atrial fibrillation. *J Formosan Med Assoc* 1990; **89**: 270–274
15. Black IW, Hopkins AP, Lee LCL, Walsh WF: Left atrial spontaneous echo contrast: A clinical and echocardiographic analysis. *J Am Coll Cardiol* 1991; **18**: 398–404
16. Sigel B, Coelho JC, Spigos DG, Flanigan DP, Schuler JJ, Kasprisin DO, et al: Ultrasonography of blood during stasis and coagulation. *Invest Radiol* 1981; **16**: 71–76
17. Daniel WG, Nellessen U, Schroder E, Nonnast-Daniel B, Bednarski P, Nikutta P, et al: Left atrial spontaneous echo contrast in mitral valve disease: An indicator for an increased thromboembolic risk. *J Am Coll Cardiol* 1988; **11**: 1204–1211
18. Brown J, Sadler DB: Left atrial thrombus in non-rheumatic atrial fibrillation: Assessment of prevalence by transesophageal echocardiography. *Int J Card Imaging* 1993; **9**: 65–72
19. Stollberger C, Bachl C, Kronik G, Chnoup P: Embolism in left atrial/appendage thrombi (ELAT). *Circulation* 1991; **84**(Suppl II): 450
20. Manning WJ, Silverman DI, Keighley CS, Oettgen P, Douglas PS: Transesophageal echocardiography facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: Final result of a prospective 4.5-year study. *J Am Coll Cardiol* 1995; **25**: 1354–1361
21. Sahn DJ, DeMaria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978; **58**: 1072–1083
22. Teichholz LE, Kreulen T, Herman MV, Gorlin R: Problems in echocardiographic volume determinations: Echocardiographic–angiographic correlations in the presence or absence of asynergy. *Am J Cardiol* 1976; **37**: 7–11
23. Yamaguchi T: Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation. *Stroke* 2000; **31**: 817–821
24. Lowe GDO: Antithrombotic treatment and atrial fibrillation. *BMJ* 1992; **305**: 1445–1446
25. Adjusted-dose warfarin therapy versus low-intensity, fixed-dose warfarin therapy plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; **348**: 633–638