Association of Follow-up Change of Left Atrial Appendage Blood Flow Velocity With Spontaneous Echo Contrast in Nonrheumatic Atrial Fibrillation*

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Study objectives: To evaluate the time-related change of left atrial (LA) appendage flow velocity in chronic atrial fibrillation (AF) by follow-up transesophageal echocardiography (TEE) and to investigate its association with the occurrence of LA spontaneous echo contrast.

Design: Prospective follow-up study.

Setting: University-based, tertiary referral medical center.

Patients: Forty-seven patients with chronic nonrheumatic AF.

Interventions: All studied patients underwent both a baseline and follow-up TEE during a mean period of 13 ± 7 months.

Measurements and results: Baseline TEE revealed that LA spontaneous echo contrast was present in 28 patients (group 1) and was absent in 19 patients (group 2). The LA appendage flow velocity profiles at baseline were significantly lower in group 1 than in group 2; on follow-up, the appendage flow velocities decreased significantly in group 2, but were not significantly changed in group 1. Follow-up TEE revealed that spontaneous echo contrast was persistent in all group 1 patients. In group 2, LA spontaneous echo contrast was newly observed in 9 patients (group 2A) but was persistently absent in 10 patients (group 2B). In group 2A, all of the LA appendage flow velocity profiles decreased significantly at the follow-up study. In group 2B, however, only LA appendage inflow velocity integral showed significant decrease on follow-up; there were no significant changes in LA appendage outflow velocity indexes and peak inflow velocity.

Conclusions: LA appendage flow velocity may decrease with time in some patients with AF, and this change is associated with a new occurrence of LA spontaneous echo contrast. For patients without LA spontaneous echo contrast, serial follow-up of the LA appendage flow velocity profiles may be useful for predicting future development of spontaneous echo contrast. Once LA spontaneous echo contrast occurs in AF patients, it tends to persist with time and the LA appendage is usually under a persistently low flow state.

Key words: atrium; fibrillation; thrombosis

Abbreviations: AF = atrial fibrillation; LA = left atrial; TEE = transesophageal echocardiography

L left atrial (LA) spontaneous echo contrast has been proposed as an important cardioembolic source in patients with nonrheumatic atrial fibrillation (AF).1–3 This echo phenomenon is caused by LA blood stasis, and its presence is related to a variety of hemodynamic and hematologic factors. In view of the well-known predilection of LA appendage for thrombus formation, the LA appendage contractile function as assessed by transesophageal Doppler echocardiography is believed to have important implications for the development of LA thrombus in chronic AF.4,5 In support of this hypothesis, previous studies have also shown that patients with LA spon-
taneous echo contrast have a lower LA appendage flow velocity than patients without spontaneous echo. However, without serial transesophageal echocardiography (TEE), the potential change of the appendage flow velocity with time is unknown and the association of impaired LA appendage function with spontaneous echo contrast cannot be well established in a prospective manner. A recent follow-up study has shown that, with serial TEE, patients with chronic AF that do not initially have LA spontaneous echo contrast may subsequently have an occurrence of this finding. The purpose of this study was to evaluate the change of LA appendage flow velocity with time by follow-up TEE and to investigate its association with the occurrence of spontaneous echo contrast in chronic nonrheumatic AF.

**Materials and Methods**

**Study Population**

This study consisted of a total of 47 patients with chronic nonrheumatic AF who underwent both a baseline and follow-up TEE during a mean ± SD study period of 13 ± 7 months (range, 6 to 33). There were 37 men and 10 women, with a mean ± SD age of 64 ± 8 years (range, 43 to 79). All patients had an AF rhythm that was persistent for >30 days as documented by serial ECG, and none had physical or echocardiographic evidence of rheumatic mitral stenosis or prosthetic mitral valve. The underlying etiologies of AF included hypertension (n = 24), dilated cardiomyopathy (n = 8), ischemic heart disease (n = 2), hyperthyroidism (n = 2), nonrheumatic valvular disease (n = 2), and hypertrophic cardiomyopathy (n = 1). The remaining eight patients were considered to have lone AF. At the time of the study, 17 patients (36%) had a history of thromboembolism. Of these, seven patients had ischemic stroke, eight patients had transient ischemic attack, and the remaining two had both ischemic stroke and peripheral embolism. All patients gave informed consent before enrollment.

**Echocardiography**

Both transthoracic and transesophageal echo studies were performed during baseline and follow-up examinations. Transthoracic echocardiography was performed with a commercially available ultrasound system (Sonos 500 or Sonos 1500; Hewlett-Packard; Andover, MA), using a 2.0-MHz or 2.5-MHz phased-array transducer. M-mode echocardiographic measurements were made according to the recommendation of the American Society of Echocardiography, and five consecutive beats were averaged. The left ventricular ejection fraction was calculated using the method of Teichholz et al. Mitral regurgitation was evaluated by color flow imaging and was graded as mild, moderate, or severe. TEE was performed with a 5-MHz monoplane (n = 12) or a 5-MHz multiplane (n = 35) probe (models 21362A and 23164A, respectively; Hewlett-Packard). For each subject, all follow-up studies were performed using the same ultrasound imaging system and the same transesophageal probe as was used in the baseline studies. LA spontaneous echo contrast was diagnosed by the presence of the dynamic smoke-like echo in the LA cavity or appendage, and particular care was taken to differentiate a thrombus from the pectinate muscles in the atrial appendage. LA appendage flow velocity profiles were obtained by pulsed-wave Doppler echocardiography with sample volume placed at the orifice of appendage. The peak outflow and inflow velocity waves within each R-R interval were measured and averaged over a minimum of six consecutive cardiac cycles. When the multiplane transesophageal probe was used in the baseline study, the angulation of the image plane was adjusted to obtain the optimal flow velocity signals, and the same angulation setting was used in the follow-up study whenever possible. During the follow-up period, 17 patients were placed on warfarin therapy and 12 patients were placed on aspirin therapy.

**Statistical Analysis**

Results are expressed as mean ± SD. Continuous variables were compared with unpaired or paired Student’s t test when appropriate. Categorical variables were compared using χ² test with Yates correction. A p value < 0.05 was considered statistically significant.

**Results**

**Patient Characteristics and Follow-up Echocardiographic Variables**

Baseline TEE revealed that LA spontaneous echo contrast was present in 28 patients (group 1) and was absent in 19 patients (group 2). Table 1 lists the baseline clinical variables and follow-up echocardiographic data of these two groups. LA thrombus was observed in four patients in group 1 but in no patients in group 2. Group 1 patients were more frequently associated with a history of thromboembolism. The age, duration of AF, and baseline echocardiographic variables including LA dimension, left ventricular ejection fraction, and prevalence of significant mitral regurgitation were not significantly different between groups. Baseline data revealed that LA appendage outflow and inflow velocities and velocity integrals were significantly lower in group 1 patients than in group 2 patients. Follow-up echocardiography was performed after a mean ± SD period of 13 ± 7 months in group 1 and of 14 ± 7 months in group 2. In both groups, there were no significant changes in LA dimension, left ventricular ejection fraction, or severity of mitral regurgitation between baseline and follow-up studies. However, when follow-up data were compared between groups, the LA dimension was higher and the left ventricular ejection fraction was lower in group 1 than in group 2. In group 2, there were significant decreases in the LA appendage outflow, inflow velocities, and velocity integrals on follow-up echocardiography, but none of these LA appendage flow profiles was significantly changed in group 1.
Follow-up Changes of LA Spontaneous Echo Contrast, Thrombus, and Thromboembolic Events

During follow-up period, all patients in group 1 were receiving antithrombotic therapy: 17 patients were receiving warfarin, and the remaining 11 patients were receiving aspirin. In group 2, only one patient was receiving aspirin and none were receiving warfarin. Follow-up TEE revealed that LA spontaneous echo contrast was persistent in all patients in group 1. In group 2, LA spontaneous echo contrast was newly observed by follow-up study in 9 patients (group 2A) and was persistently absent in 10 patients (group 2B). All four patients with LA thrombus were treated with warfarin, and complete resolution of all the thrombi was observed on follow-up examinations. During the study period, only three patients developed transient ischemic attack. Of these, two patients were in group 1 and one was in group 2.

Association of LA Appendage Flow Changes With Occurrence of Spontaneous Echo Contrast

The clinical and echocardiographic variables in groups 2A and 2B are listed in Table 2. The age, duration of AF, follow-up period, and baseline echocardiographic data including LA dimension, left ventricular ejection fraction, and prevalence of significant mitral regurgitation were not significantly different between these two groups. In both groups, the LA dimension, left ventricular ejection fraction, and severity of mitral regurgitation were not signifi-

Table 1—Baseline Variables and Follow-up Echocardiographic Data in Patients With and Without LA Spontaneous Echo Contrast on Initial TEE*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1, n = 28</th>
<th>Group 2, n = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>65 ± 9</td>
<td>65 ± 7</td>
</tr>
<tr>
<td>Duration of AF, yr</td>
<td>4.6 ± 3.1</td>
<td>4.6 ± 5.3</td>
</tr>
<tr>
<td>History of embolism</td>
<td>16 (57)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>LA thrombus</td>
<td>4 (14)</td>
<td>0</td>
</tr>
<tr>
<td>LA dimension, mm</td>
<td>42 ± 6</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>53 ± 14</td>
<td>53 ± 15</td>
</tr>
<tr>
<td>Moderate or greater mitral regurgitation</td>
<td>6 (21)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>LAAO velocity, cm/s</td>
<td>16 ± 7</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>LAAO velocity integral, cm</td>
<td>1.0 ± 0.4</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>LAAI velocity, cm/s</td>
<td>16 ± 7</td>
<td>14 ± 6</td>
</tr>
<tr>
<td>LAAI velocity integral, cm</td>
<td>1.0 ± 0.5</td>
<td>0.9 ± 0.5</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SD or as No. of patients (percent of total); LAAI = LA appendage inflow; LAAO = LA appendage outflow.

†p < 0.05 vs group 1.
‡p < 0.05 vs baseline.
§p < 0.005 vs group 1.
¶p < 0.001 vs baseline.

Table 2—Baseline Variables and Follow-up Echocardiographic Data in Patients Without LA Spontaneous Echo Contrast on Initial TEE*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 2A, n = 9</th>
<th>Group 2B, n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>65 ± 7</td>
<td>59 ± 6</td>
</tr>
<tr>
<td>Duration of AF, yr</td>
<td>4.0 ± 3.7</td>
<td>5.2 ± 6.6</td>
</tr>
<tr>
<td>Follow-up period, mo</td>
<td>13 ± 7</td>
<td>15 ± 8</td>
</tr>
<tr>
<td>LA dimension, mm</td>
<td>38 ± 2</td>
<td>37 ± 3</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>64 ± 10</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>Moderate or greater mitral regurgitation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LAAO velocity, cm/s</td>
<td>25 ± 9</td>
<td>16 ± 7†</td>
</tr>
<tr>
<td>LAAO velocity integral, cm</td>
<td>2.0 ± 1.1</td>
<td>1.0 ± 0.5§</td>
</tr>
<tr>
<td>LAAI velocity, cm/s</td>
<td>22 ± 8</td>
<td>13 ± 6§</td>
</tr>
<tr>
<td>LAAI velocity integral, cm</td>
<td>1.6 ± 0.7</td>
<td>0.8 ± 0.4§</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SD or as No. of patients (percent of total); see Table 1 for expansion of abbreviations.
†p < 0.05 vs baseline.
‡p < 0.01 vs group 2A.
§p < 0.01 vs baseline.
cantly changed on follow-up echocardiography. However, the percentage of significant mitral regurgitation at the time of the follow-up study was significantly higher in group 2B than in group 2A. In group 2A, all LA appendage flow velocity profiles decreased significantly on follow-up echocardiography. In group 2B, however, only LA appendage inflow velocity integral decreased significantly on follow-up; there were no significant changes in LA appendage outflow velocity indexes and peak inflow velocity. Figure 1 demonstrates the significant decrease of LA appendage flow velocity from baseline to follow-up study in a group 2A patient and the persistent low LA appendage flow velocity in a group 1 patient.

**Discussion**

Patients with nonrheumatic AF are associated with a higher risk of thromboembolism, presumably from LA clot formation.\(^2\)\(^{14-16}\) The recent advent of TEE has increased the echocardiographic spectrum for risk stratification in AF patients.\(^17\) TEE is an excellent tool for the detection of spontaneous echo contrast and atrial thrombus.\(^18\)\(^-\)\(^21\) LA spontaneous echo contrast, a likely precursor of thrombus formation, is probably a more sensitive marker than LA thrombus in predicting an increased thromboembolic risk.\(^2\)\(^22\) This echo contrast has been reported to be related to an enlarged LA size,\(^1\)\(^,\)\(^3\) a lower left ventricular ejection fraction,\(^22\) the absence of significant mitral regurgitation,\(^1\)\(^,\)\(^2\) and increased levels of several hematologic markers of hypercoagulable state.\(^23\)\(^-\)\(^25\) Our results also show a trend toward the preventive effect of significant mitral regurgitation on LA blood stasis. Recently, the contractile function of LA appendage has been proposed as an important indicator for atrial thrombus formation\(^4\)\(^,\)\(^5\) and systemic embolism.\(^6\)\(^,\)\(^17\) In support of this hypothesis, we found patients with spontaneous echo contrast to have significantly lower LA appendage blood flow velocities than those without this echo phenomenon.

The association of LA appendage function with spontaneous echo contrast in chronic AF has never been prospectively studied by follow-up TEE. Our study uniquely demonstrates that LA appendage flow velocity in AF patients without spontaneous echo contrast may significantly decrease with time on follow-up echocardiography, and this change is only apparently observed in those who develop a new formation of LA spontaneous echo contrast. The changes of LA appendage flow velocities were better correlated to the development of spontaneous echo contrast than were the changes of LA dimension and left ventricular ejection fraction. These findings, in a prospective manner, provide strong evidence supporting that the progressive reduction of LA appendage contractile function plays an important role in the pathogenesis of LA blood stasis; also suggested is that, for patients without spontaneous echo contrast, serial follow-up of the LA appendage flow velocity profiles may be helpful for predicting future occurrence of this echo contrast.

In the subgroup with LA spontaneous echo contrast on baseline TEE, the follow-up LA appendage flow velocity indexes were not significantly changed compared to baseline data. In contrast to the observation that LA thrombi could be resolved after warfarin therapy, we found the spontaneous echo contrast to be persistent on follow-up in spite of antithrombotic therapy. Therefore, once the LA spontaneous echo contrast develops in patients with chronic AF, it tends to persist with time. It is reasonable to postulate that the persistently low flow state of the LA appendage in patients with spontaneous echo contrast may contribute to the stability of this echo phenomenon.

**Study Limitations**

This study is limited by the modest number of the study population. The changes of LA appendage flow profiles with time in each patient were evaluated by only one follow-up TEE. Therefore, a more detailed time-course change of these variables could not be provided, and whether a reduced LA appendage flow velocity precedes the occurrence of spontaneous echo contrast remains unknown. Based on our results, it is reasonable to speculate that the LA appendage flow velocity in some patients with chronic AF may progressively decrease with time until the occurrence of spontaneous echo contrast. Further serial follow-up study in a larger scale should...
be warranted, particularly for patients without spontaneous echo contrast, to clarify these issues. Since most of our patients in group 2 were not receiving antithrombotic therapy during follow-up, it remains unclear whether antithrombotic therapy could prevent future development of spontaneous echo contrast. We used only LA appendage flow velocity as the index of atrial appendage function. The LA appendage diameter, area, or ejection fraction were not measured in this study. The derangement of these parameters is usually associated with reduction of the appendage flow velocity. We believe these measurements are unlikely to be more informative than the assessment of Doppler flow velocity. The left ventricular ejection fraction was calculated by M-mode instead of two-dimensional echocardiographic measurements. The beat-to-beat variation of left ventricular chamber size under AF rhythm usually makes two-dimensional quantitative measurements of consecutive beats difficult. The major concern about the accuracy of left ventricular ejection fraction by M-mode measurement comes from the cases with abnormal regional wall motion. Only two of our patients had ischemic heart disease, and none had apparent regional wall-motion abnormality. Finally, we did not include other potential precipitating factors of spontaneous echo contrast, such as hematologic markers. Nevertheless, the LA appendage flow velocity appeared to be more significantly related to the occurrence of spontaneous echo contrast than other clinical and echocardiographic variables.

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REFERENCES
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