Complex Left Atrial Appendage Morphology and Left Atrial Appendage Thrombus Formation in Patients With Atrial Fibrillation

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Background—In patients with atrial fibrillation (AF), most thrombus forms in the left atrial appendage (LAA). However, the relation of LAA morphology with LAA thrombus is unknown.

Methods and Results—We prospectively enrolled 633 consecutive patients who were candidates for catheter ablation for symptomatic drug-resistant AF. Transesophageal echocardiography (TEE) was performed to assess LAA thrombus. LAA structure was assessed by 3-dimensional TEE. LAA orifice area, depth, volume, and number of lobes were measured on reconstructed 3-dimensional images. Clinical characteristics and echocardiographic measures were compared to determine variables predicting LAA thrombus. Excluded were 69 (10.9%) patients who met the exclusion criteria. Finally, this study comprised 564 patients, of whom LAA thrombus was observed in 36 (6.4%) patients. Multivariate analysis revealed CHADS2 (Congestive heart failure, Hypertension Age>75, Diabetes mellitus and prior Stroke or transient ischemic attack) score (\(P=0.002\)), left ventricular ejection fraction (\(P=0.01\)), degree of spontaneous echo contrast (\(P=0.02\)), left atrial volume (\(P=0.02\)), and number of LAA lobes (\(P<0.001\)) to be independently associated with thrombus formation. Most patients with LAA thrombus (32/34, 94.4%) had ≥3 LAA lobes, whereas LAA thrombus was observed in only 2 (0.7%) of 296 patients with 1 or 2 lobes. LAA volume significantly decreased in patients maintaining sinus rhythm after catheter ablation (\(P=0.0009\)). Number of LAA lobes did not change in any patient.

Conclusions—Complex LAA morphology characterized by an increased number of LAA lobes was associated with the presence of LAA thrombus independently of clinical risk and blood stasis. This study suggests that LAA morphology might be a congenital risk factor for LAA thrombus formation in patients with AF. (Circ Cardiovasc Imaging. 2014;7:337-343.)

Key Words: anticoagulants • atrial appendage • atrial fibrillation • catheter ablation • echocardiography • stroke • thrombosis

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Methods

Study Population and Study Protocol

Between April 2008 and February 2012, a total of 633 consecutive patients who were candidates for catheter ablation for symptomatic drug-resistant AF at the University of Tsukuba Hospital were prospectively enrolled in this study (Table 1). Among them, patients with inadequate TEE imaging quality and severe mitral or aortic valvular diseases and those undergoing hemodialysis or not receiving anticoagulation therapy with warfarin were excluded.

On the day before catheter ablation, transthoracic echocardiography and TEE examinations were performed to identify the presence of LAA thrombus in all patients. Anticoagulation management of warfarin was in accordance with the guideline of The Japanese Circulation Society.12 In the guideline, the target international normalized ratio (INR) is 2.0 to 3.0 for patients under 70 years of age and 1.6 to 2.6 for patients 70 years of age or older because an INR >2.6 increases the risk for serious bleeding complications in the Japanese elderly population. All patients received therapeutic anticoagulation therapy at least during the 3 weeks before TEE.

Sequential TEE examinations were also performed in patients who had maintained sinus rhythm for ≥1 year after catheter ablation to clarify the contribution of AF to left atrium and LAA morphology and function. Ethical approval of the present study was obtained from the local review committee, and all patients provided their written informed consent.

Echocardiographic Studies

Standard 2D transthoracic echocardiographic examinations were performed with an iE33 ultrasound system and S5-2 probe (Philips Medical Systems, Andover, MA). Left ventricular end-diastolic volume, end-systolic volume, and ejection fraction (LVEF) were measured using the modified Simpson’s method from the apical view.13 The left atrial (LA) volume was measured using the modified Simpson’s method from the apical view.14 TEE was performed with an iE33 ultrasound system and S7-2 probe (Philips Medical Systems). SEC was visually classified into 4 grades by careful attention to the gain settings adjusted to distinguish background white noise.15 The severity of SEC was scored as follows: 0, absence of echogenicity; 1+, mild (minimal echogenicity detectable in only a part of the LA cavity with high gain settings); 2+, moderate (denser swirling during the entire cardiac cycle); and 3+, severe (intense echodensity and slow swirling patterns in the LAA usually with similar density in the main cavity) as defined in a previous report. Reproducibility of the SEC grade was evaluated between 2 observers in 50 patients selected at random, and the concordance rate was 92% (46/50). Based on the recommendations from the American Society of Echocardiography,16 blood stasis was quantified by LAA flow velocities, which were measured at ≈ 1 cm below the outlet of the LAA cavity using pulsed Doppler. LAA emptying flow velocity was measured in the basal short-axis view from the transverse scan (45° views). The LAA emptying and filling flow velocities were measured as the average of 3 consecutive cardiac cycles in patients with normal sinus rhythm and 5 consecutive cardiac cycles in patients with AF. Full-volume mode examinations were performed from 45° views during apnea at end-expiration. To obtain these data sets, 6 sectors were scanned with gating to the electrocardiographic R wave and were automatically integrated into a wide-angle (76x69 degrees) pyramidal data image covering the entire LAA. The frame rate of each image was set at ≈ 20 to 30 frames/s. In patients with AF during the examination, zoom mode, which magnified the pyramidal scan by 1 cardiac beat, was used. The frame rate of each image was set at ≈ 10 frames/s.

Quantification of LAA Morphology

Quantification of LAA morphology was performed with QLAB GI-3DQ software (Philips Medical Systems). First, multireconstruction planes of the LAA were obtained from 3D data sets (pyramidal images) including the LAA at end-systole. The method of determining LAA orifice size is shown in Figure 1A and 1B.15,16 We measured the LAA orifice long and short diameters, orifice area (Figure 1C), and depth of the orifice to a lobe tip (Figure 1B).

The inner border of the LAA was manually traced within the distal area of the orifice, and the transverse images of the longest axis of the LAA trace area were automatically sliced at 10 levels from the orifice to the most distal site. On each sliced transverse image, the inner border was manually traced and reconstructed into a 3D image (Figure 2). On a reconstructed image, we measured LAA volume and the number of LAA lobes, which was assessed based on the definitions by Veinot et al17 as follows: (1) LAA lobe was a visible out-pouching from the main tubular body of the LAA, usually demarcated by an external crease; (2) it was internally capable of admitting a 2-mm probe (ie, it was not simply a tag of external adipose tissue); (3) it was occasionally but not necessarily associated with a change in direction of the main tubular body of the LAA; (4) it could lie in a different anatomic plane than the main tubular body; and (5) by definition, the LAA must have ≥ 1 lobe. Intraobserver and interobserver variability of these parameters was <10% in our previous study.18

Clinical Risk Stratification

We calculated CHADS2 score for clinical risk stratification of stroke in patients with AF.2 Some clinical studies have reported a relation between inflammation and AF,20 and C-reactive protein (CRP) is a representative marker of vascular inflammation. B-type natriuretic peptide (BNP) is a marker that increases in patients with structural heart disease, heart failure, and lone AF. It has been reported that the

Table 1. Baseline Characteristics and Echocardiographic Measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>(N=633)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>512/121</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62±11</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>67±16</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>373 (59%)</td>
<td></td>
</tr>
<tr>
<td>Nonparoxysmal atrial fibrillation</td>
<td>260 (41%)</td>
<td></td>
</tr>
<tr>
<td>Rhythm at examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal sinus rhythm</td>
<td>365 (58%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>268 (42%)</td>
<td></td>
</tr>
<tr>
<td>Measurements on 2D TEE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume, ml</td>
<td>101±36</td>
<td></td>
</tr>
<tr>
<td>Left ventricular end-systolic volume, ml</td>
<td>38±26</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>63±11</td>
<td></td>
</tr>
<tr>
<td>Left atrial volume, ml</td>
<td>63±29</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or as number (percentage).

Figure 1. Determination of the left atrial appendage (LAA) orifice. A. LAA long-axis view at the level including the mitral valve annulus, left coronary artery (white arrow), and lateral ridge of the left superior pulmonary vein (white arrowhead). B. LAA long-axis view at the level including the aortic valve annulus (white arrows). The dashed line with double-headed white arrows in both (A) and (B) corresponds to the line used to determine the orifice of the LAA as shown in (C). In (B), the dashed line shows LAA depth. C. LAA orifice area and long and short diameters.
atrium, and not the ventricle, is the main source of BNP in patients with AF, and BNP is higher in patients with a history of thromboembolism than in patients without this complication. Therefore, blood samples to measure plasma high-sensitivity CRP, BNP concentration, and prothrombin time/INR were obtained at the time of TEE examinations.

### Statistical Analysis

Results are expressed as number (%) or mean±SD. Comparisons between the 2 groups were performed by the Student t test for continuous variables and the Fisher exact test for categorical variables. One-way analysis of variance with the post hoc Tukey–Kramer test was used to compare variables in ≥3 groups. Multiple logistic analysis was performed to identify independent risk factors for LAA thrombus. A P value of <0.05 was considered to indicate statistical significance. These analyses were performed with SPSS version 17.0 for Windows (SPSS Inc, Chicago, IL).

### Results

TEE examinations were successfully performed in all patients. We excluded 69 (10.9%) patients because of inadequate imaging quality for LAA analysis (n=42), not receiving anticoagulation therapy with warfarin (n=12), severe mitral regurgitation (n=8), undergoing hemodialysis (n=5), and severe mitral stenosis (n=2). Finally, this study comprised 564 patients. Among them, LAA thrombus was observed in 36 (6.4%) patients. Comparisons between patients with and without LAA thrombus are summarized in Table 2. Patients with LAA thrombus had a significantly higher prevalence of nonparoxysmal AF (P<0.001). Patients with LAA thrombus were significantly older (P=0.003), and their LVEF was lower (P<0.001) and CHADS2 score higher (P<0.001) than those in patients without LAA thrombus. There was no significant difference in prothrombin time/INR between the 2 groups. In patients with LAA thrombus, plasma high-sensitivity CRP (P<0.001) and BNP (P<0.001) concentrations were significantly higher than those in patients without LAA thrombus. In patients with LAA thrombus, LAA volume (P<0.001) and LA emptying velocity (P<0.001) were significantly larger than in patients without LAA thrombus. In addition, the number of LAA lobes was significantly higher (P<0.001) than that of the patients without LAA thrombus. Degree of SEC was significantly higher (P<0.001) with lower LAA emptying velocities (P<0.001) compared with those in patients without LAA thrombus.

### Risk Factors for LAA Thrombus

Various factors had a significant relation with the presence of LAA thrombus as shown in Table 3. In a multivariate logistic analysis, number of LAA lobes (odds ratio [OR], 2.469; 95% confidence interval [CI] 1.495–4.078); P=0.001) was identified as an independent risk factor for presence of LAA thrombus, as were CHADS2 score (OR, 1.752; 95% CI 1.237–2.483; P=0.002), LVEF (OR, 0.962; 95% CI [0.934–0.992]; P=0.01), LA volume (OR, 1.018; 95% CI [1.003–1.032]; P=0.02), and degree of SEC (OR, 1.783; 95% CI [1.102–2.740]; P=0.02). Prevalence of the number of LAA lobes is shown in Figure 3. The majority of patients with LAA thrombus (32/34, 94.4%) had ≥3 LAA lobes. In contrast, LAA thrombus was observed in only 2 (0.7%) of 296 patients with 1 or 2 lobes. In a multiple logistic regression analysis model, as compared with an
LAA with 1 or 2 lobes, an LAA with 3 lobes was 8.6 times (OR, 8.6; 95% CI [1.9–39.8]; P =0.006), 4 or 5 lobes was 10 times (OR, 10.0; 95% CI [2.2–42.1]; P=0.004), and ≥3 lobes was 9.2 times (OR, 9.2; 95% CI [2.0–41.1]; P=0.004) more likely to have thrombus.

The relation of number of LAA lobes with degree of SEC and LAA emptying velocity is shown in Figure 4. In patients with ≥3 LAA lobes, a higher degree of SEC (Figure 4A) and lower LAA emptying velocity (Figure 4B) were observed as compared with those in patients with 1 or 2 LAA lobes.

**Risk Factors for LAA Thrombus in Patients with Low CHADS2 Score**

Patients with LAA thrombus included 13 (13/198, 6.6%) with a CHADS2 score of 1 and 1 (1/185, 0.5%) patient with a CHADS2 score of 0. In a multiple logistic regression analysis model for LA thrombus in only limited patients with CHADS2 score 0/1, number of LAA lobes (OR, 2.8; 95% CI [1.3–6.1]; P=0.008) was identified as a significant predictor as were SEC (OR, 3.1; 95% CI [1.5–6.6]; P=0.003) and LVEF (OR, 0.9; 95% CI [0.89–0.98]; P=0.022). Unlike the analysis in the overall population, LA volume was not a significant predictor.

**Functional and Morphological Changes After Catheter Ablation**

Repeat TEE examinations were performed in 46 patients who maintained sinus rhythm during 1 year after catheter ablation. Average term from catheter ablation to next TEE examination was 1 year.

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**Table 3. Univariate and Multivariate Analyses for Presence of LAA Thrombus**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate OR (95% CI)</th>
<th>P Value</th>
<th>Multivariate OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF type (nonparoxysmal AF)</td>
<td>4.785 (2.26–10.10)</td>
<td>&lt;0.001</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>1.915 (1.486–2.467)</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Degree of spontaneous echo contrast</td>
<td>3.128 (2.262–4.326)</td>
<td>&lt;0.001</td>
<td>1.752 (1.237–2.483)</td>
<td>0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>0.935 (0.914–0.956)</td>
<td>&lt;0.001</td>
<td>0.962 (0.934–0.992)</td>
<td>0.01</td>
</tr>
<tr>
<td>LA volume, ml</td>
<td>1.031 (1.021–1.041)</td>
<td>&lt;0.001</td>
<td>1.018 (1.003–1.032)</td>
<td>0.02</td>
</tr>
<tr>
<td>LAA emptying velocity, cm/s</td>
<td>0.947 (0.925–0.970)</td>
<td>&lt;0.001</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>LAA volume, ml</td>
<td>1.038 (1.007–1.070)</td>
<td>0.02</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Number of LAA lobes</td>
<td>3.318 (2.179–5.052)</td>
<td>&lt;0.001</td>
<td>2.469 (1.495–4.078)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CHADS2, Congestive heart failure, Hypertension Age>75, Diabetes mellitus and prior Stroke or transient ischemic attack; CI, confidence interval; LA, left atrium; LAA, left atrial appendage; and OR, odds ratio.

*P*<0.05 vs 1 lobe group; †*P*<0.05 vs 2 lobe group; ‡*P*<0.05 vs 3 lobe group.
was 19.2±5.3 months. A representative case is shown in Figure 5. The LAA volume decreased after catheter ablation from 17.8 to 10.3 mL, whereas the number of lobes and fundamental morphology were maintained. Comparison of clinical characteristics and echocardiographic measurements between baseline and after catheter ablation are summarized in Table 4. After catheter ablation, plasma high-sensitivity CRP \( (P=0.04) \) and BNP \( (P<0.001) \) concentrations were decreased, and LVEF \( (P=0.002) \) was increased. In addition, significant reverse remodeling of both the LA \( (P<0.001) \) and LAA \( (P<0.001) \) were observed with improvements of blood stasis represented as SEC \( (P<0.001) \) and LAA emptying velocity \( (P=0.02) \). However, the number of lobes did not change in any of the patients.

### Discussion

This is the first study, to our knowledge, to examine the relation between LAA morphology assessed by 3D-TEE and LAA thrombus formation in patients with AF. We found a significant relation between LAA morphology and the prevalence of LAA thrombus formation; in particular, number of LAA lobes, may be a congenital and fundamental characteristic and is not influenced by LAA remodeling. Accordingly, the complexity of the LAA, which is represented by the number of LAA lobes, may be a congenital and specific factor in each individual. Several previous studies have reported on the diversity of LAA lobes and their geometry. \(^5\) \(^6\) \(^10\) \(^19\) \(^23\) In a large autopsy series comprising 500 normal human hearts (age range, 0–100 years), the distribution of the number of LAA lobes was 2 (54% of hearts), 3 (23%), 1 (20%), and 4 (3%). \(^19\) In our study, the distribution was 2 (42.2%), 3 (34.9%), 1 (10.3%), 4 (11.3%), and 5 (1.2%). The mean number of LAA lobes was 2.1 in the autopsy study and 2.5 in our study, and there was a statistically significant difference by \( \chi^2 \) test \( (P<0.01) \). The difference might be caused by study populations, namely, our study consisted of patients with AF, in contrast to the normal hearts in the autopsy study.

Di Biase et al. \(^6\) categorized LAA into 4 different morphologies and reported that the Chicken Wing LAA morphology was less likely to produce an embolic event. We did not analyze morphology type in the present study; however, morphology such as the Chicken Wing type is the simplest among the Di Biase et al. classification and may correspond to the LAA with 1 or 2 lobes in our study. Di Biase et al. did not discuss the reason that simple LAA morphology was related to a lower embolic event rate. Because it is assumed that a simple morphology is less likely to induce blood stasis, the present study clearly revealed that an increase in the number...
of LAA lobes was related to a high degree of SEC and low LAA emptying velocity. The findings suggest that complex LAA morphology characterized by an increased number of lobes is likely to induce blood stasis, which is a fundamental cause of thrombus formation.

CT and MRI are useful methods of characterizing the LAA; however, image quality is severely deteriorated by stitching artifact in patients with AF during the examination. We used zoom mode, which magnified the pyramidal scan by 1 cardiac beat in patients with AF during the examination, so we could avoid stitching artifact. Moreover, CT has a problem of radiation exposure, and both methods require use of a contrast agent, so it is difficult to use in patients with severe renal dysfunction. In most hospitals, TEE was generally performed before catheter ablation for AF to assess LAA thrombus. TEE has the advantage of assessing LAA morphology in routine clinical practice.

Because we managed anticoagulation based on the guideline of the Japanese Circulation Society, the target ranges differ slightly from those in the AHA guidelines or those of other Western countries. The Japanese Circulation Society guideline recommends a basic target INR of 2.0 to 3.0. However, in patients ≥70 years of age, the recommended target INR is 1.6 to 2.6 because an INR of >2.6 increases the risk for serious bleeding complications in the Japanese elderly population. In our patients without thrombus, 482 (482/528, 91.3%) achieved the target INR, and in patients with thrombus, 33 (33/36, 91.7%) achieved the target INR. In the 3 patients with thrombus who did not achieve the target INR, thrombus formation might be because of poor warfarin control. However, the INR in these 3 patients was not much lower than the target INR (every patient exceeded an INR of 1.5) because they were all >70 years of age. Therefore, most patients with thrombus were treated within the target INR.

Plasma CRP concentrations in patients with LAA thrombus were increased over those in patients without LAA thrombus. Previous studies reported that CRP and interleukin-6 were elevated in patients with AF, and elevated inflammatory markers are related to embolic events. Our findings support these results, but multivariate analysis could not identify the independent strength of the association of these variables with LAA thrombus as compared with that of LAA morphology and blood stasis. Because a significant relation between inflammation and LA remodeling has been observed, the inflammation process may indirectly contribute to LAA thrombus formation via LA and LAA remodeling.

Clinical Implications

In this study, we clarified the relation between LAA morphology and thrombus formation. In the clinical setting, we have used the CHADS2 or CHA2DS2-VASC score for thromboembolic risk stratification. However, in cases of high bleeding risk or low CHADS2 score (0 or 1), both bleeding risk because of anticoagulation therapy and thromboembolic risk should be considered. Furthermore, in patients who have maintained sinus rhythm for a long time after catheter ablation, we wonder whether anticoagulation therapy should be continued. Knowledge of the number of LAA lobes would be helpful in making clinical decisions on antithrombotic therapy in such controversial cases. However, thrombus is a cause of stroke, and thrombus formation is no more than a surrogate for stroke risk. In the future, long-term follow-up studies identifying how the number of LAA lobes together with the CHADS2 score influences the risk of stroke as an end point are needed.

Study Limitations

Forty-two patients (6.6%), most of whom were in an AF rhythm at the time of TEE examination, were excluded because of inadequate 3D LAA image quality. Because the full-volume imaging method derived from 6 cardiac beats was not available in patients with AF, the single-beat image acquisition method (zoom-mode imaging) was used, which may exacerbate image quality in assessing LAA morphology in patients with AF. From the statistical aspect, there is a great difference between the number of patients with thrombus (n=528) and without thrombus (n=36). Therefore, comparisons between the 2 groups are limited statistically. Furthermore, our study was a single-center study, and the study population was limited to patients undergoing catheter ablation and anticoagulation therapy with warfarin for AF. To confirm whether this study is applicable to a wider population not undergoing catheter ablation or taking warfarin, a multicenter study consisting of a larger number of participants with diverse diagnoses is necessary.

Conclusions

Complex LAA morphology that was characterized by an increased number of LAA lobes was associated with the presence of LAA thrombus, independently of clinical risk and blood stasis. Our study suggested that LAA morphology might be a congenital risk factor for LAA thrombus formation in patients with AF. Accordingly, analysis of LAA morphology may provide additional information in the diagnosis of LAA thrombus and in decision making and formulation of medical strategies including anticoagulation management.

Disclosures

None.

References

In patients with atrial fibrillation (AF), most thrombus formation occurs in the left atrial appendage (LAA) in part because the complex morphology of the LAA predisposes to blood flow stasis. Three-dimensional transesophageal echocardiography (3D-TEE) allows detailed imaging of the LAA and could help evaluate morphological characteristics that predispose to thrombus formation. In the present study, 564 patients who were candidates for catheter ablation for symptomatic drug-resistant AF were studied, and LAA thrombus was observed in 36 patients (6.4%). Independent of clinical risk factors and blood stasis, the presence of LAA thrombus was strongly associated with complex LAA morphology characterized by more numbers of LAA lobes. In patients who maintained sinus rhythm during 1 year after catheter ablation, LA and LAA volumes decreased, but, not unexpectedly, the number of LAA lobes did not change. This finding is consistent with the fact that the number of LAA lobes is a structural feature and is not influenced by LAA remodeling. This study contributes to our understanding of risk stratification for LAA thrombus formation and may provide additional information to be incorporated into decisions around anticoagulation in patients with AF. Long-term follow-up studies will be required to assess how the LAA morphology influences stroke risk, and whether this information provides incremental benefit over traditional risk scoring systems.
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