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【 ORIGINAL ARTICLE 】

Clinical Significance of the Left Atrial Appendage Orifice Area

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Abstract:

Objective The left atrial appendage (LAA) is one of the major sources of cardiac thrombus formation. Three-dimensional transesophageal echocardiography (TEE) made it possible to perform a detailed evaluation of the LAA morphologies. This study aimed to evaluate the clinical implications of the LAA orifice area.

Methods A total of 149 patients who underwent TEE without significant valvular disease were studied. The LAA orifice area was measured using three-dimensional TEE. The patients were divided into two groups according to the LAA orifice area (large LAA orifice group, ≥median value, and small LAA orifice group). The clinical characteristics and echocardiographic findings were evaluated.

Results The median LAA orifice area among all patients was 4.09 cm^2 (interquartile range 2.92-5.40). The large LAA orifice group were older (67.2±10.4 vs. 62.4±15.3 years, p=0.02), more often had hypertension (66.7% vs. 44.6%, p=0.007), and atrial fibrillation (70.7% vs. 39.2%, p<0.001) than the small LAA orifice group. Regarding the TEE findings, the LAA flow velocity was significantly lower (33.7±20.0 vs. 50.2±24.3, p<0.001) and spontaneous echo contrast was more often observed (21.3% vs. 8.1%, p=0.02) in the large LAA orifice group. Multivariate models demonstrated that atrial fibrillation was an independent predictor of the LAA orifice area. In the analysis of atrial fibrillation duration, the LAA orifice area tended to be larger as patients had a longer duration of atrial fibrillation.

Conclusion Our findings indicated that a larger LAA orifice area was associated with the presence of atrial fibrillation and high thromboembolic risk based on TEE findings. A continuation of the atrial fibrillation rhythm might lead to the gradual expansion of the LAA orifice.

Key words: left atrial appendage, atrial fibrillation, echocardiography

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Introduction

The left atrial appendage (LAA) is one of the major sources of cardiac thrombus formation (1-3). Three-dimensional transesophageal echocardiography (TEE) made it possible to evaluate the LAA morphologies. Previous studies have shown that large and complex LAA are related to an increased risk of LAA thrombus formation and embolic stroke in patients with atrial fibrillation (AF) (4-6). Recently, transcatheter LAA occlusion has been expanding in clinical practice, and additional attention has been paid to the LAA morphology. However, the clinical significance of the LAA morphology has not yet been fully elucidated. This study aimed to investigate the clinical implications of the LAA orifice area, which can be easily obtained by TEE, among patients with and without AF.

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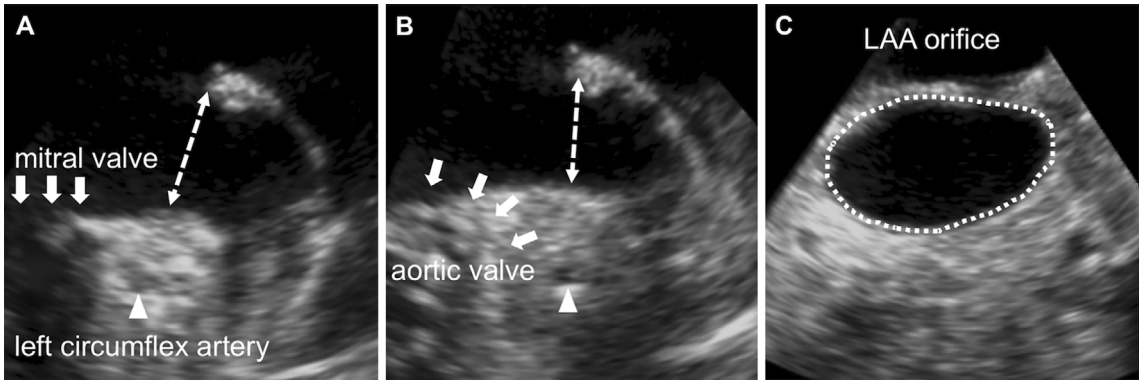

Figure 1. Measurement of the left atrial appendage (LAA) orifice area by three-dimensional transesophageal echocardiography. A: In the LAA long-axis view at the level including the mitral valve, a first line was drawn from the left circumflex artery and the lateral ridge of the left pulmonary vein. B: In the LAA long-axis view at the level including the aortic valve, a second line was drawn from the left circumflex artery and the ridge or the left pulmonary vein. C: Determine the plane of the LAA orifice from the two lines and then measure the LAA orifice area.

Materials and Methods

Subjects

We retrospectively identified 269 consecutive patients who underwent TEE at the Yokkaichi Municipal Hospital between June 2013 and December 2014. Any patients who underwent TEE for assessment of moderate/severe valvular disease (n=105) or had a history of cardiac surgery (n=15) were excluded. Finally, 149 patients were included for the analysis. This study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee.

Echocardiographic assessments

All transthoracic echocardiographic (TTE) images were obtained using an iE33 ultrasound system and S5-2 probe (Philips Medical Systems, Andover, USA). Left ventricular ejection fraction and left atrial volume were measured using the modified Simpson's method.

All TEE images were obtained using an iE33 ultrasound system and S7-2 probe (Philips Medical Systems, Andover, USA). LAA thrombus and left atrium spontaneous echo contrast were determined by visual assessment. Spontaneous echo contrast was defined as dynamic, swirling, and smoke-like echoes within the left atrium and LAA, after gain settings were adjusted to distinguish any background excessive noise (7).

The LAA-emptying velocity was evaluated using pulsed-wave Doppler with a sampled volume placed 1 cm below the outlet of the LAA cavity at the basal short-axis view from the transverse scan. The LAA-emptying velocity was measured at three cardiac cycles and averaged in patients with sinus rhythm and at five cardiac cycles in patients with AF (8).

Real-time three-dimensional TEE was performed from 45° views. The region of interest was adjusted to the smallest pyramidal dataset, which sufficiently included the entire LAA. Three-dimensional TEE imaging data were reviewed using an offline QLAB-3DQ software program (Philips Medical Systems).

The LAA orifice was determined as follows: 1) At the LAA long-axis view at the level including the mitral valve, a first line was drawn from the left circumflex artery and the lateral ridge of the left pulmonary vein. 2) At the LAA long-axis view at the level including the aortic valve, a second line was drawn from the left circumflex artery and the ridge or the left pulmonary vein. 3) Determine the plane of the LAA orifice from the two lines and then measure the LAA orifice area (Fig. 1) (6, 9). Patients were divided into two groups according to the value: those with larger than the median value (large LAA orifice group) and those smaller than the median value (small LAA orifice group).

Other definitions

The clinical data, including congestive heart failure, hypertension, age 75 years, diabetes mellitus, stroke ($CHADS_2$) score (10) and congestive heart failure, hypertension, age ≥75 years (double score), diabetes, prior stroke or transient ischemic attack (TIA; double score) (CHA_2DS_2-VASc) score (11), were obtained at the time of TEE.

Statistical analysis

The data are expressed as the mean ± standard deviation or median (interquartile range). Categorical variables were expressed as numbers and percentages. Continuous data were compared using the unpaired *t* test or Mann-Whitney U test. Among the three groups, continuous data were compared by an analysis of variance. Categorical variables were compared using the chi-square test or Fisher's exact test. Univariate and multivariate linear regression analyses were performed to identify the predictors related to LAA orifice area and LAA flow velocity. Factors with $p<0.05$ according

Table 1. Patient Characteristics.

	All n=149	Large LAA orifice n=75	Small LAA orifice n=74	p value*
Age, y	64.8±13.2	67.2±10.4	62.4±15.3	0.03
Male, n (%)	99 (66.4)	52 (69.3)	47 (63.5)	0.45
Hypertension, n (%)	83 (55.7)	50 (66.7)	33 (44.6)	0.007
Diabetes mellitus, n (%)	28 (18.8)	14 (18.7)	14 (18.9)	0.97
Heart failure, n (%)	37 (24.8)	18 (24.0)	19 (25.7)	0.81
Prior stroke/transit ischemic attack, n (%)	51 (34.2)	23 (30.7)	28 (37.8)	0.36
Vascular disease, n (%)	40 (26.8)	23 (30.7)	17 (23.0)	0.29
$CHADS_2$ score	1.93±1.35	1.96±1.31	1.91±1.31	0.81
CHA_2DS_2-VASc score	3.13±1.88	3.25±1.89	3.01±1.88	0.44
Atrial fibrillation, n (%)	82 (55)	53 (70.7)	29 (39.2)	<0.001
Paroxysmal or persistent	55	33	22	
Long persistent-chronic	27	20	7	
TEE indication, n (%)				
Source for cardiac embolism	47	20	27	
Evaluation of LA thrombus	78	47	31	
Assessment for endocarditis	15	5	10	
Other	9	3	6	

LAA: left atrial appendage

*Comparison between Large LAA group and Small LAA group

to univariate analyses were entered into the multivariate model. A p-value <0.05 was considered to be statistically significant. All analyses were performed using the SPSS Statistics software program version 26.0 (IBM, Armonk, USA).

Results

The baseline characteristics of all patients are shown in Table 1. The mean age was 64.8±13.2 years, and 66.4% (99/149) were male. Fifty-one patients (34.2%) had a history of stroke or transient ischemic attack. The mean $CHADS_2$ score was 1.9±1.4, and the CHA_2DS_2-VASc score was 3.1±1.9. Eighty-two patients (55%) had AF, 55 had paroxysmal or persistent AF, and 27 had long-persistent or chronic AF. The indications for TEE are also shown in Table 1. TEE was performed to identify the cardiac source of embolism after cerebral infarction in 47 (31.5%) patients, to confirm the absence of thrombus during AF management or before cardioversion/catheter ablation in 78 patients (52.3%), to assess endocarditis in 15 (10.0%), and others in 9 (6.4%).

Fig. 2 shows the distribution of the LAA orifice area among all patients. The median LAA orifice area was 4.09 cm^2 (interquartile range, 2.92-5.40 cm^2). The patients were divided into two groups according to the LAA orifice area: large LAA orifice group (≥4.09 cm^2) or small LAA orifice group (<4.09 cm^2).

Table 1 also shows a comparison of the baseline characteristics between the two groups. The patients in the large LAA orifice group were older and more often had hypertension and AF than those in the small LAA orifice group. No significant differences were found in $CHADS_2$ and CHA_2DS_2-VASc scores between the two groups.

Table 2 shows the TTE and TEE findings in both groups. The LA diameter, LA volume and LA volume index were significantly larger in the large LAA orifice group. There was a significant correlation between the LA volume and LAA orifice area (Supplementary material 1). The LAA flow velocity was significantly lower and spontaneous echo contrast was more often seen in the large LAA orifice group. LAA thrombus was detected in four patients: 2 in large LAA orifice group and 2 in small LAA orifice group. When dividing the patients into two groups according to the sinus rhythm or AF at TEE, a significant negative correlation between LAA orifice area and LAA flow velocity was observed among the patients with AF at TEE (Supplementary material 2).

The results of the univariate and multivariate linear regression analyses for the LAA orifice area are shown in Table 3. According to the univariate analysis, age, hypertension, and AF were associated with the LAA orifice area. A multivariate analysis indicated that the presence of AF was an independent predictor of the LAA orifice area. Further, Supplementary material 3 shows the liner regression analyses for the LAA flow velocity. A multivariate liner regression analysis indicated the LAA orifice area to be an independent predictor of the LAA flow velocity as well as for a history of heart failure and the presence of AF.

We compared the LAA orifice area among patients with sinus rhythm, paroxysmal/persistent AF (≤1 year), and long-persistent/chronic AF (>1 year) (Fig. 3). The LAA orifice area was significantly larger as the patients had a longer AF

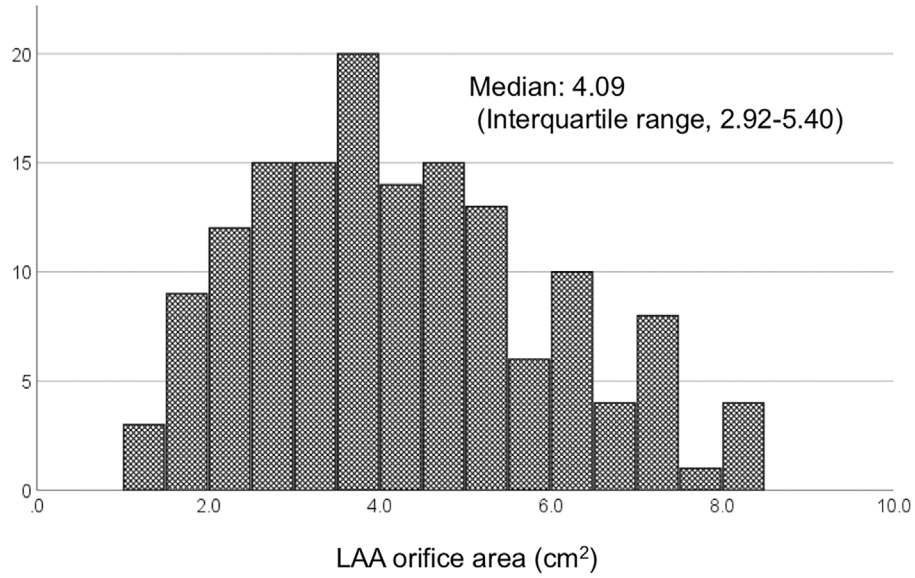

Figure 2. **The distribution of the left atrial appendage orifice area by three-dimensional transesophageal echocardiography.**

Table 2. **Transthoracic and Transesophageal Echocardiographic Findings.**

	All n=149	Large LAA orifice n=75	Small LAA orifice n=74	p value*
Transthoracic				
LV end-diastolic diameter, mm	47.3±7.9	47.9±7.6	46.2±8.1	0.22
LV end-systolic diameter, mm	32.6±8.6	33.4±8.4	31.8±8.7	0.25
LVEF, (%)	56.6±11.4	56.3±11.1	57.0±11.8	0.78
LA diameter, mm	39.2±6.8	42.0±5.7	36.4±6.7	<0.01
LA volume, mL	61 (48-83)	71 (52-64)	52 (41-64)	<0.01
LA volume index,	37.2 (27.3-46.6)	39.3 (30.5-55.8)	32.0 (24.4-42.0)	0.01
Mitral valve regurgitation, (none-trivial/mild/moderate/severe)	87/62/0/0	38/37/0/0	49/25/0/0	0.07
DcT, ms	190 (130-230)	190 (150-240)	200 (170-230)	0.66
E/e'	13.6 (10.4-18.1)	14.3 (11.9-17.6)	12.6 (9.5-18.6)	0.15
Transesophageal				
LAA flow velocity, cm/s	41.8±23.6	33.7±20.0	50.2±24.3	<0.001
Presence of thrombus, n (%)	4 (2.7)	2 (2.7)	2 (2.7)	0.99
Spontaneous echo contrast, n (%)	22 (14.8)	16 (21.3)	6 (8.1)	0.02
AF at exam	69 (46.3)	47 (62.7)	22 (29.7)	<0.001
Sinus rhythm at exam	*n=80*	*n=28*	*n=52*	
LAA flow velocity, cm/s	54.8±22.4	48.4±20.6	58.4±22.8	0.06
Presence of thrombus, n (%)	0 (0)	0 (0)	0 (0)	
Spontaneous echo contrast, n (%)	3 (3.8)	2 (7.1)	1 (1.9)	0.28
AF at exam	*n=69*	*n=47*	*n=22*	
LAA flow velocity, cm/s	27.3±14.9	25.1±13.6	32.0±16.6	0.07
Presence of thrombus, n (%)	4 (5.8)	2 (4.3)	2 (9.1)	0.59
Spontaneous echo contrast, n (%)	19 (27.5)	14 (29.8)	5 (22.7)	0.54

LAA: left atrial appendage, LV: left ventricular, LVEF: left ventricular ejection fraction, LA: left atrial, DcT: deceleration time of early transmitral velocity, E: peak mitral inflow velocity during early diastole, e': peak mitral annular velocity during early diastole, AF: atrial fibrillation

*Comparison between Large LAA group and Small LAA group

Table 3. Liner Regression Analyses for Left Atrial Appendage Orifice Area.

	Univariate		Multivariate		
	Regression coefficient	p value	Regression coefficient	Beta coefficient	p value
Age	0.03	0.01	0.009	0.07	0.41
Male	0.21	0.94			
Hypertension	0.65	0.02	0.39	0.12	0.15
Diabetes mellitus	-0.40	0.26			
Heart failure	0.37	0.25			
Stroke/Transit ischemic attack	-0.22	0.44			
Vascular disease	0.57	0.07			
Atrial fibrillation	1.40	<0.01	1.28	0.38	<0.001

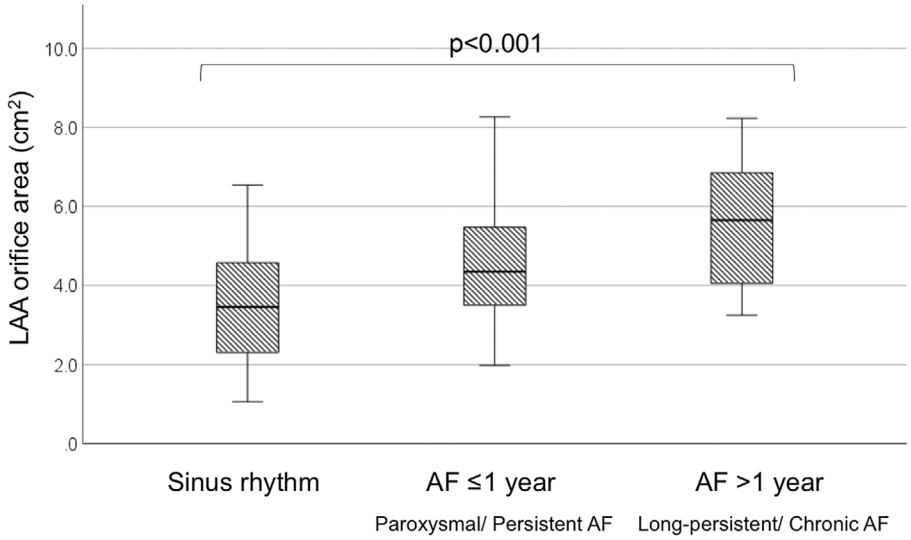

Figure 3. Comparison of the left atrial appendage orifice area among patients with sinus rhythm, paroxysmal/persistent atrial fibrillation (≤1 year), and long-persistent/chronic atrial fibrillation (>1 year).

duration.

Discussion

The main findings of this study are shown below:

1) Patients with a large LAA orifice area were older and more often had hypertension and AF than those with a small LAA orifice area.

2) Patients with a large LAA orifice area had lower LAA velocity and more often a spontaneous contrast echo than those with a small LAA orifice area.

3) The presence of AF was an independent predictor of the LAA orifice area.

4) The LAA orifice area was larger as the patients had a longer AF duration.

Recently, much attention has been focused on the LAA morphology, as catheter ablation and percutaneous LAA closure are expanding in clinical practice (12-14). LAA morphology can be evaluated by TEE, cardiac magnetic resonance, and computed tomography, and previous reports have focused on various anatomical features, including the volume, number of lobes, and orifice size (15, 16). Furthermore, racial differences have also been reported (17), and data regarding the clinical significance of various anatomical features in each population are still limited and more data are required. In this study, we focused on the LAA orifice area among the Japanese population, which has not yet been fully elucidated and also examined its clinical significance.

A few studies, which focused on the LAA orifice area, have reported a mean value of 4.4-4.6 cm^2 among patients with AF (6, 18), and similar values were seen among patients with AF in our study. The values in the overall population appeared to be smaller than those in previous reports, and this can be explained by the difference in the studied population because the present study included patients with sinus rhythm. To date, the data regarding the factors associated with the LAA orifice area are limited. Our study showed that patients with a larger LAA orifice area were older and more often had hypertension and AF. In particular, the presence of AF was independently associated with the LAA orifice area, and patients with longer AF duration had a larger LAA orifice area. The results of this study suggest

that a sustained AF rhythm might lead to the gradual expansion of the LAA orifice along with LA dilatation, even though this was a cross-sectional study.

The clinical significance of the LAA orifice size has not yet been adequately determined. Some studies have shown that a larger LAA orifice area/diameter is associated with an increased thromboembolic risk in patients with AF (4, 6). Other reports have shown that a smaller LAA orifice area is associated with thromboembolic risk (17), or no significant association was noted between the LAA orifice size and thromboembolic risk (18-21). In our study, a larger LAA orifice area was associated with a lower LAA flow velocity and more frequent spontaneous echo contrast, which are well known to be thromboembolic risks of TEE findings. Therefore, our study might support the theory that a larger LAA orifice area has higher thromboembolic risk than a smaller one. In clinical practice, when considering the indications for LAA closure, we might be able to regard a patient with a large LAA orifice as a more appropriate candidate in terms of thromboembolic risk.

This study is associated with several limitations. First, this was a retrospective, single-center observational study, and the sample size was relatively small. Second, there might be some differences in the measurement position from that measured for other purposes, including percutaneous LAA closure. However, it would not be a concern when the clinical significance of the LAA orifice area is considered. Third, this study only included patients who had clinical indications for TEE, and thus some selection bias might exist.

Conclusion

A larger LAA orifice area was associated with the presence of AF and thromboembolic risk of TEE findings. Our findings suggest that the persistence of AF rhythm might lead to the expansion of the LAA orifice over time, and this phenomenon is considered to be important in clinical practice.

Author's disclosure of potential Conflicts of Interest (COI).
Hideki Ishii: Honoraria, Astellas Pharma, Astrazeneca, Daiichi-Sankyo Pharma and MSD. Toyoaki Murohara: Honoraria, Bayel Pharmaceutical, Daiichi-Sankyo, Dainippon Sumitomo Pharma, Kowa, MSD, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, Sanofi-aventis and Takeda Pharmaceutical.

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