Characteristics of Anatomy and Function of the Left Atrial Appendage and Their Relationships in Patients with Cardioembolic Stroke: A 3-Dimensional Transesophageal Echocardiography Study

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Background: Increasing attention is being paid to the left atrial appendage (LAA) in the context of risk stratification in cardioembolic stroke (CES) and the requirement for meticulous planning of percutaneous closure device implantation. However, detailed systematic assessment of the LAA remains limited. *Methods:* This study evaluated the anatomy and function of LAA using 3-dimensional transesophageal echocardiography (3D-TEE) on 194 consecutive patients older than 50 years old hospitalized exclusively for CES. Patients were stratified into 3 groups on the basis of cardiac rhythm: (1) chronic atrial fibrillation (AF), n = 53; (2) paroxysmal AF, n = 26; and (3) no detected AF, n = 115. *Results:* Significant differences between the groups were observed for anatomical (orifice area [OA], depth, diastolic volume) and functional parameters (ejection fraction [EF], flow velocity [FV]), as measured by 3D-TEE. The anatomical parameters were consistently the greatest, and functional parameters were the poorest, in the group with chronic AF. There were significant inverse correlations between them ($r = -.33$, $P = .0003$ for depth and EF; $r = -.27$, $P = .0020$ for depth and FV; $r = -.22$, $P = .016$ for OA and EF; and $r = -.38$, $P < .0001$ for OA and FV). *Conclusions:* LAA morphology and function were strongly affected by cardiac rhythm disturbances. Patients with chronic AF had the greatest LAA dimensions, areas, and volumes as well as the lowest LAA functions. An inverse correlation was observed between LAA size and function. **Key Words:** Left atrial appendage—embolic stroke—transesophageal echocardiography—atrial fibrillation.

Introduction

Cardioembolic stroke (CES) accounts for 14%-30% of all strokes and tends to result in large infarcts and often in death or severe functional disorders. It is well-known that atrial fibrillation (AF) is the most common cause of CES. Relative to patients without AF, the risk of stroke is estimated at up to 5 times higher than in those with AF. Because the prevalence of AF increases with patient age, the risk of CES also becomes greater as the population ages.[1,2]

Generally, by summing clinical risk factors, CHADS2 and CHA2DS2-VASc scores determine the risk of cerebral infarction in patients with AF quite well.[3,4] In addition to these clinical determinants, imaging findings may impact

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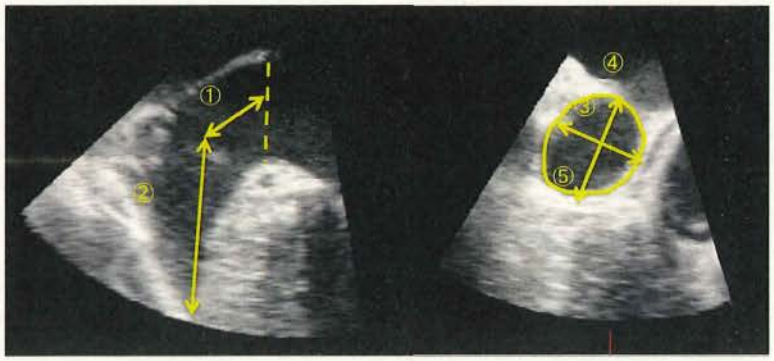

Figure 1. *Schematic representation of definition of measurements of transesophageal echocardiography images of the left atrial appendage (LAA). LAA long-axis view at the level including the mitral valve annulus and the lateral ridge of the left superior pulmonary vein was used to determine the LAA orifice plane as well as to calculate LAA depth (① + ②). The LAA orifice short-axis view, determined by a vertical cross section of the LAA (along the dotted line in the long-axis view), was used to measure the orifice area (③), minor axis diameter (④), and major axis diameter (⑤).*

to ventricular "diastole." Accordingly, the atrial diastolic (ventricle systolic) phase was exclusively used for 2D-TEE assessment in this study. For 3D-TEE analyses, each slice of the LAA from orifice to bottom was integrated by GI-3DQ, and LAA systolic and diastolic volumes were calculated using Simpson's method. These slices ranged from about 5-10 mm thick without gaps (Fig 2). LAA ejection fractions were calculated as diastolic LAA volume minus systolic LAA volume divided by diastolic LAA volume.

Patient Stratification

For convenience, we decided to designate permanent AF as chronic atrial fibrillation (CAF). We divided the patients into 3 groups according to cardiac rhythm, comprising CAF, paroxysmal atrial fibrillation (PAF), and no detected atrial fibrillation (NAF), based on electrocardiograms on admission, history of AF, and electrocardiographic monitoring in the hospital. Moreover, Holter electrocardiography was performed at least twice to determine PAF when patients had no evident AF history. The group of patients with no detected AF was defined as those with no history of AF and no AF documented by monitoring. Anatomical or functional ultrasound parameters of LAA were multidirectionally compared between these 3 groups.

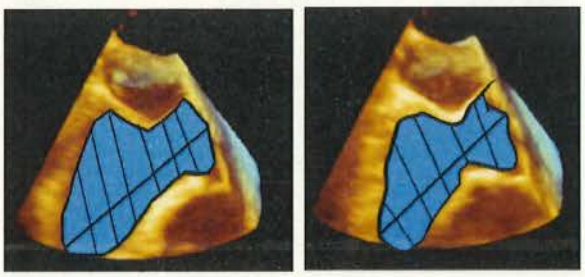

Figure 2. *Images of multisliced left atrial appendage integrated volumes.*

Statistical Analysis

All analyses were performed using JMP version 12.0 for Windows (SAS Institute Inc., Cary, NC). All quantitative data were expressed as the mean ± standard deviation, compared using Student's *t*-test and analysis of variance for 2 levels and more. Continuous variables were compared using Student's *t*-test. Values with $P < .05$ were considered significant. The relationships between the parameters were investigated by Pearson correlation coefficient testing. Simple linear regression analysis was performed to investigate correlations between echo parameters.

Results

Patients' Characteristics

Fifty-three patients were diagnosed as having CAF, of which 26 had an evident history of PAF according to the initial examination. The remaining 115 patients were classified as NAF. Clinical characteristics of the enrolled patients and comparisons between CAF, PAF, and NAF groups are shown in Table 1. Overall, this study recruited patients with a mean age of 69 ± 10 years, 65% of whom were men. Significant differences were seen between the 3 groups, including gender, height, hyperuricemia, CHADS2-VASc score, serum B-type natriuretic peptide, heart rate at the examination, prothrombin time international normalized ratio, and use of antiarrhythmic drugs and oral anticoagulants. No differences were observed in the other clinical characteristics assessed. Oral anticoagulants included warfarin, dabigatran etexilate, rivaroxaban, apixaban, and edoxaban.

Results of TTE

The results of 2D quantitative TTE analysis are summarized in Table 2. In terms of assessment of LV, no significant differences were observed between the 3 groups

Table 3. *Qualitative and quantitative assessment of LAA by 3D transesophageal echocardiography*

	CAF (n = 45)	PAF (n = 28)	NAF (n = 115)	*P* value
LAA orifice				
Major axis, cm	3.74 ± .94	2.88 ± .77	2.74 ± .59	<.0001
Minor axis, cm	2.73 ± .75	2.08 ± .61	1.91 ± .46	<.0001
Symmetry	.73 ± .08	.72 ± .13	.70 ± .11	.4505
Orifice area, cm^2	7.85 ± 3.9	4.80 ± 2.9	4.03 ± 1.8	<.0001
LAA depth, cm	4.47 ± 1.18	3.91 ± 1.25	3.18 ± .87	<.0001
LAA volumetric measurements				
Systolic volume, cm^3	16.5 ± 12.9	7.3 ± 5.2	5.1 ± 2.8	<.0001
Diastolic volume, cm^3	18.7 ± 14.6	9.7 ± 6.4	6.9 ± 3.5	<.0001
Ejection fraction, %	12.7 ± 13.5	20.3 ± 13.7	25.8 ± 15.2	.0002
Spontaneous echo contrast, n(%)	32(60%)	6(23%)	0(0%)	<.0001
LAA thrombus, n(%)	12(23%)	4(15%)	3(2%)	<.0001
LAA flow, cm/s	39.7 ± 30.3	61.7 ± 27.4	80.8 ± 22.7	<.0001

Abbreviations: 3D, 3-dimensional; CAF, chronic atrial fibrillation; LAA, left atrial appendage; NAF, no detected atrial fibrillation; PAF, paroxysmal atrial fibrillation.

differences were observed in the anatomical parameters of LAA between the 3 groups, except for the symmetry index of the orifice. Many anatomical parameters of the LAA were most marked in the CAF group. A slight differential tendency was observed in the symmetry index of the LAA orifice ($P = .089$). Comparing the symmetry indices between the CAF group and the NAF group showed that it was significantly larger in the CAF group ($P = .028$). In terms of LAA function, the LAAEF was significantly lower in the CAF group than in the PAF group ($P = .0031$) or NAF group ($P < .0001$). A slight tendency toward a reduced LAAEF was observed in the PAF group compared with the NAF group, but this was not statistically significant ($P = .073$).

Correlation of LAA Parameters

Correlations between LAA parameters were assessed. Figure 3 displays relationships between 3D anatomical parameters (LAA depth and LAA orifice area) and LAA function (LAAEF and LAA flow velocity). An inverse correlation was observed between the LAA depth and the LAAEF ($P = .0003$, $r = -.33$) as well as between the LAA depth and the LAA flow velocity ($P = .0020$, $r = -.27$) (Fig 4). Similar relationships were seen between the LAA orifice area and LAAEF ($P = .016$, $r = -.22$) and the LAA flow velocity ($P < .0001$, $r = -.38$). Importantly, a positive correlation was observed between left atrial appendage ejection fraction (LAAEF) and LAA flow velocity ($P < .0001$, $r = .35$) (Fig 5).

Relationships between a representative TTE parameter (LAD, LAVI) and 3D-TEE anatomical and functional parameters were also investigated (Fig 6). Positive correlations were observed between LAD, assessed by TTE and LAA depth ($P < .001$, $r = .31$), and LAA orifice area ($P < .001$, $r = .40$), assessed by TEE. Furthermore, positive correlations between LAVI and LAA depth ($P < .001$, $r = .46$) and LAA orifice area ($P < .0001$, $r = .56$) were also present (Fig 7). On the other hand, inverse correlations were noted between LAD assessed by TTE and LAAEF ($P = .0014$, $r = -.29$), and LAA flow velocity ($P < .0001$, $r = -.48$) assessed by TEE. Additionally, as with the results for LAD, inverse correlations were documented between LAVI and LAAEF ($P = .0014$, $r = -.41$), and LAVI and LAA flow velocity ($P < .0001$, $r = -.50$).

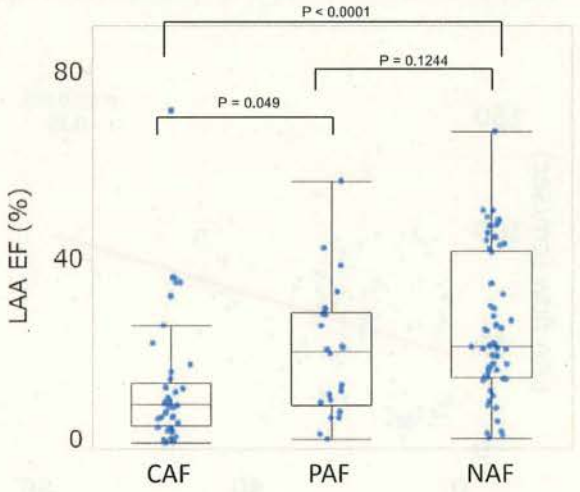

Figure 3. *Comparison of ejection fraction of the left atrial appendage (LAAEF) between CAF, PAF, and NAF. LAAEF was significantly lower in the CAF group (12.4 ± 12.7%) than in the PAF (18.0 ± 9.5%) and NAF (27.9 ± 15.5%) groups. Abbreviations: CAF, chronic atrial fibrillation; NAF, no detected atrial fibrillation; PAF, paroxysmal atrial fibrillation.*

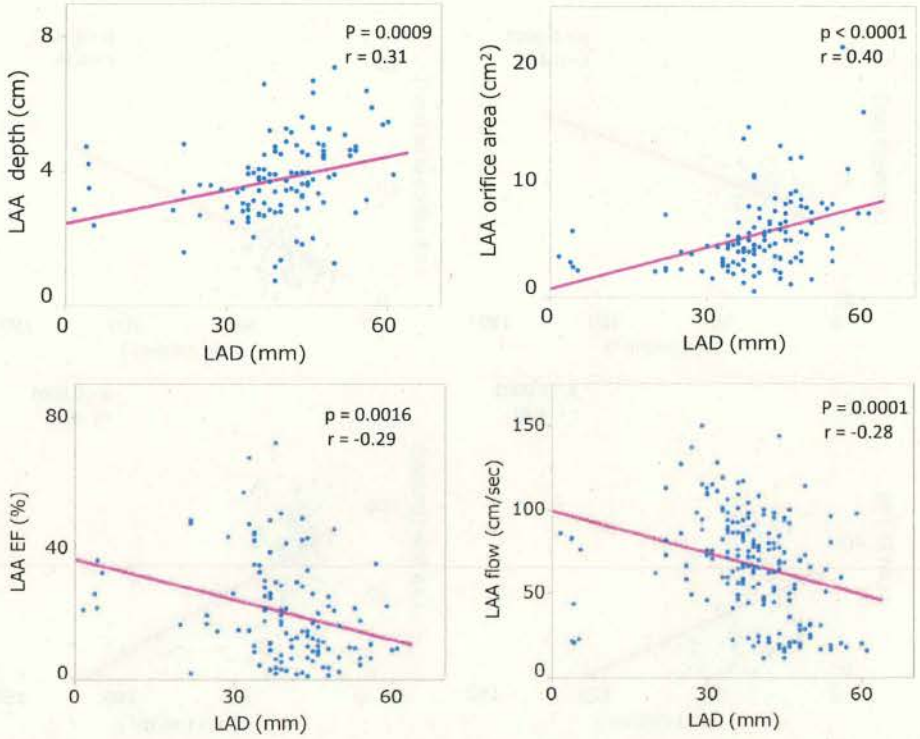

Figure 6. *Relationships between left atrial diameter (LAD) by transthoracic echocardiography (TTE) and 3D-TEE left atrial appendage (LAA) parameters (anatomical parameters: LAA depth, LAA orifice area; functional parameters: LAA ejection fraction, LAA flow velocity). Positive correlations were observed between LAD and 3D-TEE anatomical parameters (upper graphs) and inverse correlations between LAD and 3D-TEE functional parameters (lower graphs). Abbreviation: 3D-TEE, 3-dimensional transesophageal echocardiography.*

well as the other morphological parameters compared with conventional 2D-based TEE analyses.

Differences in Anatomical and Functional Characteristics of LAA in Different Cardiac Rhythm Patterns

There have been several previous reports regarding the relationship between the morphology of LAA and CES.[25-27] These relationships are reasonable, considering that most thrombi in patients with AF were present in the LAA, the morphology of which is very important for evaluating risk factors for CES. In addition, the demand for a profound understanding of morphology of LAA is increasing since the development and wider application of percutaneous LAA closure treatment: it is essential for visual guidance for accurate device sizing or positioning. From the present study, we learned that many elements of LAA, including depth, orifice diameter or area, and volume, are always greater in patients with CAF than in patients with NAF or PAF. Functions of the LAA in patients with CAF were much reduced, whereas in patients with PAF they were relatively well preserved.

Other findings of interest in this study can be derived from a general comparison with historical controls. Our study exclusively recruited patients who actually had CES, whereas previous studies had examined patients with AF in general. According to an earlier comparison of LAA by 3D-based assessment, LAA depth was 40.5 ± 8.0 mm, and orifice long- and short-axis diameters were 28.2 ± 7.2 mm and 9.2 ± 5.7 mm, respectively.[13] These values appeared to be smaller than those in our study (44.7 ± 11.8 mm; 37.4 ± 1.94 mm and 27.3 ± 7.5 mm, respectively), although direct comparison is difficult. If such differences are truly present, they may be due to differences in the recruited population. Our study demonstrated that LAA size correlated inversely with LAAEF and LAA flow velocity, findings which at least in part support this potential difference. In general, it is said that LAA morphology in patients with PAF is more likely to be similar to patients with NAF. However, our study indicated that LAA in PAF was significantly larger than in NAF. A slight morphological change of LAA may have already been present when the patients began to show PAF. Enlargement of LAA in patients with AF could have several reasons. When patients have AF, it is known that LA becomes larger.[28] LAA derives from primordial LA. LAA becomes larger as LA increases because they are histologically the same. The remodeling process associated with AF causes the LAA to function as a static pouch, predisposing to stagnation. LAA fills the space that is created within the pericardial sac during ventricular systole as

an inevitable inherent limitation in such clinical investigations. Fourth, quantitative 3D-TTE analyses were performed with methodology involving manual tracing. It is sometimes difficult to determine optimal phases of left ventricular systolic and diastolic periods during AF, which potentially cause errors in the measurement of LAA volume or function. To minimize such errors, we extracted information on systolic and diastolic phases to reduce mistakes as much as possible to derive visual maxima and minima. Some patients who had particularly complex LAA structures, such as multi-lobes, were very difficult to assess in 3D measurements. In the future, a similar examination using multislice computed tomography, magnetic resonance imaging synchronized with echocardiogram, should give us supporting results. Finally, this study focused only on patients with CES. At this time, we believe it is more meaningful to survey LAA morphology and function exclusively for the patients who had resultant clinical events. On the other hand, this makes it difficult to apply the obtained data to the overall AF population.

Conclusions

This detailed 3D-TEE study confirmed that LAA morphology and function were strongly affected by cardiac rhythms. Patients with CAF had the greatest dimension, area, and volume of any anatomical parameters of the LAA, as well as the poorest LAA function. An inverse correlation was observed between LAA size and LAA function. These basic findings could be useful for risk stratification of CES.

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