Impact of Increased Orifice Size and Decreased Flow Velocity of Left Atrial Appendage on Stroke in Nonvalvular Atrial Fibrillation

Jung Myung Lee, MD, Jaemin Shim, MD, Jae-Sun Uhlm, MD, Young Jin Kim, MD, PhD, Hye-Jeong Lee, MD, PhD, Hui-Nam Pak, MD, PhD, Moon-Hyoung Lee, MD, PhD, and Boyoung Joung, MD, PhD*

The structural and functional characteristics of left atrial appendage (LAA) in patients with atrial fibrillation (AF) with previous stroke remain incompletely elucidated. This study investigated whether a larger LAA orifice is related to decreased LAA flow velocity and stroke in nonvalvular AF. The dimension, morphology, and flow velocity of LAA were compared in patients with nonvalvular AF with (stroke group, n = 67, mean age 66 ± 9 years) and without ischemic stroke (no-stroke group, n = 151, mean age 56 ± 10 years). Compared with no-stroke group, the stroke group had larger LA dimension (4.7 ± 0.8 vs 4.2 ± 0.6 cm, p <0.001), larger LAA orifice area (4.5 ± 1.5 vs 3.0 ± 1.1 cm², p <0.001), and slower LAA flow velocity (36 ± 19 vs 55 ± 20 cm/s, p <0.001). LAA flow velocity was negatively correlated with LAA orifice size (R = −0.48, p <0.001). After adjustment for multiple potential confounding factors including CHA2DS2-VASc score, persistent AF, and LA dimension, large LAA orifice area (odds ratio 6.16, 95% confidence interval 2.67 to 14.18, p <0.001) and slow LAA velocity (odds ratio 3.59, 95% confidence interval 1.42 to 9.08, p = 0.007) were found to be significant risk factors of stroke. In patients with LAA flow velocity <37.0 cm/s, patients with large LAA orifice (>3.5 cm²) had greater incidence of stroke than those with LAA orifice of ≤3.5 cm² (75% vs 23%, p <0.001). In conclusion, LAA orifice enlargement was related to stroke risk in patients with nonvalvular AF even after adjustment for other risk factors, and it could be the cause of decreased flow velocity in LAA. © 2014 Elsevier Inc. All rights reserved. (Am J Cardiol 2014;113:963–969)

Methods

In this study, we hypothesized that increased orifice size of the left atrial appendage (LAA) is related to decreased flow velocity in the LAA and stroke in patients with atrial fibrillation (AF). To test this hypothesis, we analyzed the geometry, dimensions, and flow velocity of LAA using multidetector computed tomography (MDCT) and transesophageal echocardiography (TEE) in a series of patients with nonvalvular AF with and without ischemic stroke. We also evaluated whether large LAA orifices were related to decreased flow velocity of LAA and stroke in patients with nonvalvular AF.

In this study, we hypothesized that increased orifice size of the left atrial appendage (LAA) is related to decreased flow velocity in the LAA and stroke in patients with atrial fibrillation (AF). To test this hypothesis, we analyzed the geometry, dimensions, and flow velocity of LAA using multidetector computed tomography (MDCT) and transesophageal echocardiography (TEE) in a series of patients with nonvalvular AF with and without ischemic stroke. We also evaluated whether large LAA orifices were related to decreased flow velocity of LAA and stroke in patients with nonvalvular AF.

In this study, we hypothesized that increased orifice size of the left atrial appendage (LAA) is related to decreased flow velocity in the LAA and stroke in patients with atrial fibrillation (AF). To test this hypothesis, we analyzed the geometry, dimensions, and flow velocity of LAA using multidetector computed tomography (MDCT) and transesophageal echocardiography (TEE) in a series of patients with nonvalvular AF with and without ischemic stroke. We also evaluated whether large LAA orifices were related to decreased flow velocity of LAA and stroke in patients with nonvalvular AF.
pressure $\geq 140$ mm Hg or diastolic blood pressure $\geq 90$ mm Hg at 2 or more visits or medical history of hypertension. Dyslipidemia was defined by fasting triglyceride plasma levels $\geq 150$ mg/dl and/or fasting total cholesterol $\geq 200$ mg/dl and/or low-density lipoprotein-C $\geq 130$ mg/dl and/or high-density lipoprotein-C $< 40$ mg/dl or current use of lipid-lowering medications such as hydroxymethylglutaryl-CoA reductase inhibitors, bile acid sequestrants, and fibric acid derivatives. AF was classified as paroxysmal AF that self-terminates within 7 days and persistent AF that either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion.

TEE was performed with a 5-MHz multiplane transesophageal transducer connected to an ultrasound system (iE33; Philips Medical Systems, Andover, Massachusetts). After local pharyngeal anesthesia with lidocaine spray, the patient was placed in the left lateral position, and the transesophageal transducer was inserted into the esophagus. The LAA was observed in $0^\circ$, $45^\circ$, $90^\circ$, and $135^\circ$ to detect spontaneous echocontrast or thrombus. Then, a sample volume was placed at the middle portion of the LAA, and peak velocities of flow out of the LAA (emptying velocity) were measured. LAA peak emptying velocities were determined during 10 cardiac cycles, and the average value was used for analyses.

Contrast-enhanced cardiac CT scans were performed using a 64-slice MDCT (Somatom Sensation 64; Siemens Medical Solutions, Forchheim, Germany). A bolus of 60 to 80 ml iopamidol (Iopamiro 370; Bracco, Italy) was injected into an antecubital vein at a flow rate of 5 ml/s and then followed by a 50 ml saline chasing bolus at 5 ml/s. The start delay was defined by bolus tracking in the ascending aorta, and the scan was automatically initiated 5 seconds after reaching the contrast threshold of 140 H. Scans were performed using the following parameters: retrospective electrocardiographic-gated acquisitions, 80 to 120 kVp, 500 to 700 mAs depending on patient size, and 64 $\times$ 0.6 mm slice collimation. Scans were performed from the tracheal bifurcation to the diaphragm. The field of view was adjusted according to the size of the heart. The cardiac CT was reconstructed at the end-systolic and the mid-diastolic phases using a slice thickness of 0.75 mm, an increment interval of 0.5 mm, and a medium-smooth convolution kernel of B36f. We used end-systolic CT images for this study.

Two experienced radiologists (YJK and HJL, with 4 years and 8 years of experience with cardiac MDCT, respectively) measured the LAA long (D1) and short (D2) diameters by using the CT images and associated software (Vitrea; Toshiba, Japan). The LAA orifice was manually transected by multiplanar reformatted images. The size of the LAA orifice was defined by its narrowest portion. Then, cross-sectional views for LAA were produced by creating a plane perpendicular to the transverse multiplanar reformatted image (Figure 1). Because the LAA orifice is elliptical in

![Figure 1. Measurement of LAA orifice size by multiplanar reformatted images of MDCT. (A) 3D reconstruction image of LA, LAA (Windsock type), and pulmonary veins. (B) Coronal, (C) sagittal, and (D) tangential images of heart.](image-url)
Table 1
The clinical characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stroke p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 151)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>Women</td>
<td>33 (22)</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>98 (65)</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>53 (35)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67 (44)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>0</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>33 (22)</td>
</tr>
<tr>
<td>CHADS₂ score</td>
<td>0.8 ± 1.0</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score</td>
<td>1.0 ± 1.1</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>63.0 ± 7.5</td>
</tr>
<tr>
<td>E/E'</td>
<td>9.9 ± 4.1</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>78 (52)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) and mean ± SD.

* Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at 2 or more visits or medical history of hypertension.

† Dyslipidemia was defined by fasting triglyceride plasma levels ≥150 mg/dl and/or fasting total cholesterol ≥200 mg/dl and/or low-density lipoprotein-C ≥130 mg/dl and/or high-density lipoprotein-C <40 mg/dl, or current use of lipid-lowering medication.

Results

Table 1 lists a comparison of clinical characteristics between the stroke and no-stroke groups. The stroke group was older and had a greater prevalence of co-morbidities and higher CHADS₂ and CHA₂DS₂-VASc scores than the no-stroke group. The CHADS₂ and CHA₂DS₂-VASc scores were calculated according to the clinical status before stroke onset. Body mass index was lower in the stroke group than in the no-stroke group. E/E' ratio was significantly higher in the stroke group than that in the no-stroke group. Reasons for withholding anticoagulant therapy in the stroke group included stroke as the presenting symptom of AF (41%), low-risk patients (24%), unawareness (6%), physician discretion (19%), patient preferences (6%), history of bleeding (2%), and unknown reasons (2%). This study included patients who underwent TEE and CT during the same rhythm. In total, 137 (63%) patients had undergone TEE and CT during AF.

Table 2 lists LA and LAA parameters measured by MDCT and TEE. The stroke group had larger LA dimensions and larger LA volume than the no-stroke group. LA orifice area, LA depth, and LAA volume were also significantly larger in the stroke group. LAA emptying velocity was lower in the stroke group than the no-stroke group. There was no significant difference in the number of LAA lobes between the 2 groups. Morphologic types of LAA were not significantly different between the 2 groups. In the same study period, 24 patients with nonvalvular AF and on anticoagulation developed ischemic stroke and underwent cardiac MDCT and TEE. When we added this population to the stroke group, the MDCT and TEE parameters did not change significantly (Supplemental Table 1).

LAA orifice area was small, and LAA flow velocity was normal in no-stroke group (Figure 2). However, stroke group showed an enlarged LAA orifice and decreased LAA flow velocity (Figure 2). Figure 3 shows the relation between LAA flow velocity and the structural characteristics...
of LAA and LA. LAA flow velocity was shown to have a negative correlation with LAA orifice area ($R = -0.48$, $p < 0.001$), LAA volume ($R = -0.22$, $p < 0.001$), and LA volume ($R = -0.49$, $p < 0.001$) (Figure 3). Moreover, LAA flow velocity was negatively correlated with E/E’ ratio ($R = -0.31$, $p < 0.001$). The LAA flow velocity of $<37.0$ cm/s predicted stroke with a sensitivity of 60% and a specificity of 81% with an area under the curve of 0.75. The
LAA orifice area of $>3.5$ cm$^2$ predicted stroke with a sensitivity of 79% and a specificity of 78% with an area under the curve of 0.82.

Multiple possible clinical risk factors and CT measurements were assessed as univariate risk factors of stroke. The significant univariate risk factors of stroke were age, hypertension, diabetes mellitus, persistent AF, body mass index, E/E', LA dimension, LAA velocity, and LAA orifice area (Table 3). In multivariate analysis, larger LAA orifice area, slower LAA velocity, and CHA2DS2-VASc score were all significant risk factors of stroke. In patients with LAA flow velocity $<37.0$ cm/s, patients with large LAA orifice ($>3.5$ cm$^2$) had greater incidence of stroke than those with LAA orifice of $\leq3.5$ cm$^2$ (75% vs 23%, $p < 0.001$, Figure 4). The larger LAA orifice and slower LAA velocity predicted stroke with a sensitivity of 52% and a specificity of 92%.

Discussion

We found that the LAA orifice enlargement is related to the risk of stroke in patients with nonvalvular AF even after adjustment for other risk factors. Second, the LAA orifice enlargement was closely related with the decreased flow velocity of LAA. Finally, large LAA orifice accompanied with decreased flow velocity was a strong risk factor of stroke in nonvalvular AF. Our findings support the hypothesis that the size and function of LAA may be involved in the development of cardioembolic accidents.9,10

It could be hypothesized that small LAA orifice can interfere with blood flow, and therefore patients with small orifice are more prone to blood stasis, clot formation, and cardioembolic events than patients with large LAA orifice. However, in this study, the enlargement of the LAA orifice was closely related with stroke and was an independent risk factor of stroke. Because larger LAA promotes slow blood flow, blood stasis, and eventually thrombus formation11–14, it is plausible that larger LAA is associated with greater stroke risk. However, it is still controversial whether LAA size can predict the risk of cardioembolic events or not.15–18

Most of the previous studies have not focused on the patients with nonvalvular AF. Moreover, LAA size was often assessed by TEE, which can result in inaccurate dimensional estimates. Recently, MDCT can determine the volume of the cardiac chambers accurately with good interobserver and intraobserver variations. Furthermore, it provides reliable 3-dimensional images of cardiac chambers. Thus, MDCT evaluation of the volume and anatomical characteristics of LAA can be more reliable than TEE. Using MDCT, our study showed that LAA orifice enlargement was related with stroke in patients with nonvalvular AF. Moreover, persistent AF showed larger LAA than paroxysmal AF (Supplemental Table 2).

Recently, it was reported that patients with non-Chicken Wing LAA morphology were more likely to have embolic events than those with Chicken Wing-type LAA.8 However, the relation between LAA morphology and stroke is still controversial.19 In this study, there was no significant difference in LAA morphology between patients with AF with stroke and without stroke.

Handke et al reported that LVEF, LA diameter, paroxysmal AF, age, and sex were independent parameters influencing LAA flow velocity.20 Consistent with this report, we found that LA enlargement was related with a decrease in LAA flow velocity. An interesting finding of our study was that the LAA orifice enlargement was also closely related with decreased LAA flow velocity. Previously, Agmon et al reported that LAA emptying velocity was correlated negatively ($R = -0.29, p = 0.002$) with LAA orifice diameter measured by TEE.14 According to the continuity equation, the flow velocity became slower as the cross-sectional area became wider. The flow velocity became faster as the cross-sectional area got smaller, if the flow rate remains unchanged. Our data suggest that the same rule is applied to the relation of the cross-sectional area of LAA and its velocity, and therefore LAA orifice area is considered as an important factor that determines LAA flow velocity. Another explanation is that the decreased contractility of LA could be related with the enlarged LAA. A decreased LAA flow velocity is a sign of worsened LAA dysfunction in a continuous process, resulting in a steadily increasing probability of spontaneous echocoontrast and thrombi formation.21

The importance of LAA flow velocity for estimating the risk of embolism has primarily been examined in patients with AF. Several studies showed that among patients with AF, subgroups with low LAA velocity have a greater risk of thromboembolic events than those with a high LAA velocity.22–24 AF is coupled with a marked decrease in LAA flow velocity.11,24 Previous studies on patients with AF have shown that subgroups with LAA flow velocity $\leq20$ cm/s, $22 \leq25$ cm/s, $24,25$ and $\leq35$ cm/s$^2$ are at greater embolic risk than other patients. Handke et al reported that the risk of thrombus/spontaneous echocoontrast was increased significantly at an LAA flow velocity $\leq55$ cm/s independent of the rhythm.20 In
this study, the LAA flow velocity of <37.0 cm/s maximized the sum of sensitivity and specificity for predicting stroke. Interestingly, the patients with LAA flow velocity <37.0 cm/s and larger (>3.5 cm²) LAA orifice had high incidence of stroke of 75%. Therefore, these subpopulation will need strict anticoagulation to prevent stroke.

There are several limitations to our study. First, because this study was a case-control study, it is prone to recall and selection bias. However, although selection bias might exist, we provided evidence that the LAA orifice size is an independent risk factor of stroke using age- and sex-matched analysis using the largest number of patients compared with previously reported studies. Whether LAA velocity and orifice size would provide similar risk stratification among a cohort of patients without history of stroke can only be assessed in a prospective cohort study. Second, silent cerebral infarctions, which are reported in 13% to 48% of patients with AF, might have occurred in patients who were classified as having no history of embolic events. Third, we did not have data regarding the loading condition before MDCT or TEE. Therefore, individual loading conditions may vary from patient to patient and could influence the MDCT and TEE parameters. However, MDCT and TEE were performed by the same nι per os duration of 8 hours, and the 2 examinations were done within 2.2 ± 2.6 days to minimize the variation of volume status.

Disclosures

This study was supported in part by research grants of the Basic Science Research Program through the National Research Foundation of Korea, funded by the Ministry of Education, Science and Technology (2012-0007604, 2012-045367), and a grant of the Korean Healthcare technology R&D project, Ministry of Health & Welfare (A121668). No other potential conflicts of interest relating to this article were reported.

Supplementary Data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2013.11.058.


学霸图书馆

www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页  文献云下载  图书馆入口  外文数据库大全  疑难文献辅助工具