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Association of Left Atrial Appendage Voltage with Ischemic Stroke in Patients with Atrial Fibrillation

Binhao Wang, Huimin Chu, Bin He, Guohua Fu, Xianfeng Du, Yibo Yu, Jing Liu and Mingjun Feng

Background: Low atrial voltage is associated with an increased risk of stroke. The relationship between left atrial appendage voltage (LAAV) and ischemic stroke remains unknown. Low LAAV may predict the prevalence of ischemic stroke in patients with atrial fibrillation (AF).

Methods: A total of 1108 patients with AF referred for catheter ablation were consecutively included from January 2015 to May 2018. The patients were divided into stroke and control groups based on previous ischemic stroke by neuroimaging criteria. LAAV was measured with a circular mapping catheter in sinus rhythm after ablation. Variables were compared, and logistic regression was performed to assess the relationship between LAAV and stroke.

Results: A total of 120 patients (10.8%) had a history of ischemic stroke. The patients in the stroke group were older and had higher percentages of hypertension, diabetes mellitus and coronary/vascular disease. The CHA_2DS_2-VASc score was higher and left atrial diameter was larger in the patients with stroke. More left atrial appendage thrombi and spontaneous echo contrast were detected in the stroke group. LAAV was significantly lower in the stroke group compared with the controls (5.3 ± 1.8 mV vs. 6.5 ± 1.8 mV; $p < 0.001$). Multivariate logistic regression revealed that a lower LAAV was associated with increased stroke prevalence [odds ratio = 0.75; 95% confidence interval (CI) 0.65-0.87; $p < 0.001$]. LAAV had a predictive value, with an area under the curve of 0.83 (95% CI 0.79-0.87; $p < 0.001$). With an optimal cut-off value of 5.2 mV for LAAV, the sensitivity and specificity were 75% and 74%, respectively.

Conclusions: Lower LAAV in AF patients was associated with increased ischemic stroke prevalence. Whether LAAV is related to incident stroke requires further studies.

Key Words: Atrial fibrillation • Ischemic stroke • Left atrial appendage • Voltage

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia.[1] It is linked to several forms of cardiovascular disease, but may also occur in otherwise normal hearts.[2] The Framingham Study demonstrated that AF is an independent risk factor for stroke, increasing its incidence by 5 folds.[3] The majority of left atrial (LA) thrombi originate from the LA appendage (LAA).[4-6] Multiple studies assessing LAA have demonstrated that morphology,[7-9] volume,[10-12] and flow velocity[13-15] are associated with an elevated risk of stroke.

Atrial remodeling includes electrical and structural remodeling. Electrical remodeling alters ion channel expression and/or function in a way that promotes AF. Structural remodeling, particularly fibrosis, is important in many forms of AF,[16] and low atrial voltage is an indicator of atrial fibrosis.[17] Previous findings have revealed that atrial fibrosis is significantly higher in patients with a history of stroke compared to those who never experienced stroke.[18]

Theoretically, LAA remodeling may result in LAA fibrosis, low LAA voltage (LAAV) and decreased LAA contractility. Impaired LAA function has been shown to be correlated with ischemic stroke and thrombus formation.[19] In the present study, we measured the LAAV dur-

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Arrhythmia Center, Ningbo First Hospital, Ningbo, Zhejiang, China.
Corresponding author: Dr. Huimin Chu, Arrhythmia Center, Ningbo First Hospital, No. 59, Liuting Street, 315010, Ningbo, Zhejiang, China. Tel: +86-574-87085211; Fax: +86-574-87085009; E-mail: epnbheart@163.com

ing ablation procedures in AF patients, and studied whether LAAV was associated with prior ischemic stroke.

METHODS

Study patients

Upon approval by the Ethics Committee of Ningbo First Hospital, we conducted this retrospective study. The study population was composed of consecutively enrolled patients with non-valvular AF referred for catheter ablation at the Department of Cardiology, Ningbo First Hospital, from January 2015 to May 2018. All patients were derived from the outpatient department. Most patients received cerebral MRI to confirm the history of ischemic stroke before ablation, which was determined by at least two radiologists or neurologists. Computed tomography (CT) was used if the patients presented with contraindications or refusal to undergo MRI. CHA_2DS_2-VASc scores [congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex (female)] before stroke occurrence were calculated by two investigators for each patient based on comorbidities.

Collection and definitions of potential covariates

Anticoagulation medication status was collected at the time of the outpatient visit. All patients were given anticoagulation therapy for at least 3 weeks before admission for catheter ablation. Information regarding previous disease history was collected at the time of hospital admission for diabetes mellitus, hypertension, congestive heart failure, and coronary/vascular disease. Body mass index was determined as weight (kg) divided by height squared (m^2). Transthoracic echocardiography was performed to obtain left ventricular (LV) ejection fraction, LA diameter and LV end-systolic diameter for each patient. Transesophageal echocardiography (TEE) was performed, and the LAA orifice diameter was measured. LAA thrombus (LAAT) and spontaneous echo contrast (SEC) were detected. Patients with LAAT were prescribed with anticoagulants until no thrombus was detected by TEE, and they were re-admitted to hospital for ablation.

Measurement of LAAV

Antiarrhythmic drug therapy was stopped five half-lives before measurements. The patients were placed in the supine position under deep sedation for ablation. A decapolar diagnostic catheter was positioned in the coronary sinus via the left femoral venous access. Through the right femoral vein, two transseptal accesses were obtained for the placement of two sheaths (SWARTZ, St. Jude Medical). A circular mapping catheter (Inquiry™ Afocus™ II, St. Jude Medical) was used to map pulmonary vein potential and LAAV. Three-dimensional reconstruction of the left atrium and pulmonary veins was performed based on CT scan data using Ensite NavX Verismo software (St. Jude Medical, St Paul, MN, USA).

A 4.0-mm 7F irrigated-tip ablation catheter (Therapy™, Cool Flex™, St. Jude Medical, St. Paul, MN, USA) was used to perform ablation. The radiofrequency ablation settings used were 35 W/43 °C/13 mL per minute. Circumferential pulmonary vein isolation (CPVI) was performed using contiguous point-by-point radiofrequency. Lines and complex fractionated atrial electrograms (CFAEs) were performed if necessary. No patients underwent electrical LAA isolation. Patients were cardioverted to sinus rhythm if AF rhythm persisted after ablation.

Thirty minutes after ablation, the circular mapping catheter was placed in the LAA with satisfactory contact for voltage measurement in sinus rhythm (Figure 1). The catheter position in the LAA was confirmed by snapshot or angiography through the sheath when necessary. Local LAAV was defined as the amplitude of bipolar intracardiac electrogram with filtration set at HighPass 30 Hz - LowPass 500 Hz (Figure 2). Electrograms for each measurement were recorded for 10 seconds. All of the procedures were performed by a senior electrophysiologist (H.C.). LAAV was measured by two investigators who were blinded to the information of the subjects, and the

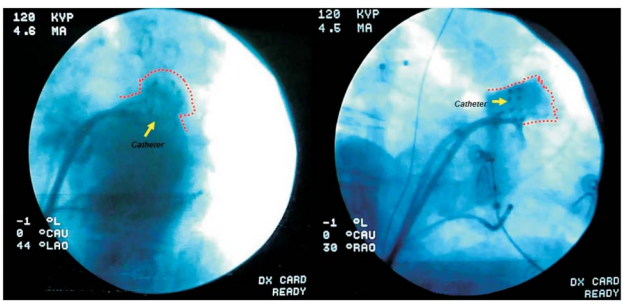

Figure 1. *The position of catheter in LA appendage (LAA). LAA angiography showed that the catheter (yellow arrow) was positioned at the place with satisfactory contactin LAA for voltage measurement.*

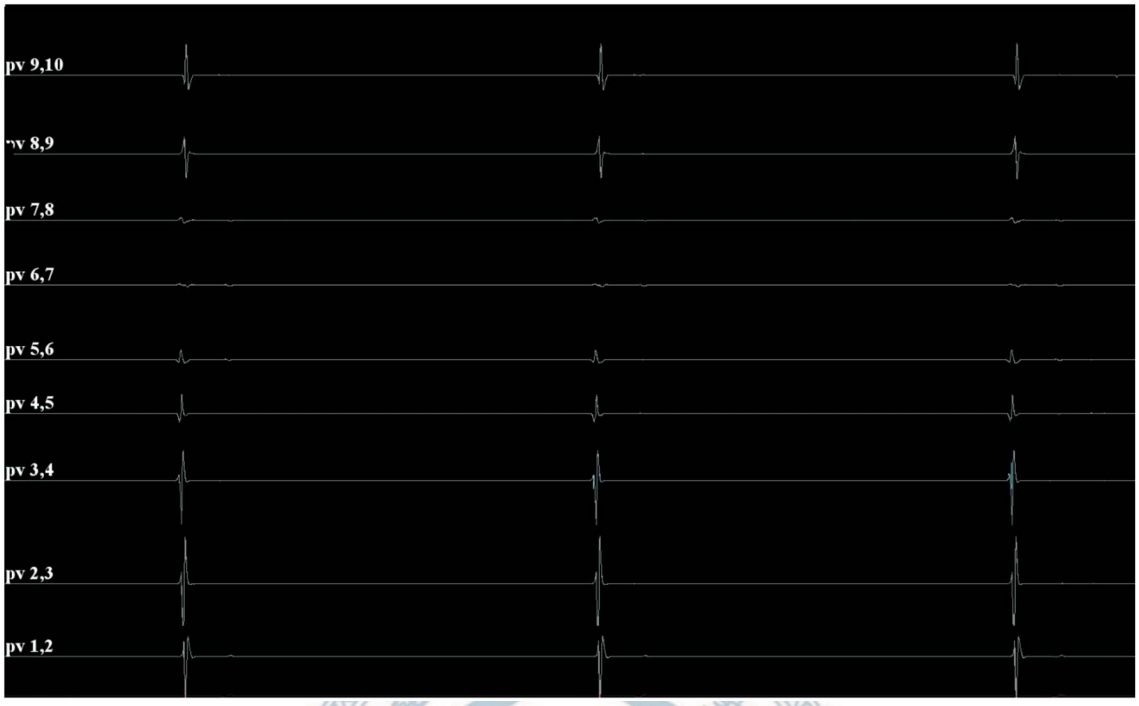

Figure 2. *LA appendage (LAA) voltage in sinus rhythms. Local LAA voltage was defined as the amplitude of bipolar intracardiac electrogram with filtration set at HighPass 30 Hz - LowPass 500 Hz.*

mean value was recorded. LAAVs of all electrodes were collected and the mean value was used.

Statistical analysis

The study patients were divided into stroke (subjects with prevalent stroke) and control (individuals without previous stroke) groups. Normally distributed continuous variables were expressed as mean (standard deviation), while median (inter-quartile range) was used for variables with a skewed distribution. Normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov goodness-of-fit test. Categorical variables were expressed as absolute number (percentage). Continuous variables were compared using the *t* test and Mann-Whitney *U* test for normally and non-normally distributed data, respectively. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate.

Logistic regression was performed to analyze the associations of potential variables with prevalent stroke. The initial model was adjusted for age and gender. The multivariate model included the variables with statistical significance in the initial model. Furthermore, subgroup analysis was conducted with the same potential variables as the multivariate model. Odds ratio (OR) and 95% confidence interval (CI) were calculated.

A receiver operating characteristic curve (ROC) was used to assess the ability of LAAV to predict stroke. The optimal cut-off value was determined as well as the area under the curve (AUC). Statistical analyses were performed with SPSS 19.0 (IBM, Armonk, NY, USA), and $p < 0.05$ (2-tailed) was considered to be statistically significant.

RESULTS

Baseline characteristics

Of the 1108 included patients, 1053 (95.0%) underwent cerebral MRI and 120 (10.8%) had prevalent ischemic stroke. Compared with the control group, the stroke group was older, and had higher percentages of CHA_2DS_2-VASc score ≥ 2, diabetes mellitus, and coronary/vascular disease. The median period of AF history was longer in the stroke group, although no statistical difference was indicated (36 vs. 24 months, $p = 0.119$). There was no significant difference in pre-procedural anticoagulation treatment between the two groups. All

patients received anticoagulation therapy for at least 3 weeks before admission for catheter ablation. In the stroke group, the mean period from the index ischemic stroke to the LAAV measurement was 4.2 ± 2.9 months.

Echocardiographic data for the cases and controls are listed in Table 1. No significant differences were found in LV ejection fraction (62 ± 7% in the stroke group vs. 64 ± 19% in the control group; p = 0.190) and LV end-diastolic diameter (48 ± 5 mm vs. 48 ± 5 mm; p = 0.369). The LA diameter was greater in the stroke group than in the control group (42 ± 6 mm vs. 39 ± 6 mm; p < 0.001). The mean LAA orifice diameter was comparable between the two groups (21 ± 7 mm vs. 22 ± 6 mm; p = 0.260). LAAT and SEC were detected in 9 (8%) and 12 (10%) patients in the stroke group, respectively, compared to 10 (1%) and 15 (2%) in the control group.

The study population included 683 patients with paroxysmal AF and 425 with persistent AF. A total of 651 patients were in sinus rhythm at the beginning of the procedure, and 457 in AF rhythm. Ablation strategy was comparable between the two groups.

LAAV was associated with ischemic stroke

LAAV data are displayed in Table 1, Figure 3 and Fig-

Table 1. Baseline characteristics of the study patients

Characteristic	Stroke group	Control group	p value
No. of patients	120	988	-
Age, years	66 ± 8	61 ± 10	< 0.001
Male gender, *n* (%)	75 (63)	648 (66)	0.502
Paroxysmal AF, *n* (%)	67 (56)	616 (62)	0.166
History of AF, month	36 (8-70)	24 (6-60)	0.119
Cerebral imagine examination			0.670
MRI, *n* (%)	115 (95.8)	938 (94.9)	
CT, *n* (%)	5 (4.2)	50 (5.1)	
Body mass index, kg/m^2	24.5 ± 3.5	24.6 ± 3.6	0.882
Hypertension, *n* (%)	76 (63)	540 (55)	0.071
Diabetes mellitus, *n* (%)	27 (23)	131 (13)	0.006
Congestive heart failure, *n* (%)	7 (6)	35 (4)	0.207
Coronary/vascular disease, *n* (%)	79 (66)	455 (46)	< 0.001
CHA_2DS_2-VASc score ≥ 2	86 (72)	587 (59)	0.009
Anticoagulants			0.964
Warfarin, *n* (%)	4 (3)	42 (4)	
Dabigatran, *n* (%)	22 (18)	185 (19)	
Rivaroxaban, *n* (%)	9 (8)	77 (8)	
Anti-arrhythmic drugs, *n* (%)	74 (62)	559 (57)	0.288
Echocardiographic data			
LV ejection fraction, %	62 ± 7	64 ± 19	0.190
LV end-diastolic diameter, mm	48 ± 5	48 ± 5	0.369
LA diameter, mm	42 ± 6	39 ± 6	< 0.001
LAA orifice diameter, mm	21 ± 7	22 ± 6	0.260
LAA thrombus, *n* (%)	9 (8)	10 (1)	< 0.001
Spontaneous echo contrast, *n* (%)	12 (10)	15 (2)	< 0.001
Ablation strategy			0.559
CPVI only, *n* (%)	74 (62)	632 (64)	
CPVI + line(s), *n* (%)	35 (29)	247 (25)	
CPVI + line(s) + CFAEs, *n* (%)	11 (9)	109 (11)	
LAA voltage, mV	5.3 ± 1.8	6.5 ± 1.8	< 0.001

Data are mean ± SD, median (inter-quartile range) or *n* (%).

AF, atrial fibrillation; CFAEs, complex fractionated atrial electrograms; CT, computed tomography; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; MRI, magnetic resonance imaging.

* The reported CHA_2DS_2-VASc scores were calculated before any thromboembolic event.

ure 4. LAAV was significantly lower in the stroke group than in the control group (5.3 ± 1.8 mV vs. 6.5 ± 1.8 mV; p < 0.001), and this result was consistent in the patients with both paroxysmal and persistent AF. The mean values of LAAV in the patients with and without LAAT and SEC were 4.5 ± 1.2 mV and 6.4 ± 1.8 mV, respectively (p < 0.001).

Table 2 shows that lower LAAV, increasing age, coronary/vascular disease, LAAT/SEC, and larger LA diameter were associated with a higher percentage of prevalent stroke. The patients with a higher LAAV had lower odds of having a previous ischemic stroke (OR = 0.75; 95% CI 0.65-0.87; p < 0.001) after multivariate logistic regression analysis. Subgroup analysis demonstrated that a lower LAAV was associated with a higher percentage of prevalent stroke in almost all of the groups (Figure 5).

ROC analysis for LAAV showed an AUC of 0.83 (95% CI 0.79-0.87; p < 0.001). The optimal cut-off value was 5.2 mV for LAAV, yielding a sensitivity and specificity of 75% and 74%, respectively (Figure 6).

DISCUSSION

The present study is the first to assess the relationship between LAAV and prevalent ischemic stroke in AF patients. We found that a lower LAAV was associated with higher ischemic stroke prevalence. This novel result could be clinically relevant for AF patients.

In AF patients, heart rate control and anticoagulation medication constitute the cornerstone of clinical therapy, in addition to rhythm control when possible.[20] Catheter ablation is more effective than antiarrhythmic

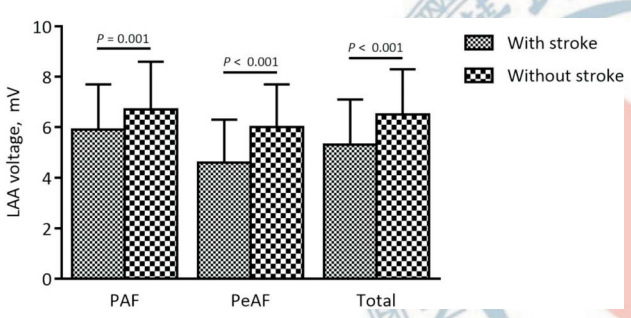

Figure 3. *Comparisons of LAA voltage between patients with and without prevalent stroke. LAA, left atrial appendage; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation.*

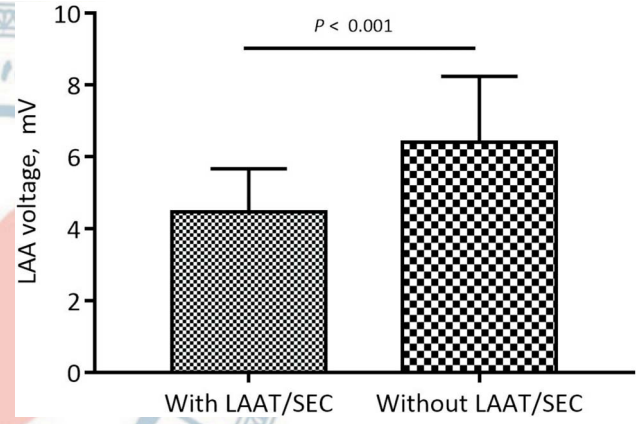

Figure 4. *Comparisons of LAA voltage between patients with and without LAAT/SEC. LAA, left atrial appendage; LAAT, LAA thrombus; SEC, spontaneous echo contrast.*

Table 2. Logistic regression data for identifying relationship between LAA voltage and prevalent ischemic stroke in patients with AF

	Univariable analysis*		Multivariable analysis#	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age	1.05 (1.03-1.08)	< 0.001	1.03 (1.01-1.06)	0.010
History of AF	1.00 (0.99-1.01)	0.990	-	-
Paroxysmal AF	0.76 (0.52-1.12)	0.162	-	-
Hypertension	1.13 (0.76-1.70)	0.548	-	-
Diabetes mellitus	1.54 (0.96-2.49)	0.075	-	-
Coronary/vascular disease	1.75 (1.16-2.66)	0.008	1.77 (1.14-2.73)	0.010
The use of anticoagulants	0.93 (0.61-1.41)	0.719	0.98 (0.63-1.52)	0.914
LAA thrombus/SEC	8.52 (4.58-15.86)	< 0.001	5.13 (2.62-10.07)	< 0.001
CHA_2DS_2-VASc score ≥ 2	0.98 (0.60-1.61)	0.941	-	-
LA diameter	1.06 (1.03-1.10)	< 0.001	1.05 (1.01-1.08)	0.007
LAA voltage	0.67 (0.59-0.77)	< 0.001	0.75 (0.65-0.87)	< 0.001

AF, atrial fibrillation; CI, confidence interval; LA, left atrial; LAA, left atrial appendage; SEC, spontaneous echo contrast.
* Adjusted for age and gender; # Adjusted for variables with statistical significance in univariable analysis.

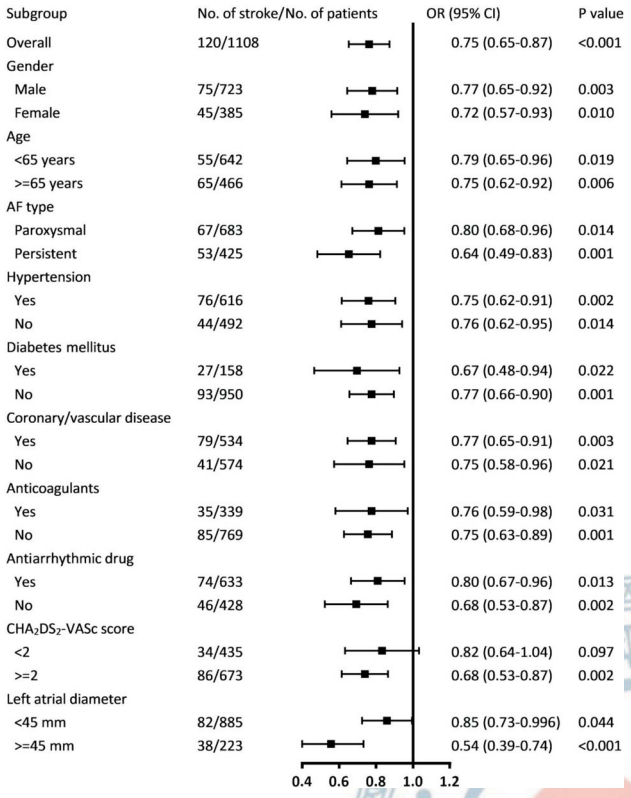

Figure 5. *The relationship between left atrial appendage voltage and prevalent stroke in subgroups. Odds ratios (ORs) was calculated using multivariable adjusted logistic regression. The variables included age, coronary/vascular disease, the use of anticoagulation, LAA thrombus/spontaneous echo contrast, and LA diameter.*

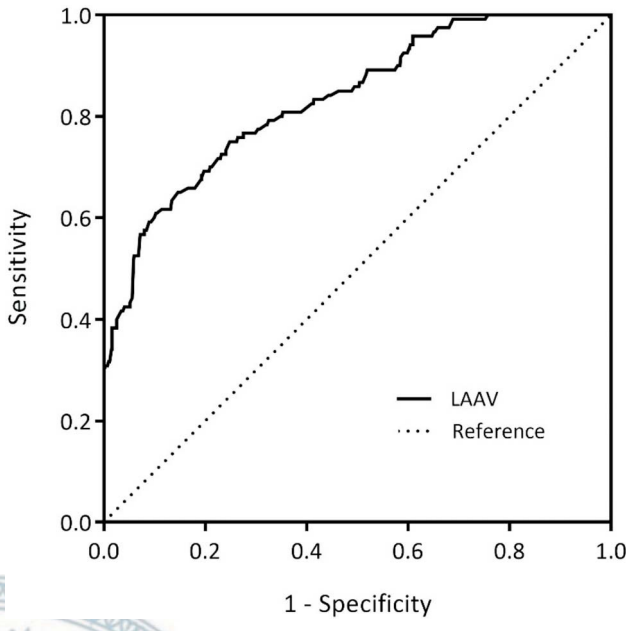

Figure 6. *ROC curve of LAAV in predicting prior ischemic stroke. LAAV, left atrial appendage voltage. AUC was 0.83 (95% CI 0.79-0.87; p < 0.001). The optimal cut-off value was 5.2 mV for LAAV (sensitivity, 75%; specificity, 74%).*

drug therapy in maintaining sinus rhythm.[21] The CHA_2DS_2-VASc score system was introduced into guidelines and implemented into clinical practice to assess the risk of thromboembolism in patients with AF. Individuals with CHA_2DS_2-VASc scores ≥ 2 should receive oral anticoagulation therapy.[22] However, several studies have revealed that stroke prevalence in patients with a CHA_2DS_2-VASc score < 2 varies by region and race.[23-25] The clinical decision making for anti-coagulation medication remains controversial in patients with low CHA_2DS_2-VASc scores in the absence of controlled trial data.

In the current study, a lower LAAV was associated with increased stroke prevalence. The LAAV was lower in the stroke group, and also in the patients with LAAT/SEC. The history of AF was longer in the patients with prevalent stroke, but no statistical significance was indicated. Longer AF history may be one of the determining factors of lower LAAV in stroke patients. It is well known that regular electrical activity (LAAV) can represent the substrate, and LAAV was lower in the stroke group in this study, which may indicate more fibrosis of the LAA. Fibrosis is a "stable" feature that progresses over time without abrupt changes, as opposed to other features such as LAA diameter or volume. Few studies have investigated the relationship between LAAV and fibrosis. Van Brakel et al.[26] reported that the percentage of interstitial fibrosis in LAA was higher in patients with persistent AF than in those with paroxysmal AF. However, surprisingly, no correlation was found between fibrosis and electrogram voltage. Two important points should be noted. (1) The electrograms were recorded from the LAA in only 4 patients, and thus the lack of association may be due to the small study sample. (2) The analysis of fibrosis was performed in tissue with two-dimensional cut from the LAA, which was definitely a major limitation of the study. Therefore, the degree of fibrosis in the study may not be very accurate. Thus, further investigations are needed to elucidate the association between LAAV and LAA fibrosis.

In addition to LAA fibrosis, the function of LAA may play a role in prevalent stroke. It is possible that in patients with a history of stroke, the activation of LAA is less organized, which may lead to less emptying and more stasis of the LAA. Previous studies have reported

that lower flow velocity in the LAA is related with an elevated stroke risk.[13-15] Our investigation also showed that LAAT/SEC was significantly higher in the stroke group (Table 1). However, the above potential mechanism is merely speculative.

LA and LAA remodeling have been associated with AF and stroke,[27,28] and it may coexist in AF patients. A previous study showed that decreased LA peak systolic strain was independently associated with LAA dysfunction in patients with acute ischemic stroke.[29] LAAV had a negative relationship with LA size in the present study (data not shown). However, the link between LA voltage and LAAV is unclear, and further studies are needed to elucidate this issue.

CHA_2DS_2-VASc score was not a risk predictor for prior ischemic stroke in the current study (Table 2). We calculated the CHA_2DS_2-VASc score before stroke occurrence, as also reported in previous studies.[9,12] Khurram et al.[9] and Kong et al.[30] retrospectively studied the relationship between LAA morphology and prior stroke, and CHA_2DS_2-VASc score was also not a risk predictor for stroke in both studies. CHA_2DS_2-VASc score is a risk prediction system for incident ischemic stroke, which may not be a suitable predictor of prior stroke.

The potential limitations of the current study should be mentioned. First, this was a retrospective study of an AF ablation cohort, with data derived from a selected population of patients undergoing AF ablation. Therefore, further studies are required to establish whether the current findings can be extended to the general population with AF. Second, we mentioned that lower LAAV may indicate more fibrosis of the LAA. However, cardiac MRI was not available due to restrictions of the medical insurance policy. Further studies are needed to investigate the relationship between LAAV and LAA fibrosis. Third, the anticoagulation status could not be determined at the time of stroke, which is similar to prior studies.[8,9] However, the association between prior stroke and LAAV was significant. The results, therefore, are likely to be accurate, but warrant validation in a prospective study.

CONCLUSIONS

The current findings revealed that a lower LAAV was independently associated with a higher prevalence of ischemic stroke. However, whether LAAV is associated with newly-acquired stroke remains unclear.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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