

The electroanatomical remodelling of the left atrium is related to CHADS₂/CHA₂DS₂VASc score and events of stroke in patients with atrial fibrillation

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Background

Although atrial fibrillation (AF) increases the risk of stroke, its relationship with atrial remodelling has not yet been studied. We hypothesized that the degree of electroanatomical remodelling of the left atrium (LA) is related to CHADS₂/CHA₂DS₂VASc score and events of stroke.

Methods and results

We compared CHADS₂/CHA₂DS₂VASc score (0, 1, ≥ 2) or events of stroke with mean and regional LA volume [by three-dimensional (3D) computed tomography images] or LA endocardial voltage (by 3D-electroanatomical map) in 348 patients who underwent catheter ablation of AF (78.4% male, 55.4 ± 11.0 years old, paroxysmal AF: persistent AF = 215:133). We graded LA volume index as Grade 1 (< 48.3 mL/m²; $n = 80$), grade 2 (48.3–63.0 mL/m², $n = 82$), grade 3 (63.0–99.0 mL/m²; $n = 94$), and grade 4 (≥ 99.0 mL/m²; $n = 92$). Results (i) The percentage volume of anterior portion of LA enlarged at the early stage of LA remodelling (Grade 1 vs. grade 2, $P = 0.006$) and the voltage of posterior venous LA was significantly reduced with the degree of LA remodelling ($P = 0.001$). (ii) Mean LA volume/body surface area (BSA), especially anterior portion of LA, was greater in patients with high CHADS₂/CHA₂DS₂VASc score ($P = 0.002$). Mean LA voltage was significantly lower in patients with high CHA₂DS₂VASc score than low score ($P = 0.007$). (iii) In patients who experience stroke ($n = 22$), LA volume/BSA, especially anterior LA, was greater ($P = 0.012$), and LA endocardial voltage was lower ($P = 0.039$) than those without stroke.

Conclusion

Electroanatomical remodelling of LA, estimated by LA volume and endocardial voltage, has significant relationship with the risk scores or events of stroke in patients with non-valvular AF.

Keywords

Atrial fibrillation • CHADS₂ score • Stroke • Left atrium • Voltage

Introduction

Atrial fibrillation (AF) is the most common arrhythmia disorder, affecting up to 9% of the population by the age of 80 years, and is a significant risk factor for thromboembolic stroke.^{1,2} CHADS₂ scores have been utilized as an excellent predictor of stroke and a guideline for anti-thrombotic therapy in patients with non-valvular AF.^{3–5} Although the CHADS₂ score is an effective predictor of ischaemic stroke in patients with AF, the pathophysiologic

mechanisms remain to be studied. Substrate or tissue factors related to CHADS₂ scores have to be considered. Recurrent fibrillatory activation of AF induces progressive electrical and tissue structural remodelling,^{6–8} and reduction of left atrial (LA) endocardial voltage in the presence of fibrosis.⁹ We previously reported that AF-related electroanatomical remodelling changes both entire and regional LA volume, endocardial voltage, conduction velocity, and distribution of complex fractionated atrial electrogram.^{10–12} However, the relationship between the degree of

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electroanatomical remodelling and CHADS₂ score and the event of stroke has not yet been studied. Therefore, we hypothesized that the degree of electroanatomical remodelling of LA is related to CHADS₂ scores and to the event of stroke. The purposes of this study were to evaluate the regional volume change of LA depending on the degree of structural remodelling, and to compare the degree of mean and regional LA volume enlargement or LA endocardial voltage depending on CHADS₂ score and the events of stroke. We also compared the degree of electroanatomical remodelling with newly suggested risk scores for stroke in non-valvular AF—CHA₂DS₂VASc score.¹³

Methods

Patient selection

The study protocol was approved by the Institutional Review Board of our institute. All patients provided written informed consent. The study enrolled 348 patients with AF (male:female = 273:75, mean age = 55.4 ± 11.0 years old) who underwent radiofrequency catheter ablation (RFCA). Among them, 215 patients had paroxysmal AF, and 133 had persistent AF (PeAF). The exclusion criteria were as follows: (i) permanent AF refractory to the electrical cardioversion; (ii) LA sizes >55 mm measured on echocardiogram; (iii) AF with rheumatic valvular disease; (iv) associated structural heart disease other than left ventricular (LV) hypertrophy; (v) prior AF ablation; and

(vi) sinus rhythm not maintained for LA voltage mapping before RFCA. The patients with the presence of an LA thrombus were excluded by transoesophageal echocardiography. We imaged all patients with a three-dimensional (3D) spiral computed tomography (CT) (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Amsterdam, Netherlands) to visually define the anatomy of LA and pulmonary veins (PVs). Trans-thoracic echocardiography was performed in every patient and LV systolic and diastolic functions were measured by ejection fraction (EF) and mitral valve area tissue Doppler (E/E'), respectively.

Electrophysiological mapping procedure

Intracardiac electrograms were recorded using the Prucka CardioLab™ Electrophysiology system (General Electric Medical Systems Inc., Easton Turnpike, Fairfield, USA), and catheter ablation procedures were performed on all patients using 3D electroanatomical mapping (NavX, St Jude Medical Inc., Minnetonka, MN, USA) merged with 3D spiral CT. Before catheter ablation, we generated an LA 3D electroanatomical map and a voltage map by obtaining contact bipolar electrograms from 350–400 points of the LA endocardium, during atrial pacing with a pacing cycle length of 500 ms. Bipolar electrograms were filtered from 32 to 300 Hz. Colour-coded voltage maps were generated by recording bipolar electrograms and measuring peak-to-peak voltage. The acquisition of an LA voltage map was abandoned if frequently re-initiating AF required electrical cardioversion more than three times. Only patients for whom the LA voltage map was available were included in the study.

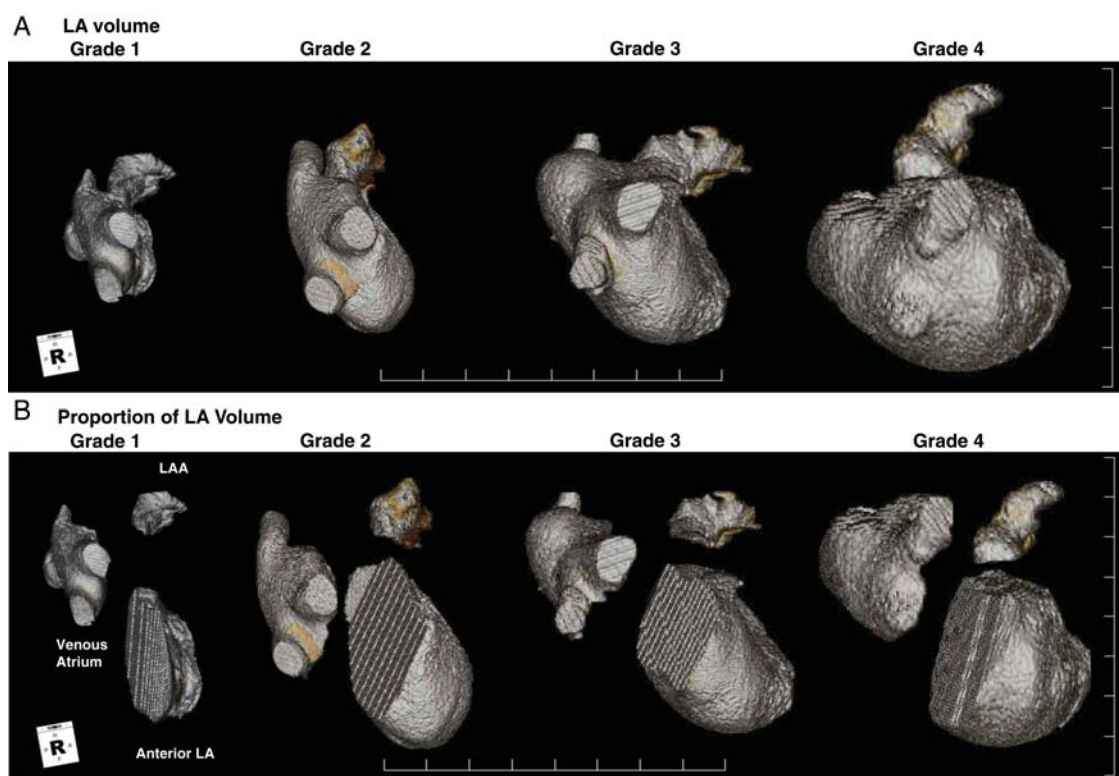


Figure 1 (A) Right lateral views of left atrium in the reconstructed three-dimensional spiral computed tomography image depending on the degree of left atrial remodelling. (B) left atrium images were divided into the venous atrium, the anterior left atrium, and the left atrial appendage. Volumetric measurement reveals significantly higher relative volume of the anterior left atrium in Stage 2 remodelling than in Stage 1.

Table 1 Comparison of left atrial morphology and left ventricular function according to atrial fibrillation-related left atrial size

	Grade 1 (n = 87)	Grade 2 (n = 87)	Grade 3 (n = 87)	Grade 4 (n = 87)	ANOVA P value	ANOVA Power
LA volumes (mL)						
Entire LA volume	74.9 ± 13.7	101.2 ± 12.1*	128.2 ± 13.7**†	170.8 ± 36.4 ^{§‡□}	P < 0.001	1
Anterior LA volume	42.4 ± 10.5	60.6 ± 12.8*	78.6 ± 11.2**†	104.4 ± 28.7 ^{§‡□}	P < 0.001	1
Venous LA volume	26.1 ± 8.2	32.3 ± 6.6*	38.8 ± 8.2**†	52.4 ± 15.0 ^{§‡□}	P < 0.001	1
LAA volume	6.5 ± 3.1	8.7 ± 3.3	10.8 ± 3.6**†	14.0 ± 5.4 ^{§‡□}	P < 0.001	1
Relative volumes of regional LA (%)						
Anterior LA volume	56.4 ± 8.5	59.5 ± 7.5	61.3 ± 5.4**	60.7 ± 8.0 [§]	P < 0.001	0.979
Venous LA volume	34.9 ± 8.4	31.9 ± 7.4	30.2 ± 5.3**	31.0 ± 7.5 [§]	P < 0.001	0.974
LAA volume	8.7 ± 3.9	8.6 ± 3.2	8.5 ± 3.1	8.3 ± 2.8	P = 0.797	0.094
LA voltage (mV)						
Mean LA voltage	1.6 ± 0.8	1.4 ± 0.6	1.3 ± 0.6	1.0 ± 0.6 [§]	P = 0.002	0.873
Anterior LA voltage	1.4 ± 0.6	1.2 ± 0.6	1.3 ± 0.6	0.9 ± 0.6 [§]	P = 0.034	0.878
Venous LA voltage	1.8 ± 1.3	1.0 ± 0.9*	1.1 ± 1.0**	0.8 ± 0.8 [§]	P = 0.001	1
LAA voltage	3.1 ± 1.7	2.8 ± 1.5	2.5 ± 1.6	2.0 ± 1.3 [§]	P = 0.018	0.708
LV function						
LVEF (%)	61.0 ± 7.2	60.9 ± 7.4	60.1 ± 8.2	57.2 ± 10.8 ^{§‡}	P = 0.012	0.806
E/E'	8.5 ± 2.6	9.2 ± 3.6	9.7 ± 4.1	10.6 ± 4.4 [§]	P = 0.014	0.781
Hypertension	26 (29.9%)	38 (43.7%)	47 (54.0%)**	45 (51.7%) [§]	P = 0.005	1
Renal insufficiency	2 (2.3%)	1 (1.1%)	2 (2.3%)	1 (1.1%)	P = 0.880	1
Recurrence	11 (12.6%)	11 (12.6%)	16 (18.4%)	24 (27.6%) [§]	P = 0.005	1

BSA, body surface area; LAA, LA appendage; LV, left ventricle; EF, ejection fraction; ANOVA, analysis of variance.

*P < 0.05, Grade 1 vs. Grade 2, **P < 0.05, Grade 1 vs. Grade 3, [§]P < 0.05, Grade 1 vs. Grade 4, [†]P < 0.05, Grade 2 vs. Grade 3, [‡]P < 0.05, Grade 2 vs. Grade 4, [□]P < 0.05, Grade 3 vs. Grade 4.

Volumetric and curvilinear analyses of three-dimensional spiral computed tomography imaging

The 3D spiral CT images of LA were analysed on an imaging processing workstation (Aquarius, Terarecon Inc., San Mateo, CA, USA) as described before.¹¹ The curvilinear lengths on LA were measured at the linear ablation sites: bilateral antral ablation line, roof line, posterior inferior line, left lateral isthmus line, anterolateral line, and anteroseptal line. Each LA image was divided into portions by embryological origin as follows: the venous LA (posterior LA including the antrum and posterior wall), LA appendage (LAA), and anterior LA (excluding the LAA and venous LA).¹⁴ Although both LAA and anterior LA are embryologically of primordial atrial origin, they differ in geometry, myocardial fibre orientations, and distribution of autonomic innervations. Therefore, we divided LAA and anterior LA, and referenced them to the points of inflection on the 3D spiral CT image. The absolute and relative volumes of each portion were calculated and compared.

Off-line analyses of colour-coded three-dimensional maps of left atriums

We analysed colour-coded voltage maps of both anterior–posterior (AP) and posterior–anterior views that had been converted to image files as previously reported.¹¹ PVs were not included in the analysis. The digital measurements of colour-coded voltage maps

were performed by a single student, using a consistent method, who was blinded to the clinical information of the maps. The percentage of colour-coded areas in each quadrant of the voltage maps was analysed by customized software (Image Pro, Silver Spring, MD, USA), and referenced to the colour scale bars. NavX detected peak-to-peak voltage differences of each contact bipolar electrogram, and changed them to colour codes. Low-voltage areas, defined as LA voltage ≤ 0.2 mV, were coded grey; high-voltage areas (> 5.0 mV) were coded purple. The mean LA voltage was calculated by summation of % area of each colour multiplied by representative voltage, and then divided by the total area of LA. The reference distance was measured by the inter-electrode distances of coronary sinus catheters (duodecath catheter, St Jude Medical Inc.).

Data analyses

We classified patients according to CHADS₂ scores (0, n = 154; 1, n = 124; and ≥ 2, n = 70), CHA₂DS₂-VASc score (0, n = 146; 1, n = 106; and ≥ 2, n = 96), the quartiles of 3D spiral CT measured LA volume index (Grade 1 ≤ 48.3 mL/m², n = 87; Grade 2, 48.3–63.0 mL/m², n = 87; Grade 3, 63.0–99.0 mL/m², n = 87; and Grade 4 ≥ 99.0 mL/m², n = 87), and the patients with (n = 22) or without (n = 326) stroke. We compared them by absolute or relative volumes or curvilinear lengths adjusted by BSA, mean LA voltage, LV systolic and diastolic function, and duration of AF. Data are expressed as the mean ± standard deviation. The statistical significance of these comparisons was assessed

using the Student *t*-test and analysis of variance (ANOVA) test. A *P* value of <0.05 was considered statistically significant.

Results

Enlargement of the anterior portion of left atrium in the early stages of left atrial remodelling

Figure 1 displays the right anterior oblique views of 3D spiral CT image of LA in each grade of remodelling. In Grade 2 LA remodelling, the anterior portion of the LA was remarkably enlarged, and the AP diameter of LA prolonged significantly. In contrast, the posterior venous LA and LAA were proportionally enlarged at Grade 3–4 of LA remodelling. Table 1 summarizes LA volumes, regional lengths, endocardial LA voltage, LV functions, and recurrence. The proportion of relative volumes of anterior LA was significantly greater ($P < 0.001$), but posterior venous LA was smaller ($P < 0.001$) in patients with high-grade remodelling than those with low-grade remodelling (Figure 2A). The increase in relative anterior LA volume was more significant in Grade 2 than in Grade 1 remodelling ($P = 0.006$, Figure 2A). Left atrial endocardial voltage was generally reduced more in patients with high-grade remodelling than in those with low-grade remodelling

($P = 0.002$), and it was most significant in venous LA ($P = 0.001$, Figure 2D).

Greater left atrial volume in patients with higher CHADS₂ score

We compared mean and regional LA volumes in terms of CHADS₂ score (0, $n = 154$; 1, $n = 124$; and ≥ 2 , $n = 70$; Table 2) and CHA₂DS₂VASc score (0, $n = 146$; 1, $n = 106$; and ≥ 2 , $n = 96$; Table 3). Mean LA volume/BSA was significantly higher in patients with high CHADS₂ score ($P = 0.002$, Figure 2B), and this difference was significant especially in the regional volume of the anterior portion of LA ($P = 0.048$, Table 2). The proportions of PeAF were 34.4% in CHADS₂ score 0, 40.3% in CHADS₂ score 1, and 42.9% in CHADS₂ score ≥ 2 ($P = \text{NS}$). In addition, EF was significantly lower ($P = 0.005$), *E/E'* was higher ($P = 0.002$), and the proportions of hypertension ($P < 0.001$) and renal insufficiency ($P = 0.016$) were higher in patients with higher CHADS₂ score than those with lower CHADS₂ score in ANOVA analyses (Table 2). When we compared depending on CHA₂DS₂VASc score (Table 3), these findings were consistent with the CHADS₂ scores, and LA volume/BSA was significantly higher in patients with high CHA₂DS₂VASc scores (Figure 2C). In the analyses of LA endocardial voltage, the mean and regional endocardial voltages tended to be lower in patients with high CHADS₂ score

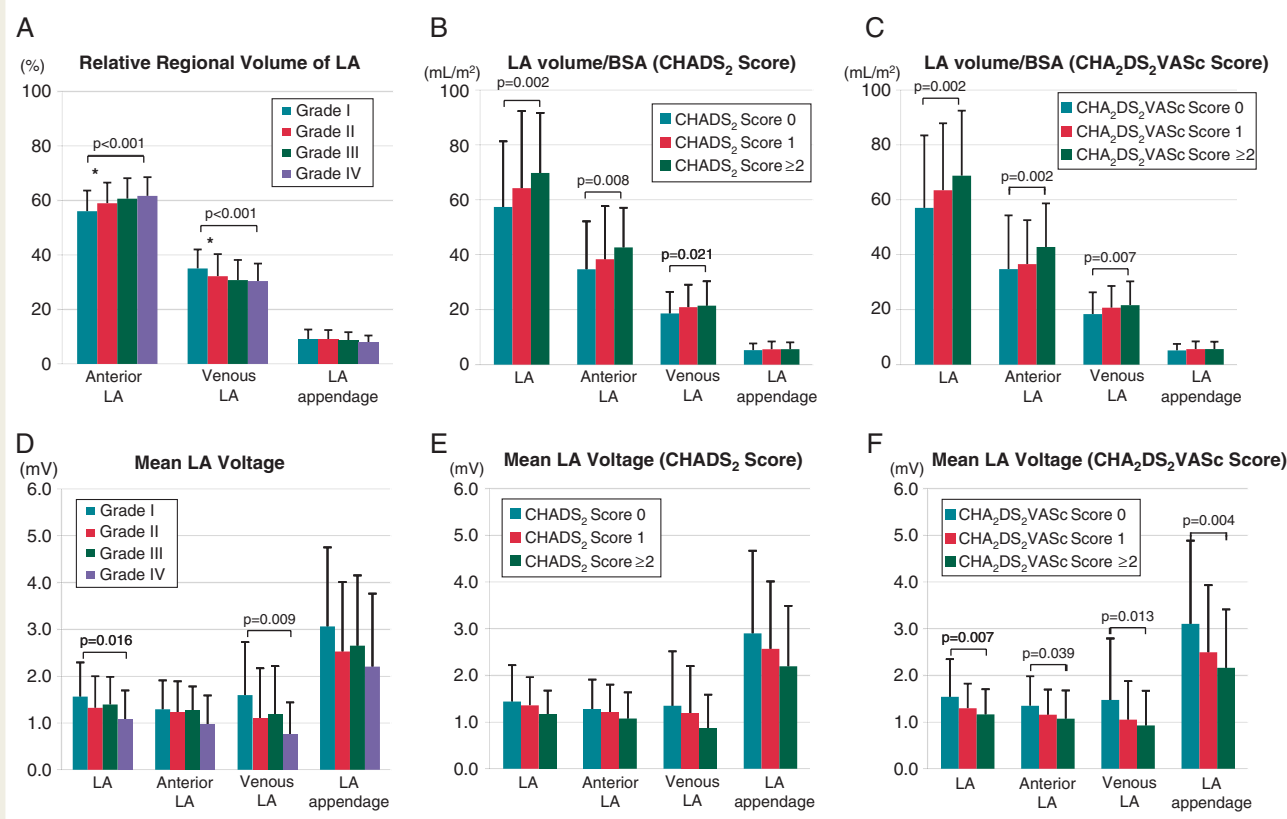


Figure 2 In high-grade remodelled left atrium, portion of anterior left atrium (A) was significantly larger, mean left atrium voltage (D) was significantly lower than those low-grade remodelled left atrium. In higher CHADS₂ score, left atrium volume/body surface area (B) was significantly larger; left atrium voltage (E) was lower than those lower CHADS₂ score. In higher CHA₂DS₂VASc score, left atrium volume/body surface area (C) was significantly larger; left atrium voltage (F) was significantly lower than in the case of lower CHADS₂ score.

Table 2 Comparison of left atrial morphology and left ventricular function according to atrial fibrillation -related CHADS₂ score

	CHADS ₂ score 0 (n = 154)	CHADS ₂ score 1 (n = 124)	CHADS ₂ score ≥2 (n = 70)	ANOVA P value	ANOVA POWER
LA volumes/BSA (mL/m ²)					
Entire LA volume	57.4 ± 23.9	64.3 ± 28.1	69.8 ± 21.9**	P = 0.002	0.882
Anterior LA volume	34.7 ± 17.5	38.4 ± 19.4	42.7 ± 14.4**	P = 0.008	0.797
Venous LA volume	18.7 ± 7.9	20.9 ± 8.2	21.5 ± 8.9	P = 0.021	0.671
LAA volume	5.3 ± 2.5	5.6 ± 2.9	5.6 ± 2.5	P = 0.520	0.140
Relative volumes of regional LA (%)					
Anterior LA volume	58.3 ± 8.6	60.3 ± 6.5	60.5 ± 7.1	P = 0.048	0.599
Venous LA volume	32.9 ± 6.9	31.2 ± 6.9*	31.3 ± 6.3	P = 0.111	0.444
LAA volume	8.7 ± 3.3	8.5 ± 3.2	8.2 ± 3.3	P = 0.555	0.142
LA voltage (mV)					
Mean LA voltage	1.4 ± 0.8	1.4 ± 0.6	1.2 ± 0.5	P = 0.110	0.288
Anterior LA voltage	1.3 ± 0.6	1.2 ± 0.6	1.1 ± 0.6	P = 0.285	0.292
Venous LA voltage	1.3 ± 1.2	1.2 ± 1.0	0.9 ± 0.7	P = 0.080	0.388
LAA voltage	2.9 ± 1.8	2.6 ± 1.4	2.2 ± 1.3	P = 0.077	0.493
LV function					
LVEF (%)	61.2 ± 5.9	57.9 ± 9.5*	59.4 ± 10.7	P = 0.005	0.817
E/E'	8.9 ± 3.3	9.4 ± 3.4	10.3 ± 5.0**	P = 0.002	0.535
Hypertension	0 (0.0%)	99 (79.8%)*	57 (81.4%)**	P < 0.001	1.000
Renal insufficiency	1 (0.6%)	1 (2.4%)	4 (5.7%)**	P = 0.016	1.000
Recurrence	23 (14.9%)	30 (24.2%)*	9 (12.9%)	P = 0.359	0.882

BSA, body surface area; LAA, LA appendage; LV, left ventricle; EF, ejection fraction; ANOVA, analysis of variance.

*P < 0.05, CHADS₂ score 0 vs. CHADS₂ score 1, **P < 0.05, CHADS₂ score 0 vs. CHADS₂ score ≥2.

than in those with low scores (Figure 2E), but it was significant in terms of CHA₂DS₂VASc score (P = 0.007, Figure 2F).

Low left atrial endocardial voltage and higher anterior left atrial volume in patients with stroke

Figure 3A and B display the representative examples of CT-merged LA voltage maps, and the patients who experienced stroke show low endocardial voltage with enlarged LA volume in comparison with the patient without stroke. We compared them with 326 patients without stroke and summarized this in Table 4. There were 22 patients who experienced episodes of stroke in this study. The stroke occurred 18.2 ± 18.4 months before catheter ablation, and CHADS₂ score was 3.2 ± 0.2 at that time. The type of stroke was ischaemic embolic stroke in all 22 patients, but haemorrhagic transformation occurred during stroke management in 2 patients. In patients who had experienced a previous stroke, mean LA volume/BSA (P = 0.012), especially anterior LA (P = 0.006), was significantly enlarged, and mean LA endocardial voltage (P = 0.039), especially venous LA voltage (P = 0.005), was significantly lower than those without stroke (Figure 3C and D). In the uni-variate analyses (t-test), LA diameter (P = 0.011), left ventricular ejection fraction (LVEF; P = 0.041), CHADS₂ score (P < 0.001), LA volume/BSA (P = 0.026), LAA volume% (P = 0.012), anterior LA volume% (P = 0.025), and LA

voltage (P = 0.039) were related with the event of stroke. In the multi-variate regression analysis, the factor most related to the episode of stroke was CHADS₂ score (OR = 3.641, CI 2.033–6.521, P < 0.001) among them.

Discussion

This is the first study that reports on the relationship between the degree of electroanatomical remodelling of LA and the risk or events of stroke in patients with non-valvular AF. We also elucidated disproportional enlargement of the anterior portion of LA in the early stages of structural remodelling and its relationship with CHADS₂ score, and low endocardial voltage of posterior venous atrium in patients with stroke. Therefore, CHADS₂ score represents not only a clinical risk factor for ischaemic stroke, but is also related to atrial substrates for thromboembolism in patients with AF.

Risks scores and potential mechanisms of stroke in patients with non-valvular atrial fibrillation

Atrial fibrillation causes a five-fold increase in the risk of ischaemic stroke or transient ischaemic attack (TIA).¹⁵ CHADS₂ score is a risk stratification scheme for ischaemic stroke in patients with non-valvular AF based on the presence of heart failure,

Table 3 Comparison of left atrial morphology and left ventricular function according to atrial fibrillation-related CHADS₂VASc score

	CHA ₂ DS ₂ VASc score 0 (n = 146)	CHA ₂ DS ₂ VASc score 1 (n = 106)	CHA ₂ DS ₂ VASc score ≥2 (n = 96)	ANOVA P value	ANOVA POWER
LA volumes/BSA (mL/m ²)					
Entire LA volume	57.1 ± 26.4	63.5 ± 24.4	68.8 ± 23.7**	P = 0.002	0.885
Anterior LA volume	34.8 ± 19.6	36.6 ± 16.0	42.8 ± 15.9**†	P = 0.002	0.873
Venous LA volume	18.4 ± 8.0	20.7 ± 7.9*	21.7 ± 8.7**	P = 0.007	0.810
LAA volume	5.2 ± 2.4	5.6 ± 2.8	5.7 ± 2.7	P = 0.256	0.269
Relative volumes of regional LA (%)					
Anterior LA volume	58.3 ± 8.5	59.6 ± 6.9	61.1 ± 6.8**	P = 0.019	0.701
Venous LA volume	33.0 ± 8.3	31.8 ± 6.8	30.7 ± 6.6	P = 0.050	0.553
LAA volume	8.7 ± 3.3	8.6 ± 3.1	8.2 ± 3.4	P = 0.525	0.170
LA voltage (mV)					
Mean LA voltage	1.5 ± 0.8	1.3 ± 0.5	1.2 ± 0.5**	P = 0.007	0.587
Anterior LA voltage	1.3 ± 0.6	1.2 ± 0.5	1.1 ± 0.6**	P = 0.039	0.332
Venous LA voltage	1.5 ± 1.3	1.1 ± 0.8	0.9 ± 0.7**	P = 0.013	0.816
LAA voltage	3.1 ± 1.8	2.5 ± 1.4	2.2 ± 1.3**	P = 0.004	0.811
LV function					
LVEF (%)	60.6 ± 6.9	57.3 ± 9.8*	61.5 ± 9.0†	P = 0.001	0.924
E/E'	9.0 ± 3.4	8.8 ± 3.2	11.0 ± 4.5**†	P < 0.001	0.968
Hypertension	0 (0.0%)	80 (75.2%)*	76 (79.2%)**	P < 0.001	1.000
Renal insufficiency	0 (0.0%)	2 (1.9%)	4 (4.2%)	P = 0.051	1.000
Recurrence	24 (16.4%)	21 (19.8%)*	17 (17.7%)	P = 0.683	1.000

BSA, body surface area; LAA, LA appendage; LV, left ventricle; EF, ejection fraction, ANOVA, analysis of variance.

*P < 0.05, CHADS₂ score 0 vs. CHADS₂ score 1, **P < 0.05, CHADS₂ score 0 vs. CHADS₂ score ≥2, †P < 0.05, CHADS₂ score 1 vs. CHADS₂ score ≥2.

hypertension, age >75 years old, diabetes, previous stroke, or TIA.¹⁶ The 2006 version of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines/European Society of Cardiology Committee for Practice Guidelines (ACC/AHA/ESC) practical guidelines for AF recommends warfarin or aspirin for patients depending on their CHADS₂ score.⁵ Recently, European Society of Cardiology have suggested new guidelines for AF management,¹³ and proposed a CHA₂DS₂-VASc score that strengthens the importance of age, sex, and combined vascular disease as risk factors for ischaemic stroke in addition to CHADS₂ score. Although both CHADS₂ and CHA₂DS₂VASc scores are effective predictors for ischaemic stroke, their pathophysiologic mechanisms remain to be clarified. Atrial contractile remodelling and blood stasis in LA during AF has generally been considered to be a major mechanism of thromboembolism in patients with AF.^{17–19} Blood stasis or hypercoagulable states are major contributors for thrombogenesis, but tissue factors cannot be underestimated. CHADS₂ score and CHA₂DS₂VASc score include risk factors related to vascular remodelling, metabolic syndrome, change of cardiac substrates, or tissue factors. The degree of electroanatomical remodelling of AF is closely related with myocardial fibrosis,^{20,21} matrix remodelling, and angiotensin II-NADPH oxidase-mediated thrombus formation.²² In this study, we demonstrated the relationship between LA volume/endocardial voltage and risk scores or events of stroke in patients with AF.

Electroanatomical remodelling process in atrial fibrillation

The mechanisms for LA remodelling include pressure or volume overload to LA by LV dysfunction, deranged plasma volume control, intensified neurohormonal activation, or atrionomyopathy itself.²³ In this study, the anterior portion of the LA was enlarged in the early stages of LA remodelling, and the potential mechanisms are as follows: first, haemodynamic overload may stretch thin the trabeculated wall of the anterior portion of LA early by Laplace's law. Secondly, the posterior venous LA and the anterosseptum about the fixed rigid structures, the spine, and the ascending aorta, respectively. Therefore, LA volume increased antero-laterally and the volume of anterior LA was enlarged in the early phases of remodelling.

The presence of fibrosis/low-voltage tissue has been postulated as a potential cause of abnormalities in atrial activation that may underlie the initiation and maintenance of fibrillation.^{24,25} The degree of voltage reduction may help grade the severity of tissue pathology underlying AF before and after catheter ablation.²⁶ Increased fibrosis has also been clearly demonstrated in human LA tissue specimens of patients with AF,^{20,21} and correlations have been observed between serum markers of atrially selective fibroblasts and clinical AF.²⁷ We also previously reported that low endocardial voltage of LA is closely related to LA volume remodelling,¹¹ reduced conduction velocity,¹⁰ and the patterns of

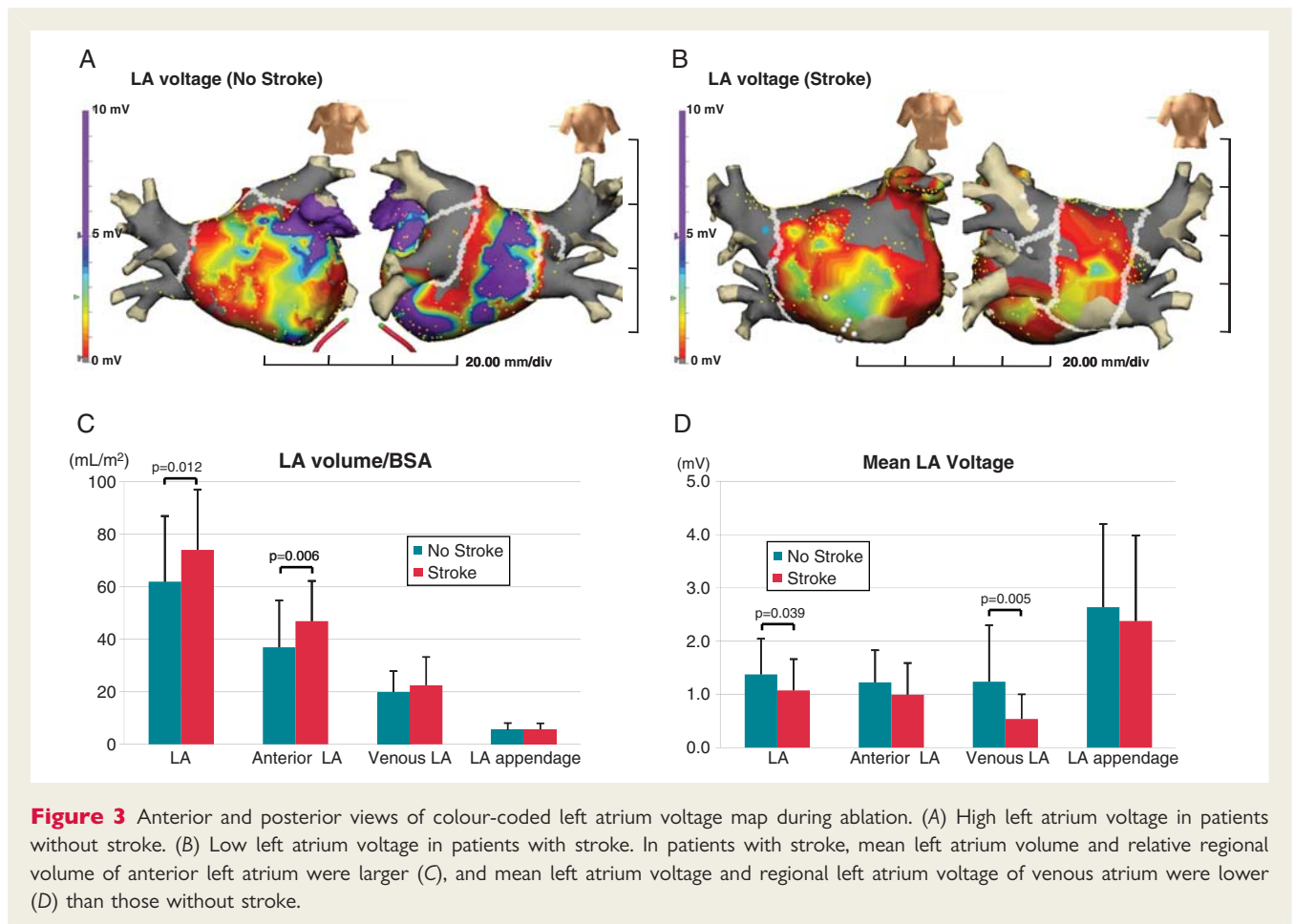


Figure 3 Anterior and posterior views of colour-coded left atrium voltage map during ablation. (A) High left atrium voltage in patients without stroke. (B) Low left atrium voltage in patients with stroke. In patients with stroke, mean left atrium volume and relative regional volume of anterior left atrium were larger (C), and mean left atrium voltage and regional left atrium voltage of venous atrium were lower (D) than those without stroke.

complex fractionated atrial electrograms in AF.¹² In this study, the degree of electroanatomical remodelling of LA was directly related to the risk or events of stroke in patients with AF. Further studies by non-invasive imaging methods, such as fibrosis on magnetic resonance imaging or stain on echocardiography, will characterize the degree of LA remodelling anatomically and functionally.²⁸

Clinical implication of left atrial structural remodelling

Electroanatomical remodelling of the atria has been known to be a predictor of AF recurrence after cardioversion²⁹ or RFCA,^{11,30} and a risk of stroke, as shown in this study. Therefore, more strict anti-coagulation is warranted in those patients with low-voltage scars and enlarged LA. Longer duration of RF energy delivery is more of a necessity for effective rhythm control in AF patients with remodelled atria than for those with less remodelled atria. However, the operator should keep in mind that profuse RF ablation can increase LA scar or atriomypathy,²⁶ and might raise the risk of stroke by electroanatomical remodelling. Whether reverse remodelling and LA voltage occurs after successful catheter ablation of AF is unclear. The appropriate strategy for anti-coagulation after abolishing AF remains to be studied. New drugs^{31,32} or devices³³ provide more options for AF management, and

customized guidelines will be required according to the symptoms, haemodynamic factors, and risks of stroke.

Study limitations

The patients included in this study were a highly selective group referred for RFCA, and the number of patients was also limited. We also excluded patients with LA size of >50 mm. Because we acquired voltage maps via point-by-point contact mapping, the maps did not reflect a spatiotemporally homogeneous distribution. We analysed 3D voltage maps using 2D measurements. Although we strictly followed ACC/AHA/ESC guideline based on the CHADS₂ score,⁵ we do not have data of the anti-thrombotic regimen at the time of ischaemic stroke because most patients included in this study were referred patients for catheter ablation. The patient group in this study was highly selected patients with relatively small LA volume with low risk of stroke. Therefore, the result of this study may not be extrapolated to the patients with permanent AF and significant LA remodelling.

Conclusion

We documented different patterns of CHADS₂ score in patients with structurally remodelled LA. In patients with non-valvular AF, LA volume was larger in patients with high CHADS₂ score than

Table 4 Degree of left atrial remodelling in patients with and without stroke

	No stroke (n = 326)	Stroke (n = 22)	P value
LA volumes/BSA (mL/m ²)			
Entire LA volume	61.5 ± 25.5	74.1 ± 23.0	P = 0.012
Anterior LA volume	36.9 ± 17.8	46.9 ± 15.3	P = 0.006
Venous LA volume	19.8 ± 8.0	22.5 ± 10.8	P = 0.074
LAA volume	5.4 ± 2.6	5.7 ± 2.3	P = 0.329
Relative volumes of regional LA (%)			
Anterior LA volume	59.3 ± 7.6	62.2 ± 8.0	P = 0.044
Venous LA volume	32.1 ± 7.4	30.6 ± 7.6	P = 0.185
LAA volume	8.6 ± 3.3	7.2 ± 2.1	P = 0.025
LA voltage (mV)			
Mean LA voltage	1.4 ± 0.7	1.1 ± 0.6	P = 0.039
Anterior LA	1.2 ± 0.6	1.0 ± 0.6	P = 0.068
Venous LA	1.2 ± 1.1	0.5 ± 0.5	P = 0.005
LAA	2.6 ± 1.6	2.4 ± 1.6	P = 0.259
LV function			
LVEF (%)	59.6 ± 8.6	63.0 ± 8.1	P = 0.041
E/E'	9.4 ± 3.8	10.5 ± 3.2	P = 0.120
Hypertension	144 (44.2%)	12 (54.5%)	P = 0.216
Renal insufficiency	6 (1.8%)	0 (0.0%)	P = 0.673
Recurrence	62 (19.0%)	0 (0.0%)	P = 0.041

BSA, body surface area; LAA, LA appendage; LV, left ventricle; EF, ejection fraction.

those with low CHADS₂ score and LA voltage was lower in patients with stroke. Thus, stroke risk factors may be related to the degree of electroanatomical remodelling of LA and anterior LA might play a role in the early phase of structural remodelling in patients with AF.

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IMAGES IN ELECTROPHYSIOLOGY

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A case of atrioventricular nodal reentrant tachycardia with high take-off coronary sinus

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A 73-year-old female with atrioventricular nodal reentrant tachycardia (AVNRT) presented with high-takeoff coronary sinus (CS). Coronary sinus venography revealed that the CS ostium was located at an unusual site where the His-bundle is supposed to be located (arrows in *Figure 1A and B*), and the successful ablation site for the slow pathway was located below the CS ostium (*Figures 1A–C*). This patient was treated by slow-pathway ablation using only the electrophysiological approach. Therefore, slow pathway ablation for AVNRT should not be guided by only anatomical approaches in cases with an anomaly of the CS.

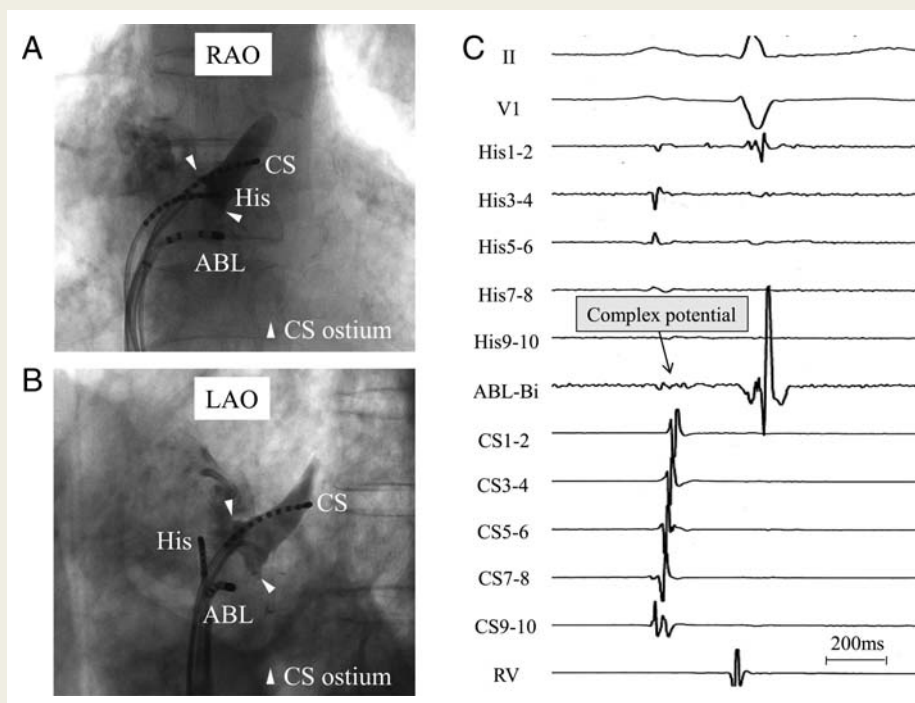


Figure 1 Radiographs demonstrating high-takeoff CS, and intracardiac electrogram.

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