Left Atrial Appendage Morphology and Function Show an Association with Stroke and Transient Ischemic Attack in Patients with Atrial Fibrillation

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Research Article

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Abstract

Background

We aimed to correlate left atrial appendage (LAA) structure and function with the history of stroke/transient ischemic attack (TIA) in patients with atrial fibrillation (AF).

Methods

We analyzed data of 649 patients with AF who were scheduled for catheter ablation. Patients underwent cardiac CT and transesophageal echocardiography prior to ablation. LAA morphologies depicted by cardiac CT were categorized into four groups: cauliflower, chicken wing, swan and windsock shapes.

Results

Mean age was 61.3±10.5 years, 33.9% were female. Prevalence of stroke/TIA was 7.1%. After adjustment for the main risk factors, LAA flow velocity ≤35.3 cm/sec (OR=2.18; 95%CI=1.09-4.61; p=0.033) and swan LAA shape (OR=2.69; 95%CI=0.96-6.86; p=0.047) independently associated with higher, while windsock LAA morphology with lower risk of stroke/TIA (OR=0.32; 95%CI=0.12-0.77; p=0.017) as compared to cauliflower LAA shape. When comparing the differences between LAA morphology groups, we measured significantly smaller LAA orifice area (389.3±137.7 mm^2 in windsock vs 428.3±158.9 ml in cauliflower, p=0.021) and LAA volume (7.4±3.0 mm^2 in windsock vs 8.5±4.8 mm^2 in cauliflower, p=0.012) in patients with windsock LAA morphology, while LAA flow velocity did not differ significantly.

Conclusion

Reduced LAA function and swan LAA morphology were independently associated with higher, while windsock LAA shape with lower prevalence of stroke/TIA. When comparing the differences between the various LAA morphology types, significantly lower LAA volume and LAA orifice area were measured in windsock LAA shape as compared to cauliflower LAA shape.

Introduction

Atrial fibrillation (AF) is the most prevalent type of sustained cardiac arrhythmia with clinical relevance, which affects 33.5 million patients worldwide [1]. Among many other factors, AF is an independent risk predictor of ischemic stroke and transient ischemic attack (TIA), with almost five-fold increase in stroke risk, as reported in the Framingham Study [2]. Moreover, a third of the patients with ischemic stroke have been found to have either clinical or subclinical AF [3]. The left atrial appendage (LAA) is a well-recognized source of cardiac thrombus responsible for stroke/TIA in patients with AF [4]. Previous studies reported that LAA morphology correlates with stroke/TIA in AF patients [5-7]. Cardiac computed tomography (CT) is commonly used for the visualization of left atrial (LA) anatomy in patients undergoing catheter ablation [8]. Moreover, cardiac CT images provide valuable data on the anatomical characteristics of the LAA, including LAA volume, orifice area and morphology. Beside cardiac CT, transesophageal echocardiographic (TEE) examinations are routinely performed in AF patients before catheter ablation for the exclusion of LAA thrombus. Moreover, TEE is the gold standard method for the evaluation of LAA flow velocity, which is a surrogate of LAA function.

In this study, we hypothesized that type of LAA morphology and LAA function were related to the risk of previous stroke/TIA. Accordingly, we analyzed geometry, dimensions and flow velocity values of the LAA using cardiac CT and TEE examinations in AF patients.

Methods

2.1. Study population

The study population consisted of 649 patients with drug-refractory AF who underwent cardiac CT before catheter ablation in the Heart and Vascular Center of Semmelweis University, Budapest, Hungary between 2014 and 2017. Exclusion criteria were age under 18 years, non-diagnostic image quality of CT, repeated ablation and patients in whom assessment of LAA flow velocity was not feasible. Those without data on the history of stroke/TIA were also excluded from the analysis. History of stroke/TIA was collected from patients' chart reviews.

2.2. Cardiac CT imaging

Cardiac CT examinations were performed with a 256-slice scanner (Brilliance iCT 256, Philips Healthcare, Best, The Netherlands) with prospective ECG-triggered axial acquisition mode. For cardiac CT, 100-120 kV with 200-300 mAs tube current was used depending on patient anthropometrics. Image acquisition was performed with 128x0.625 mm detector collimation, and 270 msec gantry rotation time. For heart rate control, a maximum of 50-100 mg metoprolol was given orally and 5-20 mg intravenously, if necessary. Iomoprol contrast material (Iomeron 400, Bracco Ltd, Milan, Italy) was used with 85-95 ml contrast agent at a flow rate of 4.5-5.5 ml/sec through an antecubital vein via an 18-gauge catheter, using a four-phasic protocol. Bolus tracking in the left atrium was used to obtain proper scan timing. 0.8 mg sublingual nitroglycerin was given between the native and CT angiography acquisitions. CT data sets were reconstructed with 0.8 mm slice thickness and 0.4 mm increment.

After defining LA and LAA borders with caution to the orifices of the pulmonary veins and the level of the mitral valve, we measured LA and LAA volumes and determined LAA morphologies based on three-dimensional volume-rendered images using a semiautomated software package (EP Planning, Philips IntelliSpace Portal, Philips Healthcare, Best, The Netherlands). Since assessment of LAA morphology can be highly subjective, LAA morphologies were determined by consensus reading of three expert readers using rigorous definitions in order to minimize inter-observer variability. LAA morphologies were classified in four different types as previously described: 1.) Cauliflower, if LAA has limited length and the distal width exceed the proximal width; 2.) Windsock, if the primary structure is one dominant lobe with sufficient length; 3.) Chicken wing, if the dominant lobe has an obvious bend in the proximal or middle part; and 4.) Swan if LAA has a second sharp curve folding the dominant lobe back [9]. Representative examples are provided in *Figure 1.*

2.3. LAA flow velocity measurement

Maximum 24h before ablation, all patients underwent TEE examination to exclude the presence of LAA thrombus. iE33 and Epiq 7C (Philips Medical System, Andover, MA) systems equipped with S5-1 phased array and X7-2t matrix TEE transducers were used. TEE was performed during conscious awake sedation. The LAA was imaged from 0°, 45°, 90° and 135° views to detect spontaneous echo contrast, sludge or thrombus. Subsequently, a sample volume was placed at the middle portion of the LAA and the peak velocity of the outflow of the LAA was measured.

2.4. Statistical analysis

Categorical variables are expressed as frequencies (percentages), and continuous values are expressed as mean±standard deviation (SD). Normality of continuous parameters was tested with Shapiro-Wilk test. Tests for significance were conducted using Mann-Whitney-Wilcoxon or Kruskal-Wallis tests for continuous variables and Pearson's chi-square or Fisher exact tests (if 5 or less observations were included) for categorical variables. The odds ratio (OR) and 95% confidence interval (CI) values of stroke/TIA were computed using uni- and multivariate logistic regression analyses. In the multivariate model, adjustment was made for CHA_2DS_2-VASc-score risk factors, such as, heart failure, left ventricular systolic dysfunction (defined as left ventricular ejection fraction (LVEF) <50%), blood pressure >140/90 mmHg or antihypertensive therapy, age >65 years, diabetes mellitus, peripheral vasculopathy, obstructive coronary artery disease (CAD; defined as >50% luminal stenosis), and female sex. Moreover, obesity (defined as body mass index (BMI) >30kg/m^2), hyperlipidemia, and renal dysfunction (defined as eGFR <60ml/min/1.73m^2) were also included in the model beyond LA and LAA parameters. Receiver operating characteristic curve analysis was performed to determine optimal cut-off points of the LAA orifice area and flow velocity for stroke/TIA based on Youden-index. Differences between the various LAA morphology types were determined with ANOVA and post-hoc Tukey's honest significant difference test. All tests were two-sided and a p-value <0.05 was considered statistically significant. All analyses were performed using statistical software R (version: 3.6.1) and its packages, namely 'pROC' (version: 1.15.3), 'yarrr' (version: 0.1.5).

The data underlying this article will be shared on reasonable request to the corresponding author.

Results

3.1. Patient population

Altogether 649 patients were included in this retrospective study. Mean age was 61.3±10.5 years, 33.9% were female. Prevalence of prior stroke/TIA was 7.1% in the study population. Altogether 15 (2.3%) patients had TIA and 31 (4.8%) had ischemic stroke prior to the preablational cardiac CT. The prevalence of cauliflower, windsock, chicken wing and swan morphologies were 50.2%, 32.5%, 12.4% and 4.8% in patients without prior stroke/TIA versus 63.0%. 13.0%, 8.7% and 15.2% in those with prior stroke/TIA, respectively (p=0.002). Demographic and clinical characteristics, LA and LAA measurements of the patients are presented in Table 1 and Figure 2.

3.2. Associates of prior stroke/TIA

Optimal cut-off point of LAA orifice area was 561.5 mm^2, and 35.3 cm/sec for LAA flow velocity (sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 21.7%, 87.3%, 11.5%, 93.6% and 82.6% for LAA orifice area and 73.9%, 43.3%, 9.0% 95.6% and 45.5% for LAA flow velocity, respectively). Uni- and multivariate logistic regression analyses were performed to determine the significant associates of stroke/TIA. In the univariate analysis, hyperlipidemia (OR=2.01; 95%CI=1.07-3.72; p=0.027), heart failure (OR=3.75; 95%CI=1.20-9.88; p=0.012); LVEF <50% (OR=2.26; 95%CI=1.02-4.61; p=0.032), LAA flow velocity ≤35.3 cm/sec (OR=2.16; 95%CI=1.13-4.43; p=0.026), and swan LAA morphology (OR=2.52; 95%CI=0.95-6.00; p=0.026) were significantly associated with increased risk of stroke/TIA, while windsock LAA morphology with lower risk of stroke/TIA (OR=0.32; 95%CI=0.12-0.73; p=0.013). After adjustment for the main risk factors, reduced LAA flow velocity (multivariate OR=2.18; 95%CI=1.09-4.61; p=0.033) and swan LAA shape (multivariate OR=2.69; 95%CI=0.96-6.86; p=0.047) were independent associates of stroke/TIA, while windsock LAA morphology with lower risk of stroke/TIA (multivariate OR=0.32; 95%CI=0.12-0.77; p=0.017). Detailed results of the logistic regression analyses are reported in *Table 2.*

3.3. Differences among LAA morphologies

When comparing the differences between LAA morphology groups, we measured significantly smaller LAA orifice area (389.3±137.7 mm^2 in windsock type vs 428.3±158.9 ml in cauliflower type, p=0.021) and LAA volume (7.4±3.0 mm^2 in windsock type vs 8.5±4.8 mm^2 in cauliflower type, p=0.012) in patients with windsock LAA morphology, while LAA flow velocity did not differ significantly between the LAA shape groups. Violin plot diagrams of the differences in LAA parameters between the LAA morphology groups are shown in *Figure 3*.

Discussion

In our retrospective study of 649 AF patients, decreased LAA flow velocity and swan LAA morphology independently associated with increased risk of stroke/TIA, while windsock LAA shape with a lower risk of stroke/TIA. When comparing the differences between the various LAA morphologies, significantly lower LAA volume and LAA orifice area were measured with cardiac CT in the windsock LAA shape group compared to cauliflower morphology. To our knowledge, this is the first study to correlate cauliflower, chicken wing, swan and windsock morphologies with the history of stroke/TIA in AF patients.

The LAA represents a frequent site of thrombus formation, since this part of the heart is prone to dysfunction, structural changes of the endothelium and abnormal blood stasis and homeostasis [10].

The anatomic morphology of the LAA is highly variable. Previous studies have reported contradictory results regarding the association between LAA morphology and the risk of ischemic stroke. While Di Biase et al suggested that non-chicken wing morphology might be associated with increased risk of stroke, other authors reported that cauliflower morphology is more common in patients with ischemic stroke [5, 6, 11]. However, these studies categorized LAA morphologies into cauliflower, windsock, chicken wing and cactus shapes, while we used another classification of cauliflower, windsock, chicken wing and swan morphologies, as previously applied by van Rosendael et al [9]. In our study population, swan morphology was associated with a more than 2.5-fold risk of stroke/TIA, while windsock morphology decreased this risk by 68%.

Even though prior autopsy study of 500 heart specimens has reported that LAA enlargement is an important contributor of stroke/TIA, imaging studies using cardiac CT and cardiovascular magnetic resonance could not confirm this correlation [5, 12]. In the current study, LAA volume was not directly associated with risk of stroke/TIA, but patients with windsock LAA morphology had significantly lower LAA volumes, compared to cauliflower morphology, suggesting that the lower risk of stroke/TIA in patients with windsock LAA morphology can be partly explained by the significantly smaller size of this morphology.

LAA flow velocity indices reflect global LA function [13]. Moreover, it has been reported as a quantitative surrogate parameter for thromboembolic risk, since lower LAA flow velocity may cause blood stasis, which is a major cause of thrombus formation [14]. In line with this finding, LAA flow velocity $\leq$35.3 cm/sec doubled the odds of stroke/TIA in our study population. Previous authors also suggested that the role of the various LAA morphologies in the occurrence of TIA/stroke might be due to the differences in LAA orifice sizes and flow velocity between the LAA categories [15, 16]. However, when analyzing the mechanisms underlying the differences in stroke/TIA rates between the LAA morphology groups, we measured significantly lower LAA orifice area values in patients with windsock LAA shape than in those with cauliflower morphology. However, there was no difference in LAA function between the groups. Moreover, we did not find any significant differences in LAA orifice area, volume and flow-velocity in those with swan LAA shape, as compared to cauliflower LAA morphology. However, it could be hypothesized that due to its curved structure, swan LAA morphology is prone to blood stasis, leading to thrombus formation and occurrence of stroke/TIA.

The current study has several limitations. First, it is a single-center, retrospective study, which needs confirmation in multi-center prospective studies. Type of stroke and medications taken at the time of stroke/TIA could not be recorded in all patients. Second, stroke/TIA rates were small, since our study is limited to AF patients undergoing catheter ablation. Moreover, it is impossible to prove that all stroke/TIA were of cardiac origin, but this is inherent to all studies focusing on this topic.

Conclusion

In this retrospective study including 649 AF patients, reduced LAA flow velocity and swan LAA morphology independently associated with higher odds of stroke/TIA, while windsock LAA morphology with a lower risk of stroke/TIA. When comparing the differences between the various LAA morphology types, significantly lower LAA volume and LAA orifice area were measured in windsock LAA shape, compared to cauliflower LAA morphology.

Declarations

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Availability of data and material

The data underlying this article will be shared on reasonable request to the corresponding author.

Code availability

The code will be shared on reasonable request to the corresponding author.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mohammed El Mahdiui, Lili Száraz, Alexander R. van Rosendael and Emese Zsarnóczay . The first draft of the manuscript was written by Judit Simon and Jeff M. Smit, and all authors commented on previous versions of the manuscript. Pál Maurovich-Horvat and Béla Merkely revised the manuscript and performed the final approval of the version to be submitted. All authors read and approved the final manuscript.

Conflict of interest

The authors have no conflicts to disclose.

Ethics approval

The study was performed according to the Declaration of Helsinki and Institutional Guidelines.

Ethical approval was waived by the local Ethics Committee of Semmelweis University in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent of publication

Patients signed informed consent regarding publishing their data and photographs.

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Tables

Table 1. Patient characteristics

	All patients (n=649)	No stroke/TIA (n=603)	Stroke/TIA (n=46)	p
Age (years)	61.3±10.5	61.2±10.6	63.0±9.3	0.295
Female, n (%)	220 (33.9)	208 (34.5)	12 (26.1)	0.263
BMI (kg/m^2)	28.8±4.6	28.8±4.6	29.0±4.5	0.722
Hypertension, n (%)	471 (72.6)	432 (71.6)	39 (84.8)	0.059
Hyperlipidemia, n (%)	164 (25.3)	146 (24.2)	18 (39.1)	**0.034**
Diabetes mellitus, n (%)	96 (14.8)	88 (14.6)	8 (17.4)	0.665
Heart failure, n (%)	24 (3.7)	19 (3.2)	5 (10.9)	**0.022**
Valvular disease, n (%)	23 (3.5)	23 (3.8)	0 (0.0)	0.397
Peripheral vasculopathy, n (%)	19 (2.9)	16 (2.7)	3 (6.5)	0.145
Obstructive CAD, n (%)	59 (9.1)	53 (8.8)	6 (13.0)	0.295
eGFR <60 ml/min/1.73m^2	153 (23.6)	144 (23.8)	9 (19.6)	0.592
CHA2DS$_2$-VASc-score >2	102 (15.7)	67 (11.1)	35 (76.1)	**<0.001**
LVEF <50%	76 (11.7)	66 (11.0)	36 (21.7)	**0.032**
LA volume (ml)	105.3±31.8	105.1±31.6	107.2±34.4	0.845
LAA volume (ml)	8.0±4.0	7.9±4.0	8.4±4.6	0.810
LAA orifice area (mm^2)	408.9±152.7	407.7±151.7	424.4±166.4	0.520
LAA flow velocity (cm/sec)	35.7±14.8	35.9±14.6	32.9±16.6	0.116
LAA morphology				
cauliflower, n (%)	332 (51.2)	303 (50.2)	29 (63.0)	**0.002**
windsock, n (%)	202 (31.1)	196 (32.5)	6 (13.0)	
chicken wing, n (%)	79 (12.2)	75 (12.4)	4 (8.7)	
swan, n (%)	36 (5.5)	29 (4.8)	7 (15.2)	

Continuous values are expressed as means±SD and categorical variables are expressed as frequencies.

Abbreviations: AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; LA = left atrium; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

Table 2. Associates of stroke/TIA

	Univariate analysis			Multivariate analysis		
	OR	95%CI	p	OR	95%CI	p
Age >65 years	1.29	0.71-2.36	0.400	1.30	0.65-2.59	0.456
Female	0.67	0.33-1.29	0.248	0.56	0.26-1.17	0.137
BMI >30 kg/m^2	0.71	0.34-1.36	0.315	0.71	0.33-1.44	0.358
Hypertension	2.21	1.03-5.47	0.060	1.96	0.83-5.26	0.148
Hyperlipidemia	**2.01**	**1.07-3.72**	**0.027**	1.54	0.76-3.04	0.225
Diabetes mellitus	1.23	0.52-2.60	0.607	0.88	0.35-2.01	0.780
Heart failure	**3.75**	**1.20-9.88**	**0.012**	3.11	0.76-11.16	0.093
Peripheral vasculopathy	2.56	0.58-8.06	0.147	2.15	0.45-7.66	0.278
eGFR <60 ml/min/1.73m^2	0.78	0.34-1.58	0.507	0.64	0.27-1.39	0.282
Obstructive CAD	1.56	0.57-3.59	0.337	1.01	0.34-2.60	0.988
LVEF <50%	**2.26**	**1.02-4.61**	**0.032**	2.05	0.78-4.97	0.125
LA volume	1.00	0.99-1.01	0.663	0.99	0.98-1.01	0.254
LAA volume	1.02	0.95-1.08	0.483	0.99	0.90-1.09	0.884
LAA orifice area >561.5 cm^2	1.90	0.86-3.85	0.090	1.90	0.74-4.58	0.163
LAA morphology						
cauliflower	Reference		...	Reference		...
windsock	**0.32**	**0.12-0.73**	**0.013**	**0.32**	**0.12-0.77**	**0.017**
chicken wing	0.56	0.16-1.47	0.287	0.52	0.15-1.45	0.257
swan	**2.52**	**0.95-6.00**	**0.046**	**2.69**	**0.96-6.86**	**0.047**
LAA flow velocity ≤35.3 cm/sec	**2.16**	**1.13-4.43**	**0.026**	**2.18**	**1.09-4.61**	**0.033**

Abbreviations: AF = atrial fibrillation; BMI = body mass index; LA = left atrium; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; OR = odds ratio; TIA = transient ischemic attack.

Figures

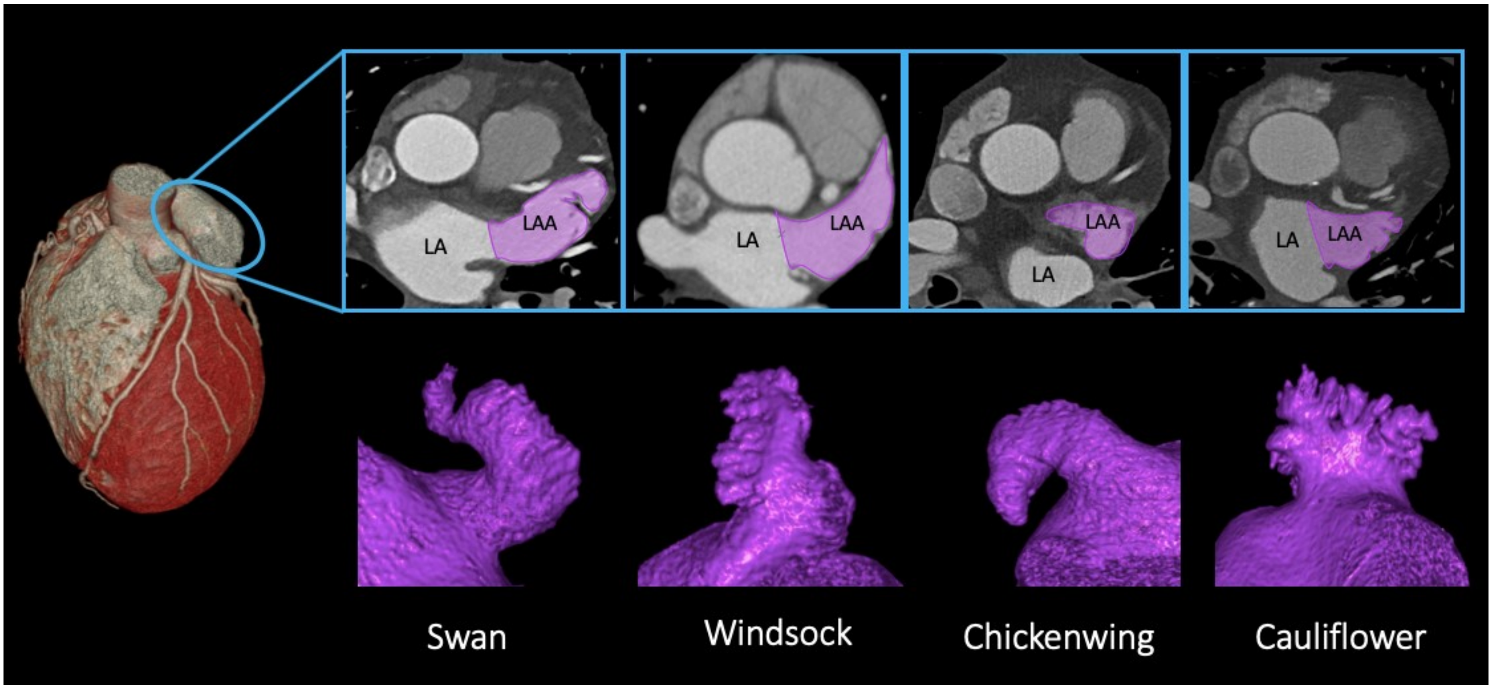

Figure 1

Representative examples of the various LAA morphology categories LAA morphologies were classified in four different types as previously described: swan if LAA has a second sharp curve folding the dominant lobe back; windsock if the primary structure is one dominant lobe with sufficient length; chicken wing, if the dominant lobe has an obvious bend in the proximal or middle part and cauliflower if LAA has limited length and the distal width exceeds the proximal width. Abbreviations: LA = left atrium LAA = left atrial appendage.

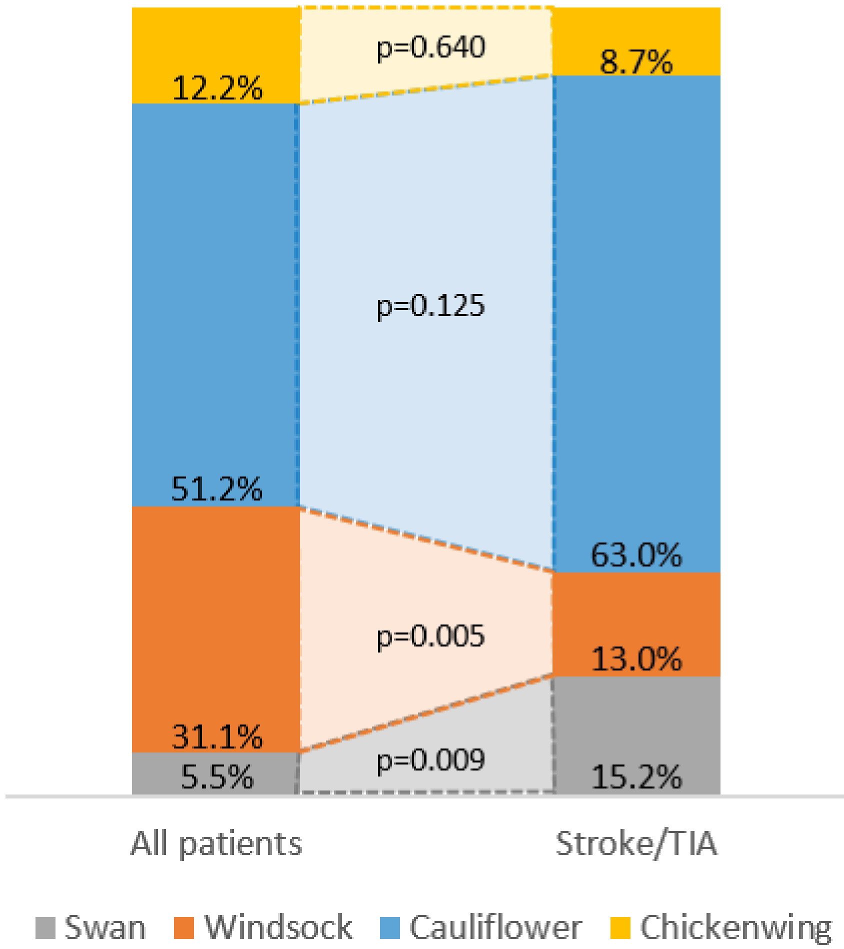

Figure 2

Comparison of LAA morphologies in the whole study group versus in those with prior stroke/TIA Patients with prior stroke/TIA had significantly higher rate of swan and lower rate of windsock LAA morphology.

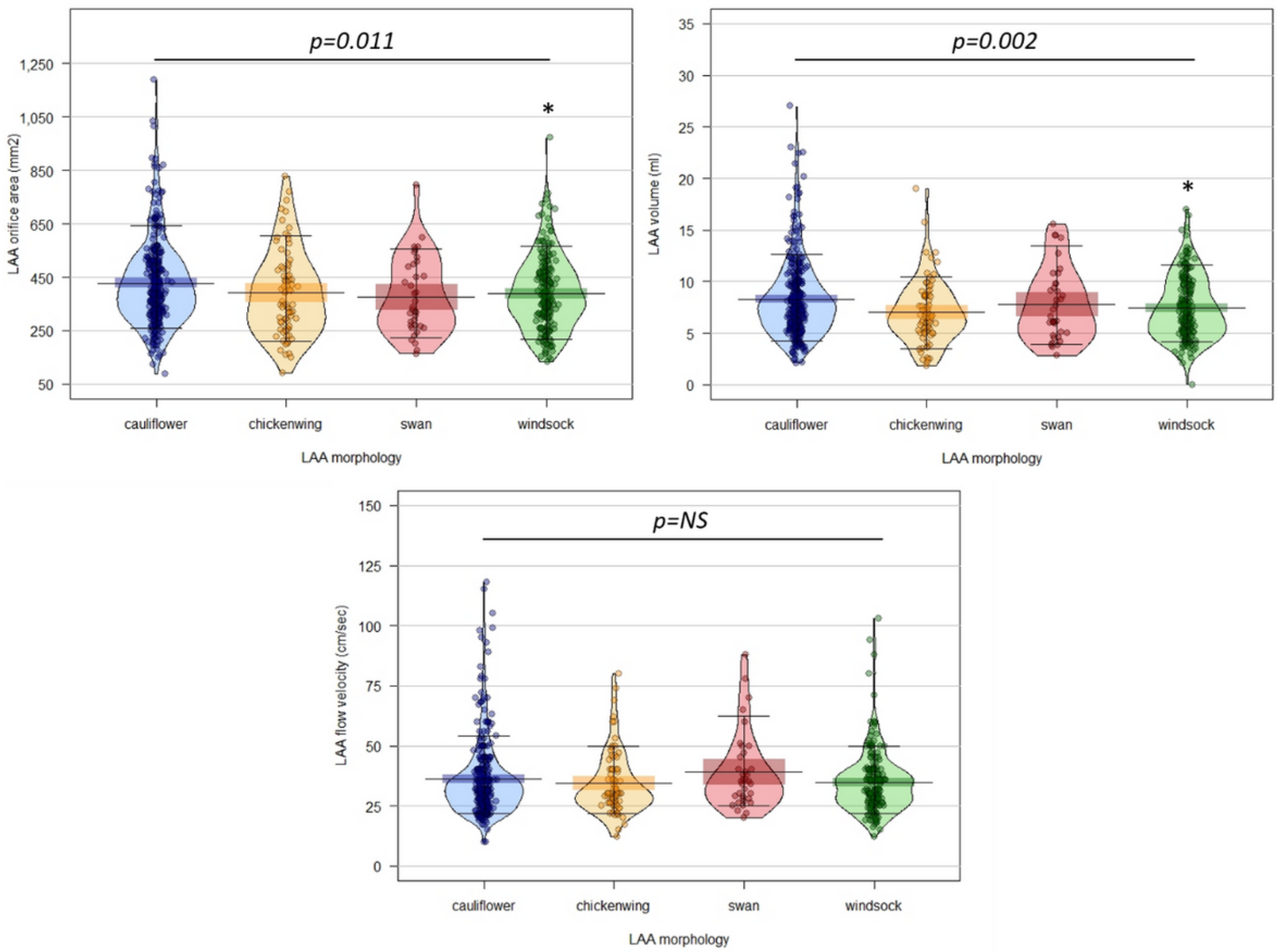

Figure 3

The relationship between LAA shape and LAA orifice area, volume and flow-velocity *p<0.05 versus cauliflower type. Violin plots show the probability density of the examined LAA parameters for each LAA morphology category. The line in the middle indicates median, box presents IQR, whiskers show 95%CI and the shape of the violin displays frequencies of the values. Abbreviations: LAA = left atrial appendage.