Journal of Cardiovascular Computed Tomography 13 (2019) 105–112

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.elsevier.com/locate/jcct

Research paper

Impact of anatomical features of the left atrial appendage on outcomes after cryoablation for atrial fibrillation

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ARTICLE INFO

Keywords:
Multidetector computed tomography
Atrial fibrillation
Cryoablation
Left atrial appendage
Morphology

ABSTRACT

Aims: Pulmonary vein isolation (PVI) using cryoballoon has been accepted as a safe and effective method for treatment of atrial fibrillation (AF). Despite advances in catheter-based technologies, some patients still experience AF recurrence. In this study, we aimed to compare left atrial appendage (LAA) morphology in AF patients and subjects with sinus rhythm and also investigate the association between LAA morphology and success of PVI using cryoballoon in subjects with AF.

Methods: In this prospective study, 359 AF patients who underwent pre-ablation computed tomographic angiography (CTA) scan between January 2013–March 2016 were included as the patient group. 100 age and gender-matched subjects in sinus rhythm who had no AF episodes in 24-h Holter monitoring that underwent CTA were included as the control group.

Results: Non-chicken wing LAA morphology was more common in AF patients ($p < 0.001$). LAA was significantly deeper ($p < 0.001$) and short-axis diameter of LAA orifice and LAA orifice area were significantly larger ($p < 0.001$) in AF patients. Low take-off type morphology of LAA was more common in controls compared to AF patients ($p = 0.006$). At a median follow-up of 37 months, only longitudinal-axis left atrial diameter on CT ($p = 0.003$) and cauliflower-type LAA morphology ($p = 0.004$) were independent predictors of AF recurrence.

Conclusion: This is the first study in the literature that investigates the relationship between anatomical variations of LAA and AF recurrence following cryoablation. Our findings demonstrate that cauliflower-type LAA morphology is associated with two-fold increased risk of AF recurrence.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia.[1] Pulmonary veins (PVs) have been reported to be the most common trigger site for initiation and maintenance of AF.[2] Considering the limited success rate with PV isolation (PVI) in persistent AF patients, anatomic regions in the left atrium other than PVs have been proposed to have a role in AF maintenance. These include the mitral isthmus, roof, septum and left atrial appendage (LAA).[3] di Biase et al.[3] have shown that LAA is responsible for arrhythmias in 27% of patients scheduled for re-do catheter ablation for AF. A recent study by our group has also demonstrated that LAA isolation as an adjunct to PVI improved one-year outcomes in persistent AF compared with the PVI-only strategy using cryoballoon.[4]

As a non-PV foci, anatomy of the LAA has been investigated in AF patients. Morphological remodelling, resultant larger LAA volumes[5,6] and a predictive role of LAA anatomy for determining the subject's thromboembolic risk[5,7] have been reported. However, there is limited information on the relationship between anatomical features of LAA and success of rhythm control strategies.

In this study, we aimed to compare LAA morphology in AF patients and subjects with sinus rhythm and also investigate the impact of LAA

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https://doi.org/10.1016/j.jcct.2019.01.011
Received 4 July 2018; Received in revised form 20 November 2018; Accepted 3 January 2019
Available online 04 January 2019

Abbreviations

AF	atrial fibrillation
CAD	coronary artery disease
CTA	computed tomographic angiography
CW	chicken wing
DLP	dose-length product
HR	hazard ratio
LA	left atrium
LAA	left atrial appendage
LAD	left atrial diamater
LVEF	left ventricular ejection fraction
MDCT	Multidetector computed tomography
PNP	phrenic nerve palsy
PVs	Pulmonary veins
PVI	Pulmonary vein isolation

morphology on AF-free survival following PV isolation (PVI) using cryoballoon in subjects with AF.

2. Methods

2.1. Study population

In this prospective study, 359 AF patients who underwent pre-ablation coronary computed tomographic angiography (CTA) scan for identifying PV anatomy between January 2013–March 2016 were included as the patient group. These patients had symptomatic paroxysmal or persistent AF episodes despite antiarrhythmic drug therapy and therefore were scheduled for cryoballoon-based AF ablation procedure using Arctic Front Advance™ Cardiac CryoAblation Catheter (Medtronic, USA) (Arc-Adv-CB) as previously described.[8] Among subjects who underwent coronary CTA at the same time interval, 100 age and gender-matched subjects in sinus rhythm who had no AF episodes in 24-h Holter monitoring were included as the control group.

Atrial fibrillation episodes that either lasted > 7 days or required termination by cardioversion, either with drugs or by direct current cardioversion were defined as persistent; whereas AF episodes self-terminating within 7 days were defined as paroxysmal AF.[9] Patients who had moderate–severe valvular disease, valvular surgery, LAA ligation, congenital heart disease, thrombus in left atrium (LA)/LAA and left ventricular ejection fraction (LVEF) < 50% were excluded. In addition, subjects who had artefacts, inadequate contrast filling that limited measurements on CT scans were not included.

Baseline demographic, clinical and imaging characteristics were recorded for all patients. Arterial hypertension was defined as having systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or self-reported use of antihypertensive medication specifically prescribed for the treatment of hypertension. Diabetes was defined as fasting plasma glucose ≥126 mg/dl and/or self-reported treatment with glucose-lowering medication. Significant coronary artery disease (CAD) was defined as 50% or greater coronary lumen stenosis of any coronary vessel. All subjects underwent transthoracic echocardiography (TTE) within 1 week prior to coronary CTA scan to assess intracavitary dimensions, LVEF and to exclude valvular heart disease.[10] Transesophageal echocardiography was performed the day before ablation only in the patient group to rule out thrombus in the LAA.

In patients on anticoagulant therapy, anticoagulation was discontinued at least 48–72 h before the procedure for warfarin; 48 h before the procedure for dabigatran and rivaroxaban. The pre-procedural interval was bridged with enoxaparin 1 mg/kg when sub-therapeutic INR levels were detected following suspension of warfarin, 12 h after suspension of dabigatran and 24 h after suspension of rivaroxaban. Last dose of enoxaparin was given 12 h prior to the scheduled procedure. Treatment with antiarrhythmic drugs was discontinued for at least 3 days prior to the procedure.

The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by the Institutional Ethics Committee (Approval number: GO 14/444-35). Informed consent was obtained from the subjects.

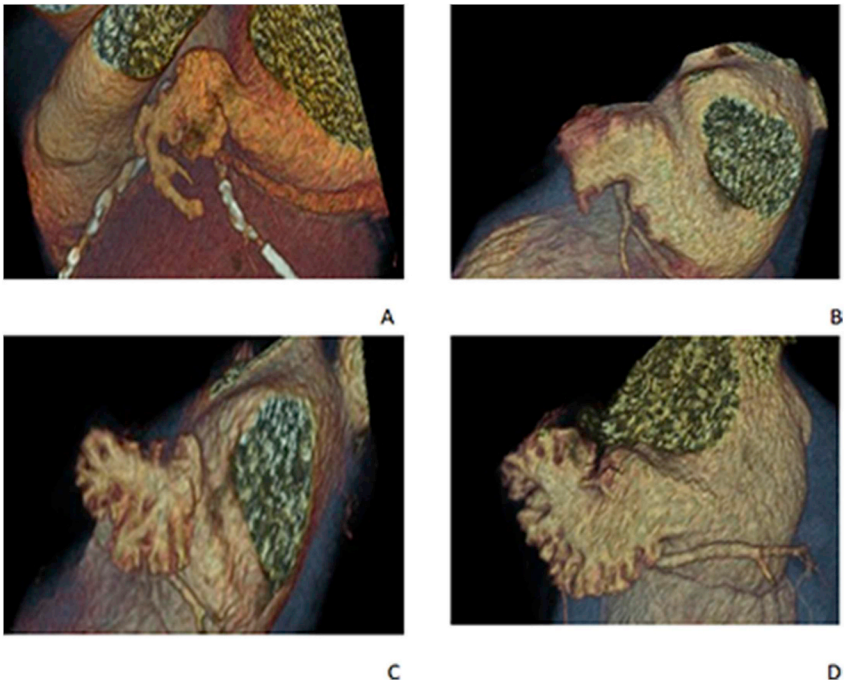

Fig. 1. Computed tomography images of the 4 most common shapes of left atrial appendage: (A) chicken wing; (B) windsock; (C) cactus; and (D) cauliflower.

2.2. Multidetector computed tomography (MDCT) scan

The study population had undergone MDCT scan with three-dimensional (3D) construction of the LA to assess detailed LA anatomy, including evaluation of the PVs, LAA and LA diverticula. CTA scans were performed using first-generation dual-source 64-slice multidetector CT scanner (Somatom Definition; Siemens, Erlangen, Germany) as described in a previous paper.[11] Sublingual nitrate (5 mg of isosorbide dinitrate, Fako Isordil) was administered 2–4 min before image acquisition to dilate the coronary arteries. The coronary angiographic scan was obtained with injection of 80 mL of nonionic contrast medium (350 mg I/mL iohexol, Omnipaque™) at a flow rate of 6 mL/s followed by 50 mL of saline solution and contrast administration was controlled with bolus tracking. The scan parameters were detector collimation, 2 × 32 × 0.6 mm; slice acquisition, 64 × 0.6 mm; gantry rotation time, 330 ms; temporal resolution, 83 ms; pitch, 0.20–0.47 adapted to the heart rate; tube current, 390 mAs per rotation; tube potential, 120 kV. Scanning time was approximately 5.7–8.4 s, depending on the cardiac dimensions and pitch and breath holding was utilized to minimize motion artifact. Prospective ECG tube-current modulation (ECG pulsing) for radiation dose reduction was used for all patients. Retrospective gating technique was used to synchronize data reconstruction with the ECG signal. The reconstructions were made in all cardiac phases at 50-ms intervals at a slice thickness of 0.75 mm and a reconstruction increment of 0.5 mm. The reconstruction interval with the fewest motion artefacts was chosen and used for further analysis. The dose-length product (DLP) was obtained from the patient protocol of the scanner, which summarizes the relevant radiation exposure parameters of each patient individually. The DLP was displayed by the CT system and was converted into effective dose values with a conversion factor of 0.017 mSv/mGy. cm, according to the Commission of the European Communities guidelines on quality criteria for CT.

During analysis, images were retrieved from the picture archiving and communication system and were retrospectively analyzed by an experienced cardiovascular radiologist. LAA morphology was classified as defined by Kimura et al.[12] as follows: chicken wing (CW), a > 4-cm-long main lobe with a folded angle of < 100°; windsock, a main lobe > 4 cm long with a folded angle of > 100°; cactus, a < 4-cm-long main lobe with more than two lobes over 1 cm; cauliflower, a < 4-cm-long main lobe with no forked lobes (Fig. 1). Intra-observer variability testing for repeated LAA morphology assessment from 50 subjects revealed an intra-class correlation coefficient of 0.989 ($p < 0.001$).

2.3. Ablation strategy and procedure during cryoablation

All procedures were performed under conscious sedation using boluses of midazolam and fentanyl. Invasive arterial blood pressure, oxygen saturation and ECG were continuously monitored throughout the procedure. Right femoral vein and left femoral vein/artery punctures were performed with Seldinger technique. A 6 Fr-steerable decapolar catheter (Dynamic Deca, Bard Electrophysiology) was placed into the coronary sinus. Single transseptal puncture by modified Brockenbrough technique (BRK-1 transseptal needle, St. Jude Medical, St. Paul, MN, USA) was performed under fluoroscopy and 8.5 Fr transseptal sheath (Fast-Cath transseptal guiding introducer, St. Jude Medical, St. Paul, MN, USA) was placed into the LA. Once LA access was obtained, unfractionated heparin boluses were repeatedly administered to maintain the activated clotting time of 300–350 s. The sheath was then exchanged with a 15 Fr-steerable sheath (Flexcath Advance, Medtronic, Minneapolis, MN, USA) over a guidewire (0.032 in., 180 cm Super Stiff, St. Jude Medical, St. Paul, MN, USA). In all patients, either the second or third-generation 28-mm CB catheter (Arctic Front Advance™ and Arctic Front Advance ™ ST, Medtronic Inc., Minneapolis, MN, USA) was used for PVI. A 20 mm-circular mapping catheter (Achieve, Medtronic, Minneapolis, MN, USA) was used in all patients to guide the CB within the LA and to attempt real-time recordings from the targeted PV. The balloon was inflated in the LA and then directed toward the PV ostia. The assessment of CB occlusion was performed through the injection of 50% diluted contrast through the CB catheter's central lumen. Ablation procedure was started after the demonstration of optimal vessel occlusion, which was defined as the retention of contrast media in the PVs without backflow into the LA. The duration of each freezing cycle was 180 s. Bonus freeze was applied even after successful isolation of the PVs. A bonus freeze was avoided in following conditions: rapid (between 60 and 120 s) and low nadir temperature achievement during the first cycle (−60 °C or below), occurrence of phrenic nerve palsy (PNP) during the first cycle or weakening of diaphragmatic capture monitored by intermittent fluoroscopy and tactile feedback.

A 6 Fr-standard decapolar catheter (Webster Decapolar Catheter, Biosense Webster, Inc., Irvine, CA, USA) was placed in the superior vena cava to pace the right phrenic nerve with a 2000-msec cycle and a 12-mA output during ablation of the right-sided PVs to prevent PNP. Capture was observed by both observation under fluoroscopy and manual palpation of the abdomen. In the case of phrenic nerve injury, cryoenergy application was aborted immediately and the balloon was deflated to avoid further damage to the nerve. Diaphragmatic contractions were followed-up for 30 min. No additional cryoenergy application was performed to the vein.

Electrical PV isolation was confirmed with entrance and exit block maneuvers by coronary sinus electrode and circular mapping catheter stimulation, respectively.

2.4. Follow-up

A TTE was performed immediately after the procedure to exclude the presence of pericardial effusion. All patients were monitored for at least 24 h in the telemetry unit. Oral anticoagulation was initiated in the evening of ablation unless pericardial effusion was detected and continued for at least 3 months after the procedure. The need for further oral anticoagulation was evaluated in the third month based on the CHA_2DS_2-VASc score. Antiarrhythmic drug treatment was also continued for at least 3 months.

Following discharge from the hospital, enrolled patients were scheduled for visits in the outpatient clinics at 1st, 3rd, 6th and 12th months after ablation and every 6 months thereafter, or earlier, if symptoms consistent with recurrent AF developed after the ablation. At each visit, patients were evaluated for the recurrence of arrhythmias with questioning for arrhythmia-related symptoms (palpitations, chest discomfort, fatigue and dizziness), physical examination and a 12-lead electrocardiogram. A 24-h ambulatory ECG monitorization was conducted at 3rd, 6th and 12th months and at every 6 months thereafter in all patients. Any episode of AF, atrial flutter or atrial tachycardia lasting at least 30 s was defined as recurrence. A blanking period of 3 months was considered for the study. Any recurrence occurring in the blanking period was classified as an early recurrence; whereas recurrence after the blanking period was considered as late recurrence.

2.5. Statistical analysis

Normally distributed continuous parameters were presented as mean ± standard deviation and compared using student's t-test or one-way ANOVA test with Tukey correction where appropriate. Skewed continuous parameters were expressed as median (interquartile range defined as 25^{th}-75th percentiles) and were compared using Mann-Whitney *U* test. Categorical data were presented as frequencies and percentages and were compared using chi-square test. To analyze the association between baseline and follow-up factors on procedural outcomes, a Cox regression model was used. A multivariable model was used to estimate hazard ratios (HR) for recurrence while controlling for baseline characteristics. Statistical analyses were performed using SPSS statistical software (IBM Corp. Released 2012. IBM SPSS Statistics for

Windows, Version 21.0. Armonk, NY: IBM Corp.). A two-tailed $p < 0.05$ was considered statistically significant.

3. Results

359 patients who were scheduled for cryoablation for AF (56.41 ± 7.88 years, 50.4% male) and 100 age and gender-matched subjects (55.35 ± 6.42 years, 50% male) were included in the study. Baseline demographic, clinical and echocardiographic parameters of the study population are listed in Table 1. Baseline characteristics did not differ between AF and control groups, except for left atrial diamater (LAD). LA were significantly larger in AF patients ($p < 0.001$). None of the patients had thrombi located in the LA or LAA.

Parameters related to LAA morphology detected in MDCT are given in Table 1. The predominant LAA morphology was CW in controls and windsock in AF patients ($p < 0.001$). Non- CW LAA morphology was more common in AF patients ($p < 0.001$). LAA was significantly deeper in AF patients ($p < 0.001$). Short-axis diameter of LAA orifice and LAA orifice area were significantly larger in AF patients ($p < 0.001$). Low take-off type morphology of LAA was more common in controls compared to patients with AF ($p = 0.006$). Number of LAA lobes or morphology of LAA orifice did not differ between two groups ($p > 0.05$). Anatomical features of the LA and LAA differed significantly among paroxysmal, persistent and long-standing persistent AF groups, regarding LA longitudinal axis diameter ($p = 0.001$), LAA diameter ($p < 0.001$) and LAA orifice area ($p = 0.008$). In the post-hoc analysis, LA long-axis size was significantly shorter in paroxysmal AF patients compared to persistent ($p = 0.007$) and long-standing persistent AF ($p = 0.020$) patients. LAA long-axis diameter was shorter ($p < 0.001$) and LAA orifice area was smaller ($p = 0.011$) in paroxysmal AF patients compared to persistent AF patients (Table 2).

All patients were followed-up for 37 (17–60) months. When blanking period of 3 months was considered, freedom from AF after a single ablation procedure was 74.37%. Among baseline characteristics, the only parameter that was significantly associated with AF recurrence at follow-up was the larger LA diameter on transthoracic echocardiography ($p < 0.001$) and MDCT ($p = 0.008$) in AF patients (Table 3). Anatomical features of LAA morphology on MDCT were found to be similar among patient groups with and without AF recurrence (Table 3).

Multivariate Cox regression analysis showed that only longitudinal-axis LA diameter on CT ($p = 0.003$) and cauliflower-type LAA morphology (compared to windsock) ($p = 0.004$) were independent predictors of AF recurrence after blanking period following cryoballoon-based PVI for AF (Table 4).

Table 1
Baseline demographic, clinical and transthoracic echocardiographic parameters and anatomic features of the left atrial appendage of the study population (n = 459).

	Control group (n = 100)	Atrial fibrillation group (n = 359)	p value
Demographic and clinical parameters			
Gender: male, n (%)	50 (50)	181 (50.42)	0.516
Age, years	55.35 ± 6.42	56.41 ± 7.88	0.216
AF type, n (%)			
Paroxysmal	–	260 (72.42)	
Persistent	–	99 (27.58)	–
Hypertension, n (%)	46 (46)	160 (44.57)	0.799
Diabetes mellitus, n (%)	10 (10)	50 (13.93)	0.303
Coronary artery disease, n (%)	16 (16)	38 (10.58)	0.137
Current smoking, n (%)	41 (41)	118 (32.87)	0.131
CHA_2DS_2- VASc score	1 (0–4)	1 (0–5)	0.946
Transthoracic echocardiographic parameters			
LVEF, %	64.61 ± 2.49	64.48 ± 3.35	0.362
LA diameter, mm	34 ± 2.2	41 ± 2.9	< 0.001*
Computed tomographic parameters			
LA diameter, mm			
- transverse axis	38.90 ± 8.53	53.99 ± 11.55	< 0.001*
- antero- posterior axis	42.83 ± 10.12	50.48 ± 13.95	< 0.001*
- longitudinal axis	50.71 ± 7.43	53.65 ± 12.77	0.028*
LAA morphology, n (%)			
- Cauliflower	15 (15)	93 (25.91)	< 0.001*
- Cactus	5 (5)	30 (8.36)	
- Chicken wing	52 (52)	67 (18.66)	
- Windsock	28 (28)	169 (47.08)	
LAA morphology, n (%)			
- Non- chicken-wing	48 (48)	292 (81.34)	< 0.001*
LAA lobe number, n (%)			
1	43 (43)	170 (47.35)	0.396
2	38 (38)	140 (39.00)	
3	19 (19)	49 (13.65)	
LAA depth, mm	42.42 ± 8.46	49.52 ± 10.41	< 0.001*
LAA diameter, mm			
- long- axis	21.46 ± 3.93	22.12 ± 5.62	0.188
- short- axis	15.64 ± 3.59	19.82 ± 5.41	< 0.001*
LAA orifice area, cm^2	2.68 ± 0.83	3.59 ± 1.41	< 0.001*
LAA orifice morphology, n (%)			
Round	15 (15)	71 (19.78)	0.191
Oval	66 (66)	199 (55.43)	
Triangular	3 (3)	26 (7.24)	
Foot	6 (6)	34 (9.47)	
Teardrop	10 (10)	29 (8.08)	
LAA take- off type, n (%)			
High take- off	9 (9)	67 (18.66)	0.006*
Mid take- off	19 (19)	95 (26.46)	
Low take- off	72 (72)	197 (54.87)	

AF, atrial fibrillation; LA, left atrial; LAA, left atrial appendege; LV, left ventricular; LVEF, left ventricular ejection fraction.
*p value < 0.05 denotes statistical significance.

4. Discussion

This is the first study in the literature that investigates the relationship between anatomical variations of LAA and AF-free survival following cryoablation. An outstanding feature of our study has been that major confounding factors for the evaluation of LAA anatomy, such as left ventricular systolic dysfunction and moderate-severe valvular heart disease, have been excluded.

Structural and electrical remodelling occurs in the left atrium of AF patients. However, there is scarce evidence related to the LAA remodelling in AF. In a necropsy study, larger LAA volumes were reported in AF patients compared to controls.[5] Another necropsy study showed that AF patients had larger LAA volumes and orifices, as well as fewer lobes.[13] Similar LAA findings were detected by MDCT when patients with paroxysmal AF and sinus rhythm were compared.[14] A higher incidence of low take-off LAA was also noted in AF patients in the same study.[14] In our study, short-axis diameter of LAA and LAA orifice area were found to be significantly larger in AF patients compared to controls. Furthermore, low take-off LAA morphology was more common in AF patients. Although lobe number of LAA was lower in AF patients compared to controls, this difference did not reach statistical significance.

When AF type is taken into account, Park et al.[15] have reported larger LAA volumes in persistent and long-standing AF patients compared to paroxysmal AF patients. Kishima et al.[6] have then reported larger LAA volumes in both persistent and paroxysmal AF patients compared to controls, nevertheless LAA volumes were comparable between persistent and paroxysmal AF patients. In our study, LAA long-axis diameter was longer and LAA orifice area was larger in persistent AF patients compared to paroxysmal AF patients. The lack of statistically significant difference between long-standing persistent AF patients and other AF patient groups may be due to relatively small sample size of long-standing persistent AF patients. Larger LAA size in AF patients

Table 2
Anatomic features of the left atrial appendage regarding type of atrial fibrillation (n = 359).

Computed tomographic parameters	Paroxysmal AF (G1) (n = 260)	Persistent AF (G2) (n = 83)	Long- standing persistent (G3) (n = 16)	p value	G1- G2	G1-G3	G2- G3
LA diameter, mm							
- Transverse axis	54.37 ± 10.99	52.33 ± 12.12	57.44 ± 16.41	0.189	–	–	–
-Antero- posterior axis	50.10 ± 13.61	51.90 ± 15.11	49.90 ± 14.30	0.566	–	–	–
-Longitudinal axis	52.11 ± 13.26	56.98 ± 9.13	60.87 ± 16.13	0.001*	0.007*	0.020*	0.493
LAA morphology, n (%)							
-Cauliflower	64 (24.62)	24 (28.92)	5 (31.25)	0.536	–	–	–
-Cactus	20 (7.69)	8 (9.64)	2 (12.5)				
-Chicken wing	52 (20.00)	15 (18.07)	0 (0)				
-Windsock	124 (47.69)	36 (43.37)	9 (56.25)				
LAA morphology, n (%)							
-Non- chicken- wing	208 (80.00)	68 (81.93)	16 (100.00)	0.115	–	–	–
LAA lobe number, n (%)							
1	144 (55.38)	49 (59.04)	7 (43.75)	0.129	–	–	–
2	107 (41.15)	27 (32.53)	6 (37.50)				
3	39 (15.00)	7 (8.43)	3 (18.75)				
LAA depth, mm	49.71 ± 9.37	48.76 ± 10.66	51.33 ± 21.13	0.617	–	–	–
LAA diameter, mm							
-Long- axis	21.31 ± 5.48	23.92 ± 5.49	25.86 ± 5.03	< 0.001*	< 0.001*	0.004	0.395
-Short- axis	19.79 ± 5.59	20.09 ± 5.12	18.95 ± 3.87	0.728	–	–	–
LAA orifice area, cm^2	3.44 ± 1.38	3.96 ± 1.42	4.01 ± 1.51	0.008*	0.011*	0.262	0.990
LAA orifice morphology, n (%)							
Round	55 (21.15)	14 (16.87)	2 (12.50)	0.804	–	–	–
Oval	140 (53.85)	48 (57.83)	11 (68.75)				
Triangular	18 (6.92)	7 (8.43)	1 (6.25)				
Foot	23 (8.85)	9 (10.84)	2 (12.50)				
Teardrop	24 (9.23)	5 (6.02)	0 (0)				
LAA take- off type, n (%)							
High take- off	53 (20.38)	13 (15.66)	1 (6.25)	0.122	–	–	–
Mid take- off	61 (23.46)	30 (36.14)	4 (25.00)				
Low take- off	144 (55.38)	40 (48.19)	11 (68.75)				

AF, atrial fibrillation; G, group; LA, left atrial; LAA, left atrial appendage.
*p value of < 0.05 denotes statistical significance.

provide evidence for LAA remodelling in AF. Despite the study by Kishima et al.,[6] findings revealed by our study and Park et al.[15] suggest that LAA remodelling reflected by increase in either LAA volume or LAA long-axis diameter and LAA orifice area is a time-dependent process, which is supported by greater LAA size in persistent and long-standing AF patients.

When morphological features other than LAA size are taken into consideration, Kishima et al.[6] have reported that patients in the persistent AF group had a significantly higher prevalence of non- CW-type LAA than those did in the paroxysmal AF and control groups, but LAA morphology was comparable between paroxysmal AF and control groups. Similarly, in our study non- CW LAA morphology was significantly more common in AF patients compared to controls. The most prevalent type was windsock in AF patients, whereas it was CW in the control group. However, type of LAA morphology did not differ between AF types. This discrepancy may be explained with the fact that LAA morphology in AF patients may differ among populations. For instance, in a study by Fukushima et al.,[16] the most prevalent LAA morphology was cactus (38.50%), followed with windsock (32.30%), cauliflower (16.70%) and CW (12.50%) in 96 paroxysmal AF patients, whereas in our study the most prevalent LAA morphology was windsock, followed with cauliflower, chicken-wing and cactus, respectively.

Current guidelines indicate that detailed LA anatomy obtained by either CT and/or magnetic resonance imaging scanning is essential for a safe and effective catheter ablation of AF.[17] A few studies have evaluated the impact of CT-derived anatomical parameters on outcomes of cryoablation for AF.[18,19] A recent study has evaluated the anatomical characteristics of the LAA in 59 persistent AF patients undergoing radiofrequency catheter ablation, including LAA volume/volume index and LAA shape, in which they were found to be comparable in patients with and without AF recurrence at a median follow-up of 13 months.[20] Our study is the first study in the literature that shows the role of anatomical features of LAA for the prediction of AF recurrence following successful cryoablation. In our study, long-axis diameter of the left atrium and cauliflower type LAA morphology (when compared to the most common LAA morphology in AF patients in this study population) were associated with increased risk of AF recurrence after cryoablation for AF when adjusted for other parameters.

Although enlarged LA size is an accepted associate of unfavourable outcomes following rhythm control strategies in AF, our study is the first to suggest that a specific LAA morphology may be related with increased AF recurrence after cryoablation. Cauliflower-type LAA is described as having a short overall length, more complex internal characteristics, a variable number of lobes with lack of a dominant lobe, and a more irregular shape of the orifice. Previous studies have suggested that extensive LAA trabeculation and multiple lobes, like in cauliflower morphology type, may cause poor emptying and slow blood filling in the LAA, increasing the risk of stroke/transient ischemic attack.[21–23] Nevertheless, data on how a specific LAA morphology may trigger AF maintenance still does not exist. However, it is of note that the increased risk of AF recurrence with the cauliflower-type LAA is present when compared to the most common LAA morphology type in AF patients in this study population, which is the windsock morphology. Further studies with larger study cohorts are necessary to understand if this is a population-specific finding or if can be replicated. In addition, redo ablation procedures including the isolation of LAA may provide a mechanistic link.

Morphological features of LAA demonstrated in MDCT prior to ablation may modify operator's therapeutic approach, such as rhythm control vs. rate control or preference of more extensive ablation strategy rather than PVI using cryoballoon. Point-by-point radiofrequency ablation in combination with a 3D-electroanatomical mapping system may be considered in subjects proven to have anatomical features associated with adverse outcomes following cryoablation,

Table 3
Baseline characteristics of the patients regarding presence of atrial fibrillation recurrence following cryoablation (n = 359).

	Study population (n = 359)	AF recurrence – (n = 267)	AF recurrence (n = 92)	p value
Demographic and clinical parameters				
Gender: male, n (%)	181 (50.42)	130 (48.69)	51 (55.43)	0.264
Age, years	56.41 ± 7.88	56.01 ± 7.97	57.58 ± 7.53	0.101
Persistent AF, n (%)	99 (27.58)	67 (25.09)	32 (34.78)	0.073
EHRA score				
2	132 (36.77)	94 (35.21)	38 (41.30)	0.536
3	193 (53.76)	148 (55.43)	45 (48.91)	
4	34 (9.47)	25 (9.36)	9 (9.78)	
Hypertension, n (%)	160 (44.57)	119 (44.57)	41 (44.57)	0.990
Diabetes mellitus, n (%)	50 (13.93)	38 (14.23)	12 (13.04)	0.776
Coronary artery disease, n (%)	38 (10.58)	26 (9.74)	12 (13.04)	0.374
Current smoking, n (%)	118 (32.87)	87 (32.58)	31 (33.70)	0.845
CHA_2DS_2- VASc score	1 (0–5)	1 (0–5)	1 (0–5)	0.863
Transthoracic echocardiographic parameters				
LVEF, %	64.48 ± 3.35	64.21 ± 3.45	64.48 ± 3.06	0.514
LA diameter, mm	41.00 ± 2.90	3.76 ± 0.50	4.01 ± 0.63	< 0.001*
Computed tomographic parameters				
LA diameter, mm				
-transverse axis	53.99 ± 11.55	53.21 ± 11.24	56.24 ± 12.21	0.030
-antero- posterior axis	50.48 ± 13.95	50.53 ± 14.17	50.34 ± 13.34	0.913
-longitudinal axis	53.65 ± 12.77	52.60 ± 12.64	56.71 ± 12.70	0.008*
LAA morphology, n (%)				
-Cauliflower	93 (25.91)	67 (25.09)	26 (28.26)	0.748
-Cactus	30 (8.36)	24 (8.99)	6 (6.52)	
- Chicken wing	67 (18.66)	52 (19.48)	15 (16.30)	
-Windsock	169 (47.08)	124 (46.44)	45 (48.91)	
LAA morphology, n (%)				
-Non- chicken- wing	292 (81.34)	215 (80.52)	77 (83.70)	0.539
LAA lobe number				
1	170 (47.35)	127 (47.57)	43 (46.74)	0.803
2	140 (39.00)	102 (38.20)	38 (41.30)	
3	49 (13.65)	38 (14.23)	11 (11.96)	
LAA depth, mm	49.52 ± 10.41	49.54 ± 10.40	49.45 ± 10.50	0.944
LAA diameter, mm				
-long- axis	22.12 ± 5.62	21.89 ± 5.37	22.79 ± 6.28	0.178
-short- axis	19.82 ± 5.41	19.70 ± 5.43	20.18 ± 5.36	0.490
LAA orifice area, cm^2	3.59 ± 1.41	3.53 ± 1.36	3.75 ± 1.55	0.204
LAA orifice morphology, n (%)				
Round	71 (19.78)	53 (19.85)	18 (19.57)	0.838
Oval	199 (55.43)	145 (54.30)	54 (58.70)	
Triangular	26 (7.24)	19 (7.12)	7 (7.61)	
Foot	34 (9.47)	28 (10.49)	6 (6.52)	
Teardrop	29 (8.08)	22 (8.24)	7 (7.61)	
LAA take- off type				
High take- off	67 (18.66)	47 (17.60)	20 (21.74)	0.675
Mid take- off	95 (26.46)	72 (26.97)	23 (25.00)	
Low take- off	197 (54.87)	148 (55.43)	49 (53.26)	

AF, atrial fibrillation; EHRA, European Heart Rhythm Association; LA, left atrial; LAA, left atrial appendege; LV, left ventricular; LVEF, left ventricular ejection fraction.
*p value < 0.05 denotes statistical significance.

instead of PVI using cryoablation. In addition, not PVI only but also ablation of complex fractionated atrial electrograms and/or linear ablation of the roof line, posterior wall, superior coronary sinus, or the mitral line, and even isolation of the superior vena cava and/or LAA may be performed in such patients. Recent studies have shown the beneficial role of LAA isolation in order to obtain higher success rate in persistent AF patients[4,24–25] but neither of them have reported data about the impact of anatomic characteristics of the LAA on procedural outcomes. Furthermore, patients with high-risk LAA features for AF recurrence may undergo a closer follow-up in the outpatient clinics.

4.1. Study limitations

There are several limitations of the study. Whether determination of LAA morphology is reproducible between different observers in different studies remain controversial due to the differences in the definition of LAA types. Nevertheless, we have tried to minimize the variability by using definitions that incorporate more objective information for the types of LAA. Second, despite regular screening of patients during outpatient visits with ECG and 24-h Holter recording, all episodes of AF paroxysms and recurrences may not have been detected. Third, longer follow-up and larger number of study population may alter results. Fourth, in this study we did not evaluate the impact of LAA morphology on outcomes of LAA isolation adjunct to PVI, which merits further studies. At last but not least, this study included a group of mono-ethnic AF patients who were scheduled for catheter ablation for AF.

5. Conclusion

Despite advances in catheter-based technology and operator experience, AF recurrence after ablation remains as a problem. Our findings demonstrate that cauliflower-type LAA morphology depicted in preprocedural CTA is associated with a two-fold increased risk of AF recurrence.

Table 4
Cox regression analysis for identifying predictors of atrial fibrillation recurrence following cryoablation.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age, years	1.028	0.998–1.058	0.067	1.026	0.996–1.057	0.095
Type of AF			0.157			0.233
- paroxysmal vs. long- standing persistent	1.597	0.988–2.581	0.056	1.377	0.619–3.063	0.433
- persistent vs. long- standing persistent	1.031	0.485–2.192	0.937	1.942	0.819–4.605	0.132
LA diameter, mm						
- transverse axis	1.003	0.986–1.021	0.704	–	–	–
- antero- posterior axis	0.988	0.974–1.002	0.100	0.991	0.977–1.006	0.247
- longitudinal axis	1.021	1.006–1.037	0.006*	1.024	1.008–1.040	0.003*
LAA morphology			0.022*			0.007*
- cauliflower vs. windsock	1.811	1.107–2.961	0.018*	2.108	1.269–3.502	0.004*
- cactus vs. windsock	1.140	0.485–2.681	0.764	1.147	0.487–2.702	0.754
- chicken wing vs. windsock	0.696	0.386–1.255	0.228	0.756	0.417–1.369	0.355
LAA morphology, n (%)						
- non- chicken- wing vs. chicken- wing	0.585	0.334–1.023	0.060	0.731	0.403–1.328	0.304
LAA lobe number	0.842	0.625–1.135	0.259	–	–	–
LAA depth, mm	1.007	0.989–1.025	0.450	–	–	–
LAA size, mm						
- long- axis	1.018	0.985–1.052	0.294			
- short- axis	1.014	0.978–1.051	0.461	–	–	–
LAA orifice area, cm^2	1.039	0.915–1.180	0.559	–	–	–
LAA orifice morphology			0.760	–	–	–
- Round vs. teardrop	0.981	0.575–1.675	0.944			
- Oval vs. teardrop	1.018	0.424–2.443	0.968			
- Triangular vs. teardrop	0.630	0.250–1.590	0.328			
- Foot vs. teardrop	1.345	0.558–3.240	0.509			
LAA take- off type			0.954			
- Mid vs. low take- off	1.079	0.640–1.817	0.776	–	–	–
- High vs. low take- off	0.994	0.605–1.632	0.981			

AF, atrial fibrillation; CI, confidence interval; CT, computed tomography; HR, hazard ratio; LA, left atrial; LAA, left atrial appendage; LV, left ventricular.
*p value $<$ 0.05 denotes statistical significance.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding sources

None.

Acknowledgements

None.

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