Acute left atrial ridge lesion after cryoballoon ablation: How it affects left atrial appendage closure combined procedure?

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Abstract

Background: Acute left atrial ridge (LAR) lesion was observed after atrial fibrillation ablation. However, the feature of LAR lesion has not been quantitatively evaluated and its influence on left atrial appendage closure (LAAC) combined procedure remained to be explored. We aimed to evaluate profile of acute LAR lesion and investigate its influence on LAAC procedure. Methods: LAR lesion profile was measured by transesophageal echocardiography (TEE) in 117 consecutive non-valvular AF patients underwent combined procedure of cryoballoon (CB) ablation and LAAC. Its correlation with baseline variables and clinical outcomes were thoroughly investigated. Results: Measurement of 96 available TEE image series showed 95 had prominent acute LAR lesion, with a greater change in width (Δwidth=3.6$\pm$2.3 mm) than thickness (Δthickness=2.6$\pm$3.5 mm), and correspondingly narrowed outer ostium (Δouter ostium diameter=-3.4$\pm$4.0 mm). While the inner ostium stayed unchanged. Logistic regression analysis showed that a higher nadir temperature when freezing left superior pulmonary vein (LSPV) led to a LAR lesion with greater width (2-fold wider) (adjusted odds ratio =1.16, 95% confidence interval 1.02-1.31). For evaluation of LAAC outcomes, residual flow occurred in 6 patients, 4 with Watchman had minimal residual flow at the inferior border, while 2 with LAmbre developed larger residual flow at the LAR side. Clinical outcomes were similar between groups divided by LAR lesion size. Conclusion: Acute LAR lesion frequently occurred following CB ablation combined procedure, and its width positively correlates with LSPV nadir temperature. It affects measurement of pacifier device but has no influence on plug device when performing combined procedure.

Introduction

Left atrial ridge (LAR)—also recognized as coumadin ridge—is the protruded convergence of left atrial appendage (LAA) and left pulmonary veins (PV). LAR is also a potential arrhythmogenic site, where embedding Bachmann's bundle and close to the ligament of Marshall (1). LAR had long been a site for atrial fibrillation (AF) ablation (2) and one of the differential diagnosis of high-echo band on echocardiography (3).

Since 2012, combining catheter ablation with left atrial appendage closure (LAAC) has been reported as a promising therapy for AF patients (4). Thenceforth, several centres worldwide have reported considerable efficacy and safety of combined procedure (5-7). Of note, prominent acute LAR lesion after combined procedure has been reported by some studies (8,9). Such phenomenon has raised the concern about its impact on LAAC procedure and overall clinical prognosis. However, neither the feature of such lesion has been quantitatively evaluated nor its influence on combined procedure has been elucidated.

Hence, we aimed to innovatively explore the influence of acute LAR lesion on combined procedure through quantitively evaluating the peri-procedural and follow-up LAR profile on transesophageal echocardiography (TEE), and analyze its relationship with preprocedural information and follow-up outcomes.

Methods

Study population

Based on the registered retrospective study Combining Left Atrial Appendage Closure with Cryoballoon Ablation in Chinese Population (CLACBAC, registry No. NCT04185142), from June 2017 to Aril 2019, 117 consecutive patients underwent combined procedure were included. Patients diagnosed with drug-refractory, non-valvular AF and met at least one of the following inclusion criteria:

a. CHA_2DS_2-VASc score[?]2 or/and HAS-BLED score[?]3,**b.** contraindications to long-term oral anticoagulants (OACs) (active major hemorrhagic diseases, inherited hemorrhagic disorders, severe side effects under OACs),**c.** refusal of OACs according to personal willingness despite comprehensive explanation.

While exclusion criteria were:

a. thrombus in LA or LAA presented and confirmed by TEE,**b.** oversized left atrium (LA, diameter¿65mm) by transthoracic echocardiography (TTE) or LAA (ostium¿35mm) by TEE,**c.** pericardial effusion ([?] 4mm by TTE or TEE),**d.** hemodynamic unstable patients,**e.** patients with active hemorrhagic diseases,**f.** ischemic or hemorrhagic stroke within 30 days.

The diagnosis of paroxysmal, persistent and long-persistent AF was in accordance with 2016 ESC guideline (10). The diagnosis of bleeding events referred to 2011 BARC consensus (11). For every patient, inform of consent was signed before the procedure with procedural risks and related complications fully informed. Our study complies with the declaration of Helsinki and approved by the ethics committee of Shanghai Tenth People's Hospital.

Combined procedure

All the procedure was performed under local anesthesia with lidocaine. Procedure details were as previously described (12). Briefly, following a transseptal puncture, a 28 mm 2^{nd} generation cryoballoon (CB, Arctic Front, Medtronic, MN, USA) was cannulated to the ostium of PV. Once complete occlusion was confirmed by angiography, cryo-energy was delivered with a time-to-isolation (TTI) guided freezing strategy (13). Phrenic pacing was applied to prevent phrenic nerve lesion. Activate clotting time (ACT) was monitored and maintained above 300 seconds during the whole procedure.

LAAC was performed instantly after CB ablation. Either Watchman (Watchman, Boston Scientific, MA, USA) or LAmbre device (Lifetech Scientific Co, Ltd, Shenzhen, China) was used. Under TEE (GE Vivid E9 and Siemens ACUSON SC2000) guidance, LAAC device was delivered and deployed. Before release, stable anchoring was confirmed by tug test and complete sealing was confirmed by TEE assessment of residual flow. Once released, TEE was applied again to reconfirm device positioning and evaluate procedure-related complications.

Post-procedure management

The anti-thrombotic therapy was recommended as follows: 1. 3-month OACs (Warfarin, dabigatran or rivaroxaban), 2. according to TEE examination in the 3rd month, double anti-platelet therapy for another 3 months 3. lifelong single anti-platelet therapy. All patients were required to have outpatient follow-up in the 1st, 3rd, 6th, 12th month, and every year after the procedure. TEE was scheduled to perform in the 3rd month and the 12th month if necessary.

Primary endpoints comprise LAAC related complications (residual flow, device related thrombosis (DRT)). Secondary endpoints encompass all-cause death, early (before the 3rd month) and late atrial arrhythmia (AA) recurrence (recorded atrial tachycardia (AT) lasting longer than 30s), stroke (confirmed by either computed tomography (CT) or magnetic resonance imaging (MRI)), major hemorrhagic events, redo-ablation, cardiovascular intervention, pericardial effusion rehospitalization due to cardiovascular events.

LAR measurement

For every patient, TEE was performed according to the ASE guideline and standards (14). Preprocedural, postprocedural and follow-up TEE were thoroughly collected. LAR profile and LAA ostium were measured on TEE at 45°/90° planes. LAR was recognized as a high-echo band between LAA and left superior PV (LSPV). The width of LAR was measured as the maximal length between LAA side and PV side, while the thickness of LAR was measured from the most proximal site of LAR to the base where a prominent reduction of echo signal was observed compared with LAR (**Figure 1**). The outer ostium was measured from the tip of LAR to the circumflex artery, as the landing zone of plug device (Watchman). While the inner ostium was measured from the circumflex artery to a point 1 to 2 cm superiorly within LAR, as the landing zone of pacifier device (LAmbre) (15). All the images were independently measured on TEE machine by 3 proficient echocardiologists, and the final LAR width, thickness, LAA inner and outer ostium diameters were acquired from the average of 3 measurements.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) if they conformed to normal distribution, while those without a normal distribution were presented as the median and interquartile ranges (IQR). The P-value was generated from 2 sample t-tests or a Mann-Whitney test according to the equality of variance, or singed-rank test if a normal distribution was not presented.

Categorical variables were described as percentages (%), and P value was generated from χ^2 test.

The changes of LAR profile were analyzed using repeated measures analysis of variance, and the correlation between width and thickness change was assessed through Spearman correlation analysis. LAR lesion was divided into mild or severe group by whether the width after procedure was larger than 2-fold of its original width or not. The association of LAR lesion size and clinical information and were evaluated by logistic regression analysis. Further multivariate model was applied that adjusted for age, gender, body mass index (BMI), LA diameter, AF type. The influence of LAR lesion on prognosis was analyzed through survival analysis with Kaplan-Meier estimate, and P value was generated from Log-Rank test.

2-side P-value < 0.05 was considered significant for all analysis. SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism 8.0.2 (GraphPad software Inc., CA, USA) adopted to conduct all the analysis.

Results

The combined procedure cohort comprised 54.7% male, with a median age of 67 years. Half of the cohort was diagnosed with persistent AF. Relatively high risks of stroke (median CHA2DS2-VASc score=3) and bleeding (median HAS-BLED score=2) can be observed (**Table 1**). Instant pulmonary vein isolation (PVI) was achieved in 117 patients, while LAAC with Watchman device failed in 2 patients who had oversized LAA ostium. During procedure, totally 9 patients, 7 with Watchman and 2 with LAmbre, required redeployment. Instant minimal residual flow was observed in 2 patients with Watchman device **(Figure 3 A & B)** . No other complications occurred. Procedure details are listed in**Table 2** .

For 96 patients with available TEE image series, acute LAR lesion was observed via TEE in almost every patient (99.0%). TEE measurement showed that LAR had a greater increase in width (Δwidth=3.6±2.3 mm, 45°) than thickness (Δthickness=2.6±3.5 mm, 45°). Correspondingly, the outer ostium was significantly narrowed (Δouter ostium diameter=-3.4±4.0 mm, 45°). However, the inner ostium remained unchanged (Δinner ostium diameter=0.4±2.2 mm, 45°). During follow-up, the lesion subsided and LAR recovered to its original width but not thickness. The LAR profile is depicted in **Figure 2.** Analysis of the association of LAR lesion size with multiple variables showed that, only LSPV nadir temperature positively correlated with over 2-fold wider LAR lesion at 45° (crude odds ratio (OR)=1.12, 95% confidence interval (CI) 1.02-1.23). Such association was still significant after adjustment (adjusted OR=1.16, 95%CI 1.02-1.31). details are presented in **Table 3** .

The influence of acute LAR lesion on LAAC was revealed by TEE. In the 3rd month, Residual flow was observed in 6 patients, 4 with Watchman and 2 with LAmbre. All four cases with Watchman device had minimal residual flow (0.9-2.1 mm) at the inferior border at 135° (**Figure 3 A-D**), while 2 cases of LAmbre device developed relatively larger (2.5 mm and 4.2 mm) residual flows at the LAR border at 90° (**Figure 3 E & F**). Besides, through a mean follow-up time of 626.4±212.2 days, survival analysis showed that there was no difference between mild and severe LAR lesion groups on AA recurrence and rehospitalization. (**Figure 4**). And the clinical outcomes were similar between groups, as listed in **Table 4** .

Discussion

Our study first quantitively illustrated the TEE feature of acute LAR lesion CB ablation combined procedure, and explored its influence on clinical outcomes. Our primary findings are: 1. Prominent acute LAR lesion after CB ablation combined procedure could be frequently observed, with a larger increment in width than thickness, 2. Higher LSPV nadir temperature poses a higher incidence of 2-fold wider LAR lesion, 3. Acute LAR lesion has no influence on overall combined procedure outcome, but it affects measurement of pacifier device.

LAR—also known as coumadin ridge—had long been mistaken as a thrombus attached to LAA revealed by transthoracic echocardiography (TTE). Until 2008, a 3-dimensional TTE study demonstrated that the high-echo attachment was a normal variant (16). LAR is an invagination between the left PVs and LAA. A recent cadaveric study by Piatek-Koziej et. al. (1) presented that the appearance of LAR varies, and the width of 7.9±3.2 mm and the whole wall thickness of 4.3±1.8 mm at the level of LSPV ostium. While in our study, we measured a smaller preprocedural width of 5.2±1.6 mm/5.7±2.2 mm and a larger thickness of 11.0±3.8 mm/13.1±4.1 mm at 45°/90° planes. We believe that the minor inconsistence is reasonable due to the difference between paraformaldehyde processed specimens and TEE measured intravital LAR.

Acute edematous change of LAR following ablation has been reported by several researches on combined procedure (8,9). Similarly, it was observed in almost every patient in our study, with a greater increment in width (Δwidth=3.6±2.3 mm) than thickness (Δthickness=2.6±3.5 mm). From a basic aspect, we believe that "edema" is rather imprecise albeit it subsides during follow-up. Study confirmed that lesion caused by thermal ablation is primarily composed of not only interstitial edema, but coagulative necrosis and hemorrhage (17). Besides, compared with radiofrequency (RF), cryo-energy ablates local tissue through a different mechanism that direct damage cellular structure and cause vascular failure (18). Yamashita et al. (19) compared ventricular lesion after cryo and RF ablation by MRI, and they found although the edematous change were compareble, the time-course of the cryo lesion differed from that of RF. We believe the feature of acute LAR lesion caused by cryo-ablation is different from RF, and it requires further imaging or histological confirmation.

Interestingly, we only found a higher balloon temperature correlates with a higher incidence of 2-fold wider LAR lesion at 45°. Previously, a study done by Miyazaki et al. (20) has demonstrated the acute PV edema in 10 patients via intracardiac echocardiography, while they found a lower right superior PV (RSPV) nadir

balloon temperature in the group with thicker edema (-49.3 +- 0.6 vs -58.8 +- 2.0). However, their sample size is relatively small and they only find such relationship at RSPV. A study has shown that a high balloon temperature indicates incomplete sealing of PV (21) that could result from mismatch of small CB and large PV antrum as commonly seen in persistent AF. In this situation, further advancement of CB into PVs is required to achieve sealing, which moves CB distally to LAR. Subsequently, less cryo-energy will be delivered to LAR, and reversible vascular impairment predominates and lead to bulked lesion. We believe a more suitably matched CB with LSPV antrum could minimize the lesion size, while more well-designed studies focusing on LAR lesion size and freezing parameters are warranted to support the idea.

Although we found the LAR lesion had no influence on either early or late recurrence and clinical outcomes, the impact on LAAC with different types of LAAC device is noteworthy. In our study, there was little change of the inner ostium diameter in the presence of LAR lesion. Therefore, it had hardly no influence on measurement and closure for plug device (Watchman) that land to the inner ostium of LAA. Follow-up TEE further confirmed that only minimal residual flow occurred in 4 patients implanted with Watchman, and all residual flow presented on the inferior border rather than LAR side.

However, the outer ostium diameter reduced significantly after the procedure (Δouter ostium diameter=-3.4$\pm$4.0 mm), and it expanded to its original size in the 3rd month follow-up. In this situation, the selection of pacifier device (that requires gauge of the outer ostium) could be masked by the acute bulked lesion. During follow-up, 2 out of 9 patients implanted with LAmbre device (size 24$\times$30 mm) developed residual flow on the LAR side. TEE reveals that both patients had distinct bulked lesion and reduced outer ostium diameter (30 mm) when performing combined procedure. Although the sample size of LAmbre combined procedure is too small to detect a statistical difference, masked outer LAA ostium interferes the selection of pacifier device size. We recommend that the size of the outer disc should refer to the measurement before ablation or a larger size outer disc should be chosen if measured after ablation. More randomized controlled studies are warranted to provide stronger evidences on choosing pacifier LAAC device during combined procedure.

Our study should be interpreted with caution. First, we uniformly applied CB ablation to achieve PVI, the conclusion cannot be extrapolated to RF and other ablation techniques. Sencondly, only 96 out of 117 TEE image series were available for measurement, the LAR lesion remained unknown in the others, and the incidence of device related event could be underestimated. Thirdly, all the TEE images were centered at LAA rather than LAR. Although the LAAC complications were precisely evaluated, the measurement of LAR and LAR lesion could be biased. Fourthly, our postprocedural images were obtained after LAAC procedure rather than instantly after CB ablation and before LAAC. Thus, the LAR could be stretched and deformed due to the expansion of LAAC device, which poses a potential bias. In addition, although we used both Watchman and LAmbre devices to explore the relationship between LAR lesion and different types of device, only 9 patients were implanted with LAmbre, which is insufficient to detect a statistical difference. Larger scaled randomized controlled studies are required to further address the issue.

Conclusions

Acute LAR lesion frequently occurred following CB ablation combined procedure, and its width positively correlates with LSPV nadir temperature. It affects measurement of pacifier device but has no influence on plug device when performing combined procedure. Further prospective randomized controlled trials are warranted.

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Variables	Combined procedure (n=117)
Male, n (%)	64 (54.7)
Age, years	67 [57, 75]
BMI, kg/m^2	20.1±10.6
LVEF, %	59 [39, 60]
OAC therapy, n (%)	39 (33.3)
AF type	
Paroxysmal AF, n (%)	58 (49.6)
Short-term persistent AF, n (%)	20 (17.1)
Long-term persistent AF, n (%)	39 (33.3)
CHA2DS2-VASc score	3 [2, 5]
Congestive heart failure, n (%)	26 (22.2)
Hypertension, n (%)	85 (72.6)
Age	
[?]75, n (%)	36 (30.8)
65-75, n (%)	46 (39.3)
Diabetes mellitus, n (%)	31 (26.5)
Stroke/TIA, n (%)	49 (41.9)
Vascular disease, n (%)	19 (16.2)
HAS-BLED score	2 [1, 3]
Abnormal liver function, n (%)	0
Abnormal renal function, n (%)	6 (5.1)
Bleeding, n (%)	13 (11.1)
Labile INR, n (%)	8 (6.8)
Drug use, n (%)	38 (32.5)
Alcohol abuse, n (%)	9 (7.7)

Table 1. Baseline information of combined procedure patients.

Continuous variables were described as mean ± SD or median with IQR. Categorical variables were described as number (proportion).

AF denotes atrial fibrillation, BMI body mass index, LA left atrium, INR international normalized ratio, LVEF left ventricular ejection fraction, OAC oral anti-coagulant.

Parameters	Value (n=117)
Pulmonary vein isolation, n (%)	117 (100)
Freeze duration, s	
LSPV	218.0±85.6

Parameters	Value (n=117)
LIPV	203.6±61.5
RSPV	160.4±41.4
RIPV	199.1±78.0
Freeze application, time	
LSPV	1.6±0.9
LIPV	1.4±0.8
RSPV	1.2±0.4
RIPV	1.4±0.8
Nadir,	
LSPV	-51.6±5.6
LIPV	-45.6±5.3
RSPV	-52.8±5.4
RIPV	-47.6±6.2
Successful LAAC, n, (%)	115 (98.3)
device	
Watchman, n (%)	106 (90.6)
LAmbre, n (%)	9 (7.7)
Re-deployment, n (%)	9 (7.8)
Residual flow, n (%)	2 (1.7)

Table 2. Cryo-ablation and LAAC procedure parameters of participants.

LAAC denotes left atrial appendage closure, LIPV left inferior pulmonary vein, LSPV left superior pulmonary vein, RIPV right inferior pulmonary vein, RSPV right superior pulmonary vein.

Table 3. Logistic regression analysis of LAR lesion and multiple variables.

Variables	Crude OR (95%CI)	Adjust OR_1 (95%CI)	Adjust OR_2 (95%CI)
Age	0.98 (0.92, 1.03)	0.97 (0.91, 1.03)	0.95 (0.87, 1.04)
Gender	1.13 (0.44, 2.90)	1.38 (0.49, 3.83)	2.50 (0.52, 12.03)
BMI	0.91 (0.77, 1.08)	0.89 (0.74, 1.06)	0.87 (0.70, 1.08)
LA diameter	1.02 (0.92, 1.13)	1.03 (0.92, 1.15)	1.11 (0.94, 1.30)
AF type	1.13 (0.44, 2.90)	1.12 (0.42, 3.00)	0.53 (0.10, 2.71)
Number of LSPV freeze application	1.04 (0.59, 1.84)	1.10 (0.61, 1.99)	1.01 (0.43, 2.37)
LSPV freeze duration	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
LSPV nadir temperature	**1.12 (1.02, 1.23) ***	**1.13 (1.01, 1.25) ***	**1.16 (1.02, 1.31) ***
LSPV time to nadir	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	0.97 (0.92, 1.03)
LSPV thawing time +	0.92 (0.80, 1.05)	0.89 (0.76, 1.04)	0.37 (0.08, 1.69)

The uni-and multi-variate logistic regression of LAR width at 45°. The multivariate model 1 was adjusted for age and gender, the model 2 was adjusted for age, gender, BMI, LA diameter and AF type.

* indicates significant p value.

+ LSPV thawing time is the time when thaw started to 0.

Events	Overall (n=114)	Mild (n=67)	Severe (n=29)
Primary endpoints			
Residual flow	6 (5.3)	4 (6.0)	2 (6.9)
DRT	0	0	0
Secondary endpoints			
Early AA recurrence	35 (31.3)	14 (20.9)	4 (13.8)
Late AA recurrence	41 (36.3)	17 (25.4)	6 (20.7)
Redo-ablation	3 (2.7)	2 (3.0)	1 (3.4)
Stroke	4 (3.5)	2 (3.0)	2 (6.9)
Major hemorrhage	1 (0.9)	1 (1.5)	0
Minor hemorrhage	3 (2.7)	3 (4.5)	0
Re-hospitalization	36 (31.6)	18 (26.9)	10 (34.5)
All-cause death	4 (6.3)	4 (6.0)	0
Heart failure	6 (5.3)	3 (4.5)	1 (3.4)
Pacemaker implantation	4 (3.5)	0	2 (6.9)
PCI	2 (1.8)	0	1 (3.4)
Pericardial effusion	3 (2.6)	2 (3.0)	1 (3.4)

Table 4. Follow-up outcomes between mild and severe injured group.

AA denotes atrial arrhythmia, PCI percutaneous coronary intervention, DRT device-related thrombosis.

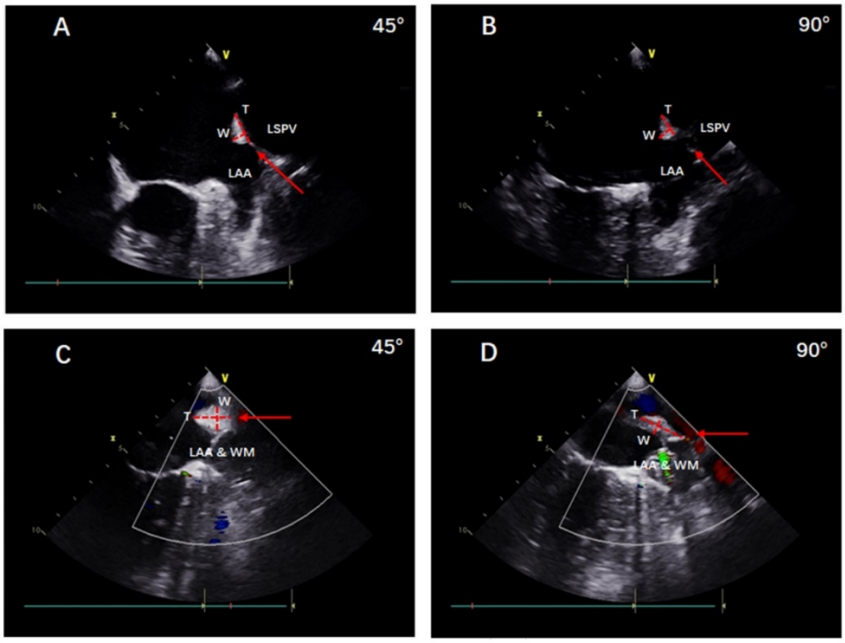

Figure 1. Measurement of LAR by TEE at 45°/90° planes. Figure A-D demonstrates the location of LAR (*red arrow*) and gauge of LAR width and thickness (*red dashed line*) at 45/90° plane. LAR width was measured as the maximum length of high-echo band between LAA side and LSPV side of LAR, while LAR thickness was measured from the free-end to the base where a distinct drop of signal was observed.**Figure**

A/B and **C/D** shows preprocedural and postprocedural measurement of LAR respectively. LAA denotes left atrial appendage, LSPV left superior pulmonary vein, W for width, WM Watchman device.

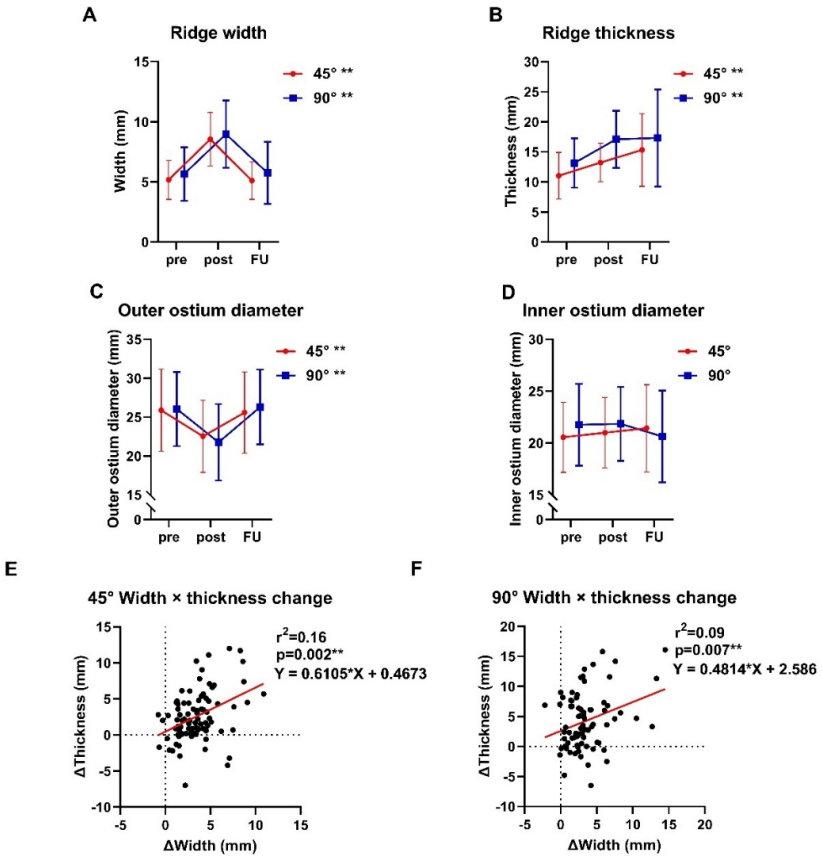

Figure 2. Periprocedural and follow-up changes of LAR width, LAR thickness, inner ostium and outer ostium diameter at 45/90° plane. Figure A & B shows LAR bulked in width and thickness significantly after combined procedure, while LAR subsided to its original width but remained thick during in the 3rd month follow-up.**Figure C & D** shows corresponding ostium diameter changes that outer ostium narrowed and expanded to its original size, while inner ostium stayed unchanged. **Figure E & F** showed the correlation of LAR width and thickness change at 45/90°after procedure. At both planes, width and thickness change were significantly correlated with each other, and the change in width were greater than thickness.

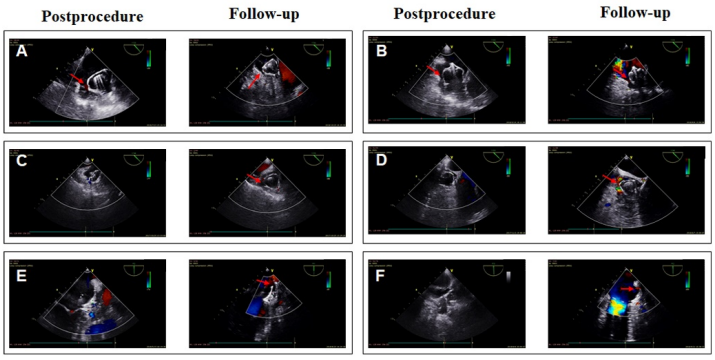

Figure 3. 6 patients with residual flow revealed by TEE. *Red arrow* indicates residual flow. **Figure A-D**demonstrated residual flow after LAAC with Watchman device. All four cases had residual flow at the inferior border at 135°, with sizes of 1.7 mm (**A**), 2.1 mm (**B**), 1.6 mm (**C**), 0.9mm (**D**) measured in the 3rd month follow-up respectively. Residual flow occurred instantly and persisted in two patients (**A** & **B**) while developed during follow-up rather instantly in the other two patients (**C** & **D**). **Figure E** & **F** showed residual flow after LAAC with LAmbre device. Both cases developed residual flow at the LAR border at 90° during follow-up, with sizes of 4.2 mm (**E**) and 2.5 mm (**F**) respectively.

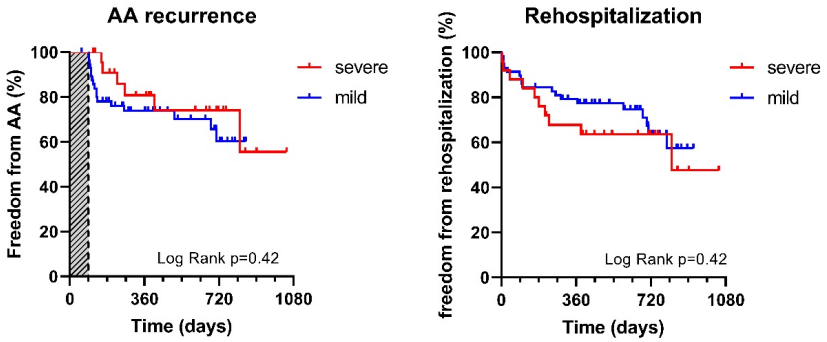

Figure 4. Survival curves between mildly and severely bulked LAR groups. None of AA recurrence, rehospitalization, or MACCE rates differed between two groups. AA denotes atrial arrhythmia.