Cardiology Research and Practice

Atrial Fibrillation Treatment in the Interventional Therapy Era

Lead Guest Editor: Rong Guo
Guest Editors: Xin Huang and Weijing Liu

Atrial Fibrillation Treatment in the Interventional Therapy Era

Cardiology Research and Practice

Atrial Fibrillation Treatment in the Interventional Therapy Era

Lead Guest Editor: Rong Guo
Guest Editors: Xin Huang and Weijing Liu

Contents

Hindawi
Cardiology Research and Practice
Volume 2020, Article ID 6573296, 10 pages
https://doi.org/10.1155/2020/6573296

Research Article

Cryoablation Combined with Left Atrial Appendage Closure: A Safe and Effective Procedure for Paroxysmal Atrial Fibrillation Patients

Zhongyuan Ren,[1,2] **Jun Zhang**,[1] **Mengyun Zhu**,[1] **Dongdong Zhao**,[1] **Shuang Li**,[1] **Haotian Yang**,[1] **Yixing Zheng**,[1] **Weilun Meng**,[1] **Jingying Zhang**,[1] **and Yawei Xu**[1]

[1]*Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China*
[2]*Soochow University Medical College, No. 199 Ren-ai Road, SIP, Suzhou, China*

Correspondence should be addressed to Jingying Zhang; mnz2009@163.com and Yawei Xu; 13916698181@139.com

Jun Zhang contributed equally to this work.

Received 20 November 2019; Revised 30 January 2020; Accepted 4 February 2020; Published 10 April 2020

Guest Editor: Xin Huang

Background. Catheter ablation combined with left atrial appendage closure (LAAC) was reported as a feasible strategy for atrial fibrillation (AF) patients with high risk of stroke or contraindications of oral anticoagulants. We aimed to observe the short-term safety and efficacy of combining cryoballoon ablation (CBA) with LAAC in paroxysmal (PAF) patients. *Method and Results*. From Jan 2016 to Dec 2017, 304 patients diagnosed with nonvalvular, drug-refractory PAF were included, who underwent either CBA alone ($n = 262$) or combined procedure ($n = 42$). Instant pulmonary vein isolation (PVI) with CBA was achieved in all patients, while successful LAAC achieved in 41 (97.6%) of combined procedure patients. 1-year freedom of AF rate was lower in combined procedure group (84.7% vs 70.7%, $p = 0.04$), with unadjusted hazard ratio (HR = 1.97) and 95% confidence interval (CI) 1.03–3.77. However, the multivariate COX model revealed left atrial diameter ($p = 0.002$, HR = 1.10, and 95% CI 1.04, 1.17), rather than procedure type ($p = 0.51$, HR = 1.34, and 95% CI 0.57, 3.17), was the predictor for freedom of AF. Only 2 patients in the CBA group had stroke, contributing to the nonsignificant higher stroke incidence ($p = 1.00$). Transoesophageal echochardiography (TEE) achieved in 35 patients (83.3%) showed complete occlusion with no obvious residual flow (>3 mm), Device-related thrombosis, or pericardial perfusion. All-cause mortality, rehospitalization, and complication rates were similar. *Conclusion*. Combining CBA with LAAC in a single procedure is a feasible strategy for PAF patients, with comparable short-term safety and efficacy to CBA alone.

1. Introduction

Atrial fibrillation (AF) is a commonly faced cardiac arrhythmia, which has been a heavy worldwide burden with a prevalence over 10 million in China [1]. Catheter ablation (CA) was established as the standardized technique to achieve rhythm control for AF patients and recently proven to be noninferior to medications by the CABANA study [2]. Furthermore, since the FIRE AND ICE trial provided the evidence of noninferiority of cryoballoon ablation (CBA) to radiofrequency ablation [3], CBA became a pervasive strategy for CA owning to its smooth learning curve and less center experience dependence [4].

To prevent stroke and embolic events in AF patients with high thrombotic risk (CHA_2DS_2-VASc score ≥2 in male and ≥3 in female), oral anticoagulants (OACs) has been suggested to be effective, with class I, level A recommendation [5]. For Chinese population, however, insufficient anticoagulation was the major obstacle of AF management, resulted from the low compliance at a great extent [6]. Furthermore, labile international normalized ratio (INR) in patients taking warfarin and insufficient dosage of new

OACs rendered anticoagulation far from enough. In addition, contraindications to long-term OACs and severe adverse effects as major hemorrhagic events limited the application in specific patients. Since left atrial appendage harbors 90% of the thrombus in nonvalvular AF patients [7], left atrial appendage closure (LAAC) is developed as an alternative to achieve stroke prevention. Recently, Dr. Lucas Boersma presented promising 2-year follow-up from the EWOLUTION trial that AF patients with contraindications of OACs benefit significantly from LAAC, reducing both ischemic and hemorrhagic events. LAAC was gradually adopted as a procedure providing effective stroke prophylaxis in nonvalvular AF patients.

Sharing the same venous access of procedure, combining CA with LAAC in a single procedure was firstly reported by Swaans and colleagues in 2012, conducted in 30 AF patients [8]. Thereafter, the feasibility, safety, and efficacy of combined procedure have been consecutively investigated by clinicians. Followed by Alexander Romanov and colleagues, their random controlled trial further proved the efficacy [9]. Combined procedure became a feasible strategy in patients with symptomatic drug-refractory AF, high risk of stroke, or contraindications to long-term OACs [10]. Nevertheless, according to our knowledge, few studies explored the combined procedure in paroxysmal AF (PAF) patients, or specifying cryoballoon ablation strategy. Moreover, no comparison between combined procedure and CBA has been reported.

In the present study, we shared our experience of CBA-combining procedure in PAF patients and validated the safety and efficacy by comparing CBA-combined procedure with CBA only.

2. Methods

2.1. Studied Population. We retrospectively investigated 399 continuous patients with documented nonvalvular, atrial fibrillation from Jan 2016 to Dec 2017, who underwent either CBA or combined procedure of CBA and LAA closure at Atrial Fibrillation Center of Shanghai Tenth people's hospital. Among them, 323 were diagnosed as paroxysmal atrial fibrillation (PAF) and included. PAF was defined as atrial fibrillation recorded and confirmed either by a 7-day or 24-hour ECG monitor, which converted to sinus rhythm spontaneously or by intervention (cardioversion or antiarrhythmic drugs) within 7 days [5]. Further, we excluded 19 patients who lost to follow-up, and eventually 304 patients were included. Before the procedure, CHA_2DS_2-VASc and HAS-BLED scores were calculated for every patient to assess the stroke and hemorrhagic risks. Two-dimensional transthoracic echocardiography (TTE) was conducted to evaluate cardiac function quantitatively, including left ventricular ejection fraction (LVEF), left atrial and ventricular size, and valvular function. Meanwhile, transoesophageal echocardiography (TEE) was applied to evaluate left atrial (LA) size and left atrial appendage (LAA) size and shape, and rule out thrombus in LA or LAA beforehand. Patients considered eligible for combined procedure are as follows: (a) drug-refractory nonvalvular paroxysmal atrial fibrillation patients and (b) patients with one of the following conditions: (a) CHA_2DS_2-VASc score ≥ 2, (b) HAS-BLED score ≥ 3, (c) contraindications to long-term OACs, and (d) refuse OACs as antithrombotic regimen according to personal willingness. Patients with the following conditions were excluded from interventional procedure: (a) thrombus in LA or LAA presented and confirmed by TEE, (b) oversized LA (LA diameter >65 mm) by TTE or LAA (LAA opening >35 mm) through TEE, (c) pericardial perfusion (volume ≥ 4 mm by TTE or TEE), (d) hemodynamic unstable patients, (e) patients with active hemorrhagic diseases, and (f) ischemic or hemorrhagic stroke within 30 days. Our study complied the Declaration of Helsinki (1964). From each patient, informed consent was obtained before the procedure, with procedural risks and possible complications fully informed. The study was approved by the Ethical Committee of Shanghai Tenth People's Hospital. Both CBA and LAAC combined procedures were performed by the same proficient electrophysiologist, with CBA procedure over 100 cases and LAA closure 50 cases per year.

2.2. Procedure Details

2.2.1. Cryoablation. The procedures were accomplished under local anesthesia by subcutaneous administration of lidocaine at the groin region. Through femoral vein access, guidewire and vessel dilator were applied ensuing a single transseptal puncture. A 23 mm or 28 mm second-generation cryoballoon (Arctic Front, Medtronic, MN, USA) was advanced through a steerable sheath (FlexCath, Medtronic, MN, USA) into the left atrium (LA). Once a pulmonary vein (PV) confirmed, the cryoballoon was inflated and advanced to the ostium of the PV, following angiography by injection contrast dye ensuring complete PV occlusion. Accompanying Achieve catheter (Achieve, Medtronic, Minneapolis, MN) cannulated distally into the PV to detect electric activity and confirm PV isolation (PVI), a standard 180 s freeze was adopted for each pulmonary vein. Freezing time was adjusted according to time to isolation (TTI) recorded. When TTI $\leq$30 s, freezing time was set to 150–180 s. While TTI between 30 and 60 s, freezing time was set to 180 s. A bonus freeze of 120 s was applied only when TTI >60 s. If TTI could not be recorded, a 180 s freeze would be adopted, with a bonus freeze of 120 s when temperature declined over −40°C before 60 s from application.

Continuous phrenic pacing (8–10 V, 30 times per minute) with electrode placed at superior vena cava was applied during freezing of right superior PV (RSPV) and right inferior PV (RIPV). Through observation of the decrement of diaphragm movement under fluoroscopy, phrenic nerve palsy was detected, when freezing procedure was subsequently halted to prevent further injury. The vital signs were continuously monitored during the procedure. Freezing was instantly halted for esophageal protection, once the patient complained about nausea, vomiting, chest distress, or pain. Additionally, a proton pump inhibitor (PPI) was prescribed to all patients till the 2nd month since the procedure. Heparin was intravenously infused during the

whole procedure with monitoring activated clotting time (ACT) between 250 and 350 s.

2.2.2. LAA Closure. Under local anesthetic state, an LAA closure device was implanted instantly after CBA in eligible patients. The first 23 patients were implanted with Lefort (Shape Memory Alloy Co., Shanghai, China), followed 11 patients with Lacbes (Shanghai Push Medical Device Technology Co., LTD, Shanghai, China), and latest 8 patients with WATCHMAN (Watchman, Boston Scientific, MA, USA), presented in Figure 1. Generally, followed by the femoral vein access from CBA procedure, 14-F guide wire and pigtail catheters were advanced into the LAA. The size, depth, and shape of LAA was observed and recorded by angiogram under fluoroscopy guidance (RCA 30° + CAU 20°/CRAN 20°) and transesophageal echocardiography (TEE) with angle approximately 0°/45°/90°/135°. According to the measured feature of LAA, the device 10–20% oversize to the LAA was chosen to ensure stable positioning and proper compression. The pigtail catheter was removed after the WATCHMAN access system advanced over into the LAA. Subsequently, the device was carefully delivered in the LAA and deployed at the ostium of the LAA by retracting the access sheath. Before release, PASS principle was fulfilled and confirmed by TEE for all devices, encompassing device position at LAA ostium, stable anchoring confirmed by tug test, and device compressed for 10–25% of the original size, sealed with residual flow ≤3 mm. Once released, LA angiography and TEE recheck for positioning, compression ratio, and residual flow were followed, simultaneously assessing for possible pericardial perfusion. Figure 2 shows procedure details about CBA and LAAC.

2.3. Follow-Up and Postprocedural Management. All patients were informed and continuously followed to reexamine at 1st, 3rd, 6th, and 12th month after the procedure. Meanwhile, transtelephonic follow-up was carried out at the same time point to evaluate individual condition and guarantee timely reexamination. For reexamination at inpatient or outpatient, medical history and physical examination were achieved, and either a 24-hour or 7-day electrocardiograph (ECG) monitor was applied to detect the recurrence of AF and other arrhythmias.

In our study, primary endpoints were stipulated as AF recurrence and stroke incidence, while secondary endpoints included all-cause mortality, acute myocardial infarction, heart failure, pericardial effusion, and device-related thrombosis. Recurrence of AF was defined as AF lasting longer than 30 s, while the time before the 3rd month from the procedure was defined as blank period, when no recorded AF was considered recurrence.

For patients who underwent combined procedure, TEE was performed at the 3rd month and the 12th month to evaluate the positioning of the device, sealing of LAA, device-related thrombosis, and other structual changes.

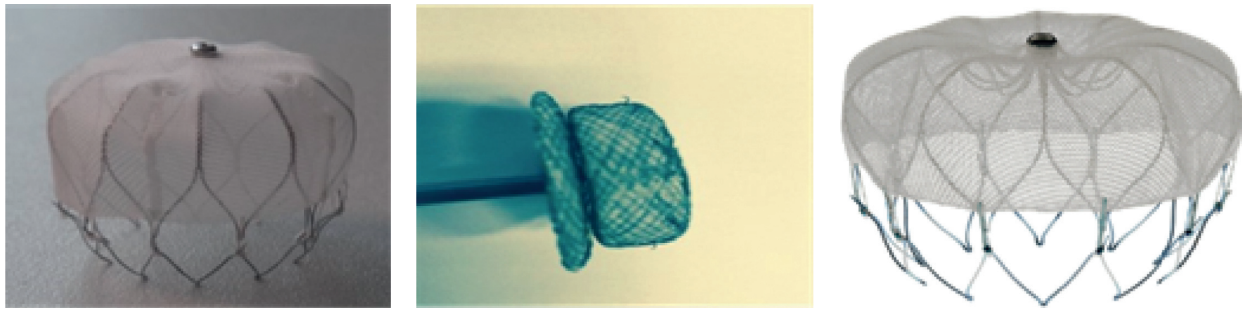
For postprocedural medications, antiarrhythmic drugs (sotalol) were generally prescribed to every patient during the blank period. Anticoagulation therapy for 2–3 months was recommended to all PAF patients underwent either procedure. For patients underwent combined procedure, warfarin or new oral anticoagulants (NOACs, dabigatran, or rivaroxaban) were prescribed and discontinued for 2–3 months. Once satisfied device positioning, no obvious residual flow (>3 mm) and no thrombus presented were confirmed by TEE; antiplatelet therapy was thenceforth substituted by double antiplatelet treatment (aspirin and clopidogrel) till the 6th month, following single antiplatelet medication as a long-term therapy (aspirin or clopidogrel), while the continuation of OACs in the CBA group was based on the CHA_2DS_2-VASc score individually. If CHA_2DS_2-VASc ≥2 in male or ≥3 in female, OACs were recommended for long-term anticoagulation.

2.4. Statistical Analysis. Continuous variables were described as mean ± standard deviation (SD) or median (interquartile range), and p value was analyzed from a two-sample t-test if the variance was equal or Mann–Whitney test if not. Categorical variables were described as percentage (%), with p value analyzed from the χ^2 test or Fisher exact test if there was theoretical frequency lower than 5. The Kaplan–Meier estimate analyzed the freedom of atrial arrhythmia with p value achieved by the log-rank test. Hazard ratio was calculated through the univariate COX proportional hazard regression model. The multivariate COX model (forward and backward stepwise selection with $p < 0.05$) was applied to determine the prognostic factors of the freedom of AF. 2-side p value <0.05 was considered significant in all analyses. We used SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) to conduct the analysis.

3. Results

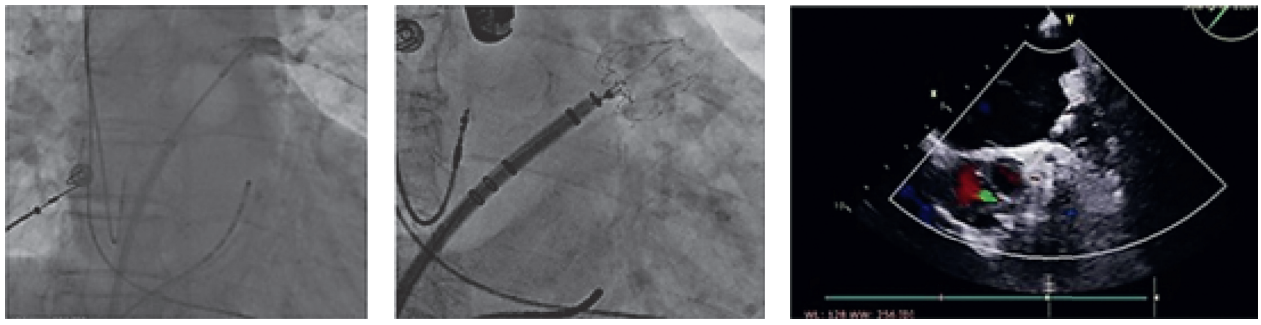
We included 42 and 262 patients underwent CBA + LAAC procedure and CBA only, respectively. Baseline characteristics are described in Table 1. Both the CHA_2DS_2-VASc score (3.8 ± 2.1 vs 2.8 ± 1.9, $p < 0.0001$) and HAS-BLED score (3.8 ± 2.1 vs 2.8 ± 1.9, $p < 0.0001$) were significantly higher in the combined procedure group than in the CBA only group. Besides, the combined procedure group was elder (70 ± 7.6 yrs vs 66.3 ± 9.5 yrs, $p = 0.01$), with larger LA diameter (45.6 ± 5.8 mm vs 40.4 ± 5.6 mm, $p < 0.0001$), higher prevalence of hyperlipidemia (14.3% vs 3.8%, $p = 0.01$), and previous stroke history (61.9% vs 23.7%, $p < 0.0001$). Routine medications also differed, with higher rate in the combined procedure group, including antiplatelet agents (46.3% vs 27.1%, $p = 0.01$) and statins (31.7% vs 15.6%, $p = 0.01$). Other characteristics were comparable between two groups.

3.1. Periprocedure Details. Details about CBA are listed in Table 2. Procedural characteristics including nadir and procedure time were comparable between the two groups. Meantime, it took similar ablation time to achieve PVI between both the groups (16.2 ± 5.1 min for CBA vs 17.7 ± 7.7 min for combined procedure, $p = 0.47$) and similar number of applications. Touch-up ablation of other



(a) (b) (c)

Figure 1: Three types of LAAC devices. (a) Lefort (Shape Memory Alloy Co, Shanghai, China), (b) Lacbes (Shanghai Push Medical Device Technology Co., LTD, Shanghai, China), and (c) Watchman device (Watchman, Boston Scientific, MA, USA).



(a) (b) (c)

Figure 2: Procedure details about CBA and LAAC. (a) Balloon ablation of left superior pulmonary vein (LSPV) that fully occluded by angiography. (b) Deployment of the WATCHMAN device under fluoroscopy. (c) Transoesophageal echocardiography (TEE) showed complete occlusion without malposition or residual flow.

arrhythmogenic sites was applied in 5 patients in the CBA only group, encompassing 2 at LAA, 1 at superior vena cava, 1 at mitral isthmus, and 1 at tricuspid isthmus.

For periprocedure complications, no obvious pericardial effusion (>3 mm) was observed in both the groups. Vagal reflex monitored by blood pressure and heart rate was observed in 11 (26.7%) and 29 (11.5%) patients and not statistically significant ($p = 0.20$). Transient phrenic nerve palsy occurred only in 3 patients in the CBA only group, observed as transient decrease of diaphragm movement in 2 patients and halted diaphragm movement in 1 patient during ablation of the right superior pulmonary vein (RSPV).

Totally 42 patients underwent LAAC immediately after CBA. Table 3 provides the details of LAAC procedure. The first 23 patients were implanted with Lacbes, followed 11 patients with Lefort, and latest 8 patients with the WATCHMAN device. Overall implantation success rate was 97.6%, where 1 patient failed to implant with the WATCHMAN device due to mismatch between oversized LAA ostium by angiography and suitable device. Device replacement occurred in 2 patients. One patient (LAA opening diameter 21 mm) firstly implanted with a 24 mm Lefort device was observed with obvious residual flow (>3 mm) and subsequently replaced with 27 mm one which deployed and fixed stably without residual flow. A 22 mm Lacbes device was implanted in the other patient (LAA opening diameter 16 mm), which was over compressed (compression ratio >25%). Proper compression ratio was then achieved by replacing a 20 mm device (compression ratio = 20%). 5 patients were observed with minimal residual flow (≤3 mm) after release (3 with Lefort and 2 with Lacbes), confirmed by TEE. Two patients recorded AF during the procedure underwent cardioversion, who were converted to sinus rhythm. No pericardial effusion or other complication was observed.

3.2. Follow-Up. Follow-up results are presented in Table 4. Follow-up time ranged from 3 months to 35 months. The median follow-up time was 22 ± 11 months in the CBA only group and 20 ± 9 months in the combined procedure group. Recurrent AF during blanking period occurred in 16 (6.2%) CBA patients and 5 (12.0%) combined procedure patients with $p = 0.30$. Correspondingly, 40 (15.3%) and 12 (29.3%) patients experienced late recurrent AF. Among which, 5 patients in the CBA group and 1 patient in the combined procedure group underwent redo-ablation. Survival analysis as presented in Figure 3 showed that 1-year freedom of AF was significantly different between the groups ($p = 0.04$, hazard ratio (HR) = 1.9, 95% confidence interval (CI) 1.0, 3.7). However, the multivariate COX regression model

Table 1: Baseline characteristics of the patients.

Parameters	CBA only group ($N = 262$)	CBA + LAAC group ($N = 42$)	p value
Age (yr)	66.3 ± 9.5	70 ± 7.6	**0.01****
Gender: male	142 (54.2)	26 (61.9)	0.35
Smoking	49 (18.7)	6 (14.3)	0.49
Wine	24 (9.2)	6 (14.3)	0.45
proBNP (pg/ml)	**298.9 (105.4, 776.2)**	**450.8 (85.8, 859.4)**	0.65
eGFR (mL/(min∗1.73 m^2))	81.5 ± 17.1	76.4 ± 16.3	0.07
Left atrial diameter (mm)	40.4 ± 5.6	45.6 ± 5.8	**<0.0001****
LVEF (%)	62.1 ± 8.1	60.9 ± 4.2	0.19
※HAS-BLED score	2.7 ± 1.2	3.7 ± 1.2	**<0.0001****
※CHA_2DS_2-VASc score	2.8 ± 1.9	3.8 ± 2.1	**0.001****
Medical history			
Hypertension	154 (58.8)	26 (61.9)	0.70
Diabetes mellitus	30 (11.5)	8 (19.1)	0.17
Hyperlipidemia	10 (3.8)	6 (14.3)	**0.01****
Hyperthyroidism	10 (3.8)	1 (2.4)	0.99
Coronary heart disease	64 (24.4)	10 (23.8)	0.93
Myocardial infarction	24 (9.2)	3 (7.1)	0.89
Previous PCI	22 (8.4)	6 (14.3)	0.35
Valvular heart disease	5 (1.9)	1 (2.4)	1.00
Cardiomyopathy	4 (1.6)	2 (4.8)	0.42
◇Previous stroke	62 (23.7)	26 (61.9)	**<0.0001** **
Medication			
Antiarrythmic drugs	79 (30.2)	17 (40.5)	0.14
Anticoagulants	44 (16.8)	12 (28.6)	0.07
Warfarin	32 (12.3)	5 (12.2)	0.99
Antiplatelet agents	69 (27.1)	19 (46.3)	**0.01****
Aspirin	61 (23.3)	17 (40.5)	**0.02****
Statins	41 (15.6)	13 (31.7)	**0.01****
ACEI/ARB	87 (33.2)	17 (40.5)	0.36
CCB	69 (26.3)	14 (33.3)	0.34
β-blocker	71 (27.2)	14 (33.3)	0.41

Continuous variables are described as mean ± SD or median (interquantile range) while categorical variables as percentage (%). CBA, cryoablation; LAAC, left atrial appendage closure; LVEF, left ventricle ejection fraction; PCI, percutaneous coronary intervention; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker. eGFR estimated glomerular filtration rate, calculated by CKD-EPI formula. ※CHA_2DS_2-VASc score is the risk estimation system of stroke in patients with atrial fibrillation, while HAS-BLED score estimates risk of hemorrhage. ◇Previous stroke encompasses documented cerebral infarction including lacunar infarction or intracerebral hemorrhage with either CT or MRI evidence.

Table 2: Cryoablation procedure details.

Parameter	CBA only group ($N = 262$)	CBA + LAAC group ($N = 42$)	p value
Procedure time (s)	1061.8 ± 462.2	974.5 ± 304.3	0.47
Nadir (°C)	−46.4 ± 5.8	−43.4 ± 8.6	0.21
Times of freeze per vein (n)			
LSPV	1.8 ± 1.1	2.4 ± 2.0	0.28
LIPV	1.6 ± 0.8	1.6 ± 0.6	0.83
RSPV	1.3 ± 0.6	1.1 ± 0.5	0.15
RIPV	1.5 ± 0.9	1.3 ± 0.6	0.37
◆Anatomic variations	13 (5.0)	5 (11.9)	0.16
RMPV	9 (3.4)	3 (7.1)	0.47
◇Ablation of other sites	5(1.9)	0(0)	0.80
Periprocedural complications			
Vagal reflex	29 (11.1)	9 (17.3)	0.20
Phrenic nerve injury	3 (1.2)	0 (0)	1.00
Cardiac tamponade	0 (0)	0 (0)	—

Continuous variables are presented as mean ± SD while categorical variables as percentage (%). PVI, pulmonary isolation; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; RMPV, right middle pulmonary vein. ◆Anatomic variations include right middle pulmonary vein, left middle pulmonary vein, and absence of inferior pulmonary vein. ◇Other sites ablated include left atrial appendage, superior vena cava, mitral isthmus, and tricuspid isthmus.

Table 3: Left atrial appendage occlusion procedure details.

Parameters	CBA + LAAC group ($N = 42$)
LAA characteristics	
LAA lobulation, *n* (%)	
One lobe	12 (28.6)
Two lobes	18 (42.9)
Three lobes	3 (7.1)
Multi-lobes	9 (21.4)
LAA opening diameter (mm)	21.2 ± 3.3
LAA depth (mm)	25.3 ± 4.3
Device characteristics	
Device company, *n* (%)	
Lefort	22 (52.4)
Lacbes	11 (26.2)
WATCHMAN	9 (21.4)
Device size (mm)	25.0 ± 3.0
Compression ratio (%)	15.9 ± 4.6
Periprocedural details	
Implantation, success	41 (97.6)
Released time (s), *n* (%)	
Once	40 (95.2)
Twice	2 (4.8)
Residual flow, *n* (%)	
≤3 mm	5 (12.0)
>3 mm	0 (0)
Cardiac tamponade	0 (0)
◆Electroversion	2 (4.8)

Continuous variables are described as mean ± SD, while categorical variables as percentage (%). CBA, cryoballoon ablation; LAAC, left atrial appendage closure. ◆Electroversion was applied when atrial fibrillation recorded during the procedure.

Table 4: Follow-up details.

Parameter	CBA only group ($N = 262$)	CBA + LAAC group ($N = 42$)	p value
Recurrence of AF, n (%)			
Early recurrence	16 (6.2)	5 (12.0)	0.30
Late recurrence	40 (15.3)	12 (29.3)	◆**0.04****
LAAC device			
TEE evaluation, *n* (%)		35 (83.3)	
Successful occlusion		**35 (100)**	
Device-related thrombosis		0 (0)	
Residual flow		0 (0)	
Pericardial effusion		0 (0)	
Complications, n (%)			
Death of any cause	2 (0.7)	0(0)	
Rehospitalizaiton due to cardiovascular events	19 (7.3)	2 (4.8)	0.79
Redo-ablation	6 (2.3)	1 (2.4)	1.00
Stroke	2 (0.7)	0 (0)	1.00
Myocardial infarction	2 (0.7)	0 (0)	1.00
Heart failure	0 (0)	0 (0)	—

Categorical variables are described as percentage (%). CBA, cryoballoon ablation; LAAC, left atrial appendage closure; AF, atrial fibrillation; TEE, transesophageal echocardiography. ◆p value of late recurrence was generated by the log-rank test.

incorporating totally 10 parameters showed only LA diameter ($p = 0.002$, HR = 1.10, and 95% CI 1.04, 1.17), rather than procedure type ($p = 0.51$, HR = 1.34, and 95% CI 0.57, 3.17), was the significant predictor of freedom of AF (Figure 4).

Among patients underwent LAA closure, 35 (83.3%) patients were reexamined by TEE, showing LAA closure device was well positioned and sealed in all 35 patients. No obvious residual flow nor device-related thrombus was observed. No obvious pericardial perfusion was detected.

Two patients in the CBA only group died at the 3rd month of follow-up, one resulted from intracerebral hemorrhage and the other from interstitial pneumonia. Besides, the rehospitalization (due to cardiovascular events) rate was comparable betweenthe CBA only and combined procedure groups (7.3% vs 4.8%, $p = 0.79$). Notably, although not statistically significant, 2 patients had intracerebral hemorrhage (1 as described above and 1 occurred at the 2nd month from the procedure) and 2 had myocardial infarction (one in 8th month

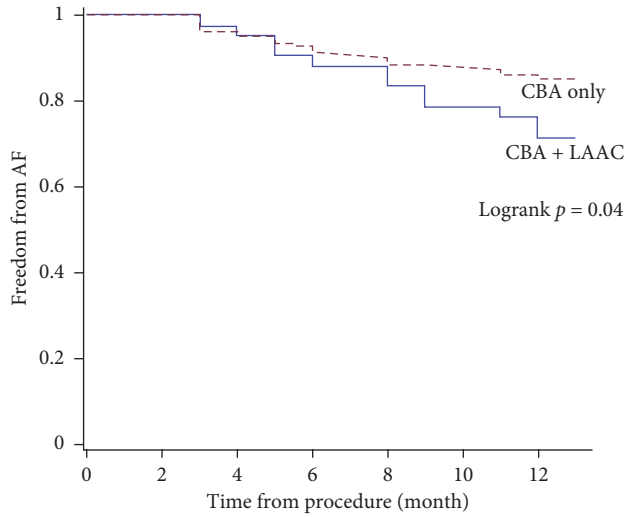


Figure 3: 1-year follow-up of freedom of AF.

and the other one in 12th month, and percutaneous coronary intervention was carried out in both patients) in the CBA only group. No stroke, myocardial infarction, or systemic embolic event occurred in the combined procedure group.

4. Discussion

Combined procedure of CA and LAA closure was developed as a novel and efficient approach which can be manipulated from the same femoral vein access and atrial septal puncture in a single procedure. Meanwhile, cryoablation, as a noninferior [3] and less experience-depended [4] strategy to radiofrequency ablation, was becoming widely adopted to achieve PVI. Based on the evidences, in 2016, the first result of combining CBA with LAAC procedure was published by Gaetano Fassini and his colleagues [11]. Incorporating 35 patients with a follow-up of 24 + 12 months, the recurrence of atrial arrhythmia rate was 28% while no device-related complications or clinical thrombotic event occurred. This was a promising result of combined procedures, nevertheless, demanded further supports from larger scale studies and randomized controlled trials. In our study, we provided our experience and validated the efficacy and safety of combined procedure.

4.1. Studied Population. Our study incorporated 304 nonvalvular PAF patients underwent either CBA only or combined procedure at our center. Because the patient was considered eligible for combined procedure only when CHA_2DS_2-VASc ≥3, or HAS-BLED score ≥2, or strictly or relatively contraindicated OACs, there were significant differences at baseline in combined procedure group compared with CBA only group, including advanced age, high CHA_2DS_2-VASc and HAS-BLED scores, large LA diameter, high prevalence of previous stroke, and high proportion of anticoagulants intake. In addition, the prevalence of hyperlipidemiaand the proportion of statins intake were higher in the combined procedure group as well, in line with the inverse relation between dyslipidemia and AF incidence during follow-up [12].

4.2. Periprocedure Evaluation. Successful PVI by CBA was achieved in all patients, and LAAC achieved in 97.6%, with 1 patient failed to implant due to unmatched device size with LAA. The success rate was in accordance with studies reported [9, 11]. Only transient phrenic nerve injury occurred in 3 patients of the CBA only group and postprocedure electroversion applied in 2 patients in the combined procedure group after LAAC who converted to sinus rhythm, while there was no significant difference of periprocedure complication rate between the groups. Additionally, 5 patients had minimal residual flow (≤3 mm) detected by TEE after implantation, which was defined as flow ≤5 mm in PREVAIL and PROTECT AF trials and proven to have no influence on placementof the device or thrombosis [13, 14]. Interestingly, distinct pulmonary vein ridge edema was observed after CBA procedure by TEE (Figure 5), even though deployment and release of WATCHMAN, Lefort, and Lacbes were unacted.We believe such phenomenon could interfere the implantation of LAAC devices that require overlaying LAA opening, such as Amplatzer Cardiac Plug (ACP) or LAmbre. Furthermore, we predicted that the incidence of device displacement and obvious residual flow would increase owning to the subsiding of edema, although not observed by TEE at the 3rd month follow-up since the procedure. In spite of the results, we still recommend plugging a LAAC device such as WATCHMAN as a first choice when considering LAAC immediately after cryoablation, in order to avoid device displacement after the ridge edema subsided. Long-term evalutation is warranted to provide stronger evidences.

4.3. Safety and Efficacy. With a meanfollow-up time of 22 ± 11 months in the CBA only group and 20 ± 9 months in the combined procedure group, the recurrence of AF was significantly higher in the latter (15.3% vs 29.3%, $p = 0.04$) and procedure type was indicated as a predictor of freedom of AF as well (HR = 1.9, 95% CI 1.0, 3.7). As discussed above, the baselinecharacteristics differed, including CHA_2DS_2-VASc [15] scores, LA diameter [16], and the prevalence of hyperlipidemia, which were significantly related to AF recurrence in a univariate model. However, through adjusting confounding parameters, the multivariate COX model showed only LA diameter ($p = 0.002$, HR = 1.10, and 95% CI 1.04, 1.17) rather than procedure type ($p = 0.51$, HR = 1.34, and 95% CI 0.57, 3.17), was the predictor of freedom of AF. Our results showed combining LAAC in CBA procedure could achieve AF rhythm control with comparable efficacy to CBA alone. . More trials are warranted to support the conclusion.

Considering stroke prophylaxis, our results showed that combined procedure seemed to be effective with a nonsignificant lower stroke risk (only 2 (0.7%) in the CBA only group). Of note, both cases were resulted from lethal intracranial hemorrhage. Results from the CABANA trial showed LAAC performed effectively in preventing hemorrhagic stroke [17]. Although we observed similar tendency in our study, prevention of hemorrhagic stroke needs to be validated in larger, prospective studies with longer follow-up period.

Among 35 patients underwent LAAC assessed by TEE, no device-related thrombosis, obvious residual flow, or

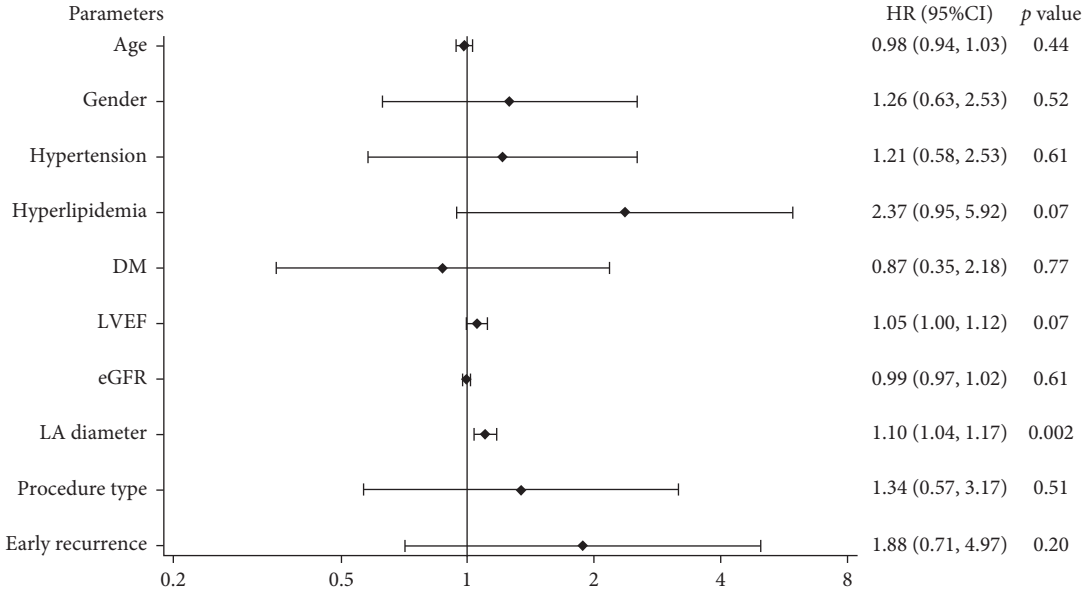
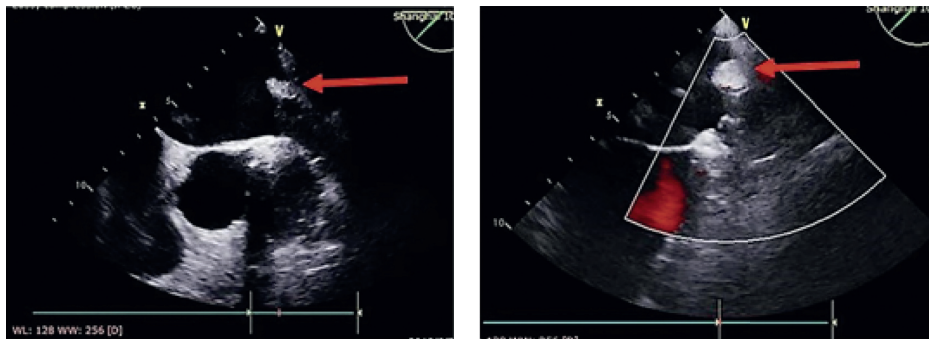


Figure 4: The multivariate COX regression model was done incorporating age, gender, hypertension, hyperlipidemia, DM, LVEF, eGFR, LA diameter, early recurrence of AF, and procedure type (0 for CBA only and 1 for combined procedure). DM, diabetes mellitus; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; LA diameter, left atrial diameter.



(a) (b)

Figure 5: Pulmonary vein-left atrial appendage ridge before and after CBA by TEE. Distinct ridge mass was observed comparing TEE evaluation (a) before (red arrow) and (b) after CBA (red arrow).

complications as pericardial perfusion was observed. Besides, severe vascular events were only observed in the CBA only group, where 2 patients who had intracerebral hemorrhage and 2 who had myocardial infarction underwent PCI. The low incidence rate of complication of combined procedure was comparable to studies with or without specifying the ablation strategy [13, 14, 18]. Hence, we believe combined procedure would not bring addtional complcations to LAAC.

From the aspect of anticoagulation, all patients received OACs therapy were discontinued (either warfarinor NOACs) for at least 2 months since the procedure in the combined procedure group, whether or not shifted to antiplatelet therapy after the reexamination by TEE at the 3rd month. Although single LAAC procedure was recommended with anticoagulation (either warfarinor NOACs) for at least 45 days [19], as there was no available guideline to recommend the proper dose and duration for patients underwent combined procedure, it was prolonged to 2 months for the patients and proven to be safe with adequate stroke prevention in most trials [11, 20]. Moreover, recently, a case reported by Steven K. Carlson presented that 45-day anticoagulation was not adequate to prevent thrombosis in patients combined procedure [21]. Hence, based on our study, in nonvalvular PAF patients combining CBA with LAAC, the anticoagulation regimen of at least 2 months either by VKA or NOACs and substituted by double antiplatelet therapy and then lifelong single antiplatelet therapy was a considerable choice for prevention of thrombotic events, without increasing risk of hemorrhagic events.

5. Limitations

Our nonrandomized, retrospective study design limited the application of the conclusion. With relatively small number of combined procedure patientsand specific inclusion criteria, the conclusion cannot be extrapolated in gerenal AF

population. Meanwhile the incidence of complications like stroke might be underestimated due to short follow-up period.Additionaly,TEE was available only in 35 (83.3%) of combining procedure group, the device-related complication rates might be higher than reported. Owning to the intolerance of TEE, a better evaluation approach and follow-up strategy should be considered in order to ensure safety and relief patients' painfulness.Furthermore, we applied 3 types of LAAC devices in our study, with only 1 case failed to implant. While the safety and efficacy among devices were not validated due to the small sample size and relatively short follow-up period. Further long-term, large scaled, randomized, prospective study is warranted to support our conclusion.

6. Conclusion

Combined procedure of CBA and LAA closure is a feasible strategy for PAF patients, with comparable safety and efficacy to CBA and OACs. Long-term, largescaled, prospective trials are warranted to provide stronger evidences.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

The manuscript was presented in the form of poster in the 40th Heart Rhythm Society scientific session on May 7th, 2019.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Supplementary file 1: the flow chart of selection and follow-up details. (*Supplementary Materials*)

References

[1] Z. Zhou and D. Hu, "An epidemiological study on the prevalence of atrial fibrillation in the Chinese population of mainland China," *Journal of Epidemiology*, vol. 18, no. 5, pp. 209–216, 2008.

[2] J. Moreno and J. L. Zamorano, "The CABANA trial," *European Heart Journal*, vol. 35, no. 35, pp. 1908-1909, 2014.

[3] K.-H. Kuck, J. Brugada, A. Fürnkranz et al., "Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation," *New England Journal of Medicine*, vol. 374, no. 23, pp. 2235–2245, 2016.

[4] M. Landolina, G. Arena, S. Iacopino et al., "Center experience does not influence long-term outcome and peri-procedural complications after cryoballoon ablation of paroxysmal atrial fibrillation: data on 860 patients from the real-world multicenter observational project," *International Journal of Cardiology*, vol. 272, pp. 130–136, 2018.

[5] P. Kirchhof, S. Benussi, D. Kotecha et al., "2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS," *European Heart Journal*, vol. 37, no. 38, pp. 2893–2962, 2016.

[6] Z.-Z. Wang, X. Du, W. Wang et al., "Long-term persistence of newly initiated warfarin therapy in Chinese patients with nonvalvular atrial fibrillation," *Circulation: Cardiovascular Quality and Outcomes*, vol. 9, no. 4, pp. 380–387, 2016.

[7] J. L. Blackshear and J. A. Odell, "Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation," *The Annals of Thoracic Surgery*, vol. 61, no. 2, pp. 755–759, 1996.

[8] M. J. Swaans, M. C. Post, B. J. Rensing, and L. V. Boersma, "Ablation for atrial fibrillation in combination with left atrial appendage closure: first results of a feasibility study," *Journal of the American Heart Association*, vol. 1, no. 5, 2012.

[9] A. Romanov, E. Pokushalov, S. Artemenko et al., "Does left atrial appendage closure improve the success of pulmonary vein isolation? results of a randomized clinical trial," *Journal of Interventional Cardiac Electrophysiology*, vol. 44, no. 1, pp. 9–16, 2015.

[10] I. G. Bolao, N. Calvo, A. Macias et al., "Ablation of atrial fibrillation in combination with left atrial appendage occlusion in a single procedure. Rationale and technique," *Journal of Atrial Fibrillation*, vol. 8, p. 1346, 2016.

[11] G. Fassini, S. Conti, M. Moltrasio et al., "Concomitant cryoballoon ablation and percutaneous closure of left atrial appendage in patients with atrial fibrillation," *Europace*, vol. 18, no. 11, pp. 1705–1710, 2016.

[12] X. Li, L. Gao, Z. Wang et al., "Lipid profile and incidence of atrial fibrillation: a prospective cohort study in China," *Clinical Cardiology*, vol. 41, no. 3, pp. 314–320, 2018.

[13] V. Y. Reddy, S. K. Doshi, H. Sievert et al., "Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation," *Circulation*, vol. 127, no. 6, pp. 720–729, 2013.

[14] D. R. Holmes Jr., S. Kar, M. J. Price et al., "Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy," *Journal of the American College of Cardiology*, vol. 64, no. 1, pp. 1–12, 2014.

[15] K. P. Letsas, M. Efremidis, G. Giannopoulos et al., "CHADS2 and CHA2DS2-VASc scores as predictors of left atrial ablation outcomes for paroxysmal atrial fibrillation," *Europace*, vol. 16, no. 2, pp. 202–207, 2014.

[16] S.-N. Wen, N. Liu, R. Bai et al., "Right atrial diameter and outcome of catheter ablation of atrial fibrillation," *Journal of Interventional Cardiac Electrophysiology*, vol. 49, no. 2, pp. 157–164, 2017.

[17] D. L. Packer, D. B. Mark, R. A. Robb et al., "Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation," *JAMA*, vol. 321, no. 13, pp. 1261–1274, 2019.

[18] L. V. Boersma, H. Ince, S. Kische et al., "Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial," *Heart Rhythm*, vol. 14, no. 9, pp. 1302–1308, 2017.

[19] G. Casu, M. M. Gulizia, G. Molon et al., "ANMCO/AIAC/SICI-GISE/SIC/SICCH consensus document: percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation patients: indications, patient selection, staff skills, organisation, and training," *European Heart Journal Supplements*, vol. 19, no. suppl_D, pp. D333–D353, 2017.

[20] K. P. Phillips, E. Pokushalov, A. Romanov et al., "Combining Watchman left atrial appendage closure and catheter ablation

for atrial fibrillation: multicentre registry results of feasibility and safety during implant and 30 days follow-up," *EP Europace*, vol. 20, no. 6, pp. 949–955, 2018.

[21] S. K. Carlson and R. N. Doshi, "Termination of anticoagulation therapy at 45 days after concomitant atrial fibrillation catheter ablation and left atrial appendage occlusion resulting in device-related thrombosis and stroke," *Heart Rhythm Case Reports*, vol. 3, no. 1, pp. 18–21, 2017.

Hindawi
Cardiology Research and Practice
Volume 2020, Article ID 5867617, 8 pages
https://doi.org/10.1155/2020/5867617

Research Article

Left Atrial Strain as Evaluated by Two-Dimensional Speckle Tracking Predicts Left Atrial Appendage Dysfunction in Chinese Patients with Atrial Fibrillation

Yu Wang[1,2] **Mingqi Li**[1,2] **Lishan Zhong**[1] **Siqi Ren**[1] **Hezhi Li**[1] **Yongwen Tang**[1] **Zhilian Li**[3] **and Hongwen Fei**[1]

[1]*Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong 510100, China*
[2]*Shantou University Medical College, Shantou, Guangdong 515000, China*
[3]*Department of Medical Imaging, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, Guangdong 515000, China*

Correspondence should be addressed to Hongwen Fei; floyd2001@sina.com

Received 6 November 2019; Revised 27 January 2020; Accepted 15 February 2020; Published 21 March 2020

Guest Editor: Rong Guo

Left atrial appendage (LAA) dysfunction identified by transesophageal echocardiography (TEE) is a powerful predictor of stroke in patients with atrial fibrillation (AF). The aim of our study is to assess if there is a correlation between the left atrial (LA) functional parameter and LAA dysfunction in the AF patients. This cross-sectional study included a total of 249 Chinese AF patients who did not have cardiac valvular diseases and were undergoing cardiac ablation. TEE was performed in all the patients who were categorized into two groups according to their left atrial appendage (LAA) function. A total of 120 of the 249 AF patients had LAA dysfunction. Univariate and multivariate logistic regression was conducted to assess the independent factors that correlated with the LAA dysfunction. Different predictive models for the LAA dysfunction were compared with the receiver operating characteristic (ROC) curve. The final ROC curve on the development and validation datasets was drawn based on the calculation of each area under the curves (AUC). Univariate and multivariate analysis showed that the peak left atrial strain (PLAS) was the most significant factor that correlated with the LAA dysfunction. PLAS did not show inferiority amongst all the models and revealed strong discrimination ability on both the development and validation datasets with AUC 0.818 and 0.817. Our study showed that a decrease in PLAS is independently associated with LAA dysfunction in the AF patients.

1. Introduction

AF is the most frequent type of arrhythmia, having a global prevalence of 1% to 2%. AF is a public health challenge associated with high comorbidity and an increased mortality risk [1–4]. For example, AF increases the risk of stroke by five times and is observed in ~33.3% of all ischemic stroke patients [5, 6]. In patients presenting with nonvalvular AF, over 90% of the thrombi originate in the LAA. Anatomical remodeling, atrial fibrosis, and a decline in the contractility of the LA myocardium are factors associated with left atrial thrombus/spontaneous echocardiographic contrast (LAT/SEC), as well as reductions in LAA flow velocities by TEE, which has been found to predispose patients to stroke [7]. Conventionally, TTE has been used to observe anatomical changes of LA following remodeling in the AF patients [8]; however, it has been increasingly replaced with two-dimensional (2D) speckle tracking echocardiography in order to evaluate LA function [9–11]. Most studies that report the association between LA and LAA function [12–15] were carried out on occidental populations. Compared to Western countries, stroke incidence in China is universally higher and the number of cases undergoing AF ablation procedures has been rapidly increasing. Moreover, stroke,

which is associated with AF, is the second leading cause of death in China [16]. Here, we aim to provide a noninvasive imaging modality to evaluate the LAA function in Chinese patients.

2. Methods

A retrospective and cross-sectional study was conducted at the Guangdong Provincial People's Hospital. This study has been approved by the institutional review board of the hospital. A total of 700 patients diagnosed with AF at the Guangdong Provincial People's Hospital from July 2014 to December 2017 (Figure 1) were included in this study. Patients exhibiting the following criteria were excluded from this study: pregnancy ($n = 105$), moderate to severe valvular dysfunction ($n = 212$), dilated/hypertrophic cardiomyopathy ($n = 50$), failed TEE ($n = 20$), and cases containing unqualified images ($n = 64$), either through failure to capture the total LA geometry (mostly incomplete contours of the LA roof) or image quality precluding speckle tracking. The patients were informed of research objectives and protocols, and they provided consent to participate in the study. Clinical information was collected at the time of their first hospital visit, including demographic data, current medications, and past medical history (PMH). The CHA2DS2-VASc score was calculated for each patient, and they underwent evaluation with TTE or/and TEE before proceeding to AF management.

2.1. Transthoracic Echocardiography. A two-dimension gray scale echocardiography was used to obtain standard view images, parasternal long-axis view, apical four-chamber view, and apical two-chamber views, where the frame rate was set between 65 and 75 frames per second. In addition, foreshortening of the left atrium was avoided [17]. Briefly, echocardiographic parameters were averaged from a total of five cardiac cycles [12], all of which contained clear image quality. TTE was measured using a Vivid E9 ultrasound instrument (GE Healthcare, Wauwatosa, WI, USA), containing a sector transducer (2.5–3.75 MHz). The left atrial anteroposterior diameter was acquired at its greatest dimension for parasternal long-axis view. The LV end-diastolic diameter (LVEDd) and LV end-systolic diameter (LVESd) were obtained at the level of the mitral valve tips using the M-mode Doppler ultrasonography. Left ventricle ejection fraction (LVEF) was automatically calculated by the system. The biplane modified Simpson's method of discs was used to separately calculate the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), maximum LA volume (LAVmax), and LA minimum volume (LAVmin) from apical 4- and 2-chamber views. The LAEF was calculated using the following formula: (LAVmax − LAVmin)/LAVmax × 100%. The left atrial transverse and longitudinal diameters were measured in a 4-chamber view of the end-ventricular systole. A spectral Doppler tissue imaging was used to measure tissue Doppler velocities at the septal and lateral annuli while pulsed Doppler echocardiography was used to record flow velocities of the valves. The ratio of the peak early mitral annular velocity to E wave (E/e') was calculated and recorded.

2.2. Transesophageal Echocardiography. During TEE examination (Figure 2), images were acquired using a transesophageal probe (2.9–7.0 MHz). Briefly, LAAeV was measured using a pulsed wave Doppler, where the sample volume was placed 1 cm distal from the mouth of the appendage. The maximum emptying velocity was calculated from an average of five well-defined emptying waves [18]. The LAT was defined as a fixed or mobile echogenic mass that clearly differed from the LA or LAA tissue. SEC was defined when dynamic, "smoke-like" echoes were seen within the atria and could not be eliminated by altering the gain settings [19, 20]. According to TEE findings, (1) the LAAeV < 40 cm/s and (2) LAT/SEC was found regardless of LAAeV; if either one is positive, the condition of LAA dysfunction was met [7].

2.3. Speckle Tracking Imaging. Cine loops were used to determine speckle tracking analysis (Figure 2) At least 5 consecutive beats from the three standard apical views were collected for analyses. Average PLAS was measured at the end of the reservoir phase with the tracking location marker placed at the end of the QRS wave calculated from 5 beats in patients with AF rhythm [21]. The LA endocardial border was manually traced in both the four- and two-chamber views with the regions of interest (ROI) encompassing the endocardial border of the mitral annulus, carefully excluding pulmonary veins and the LA appendage orifices. The thickness of the ROI was adjusted to the thinnest part to adapt to the atria. The data were analyzed using EchoPAC software (version 201) by two independent echocardiologists, who were blinded to clinical as well as other identifiers revealing patient characteristics.

2.4. Statistical Analysis. Data were analyzed using R (http://www.R-project.org) and Empower Stats software (http://www.empower.stats.com, X&Y solutions, Inc., Boston, MA, USA). Continuous variables were analyzed using the t-test (normal distribution) or Kruskal–Wallis rank sum test (nonnormal distribution), and categorical variables were analyzed using the χ^2 test. Variables associated with LAAeV were evaluated by univariate logistics regression analysis, and those with a p value <0.1 were further analyzed using the multivariable logistics regression model to test for independence. The receiver operating characteristic (ROC) curve was used to evaluate the prognostic predictive value of PLAS in LAA dysfunction. Two-sided p values with $p < 0.05$ are considered statistically significant.

Reproducibility of the PLAS measurement was assessed in 20 randomly selected subjects. The inter- and intra-observer correlation coefficients were 0.8 and 0.9, respectively, which are consistent with those of previous work [22].

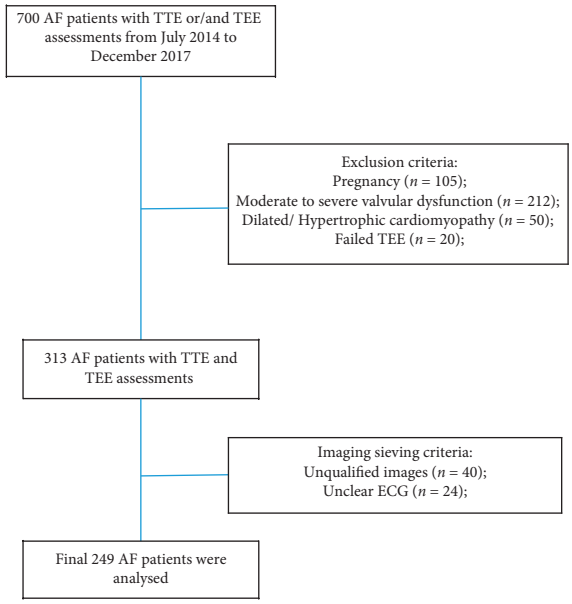


Figure 1: Flow chart of the study screening and selection process for patients used in the study.

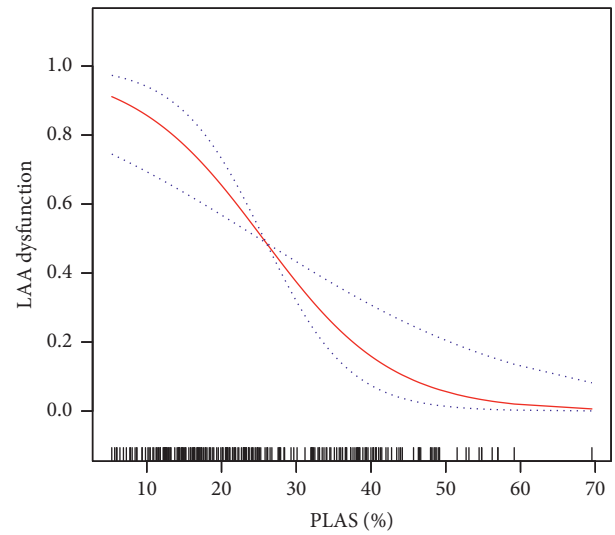


Figure 2: A linear relationship between PLAS and LAA dysfunction was observed. There was no inflection point.

3. Results

3.1. Patient Characteristics. The basic characteristics of patients used in this study are depicted by a flow diagram (Figure 1). On the basis of inclusion and exclusion criteria, a total of 249 patients undergoing both TEE and TTE were included in the study. The mean age of the patients was 59.7 years (ranging from 49.7 to 69.7 years), and the majority of the patients were male (72.7%). Following TEE measurement, it was observed that LAA dysfunction was present in 120 patients, with an incidence rate of 48.2%, where 118 patients exhibited LAAeV < 40 cm/s. Out of the 120 identified patients with the LAA dysfunction, 43 had LAT/SEC and 41 showed a LAAeV < 40 cm/s measurement. The basic characteristics of patients with and without LAA dysfunction are presented in Table 1. Patients with LAA dysfunction were older (61.4 ± 9.7 vs. 58.1 ± 12.0, $p = 0.021$) and had a higher heart rate (83.6 ± 24.2 vs. 76.7 ± 22.9, $p = 0.006$) compared to controls. The number of patients presenting both LAA dysfunction and AF rhythm (OR 3.99, 95% CI: 2.36, 6.76, $p < 0.0001$) were statistically significant.

3.2. Univariate and Multiple Logistic Regression Analysis of LAA Dysfunction. Univariate analysis showed that 18 variables, including age(OR 1.03, 95% CI: 1.00, 1.05, $p = 0.0224$), heart rhythm (OR 3.99, 95% CI: 2.36, 6.76, $p < 0.0001$), heart rate (OR 1.01, 95% CI: 1.00, 1.02, $p = 0.0243$), CHA2DS2-VASc score (OR 1.22, 95% CI: 1.04, 1.42, $p = 0.0141$), LAD (OR 1.20, 95% CI: 1.13, 1.27, $p < 0.0001$), LA longitudinal diameter (OR 1.16, 95% CI: 1.11, 1.22, $p < 0.0001$), LA transverse diameter (OR 1.17, 95% CI: 1.11, 1.23, $p < 0.0001$), LAVmax (OR 1.06, 95% CI: 1.04, 1.08, $p < 0.0001$), LAVmin (OR 1.09, 95% CI: 1.07, 1.12, $p < 0.0001$), LAEF (OR 0.92, 95% CI: 0.89, 0.94, $p < 0.0001$), E/e' (OR 1.09, 95% CI: 1.02, 1.16, $p = 0.0127$), LVDd (OR 1.18, 95% CI: 1.10, 1.25, $p < 0.0001$), LVSd (OR 1.17, 95% CI: 1.10, 1.25, $p < 0.0001$), LVDV (OR 1.03, 95% CI: 1.02, 1.05, $p < 0.0001$), LVSV (OR 1.05, 95% CI: 1.03, 1.08, $p < 0.0001$), Simpson LVEF (OR 0.95, 95% CI: 0.92, 0.98, $p = 0.0043$), and PLAS (OR 0.89, 95% CI: 0.86, 0.92, $p < 0.0001$) were associated with LAA dysfunction (Table 2). These identified variables were then further analyzed using multiple logistic regression, and PLAS (OR 0.90, 95% CI: 0.85, 0.95, $p < 0.0005$) was the only parameter significantly associated with LAA dysfunction after adjusting for sex, PMH of ablation, International Normalized Ratio (INR), AF, and isovolumic relaxation time (IVRT) (Table 2). The multivariate regression analysis showed that LAA dysfunction was consistently related to the tertials of the PLAS (Table 3). There was a linear relationship between PLAS and LAA dysfunction (Figure 3).

3.3. Sensitivity Analysis. The ROC curve for the predictive models of LAA dysfunction are presented in Figure 3. Model 1 includes the CHA2DS2-VASc score only, while Model 2 includes both the CHA2DS2-VASc score and LAEF. Model 3 includes all the three factors, viz., CHA2DS2-VASc score, LAEF, and PLAS, while Model 4 includes PLAS only. Different models performances were compared, and it was observed that PLAS of Model 4 demonstrated similar accuracy and discriminability with Model 3, including CHA2DS2-VASc score, LAEF, and PLAS. For analyses, all subjects were categorized into two equal groups, viz., development and validation groups (Figure 4). The AUC for the development group was 0.818 (95% CI: 0.744, 0.818), yielding a sensitivity of 63.33% with a specificity of 91.18% at the optimal cutoff value (PLAS = 20.44%). In the validation set, the AUC was 0.817 (95% CI: 0.741, 0.894), along with a sensitivity of 78.33% and a specificity of 78.33% at the corresponding threshold.

Table 1: Clinical characteristics of patients involved in this study.

	All patients ($n = 249$)	LAA dysfunction ($n = 120$)	Normal LAA function ($n = 129$)	p value
Age (years)	59.7 ± 11.0	61.4 ± 9.7	58.1 ± 12.0	0.021
Gender (M/F)	181/68	92/28	89/40	0.174
Course of AF, months	43.6 ± 58.0	46.8 ± 62.2	40.5 ± 53.7	0.391
History of AF ablation	30 (12.0%)	15/105	15/114	0.833
INR				0.352
<2	217 (91.6%)	103 (89.6%)	114 (93.4%)	
≥2	20 (8.4%)	12 (10.4%)	8 (6.6%)	
Heart rhythm				<0.001
Atrial fibrillation, n (%)	128 (51.4%)	79 (65.8%)	42 (32.6%)	
Sinus rhythm, n (%)	121 (48.6%)	41 (34.2%)	87v(67.4%)	
Heart rate (bpm)	80.0 ± 23.7	83.6 ± 24.2	76.7 ± 22.9	0.006
Hypertension, n (%)	111 (44.6%)	55 (45.8%)	56 (43.4%)	0.701
Diabetes mellitus, n (%)	43 (17.3%)	22 (18.3%)	21 (16.3%)	0.668
Myocardiopathy, n (%)	6 (2.4%)	3 (2.5%)	3 (2.3%)	1.000
Coronary heart disease, n (%)	35 (14.1%)	16 (13.3%)	19 (14.7%)	0.752
CHA2DS2-VASc score	2.2 ± 1.7	2.4 ± 1.8	1.9 ± 1.5	0.031
Medications, n (%)				
Antiplatelet drugs	28 (11.2%)	16 (13.3%)	12 (9.3%)	0.314
Anticoagulation drugs	77 (30.9%)	49 (40.8%)	28 (21.7%)	0.001
Antihypertension drugs	116 (46.6%)	59 (49.2%)	57 (44.2%)	0.431
Hypoglycemic agent	32 (12.9%)	16 (13.3%)	16 (12.4%)	0.827
Echocardiography				
LAAeV, n (%)				<0.001
<40 cm/s	118 (47.4%)	118 (98.3%)	0 (0.0%)	
≥40 cm/s	131 (52.6%)	2 (1.7%)	129 (100.0%)	
LAT/SEC, n (%)				<0.001
Yes	43 (17.3%)	43 (35.8%)	0 (0.0%)	
No	206 (82.7%)	77 (64.2%)	129 (100.0%)	
LAD (mm)	39.4 ± 5.9	41.9 ± 4.7	37.0 ± 6.0	<0.001
LA transverse diameter (mm)	39.5 ± 6.1	42.0 ± 5.7	37.3 ± 5.5	<0.001
LA longitudinal diameter (mm)	48.0 ± 7.2	51.2 ± 6.6	45.0 ± 6.4	<0.001
LAVmax (ml)	50.5 ± 21.7	60.2 ± 22.9	41.6 ± 16.1	<0.001
LAVmin (ml)	31.5 ± 18.6	41.0 ± 19.7	22.8 ± 12.2	<0.001
LAEF (%)	40.5 ± 14.5	33.30 ± 11.75	47.14 ± 13.55	<0.001
LVEDD (mm)	46.2 ± 4.6	47.8 ± 4.5	44.8 ± 4.3	<0.001
LVESD (mm)	29.7 ± 4.7	31.3 ± 5.1	28.2 ± 3.8	<0.001
LVEDV (ml)	58.2 ± 18.8	63.3 ± 19.5	53.4 ± 16.8	<0.001
LVESV (ml)	26.7 ± 12.8	30.6 ± 14.3	23.1 ± 10.0	<0.001
Simpson LVEF (%)	63.0 ± 7.9	61.5 ± 8.7	64.5 ± 6.9	0.003
IVRT (ms)	84.8 ± 24.8	84.1 ± 23.5	85.4 ± 26.1	0.695
E/E'	11.1 ± 4.3	11.9 ± 4.7	10.5 ± 3.7	0.010
Peak strain of LA	26.0 ± 13.2	18.6 ± 8.9	33.0 ± 12.9	<0.001

LAA dysfunction is defined as the left atrial appendage emptying velocity <40 cm/s or left atrial appendage with thrombi/spontaneous echocardiographic contrast. Data are expressed as mean ± SD, number (percentage) of subjects, or median (interquartile range). CI, confidence interval; AF, atrial fibrillation; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; LAT/SEC, left atrial thrombi/spontaneous echo contrast; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVSd, left ventricular end-systolic dimension; LVDV, left ventricular end-diastolic volume; LVSV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; E/E', the ratio of the early transmitral flow velocity to the early mitral annular velocity; IVRT, isovolumic relaxation time; LAVmax, left atrial maximum volume; LAVmin, left atrial minimum volume; LAEF, left atrial emptying fraction; LAAeV, left atrial appendage emptying flow velocity.

4. Discussion

In this study, we performed a cross-sectional study of 249 participants to investigate the association between the functions of LA and LAA. Our results revealed a positive correlation between the reduced peak LA longitudinal strain, assessed by STE, and the presence of LAA reduced emptying velocity and/or thrombus on TEE examination in AF patients. Multivariate logistic regression analysis showed that a decrease in PLAS was an independent predictor of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA thrombus and to determine subsequent needs for other imaging assessments.

CHA2DS2-VASc scores, including risk factors of age, hypertension, heart failure, and diabetes mellitus, are

Table 2: Comparison of the characteristics of patients with or without LAA dysfunction.

Covariate	Univariable			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value
Sex						
Female	Ref.			—		
Male	1.48	0.84, 2.60	0.1756	—	—	—
PMH of ablation						
No	Ref.			—		
Yes	1.09	0.51, 2.33	0.8327	—	—	—
INR						
<2	Ref.			—		
≥2	1.66	0.65, 4.22	0.2871	—	—	—
Course of AF	1.00	1.00, 1.01	0.3895	—	—	—
Heart rhythm						
Sinus rhythm	Ref.			Ref.		
AF rhythm	3.99	2.36, 6.76	<0.0001	1.88	0.65, 5.42	0.2416
Age	1.03	1.00, 1.05	0.0224	1.02	0.97, 1.06	0.4670
Heart rate	1.01	1.00, 1.02	0.0243	0.99	0.97, 1.01	0.3481
CHA2DS2-VASc score	1.22	1.04, 1.42	0.0141	0.98	0.75, 1.28	0.9004
IVRT	1.00	0.99, 1.01	0.6937	—	—	—
LAD (mm)	1.20	1.13, 1.27	<0.0001	0.97	0.88, 1.05	0.4337
LA longitudinal diameter (mm)	1.16	1.11, 1.22	<0.0001	1.00	0.92, 1.08	0.9612
LA transverse diameter (mm)	1.17	1.11, 1.23	<0.0001	0.97	0.87, 1.08	0.5679
LAVmax (ml)	1.06	1.04, 1.08	<0.0001	0.98	0.86, 1.11	0.7110
LAVmin (ml)	1.09	1.07, 1.12	<0.0001	1.07	0.88, 1.29	0.4870
LAEF (%)	0.92	0.89, 0.94	<0.0001	1.00	0.91, 1.11	0.9871
E/e'	1.09	1.02, 1.16	0.0127	1.06	0.95, 1.17	0.2920
LVDd (mm)	1.18	1.10, 1.25	<0.0001	1.18	1.02, 1.36	0.0262
LVSd (mm)	1.17	1.10, 1.25	<0.0001	0.96	0.82, 1.13	0.6274
LVDV (ml)	1.03	1.02, 1.05	<0.0001	1.04	1.00, 1.08	0.0644
LVSV (ml)	1.05	1.03, 1.08	<0.0001	0.98	0.93, 1.04	0.4685
Simpson LVEF	0.95	0.92, 0.98	0.0043	1.00	0.93, 1.07	0.9652
Peak strain of LA	0.89	0.86, 0.92	<0.0001	0.90	0.85, 0.95	0.0005

CI, confidence interval; AF, atrial fibrillation; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; LAT/SEC, left atrial thrombi/spontaneous echo contrast; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVSd, left ventricular end-systolic dimension; LVDV, left ventricular end-diastolic volume; LVSV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; E/E', the ratio of the early transmitral flow velocity to the early mitral annular velocity; IVRT, isovolumic relaxation time; LAVmax, left atrial maximum volume; LAVmin, left atrial minimum volume; LAEF, left atrial emptying fraction; LAAeV, left atrial appendage emptying flow velocity.

Table 3: The linearity between PLAS and LAA dysfunction.

Variables	Incidence, n (%)	Crude model			Multivariate-adjusted model 1			Multivariate-adjusted model 2		
		OR (95% CI)	p value	p for trend	OR (95% CI)	p value	p for trend	OR (95% CI)	p value	p for trend
PLAS (continuous, %)	Tertiles ($n = 248$)	0.90 (0.85, 0.95)	0.0005		0.87 (0.83, 0.92)	<0.0001		0.90 (0.85, 0.95)	0.0004	
T1: 5.3–17.3	82 (33.3)	1		<0.0001	1		<0.0001	1		0.0340
T2: 17.4–32.0	83 (33.3)	0.23 (0.11, 0.45)	<0.0001		0.23 (0.10, 0.53)	0.0007		0.58 (0.20, 1.65)	0.3046	
T3: 32.1–69.5	83 (33.3)	0.05 (0.02, 0.11)	<0.0001		0.04 (0.01, 0.14)	<0.0001		0.20 (0.04, 0.93)	0.0398	

Odds ratios were derived from the multivariate logistic regression analysis. Crude, no adjustment. Model I, adjusted for gender, PMH of ablation, INR, course of AF, age, heart rhythm, heart rate, and CHA2DS2-VASc score. Model II, adjusted for gender, PMH of ablation, INR, course of AF, age, heart rhythm, heart rate, CHA2DS2-VASc score, LAD, LA longitudinal diameter, LA transverse diameter, LAVmax, LAVmin, LAEF, E/e', LVDd, LVSd, LVDV, LVSV, and Simpson LVEF. PLAS, peak left atrial strain. CI, confidence interval.

clinically measurable indicators promoting atrial remodeling and are widely used to predict the risk of stroke in patients with AF. In our study, we did not find the CHA2DS2-VASc score to be significantly associated with LAA dysfunction, and this score was not an ideal platform to predict risks associated with stroke using the LAT value as a comparator. This inconsistency was also observed in previous studies [23, 24]. It is clear that the scoring system includes an assessment of the risks of early stroke, including those that cause vascular wall injury and hypercoagulable

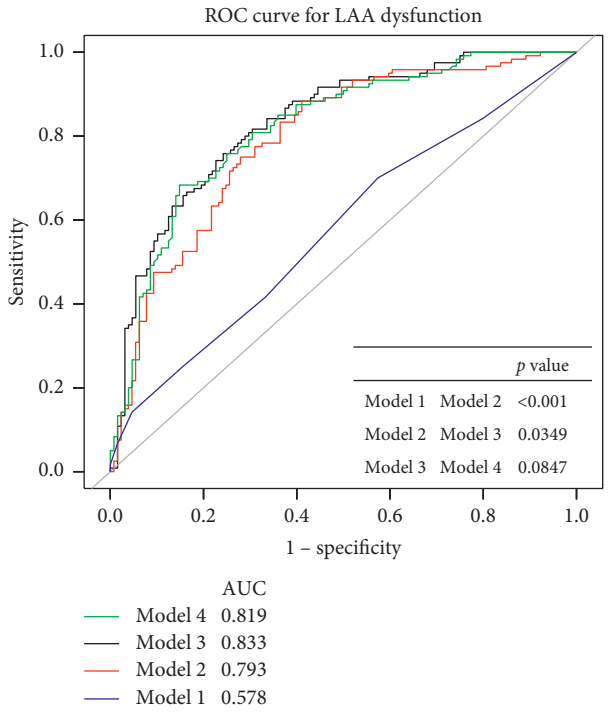


Figure 3: Comparisons among the four models used to diagnose LAA dysfunction using the ROC curve. Only the CHA2DS2-VASc score showed the lowest AUC value. CHA2DS2-VASc score, LAEF, and PLAS combined showed the highest AUC value. PLAS demonstrated similar accuracy and discriminability with Model 3. Model 1, CHA2DS2-VASc score; Model 2, CHA2DS2-VASc score + LAEF; Model 3, CHA2DS2-VASc score + LAEF + PLAS; Model 4, PLAS.

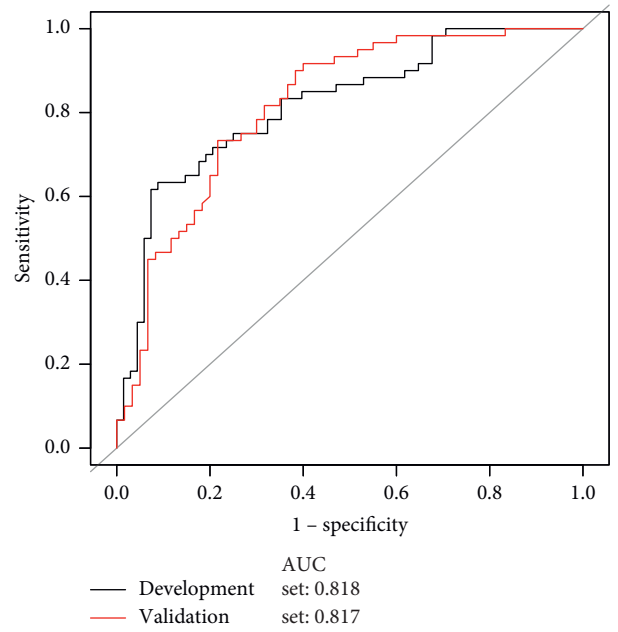


Figure 4: A receiver operating characteristic curve of PLAS that was used to predict the LAA dysfunction. The receiver operating characteristic curve of PLAS predicting the LAA dysfunction, having 50% of cases as modeling data and 50% of cases as validation data; the AUC were 0.818 and 0.817. The model showed a good discrimination ability on the validation datasets.

status [25, 26]. However, the scoring system did not analyze the effect of AF itself on cardiac remodeling which is a continuous present risk factor for stroke. Other possible variations include AF duration, structural cardiac abnormalities, race, anticoagulation adequacy, and other cardiovascular risk factors that might be associated with the observed effects. Yet, these indicators are relatively difficult to define. Consequently, recent efforts are focused on studies to refine the assessment of the risk of stroke based on cardiac structure and function [27, 28].

AF has been associated with electromechanical remodeling of the LA. LAA plays a role in maintaining LA pressure as an actively contracting structure [29]. As result of the intravascular volume status and remodeling in AF, LAA has become the primary location for the formation of thrombus [30, 31]. In the current study, we observed LAA as the site of thrombi in all patients. TEE is considered as the gold standard for the assessment of the LAA function [32]. However, as it is a semi-invasive procedure not tolerated by all patients, it remains controversial as to whether it is rational to use it as a measurement tool for the serial resolution of LAT or SEC in patients with a history of LAT or SEC [33]. Direct assessments of LAA function by TTE have also been proposed. Conventional 2D TTE has a low sensitivity of only 3–19% for the detection of thrombi in LA and especially in LAA [34]. Studies, such as those performed by Tamura et al. [35] as well as Uretsky et al. [36], were carried out to resolve the problem. These studies found that TTE-measured LAA tip Doppler tissue velocity was an independent predictor of LAA thrombus formation and may be a useful indicator for risk stratification of AF. Nevertheless, LAA is generally difficult to be clearly and totally visualized on TTE, especially in patients with small LAA.

Kuppahally et al. [13] showed that the LA strain inversely correlates with LA fibrosis in AF patients, suggesting that fibrosis decreases with LA compliance. Replacement of healthy atrial tissue with fibrotic tissue in AF leads to a reduction in the atrial contractile function and blood stasis, which results in the process of thrombus formation [37–39]. Our study observed that an impaired PLAS independently correlates with a decreased LAA function. It was also found to be the strongest independent predictor of LAA dysfunction multivariate analysis. Other conventional TTE parameters were found to be significant in univariate analysis but no longer maintained their significance in multivariate analysis. The associations between LA strain and TEE changes were also described in a previous study performed by Meng-Ruo Zhu et al. [40]. The difference here is that we defined LAA dysfunction as both decreased LAAeV and presence of LAT/SEC considering patient PMH may reduce the incidence of LAT/SEC. Therefore, we had a higher LA strain threshold for predicting LAA dysfunction compared to the one used in other studies [40]. Furthermore the diagnostic performance of PLAS to detect LAA dysfunction is strong. The addition of the CHA2DS2-VASc score and LAEF to PLAS offered no further discrimination in the detection of LAA dysfunction to

that offered by PLAS alone, which suggests that in real-world practice, when an AF patient cannot undergo TEE, the PLAS can alternatively be used to rule out the possibility of thrombus and to determine the subsequent needs for other imaging assessments.

Our study has few limitations including the fact that it is composed of a small sample size with infrequent LAT events, which impaired our ability to analyze many covariates within a single regression model. Thus, we meticulously chose the covariates to be analyzed in the logistic regression models. It is still possible that some weakly associated parameters may have been missed. Secondly, the PLAS was calculated using EchoPAC software (version 201). Vendor differences should be considered when using different machines. Finally, we used the current software for LV analysis to study the LA pattern strain because a dedicated software for LA analysis has not yet been released.

Thus, it can be concluded that a decrease in PLAS is significantly associated with LAA dysfunction in patients with nonvalvular AF, providing a parameter to identify patients with nonvalvular AF at high risk of stroke.

Abbreviations

AF: Atrial fibrillation
IVRT: Isovolumic relaxation time
LA: Left atria
LAA: Left atrial appendage
LAAeV: Left atrial appendage emptying velocity
LAD: Left atrial dimension
LAEF: Left atrial emptying fraction
LAT: Left atrial thrombi
LAVmax: Left atrial maximum volume
LAVmin: Left atrial minimum volume
LVDd: Left ventricular end-diastolic dimension
LVDV: Left ventricular end-diastolic volume
LVEF: Left ventricular ejection fraction
LVSd: Left ventricular end-systolic dimension
LVSV: Left ventricular end-systolic volume
SEC: Spontaneous echocardiographic contrast
STE: Speckle tracking echocardiography
TEE: Transesophageal echocardiography
TTE: Transthoracic echocardiography
PLAS: Peak left atrial strain.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request. The data are not publicly available due to the potential revealing of information compromising patient identity.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Yu Wang, Mingqi Li, and Lishan Zhong contributed equally to this work.

Acknowledgments

This study was supported by the National Key Research and Development Program of China (No. 2018YFC1312502), Guangdong Provincial People's Hospital Science and Technology Special Project (No. 2017zh04), Guangzhou Science and Technology Key Project (No. 323201508020261), and Guangdong Provincial Science and Technology Planning Project (No. 2014A020212676).

References

[1] S. Stewart, N. Murphy, A. Walker, A. McGuire, and J. J. V. McMurray, "Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK," *Heart*, vol. 90, no. 3, pp. 286–292, 2004.

[2] C. Blomstrom Lundqvist, G. Y. H. Lip, and P. Kirchhof, "What are the costs of atrial fibrillation?" *Europace*, vol. 13, no. 2, pp. ii9–ii12, 2011.

[3] G. Thrall, D. Lane, D. Carroll, and G. Y. Lip, "Quality of life in patients with atrial fibrillation: a systematic review," *The American Journal of Medicine*, vol. 119, pp. 448 e1–448 e19, 2006.

[4] T. Andersson, A. Magnuson, I.-L. Bryngelsson et al., "All-cause mortality in 272186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case-control study," *European Heart Journal*, vol. 34, no. 14, pp. 1061–1067, 2013.

[5] European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, A. J. Camm, P. Kirchhof et al., "Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC)," *European Heart Journal*, vol. 31, pp. 2369–2429, 2010.

[6] B. Freedman, T. S. Potpara, and G. Y. H. Lip, "Stroke prevention in atrial fibrillation," *The Lancet*, vol. 388, no. 10046, pp. 806–817, 2016.

[7] S. Yaghi, C. Song, W. A. Gray, K. L. Furie, M. S. V. Elkind, and H. Kamel, "Left atrial appendage function and stroke risk," *Stroke*, vol. 46, no. 12, pp. 3554–3559, 2015.

[8] Y. E. Yoon, I.-Y. Oh, S.-A. Kim et al., "Echocardiographic predictors of progression to persistent or permanent atrial fibrillation in patients with paroxysmal atrial fibrillation (E6P study)," *Journal of the American Society of Echocardiography*, vol. 28, no. 6, pp. 709–717, 2015.

[9] D. A. Morris, M. Takeuchi, M. Krisper et al., "Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study," *European Heart Journal-Cardiovascular Imaging*, vol. 16, no. 4, pp. 364–372, 2015.

[10] D. A. Morris, A. Parwani, M. Huemer et al., "Clinical significance of the assessment of the systolic and diastolic myocardial function of the left atrium in patients with paroxysmal atrial fibrillation and low CHADS2 index treated with Catheter ablation therapy," *The American Journal of Cardiology*, vol. 111, no. 7, pp. 1002–1011, 2013.

[11] A. Y. Shaikh, A. Maan, U. A. Khan et al., "Speckle echocardiographic left atrial strain and stiffness index as predictors of maintenance of sinus rhythm after cardioversion for atrial fibrillation: a prospective study," *Cardiovasc Ultrasound*, vol. 10, p. 48, 2012.

[12] S. Sasaki, T. Watanabe, H. Tamura et al., "Left atrial strain as evaluated by two-dimensional speckle tracking predicts left

atrial appendage dysfunction in patients with acute ischemic stroke," *BBA Clinical*, vol. 2, pp. 40–47, 2014.

[13] S. S. Kuppahally, N. Akoum, N. S. Burgon et al., "Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation," *Circulation: Cardiovascular Imaging*, vol. 3, no. 3, pp. 231–239, 2010.

[14] M. Obokata, K. Negishi, K. Kurosawa et al., "Left atrial strain provides incremental value for embolism risk stratification over CHA2DS2-VASc score and indicates prognostic impact in patients with atrial fibrillation," *Journal of the American Society of Echocardiography*, vol. 27, no. 7, pp. 709–716, 2014.

[15] D. Kim, C. Y. Shim, G.-R. Hong et al., "Clinical implications and determinants of left atrial mechanical dysfunction in patients with stroke," *Stroke*, vol. 47, no. 6, pp. 1444–1451, 2016.

[16] H. Li and J. Ge, "Cardiovascular diseases in China: current status and future perspectives," *IJC Heart & Vasculature*, vol. 6, pp. 25–31, 2014.

[17] C. Mitchell, P. S. Rahko, L. A. Blauwet et al., "Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography," *Journal of the American Society of Echocardiography*, vol. 32, no. 1, pp. 1–64, 2019.

[18] R. T. Hahn, T. Abraham, M. S. Adams et al., "Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists," *Journal of the American Society of Echocardiography*, vol. 26, no. 9, pp. 921–964, 2013.

[19] W. Aschenberg, M. Schlüter, P. Kremer, E. Schröder, V. Siglow, and W. Bleifeld, "Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus," *Journal of the American College of Cardiology*, vol. 7, no. 1, pp. 163–166, 1986.

[20] I. W. Black, A. P. Hopkins, L. C. L. Lee, and W. F. Walsh, "Left atrial spontaneous echo contrast: a clinical and echocardiographic analysis," *Journal of the American College of Cardiology*, vol. 18, no. 2, pp. 398–404, 1991.

[21] L. P. Badano, T. J. Kolias, D. Muraru et al., "Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging," *European Heart Journal-Cardiovascular Imaging*, vol. 19, no. 6, pp. 591–600, 2018.

[22] Y. Wang, Z. Li, H. Fei et al., "Left atrial strain reproducibility using vendor-dependent and vendor-independent software," *Cardiovasc Ultrasound*, vol. 17, no. 1, p. 9, 2019.

[23] R. Beigel, N. C. Wunderlich, S. Y. Ho, R. Arsanjani, and R. J. Siegel, "The left atrial appendage: anatomy, function, and noninvasive evaluation," *JACC: Cardiovascular Imaging*, vol. 7, no. 12, pp. 1251–1265, 2014.

[24] H. Yarmohammadi, B. C. Varr, S. Puwanant et al., "Role of CHADS2 score in evaluation of thromboembolic risk and mortality in patients with atrial fibrillation undergoing direct current cardioversion (from the ACUTE Trial Substudy)," *The American Journal of Cardiology*, vol. 110, no. 2, pp. 222–226, 2012.

[25] R.-B. Tang, J.-Z. Dong, X.-L. Yan et al., "Serum uric acid and risk of left atrial thrombus in patients with nonvalvular atrial fibrillation," *Canadian Journal of Cardiology*, vol. 30, no. 11, pp. 1415–1421, 2014.

[26] J. Huang, S. L. Wu, Y. M. Xue et al., "Association of CHADS2 and CHA2DS2-VASc scores with left atrial thrombus with nonvalvular atrial fibrillation: a single center based retrospective study in a cohort of 2695 Chinese subjects," *BioMed Research International*, vol. 2017, Article ID 6839589, 2017.

[27] D. R. Kumar, E. Hanlin, I. Glurich, J. J. Mazza, and S. H. Yale, "Virchow's contribution to the understanding of thrombosis and cellular biology," *Clinical Medicine & Research*, vol. 8, no. 3-4, pp. 168–172, 2010.

[28] J. Huang, H.-t. Liao, H.-w. Fei et al., "Association of thromboembolic risk score with left atrial thrombus and spontaneous echocardiographic contrast in non-anticoagulated nonvalvular atrial fibrillation patients," *Cardiology*, vol. 140, no. 2, pp. 87–95, 2018.

[29] C. J. Boos, R. A. Anderson, and G. Y. H. Lip, "Is atrial fibrillation an inflammatory disorder?" *European Heart Journal*, vol. 27, no. 2, pp. 136–149, 2006.

[30] D. Regazzoli, F. Ancona, N. Trevisi et al., "Left atrial appendage: physiology, pathology, and role as a therapeutic target," *BioMed Research International*, vol. 2015, Article ID 205013, 2015.

[31] N. M. Al-Saady, O. A. Obel, and A. J. Camm, "Left atrial appendage: structure, function, and role in thromboembolism," *Heart*, vol. 82, no. 5, pp. 547–554, 1999.

[32] J. Acar, B. Cormier, D. Grimberg et al., "Diagnosis of left atrial thrombi in mitral stenosis-usefulness of ultrasound techniques compared with other methods," *European Heart Journal*, vol. 12, no. B, pp. 70–76, 1991.

[33] G. K. Grewal, T. B. Klosterman, K. Shrestha et al., "Indications for TEE before cardioversion for atrial fibrillation: implications for appropriateness criteria," *JACC: Cardiovascular Imaging*, vol. 5, no. 6, pp. 641–648, 2012.

[34] H. Omran, W. Jung, R. Rabahieh et al., "Imaging of thrombi and assessment of left atrial appendage function: a prospective study comparing transthoracic and transoesophageal echocardiography," *Heart*, vol. 81, no. 2, pp. 192–198, 1999.

[35] H. Tamura, T. Watanabe, O. Hirono et al., "Low wall velocity of left atrial appendage measured by trans-thoracic echocardiography predicts thrombus formation caused by atrial appendage dysfunction," *Journal of the American Society of Echocardiography*, vol. 23, no. 5, pp. 545–552, 2010.

[36] S. Uretsky, A. Shah, S. Bangalore et al., "Assessment of left atrial appendage function with transthoracic tissue Doppler echocardiography," *European Journal of Echocardiography*, vol. 10, no. 3, pp. 363–371, 2009.

[37] N. Akoum, G. Fernandez, B. Wilson, C. Mcgann, E. Kholmovski, and N. Marrouche, "Association of atrial fibrosis quantified using LGE-MRI with atrial appendage thrombus and spontaneous contrast on transesophageal echocardiography in patients with atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 24, no. 24, pp. 1104–1109, 2013.

[38] M. B. Vatan, S. Yılmaz, M. T. Ağaç et al., "Relationship between CHA2DS2-VASc score and atrial electromechanical function in patients with paroxysmal atrial fibrillation: a pilot study," *Journal of Cardiology*, vol. 66, no. 5, pp. 382–387, 2015.

[39] Y. Guo, G. Y. H. Lip, and S. Apostolakis, "Inflammation in atrial fibrillation," *Journal of the American College of Cardiology*, vol. 60, no. 22, pp. 2263–2270, 2012.

[40] M.-R. Zhu, M. Wang, X.-X. Ma, D.-Y. Zheng, and Y.-L. Zhang, "The value of left atrial strain and strain rate in predicting left atrial appendage stasis in patients with nonvalvular atrial fibrillation," *Cardiology Journal*, vol. 25, no. 1, pp. 87–96, 2018.