

Comparison of cryoballoon ablation for atrial fibrillation guided by real-time three-dimensional transesophageal echocardiography vs. contrast agent injection

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Abstract

Background: Pulmonary vein (PV) occlusion generally depends on repetitive contrast agent injection when cryoballoon ablation for atrial fibrillation (AF). The present study was to compare the effect of cryoballoon ablation for AF guided by transesophageal echocardiography (TEE) vs. contrast agent injection.

Methods: Eighty patients with paroxysmal AF (PAF) were enrolled in the study. About 40 patients underwent cryoballoon ablation without TEE (non-TEE group) and the other 40 underwent cryoballoon ablation with TEE for PV occlusion (TEE group). In the TEE group during the procedure, PVs were displayed in 3-dimensional images to guide the balloon to achieve PV occlusion. The patients were followed up at regularly scheduled visits every 2 months.

Results: No differences were identified between the groups in regard to the procedure time and cryoablation time for each PV. The fluoroscopy time (6.7 ± 4.2 min vs. 17.9 ± 5.9 min, $P < 0.05$) and the amount of contrast agent (3.0 ± 5.1 mL vs. 18.1 ± 3.4 mL, $P < 0.05$) in the TEE group were both less than the non-TEE group. At a mean of 13.0 ± 3.3 month follow-up, success rates were similar between the TEE group and non-TEE group (77.5% vs. 80.0% , $P = 0.88$).

Conclusions: Cryoballoon ablation with TEE for occlusion of the PV is both safe and effective. Less fluoroscopy time and a lower contrast agent load can be achieved with the help of TEE for PV occlusion during procedure.

Keywords: Atrial fibrillation; Cryoballoon ablation; Pulmonary veins; Balloon occlusion; Transesophageal echocardiography

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia and triggers that initiate AF originate mostly from the pulmonary veins (PVs). Thus, PV isolation (PVI), with the left atrial (LA)-PV junction as the ablation target, has been regarded as the standard for an ablation strategy in drug refractory AF.^[1-3]

Radio frequency (RF) ablation is the most established approach for PVI; however, this technique has some associated risks such as thrombus formation and cardiac tamponade. The degree of hyperthermic tissue injury is related to a successful isolation of the PV. Nevertheless, excess RF ablation, including due to high contact pressure and power delivery, may lead to complications.^[4] Cryoballoon ablation, which applies liquid nitrous oxide delivered under pressure in the balloon to freeze the

surrounding tissue, is a relatively novel technology that has been demonstrated very effective for PVI in AF. Lesion formation occurs at the entire circumference of the balloon when cryoballoon ablation is performed, resulting in electrical isolation of the PVs from the LA. As demonstrated in the Fire and Ice trial, cryoballoon ablation is noninferior to RF ablation for PVI in AF, especially the 2nd-generation cryoballoon (Arctic Front Advance, Medtronic, MD, USA).^[5] Cryoballoon ablation was reported to have high acute procedural success rates with up to 97.9% of PVI with very low procedural complications.^[6] This technique is associated with a low rate of PV-stenosis, cardiac tamponade, and stroke.^[7]

Cryoballoon ablation needs complete PV occlusion to achieve complete PVI and generally, PV occlusion, which depends on repetitive contrast agent injection, often leads to prolonged radiation exposure and sometimes contrast induced kidney injury. Transesophageal echocardiography

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(TEE) might prove useful in guiding the operator to achieve complete occlusion by real-time monitoring of the balloon position at the orifice of each PV.^[8] TEE-guided PV occlusion during cryoballoon ablation might improve both safety and efficacy of the procedure and reduce fluoroscopy exposure and contrast agent dose. In the present study, we aimed to address the advantages of cryoballoon ablation guided by TEE compared with conventional procedures without TEE through mainly analyzing the fluoroscopy time and the amount of contrast agent during procedures and the success rates.

Methods

Ethical approval

The study protocol was preapproved by the Research Development and Human Ethics Committee at the First Affiliated Hospital of Dalian Medical University. All patients signed written informed consent.

Patient population

Eighty patients with drug-refractory symptomatic paroxysmal AF (PAF) who were referred for a first catheter ablation in our center from April 2016 to June in 2017 were enrolled in the present study. All patients involved were free of congenital heart diseases, thyroid dysfunction, moderate-to-severe valvular heart disease, or prior cardiac surgery, and all patients were without common PV or accessory PV. Patients were randomly divided into two groups with or without TEE monitoring during the procedure (40 individuals, respectively).

Cryoballoon ablation protocol

All antiarrhythmics were withheld for five half-lives before the procedure. Each individual received TEE for exclusion of left atrial thrombus before ablation. All patients underwent a cardiac computed tomography scan, and three-dimensional (3D) anatomical models of the LA and PVs were reconstructed. The ablation procedure was performed under general anesthesia and endotracheal intubation. All procedures were performed with the second-generation cryoballoon (Arctic Front Advance, Medtronic, MD, USA). The ostial diameter of each PV was measured to select the balloon size. A 28-mm balloon was used for all PVs.

Cryoballoon ablation without TEE

Under fluoroscopic guidance (Innova 2000, GE, WI, USA), two multipolar catheters were placed at the coronary sinus (St Jude Medical, MN, USA) and right ventricle (MicroPort, Shanghai, China) through the left femoral vein and a transseptal sheath (St. Jude Medical, MN, USA) was introduced into the right femoral vein. After transseptal puncture was performed, anticoagulation was initiated with a bolus administration of 100 IU/kg heparin followed by continuous intravenous heparin infusion to maintain an activated clotting time of 250 to 300 s and monitored every 30 min. A long guidewire was then employed to exchange for a steerable 14F delivery sheath, which accommodates

the cryoballoon. A circular mapping catheter with an eight-electrode distal loop (Achieve, Medtronic, MD, USA) was employed through the cryoballoon catheter to record PV potentials.

The quadripolar catheter positioned in the right ventricle was then moved into the superior vena cava to pace the right phrenic nerve to avoid phrenic nerve palsy caused by low temperature injury during ablation of the right-sided PVs. After confirmation of PV occlusion by contrast agent injection (Visipaque, GE Cork, Ireland), the freezing cycle was initiated. When cryoballoon ablation of the right PVs was performed, the right phrenic nerve was stimulated with the cycle length of 1000 ms. If the PV potential did not disappear within 60 s, freezing was stopped and the cryoballoon was readjusted. Each PV was ablated using two freezing cycles. The left superior PV (LSPV) was ablated firstly, followed by the left inferior PV (LIPV), then the right superior PV (RSPV), and finally the right inferior PV (RIPV).

Cryoballoon ablation with TEE

The TEE was performed by a cardiacsonographer. The initial catheter setup was the same in the procedures using TEE guidance. Transseptal puncture was performed under TEE guidance. Then the TEE probe (GE, WI, USA) was placed into the mid-esophagus [Figure 1] and PVs were displayed in a longitudinal plane, starting at an angle of 70° for the septal and 110° for the lateral veins. The plane was then gradually adjusted to optimize Doppler alignment for each single PV and to locate maximum flow.

The balloon was moved to the orifice of the PV with the guidance of fluoroscopy. Then TEE would be changed to 3D mode, and the balloon's adjustment aimed for PV occlusion with the TEE. If PV occlusion was not achieved when the balloon covered the orifice of the PV, we adjusted the position of the balloon until no PV flow was visible on the echocardiographic image [Figure 2]. The balloon was turned clockwise or counterclockwise or even slightly withdrawn according to the 3D TEE image. If TEE images still appeared incomplete occlusion of the PV after adjusting the balloon repeatedly, fluoroscopy and contrast agent injection would be performed to guide the PV occlusion. After PV occlusion was confirmed, freezing was initiated with phrenic nerve stimulation if needed.

Because of the near horizontal and longitudinal distance between the left PVs and esophagus [Figure 3], esophageal injury most commonly occurs when ablation is performed near the left PVs. The esophageal position was assessed in the 3D geometry in the postero-anterior view. If the esophagus was near the left PVs or midline (lateral borders of the esophagus were both >5 mm from the PV ostia) of the left atrium, after occlusion of the left PV, the probe of the TEE was turned in the contralateral direction (horizontal distance: about 2 cm) to push the esophagus away from the left atrium to reduce the risk of injury of esophagus from hypothermy [Figure 4]. The distance of this movement was measured using the diameter of the coronary sinus lead (5Fr, 1.7 mm) as a reference distance. The freezing time and endpoint of the ablation

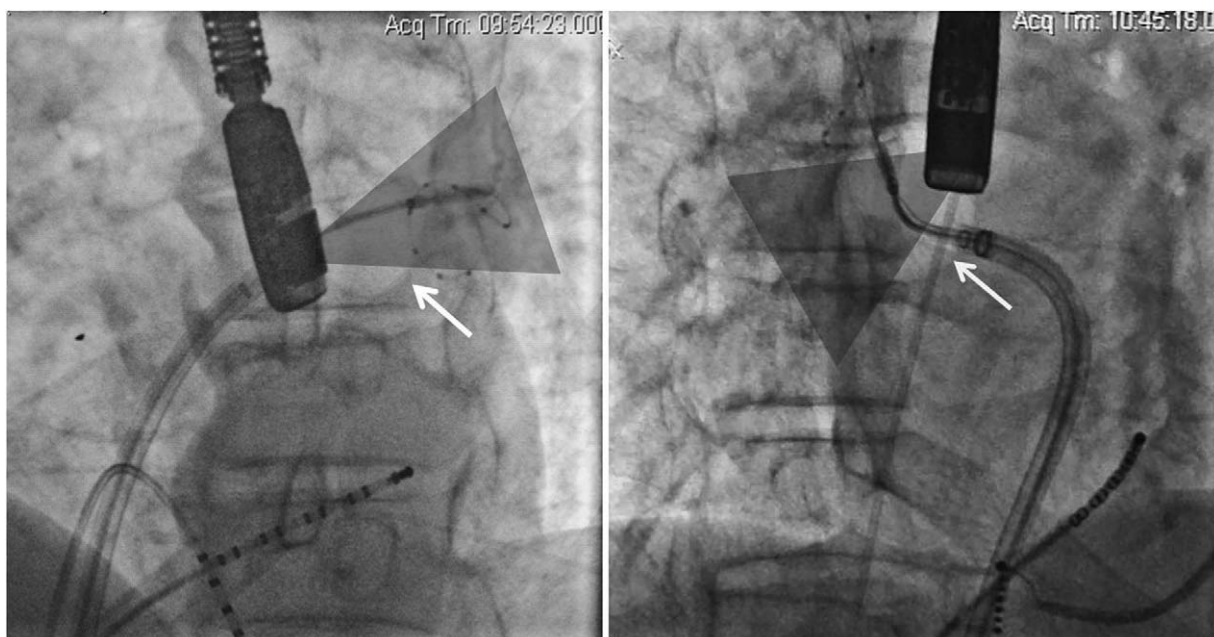


Figure 1: The position of the TEE probe on fluoroscopic images. The cryoballoon (arrows) has been inflated. The left panel shows an postero-anterior projection and the right panel is a right anterior oblique 30° projection. TEE: Transesophageal echocardiography.

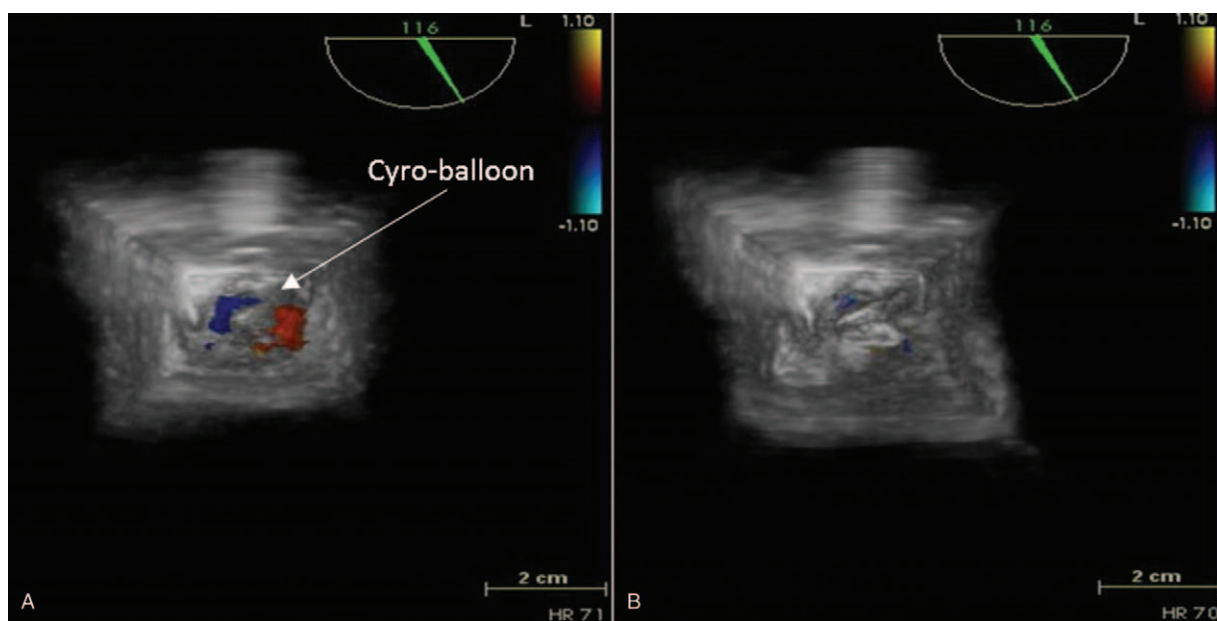


Figure 2: Three-dimensional color Doppler for adjusting the position of the balloon. At the beginning, the balloon covered the orifice of the PV, but the PV was not occluded according to the visible flow (A). After adjusting the balloon, no PV flow was visible on the echocardiographic image, which suggested the PV was occluded (B).

was the same as in procedures without TEE. The LSPV was ablated firstly, followed by the LIPV, RSPV, and RIPV.

Post-procedural management and follow-up

After the procedure, anticoagulation therapy with dabigatran (110 mg twice daily), rivaroxaban (20 mg once daily) or warfarin with target INR of 2 to 3 was administered for at least 3 months. The patients were followed up in our

center at regularly scheduled visits every 2 months. During the follow-up, a 12-lead electrocardiography (ECG) and a 24-hour Holter were obtained. When the patients experienced palpitation, ECG and Holter were also performed to assess for arrhythmia recurrence. After the 3-month blanking period, any atrial tachyarrhythmia lasting longer than 30 s was considered a recurrence. We mainly aimed to compare the fluoroscopy time and the amount of contrast agent during the procedure and success rates between the TEE group and non-TEE group.

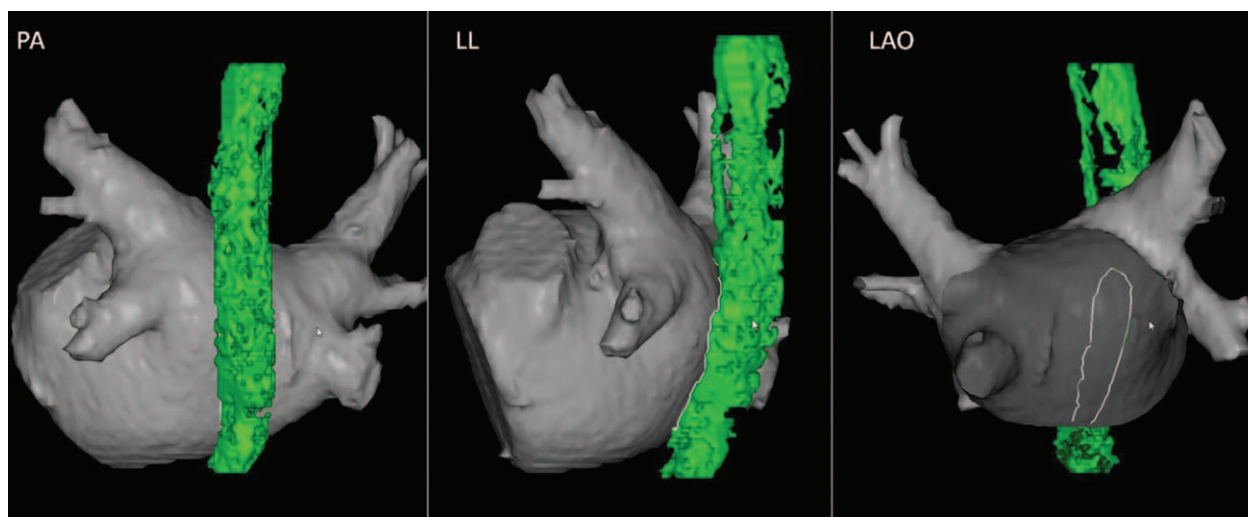


Figure 3: Postero-anterior view, left lateral view and left anterior oblique view of the CT model of the PVs, left atrium and esophagus, showing the spatial relation between the PVs and esophagus. The esophagus is nearest the left PVs, especially the LIPV, in horizontal and longitudinal distance. LAO: Left anterior oblique view; LIPV: Left inferior Pulmonary vein; LL: Left lateral view; PA: Postero-anterior view.

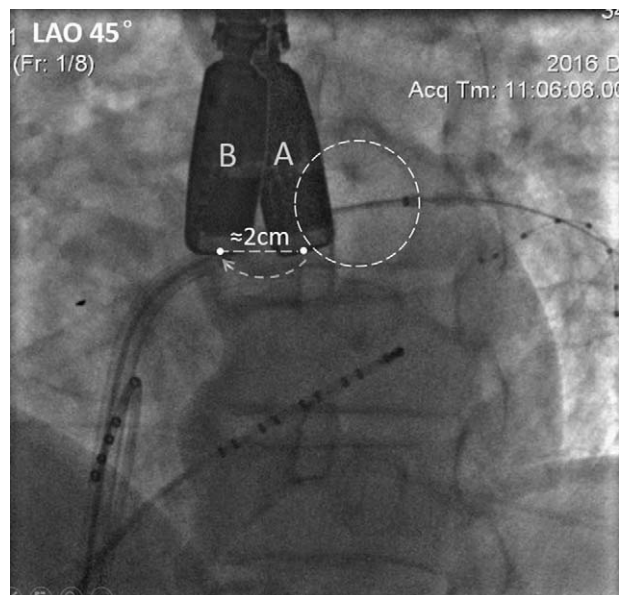


Figure 4: Movement of the TEE probe in a contralateral direction (from position A to position B) in LAO 45° (horizontal distance: 2 cm) to potentially avoid the thermal injury of the esophagus during cryablation. The circle represents the balloon. LAO: Left anterior oblique position; TEE: Transesophageal echocardiography.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation (SD). Comparisons between groups were performed with either the Student's unpaired *t*-test or Wilcoxon rank-sum test. Receiver-operator characteristic curve analysis was utilized to estimate the predictive value. The cumulative freedom from recurrence after ablation was evaluated using Kaplan-Meier event-free survival analysis. All statistical tests were two-tailed and performed using the SPSS 19.0 (SPSS Inc, USA). A *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

All patients (aged 59.2 ± 7.8 years, 51.3% males) completed the study protocol. The mean left ventricular ejection fraction (LVEF) was ($57.9 \pm 1.4\%$), and left atrial size was 37.3 ± 3.6 mm. The time course of AF was 2.9 ± 2.6 years. There was no statistical difference in the age, time course of AF, left atrial size, LVEF, CHA₂DS₂-VASc score, and ratios of gender, hypertension, coronary heart disease, and diabetes mellitus [Table 1].

Procedural data

All enrolled patients successfully completed the present study. No acute complications occurred during any procedures. Median procedural and fluoroscopy times were 116.0 ± 33.2 min and 14.3 ± 6.3 min, respectively. Eighty patients had 320 PVs (160 PVs in each group), successful PV isolation was documented in all the 320 PVs of the 80 patients. No complications occurred during the procedure.

A total of 160 PVs could be visualized by TEE during occlusion in the TEE group. Eleven PVs required fluoroscopy and contrast agent injection for occlusion. There was no significant difference between the TEE group and non-TEE group with regard to procedure time (117.3 ± 31.5 min *vs.* 114.8 ± 35.1 min, *P*=0.74) or ablation time for all PVs (LSPV: 302.6 ± 76.3 s *vs.* 312.3 ± 81.7 s, *P*=0.59; LIPV: 238.3 ± 91.3 s *vs.* 225.3 ± 72.7 s, *P*=0.48; RSPV: 334.6 ± 68.4 s *vs.* 333.3 ± 61.4 s, *P*=0.93; RIPV: 326.2 ± 71.9 s *vs.* 326.2 ± 71.9 s, *P*=0.32) [Figure 5]. About 140 PVs' potentials disappeared within 60 s of the 1st freeze application in the TEE group and 134 in non-TEE group (*P*=0.51). The fluoroscopy time in the TEE group was less compared to the non-TEE group (6.7 ± 4.2 min *vs.*

Table 1: Patient characteristics between transesophageal echocardiography (TEE) group and non-TEE group

Characteristics	TEE group (n=40)	Non-TEE group (n=40)	P
Male	21 (52.5)	20 (50.0)	0.82
Age (years)	58.8±6.8	59.7±8.7	0.60
Course of AF (years)	2.9±2.6	3.0±2.8	0.83
Left atrial size (mm)	37.7±3.2	36.8±3.5	0.25
LVEF (%)	57.7±1.3	58.0±1.5	
CHA ₂ DS ₂ -VASc score	1.4±1.2	1.3±0.9	0.75
Hypertension	19 (47.5)	17 (42.5)	0.66
Coronary disease	5 (12.5)	4 (10.0)	0.73
Diabetes mellitus	7 (17.5)	7 (17.5)	1.00

Data are presented as n (%) or mean ±SD. AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction, SD: Standard deviation.

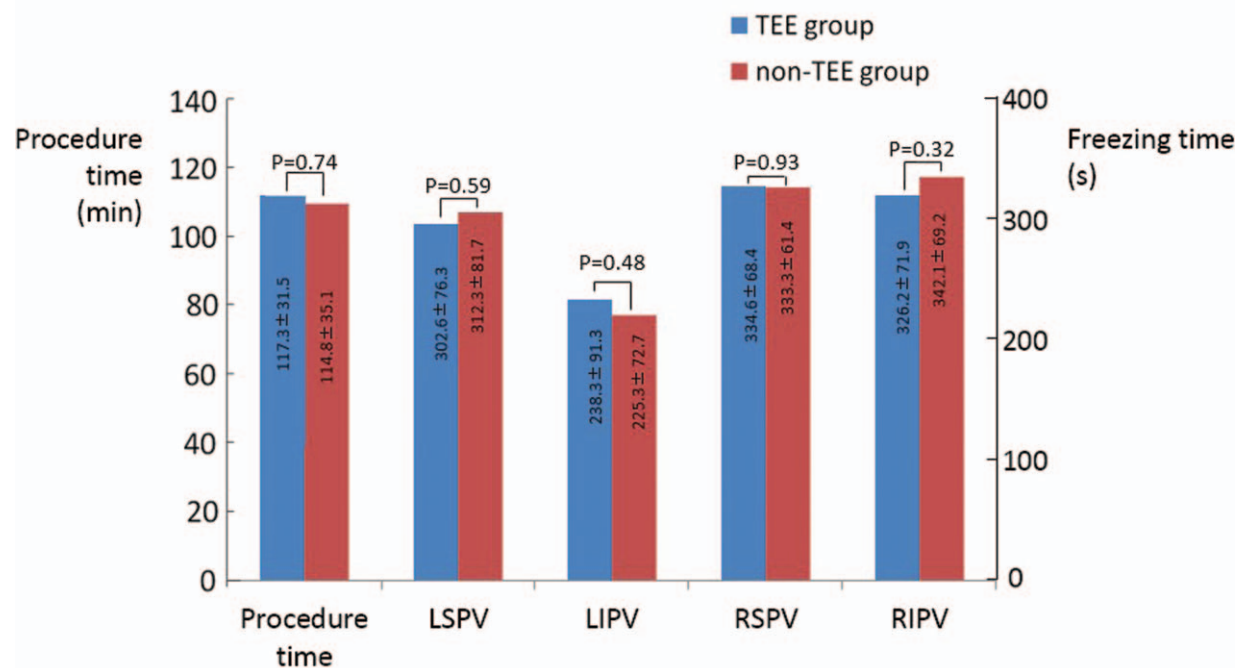


Figure 5: Comparison between the TEE group and non-TEE group for procedure time and freezing time of each PV. LIPV: Left inferior PV; LSPV: Left superior PV; PV: Pulmonary vein; RIPV: Right inferior PV; RSPV: Right superior PV; TEE: Transesophageal echocardiography.

17.9±5.9 min, $P < 0.05$). Also, the amount of contrast agent administered in the TEE group was less than the non-TEE group (3.0 ± 5.1 mL vs. 18.1 ± 3.4 mL, $P < 0.05$) [Figure 6 and Table 2].

In the TEE group, the esophagus was located near the left PVs in 28 patients (70.0%), midline of the left atrium in 7 patients (17.5%) and near the right PVs in 5 patients (12.5%). The probe of the TEE was moved in the 35 patients whose esophagus lied near the left PVs or midline of the left atrium when freezing was performed around the LSPV and LIPV. The mean distance of the movements of the probe was 2.1 ± 0.2 cm (1.8–2.4 cm) for LSPV ablation and 2.2 ± 0.2 cm (1.8–2.5 cm) for LIPV ablation [Table 3].

Follow-up

All patients were successfully followed up for a mean of 13.0 ± 3.3 months, with overall freedom from atrial tachyarrhythmia after a single procedure achieved in of 63 patients (78.8%). Similar success rates were observed between the TEE group and non-TEE group (77.5% and 80.0%, $P = 0.88$) [Figure 7]. No symptoms of pulmonary stenosis occurred during the follow-up visit.

Discussion

Major findings

The present study demonstrated the feasibility and safety of cryoballoon ablation aided by real-time TEE for PV

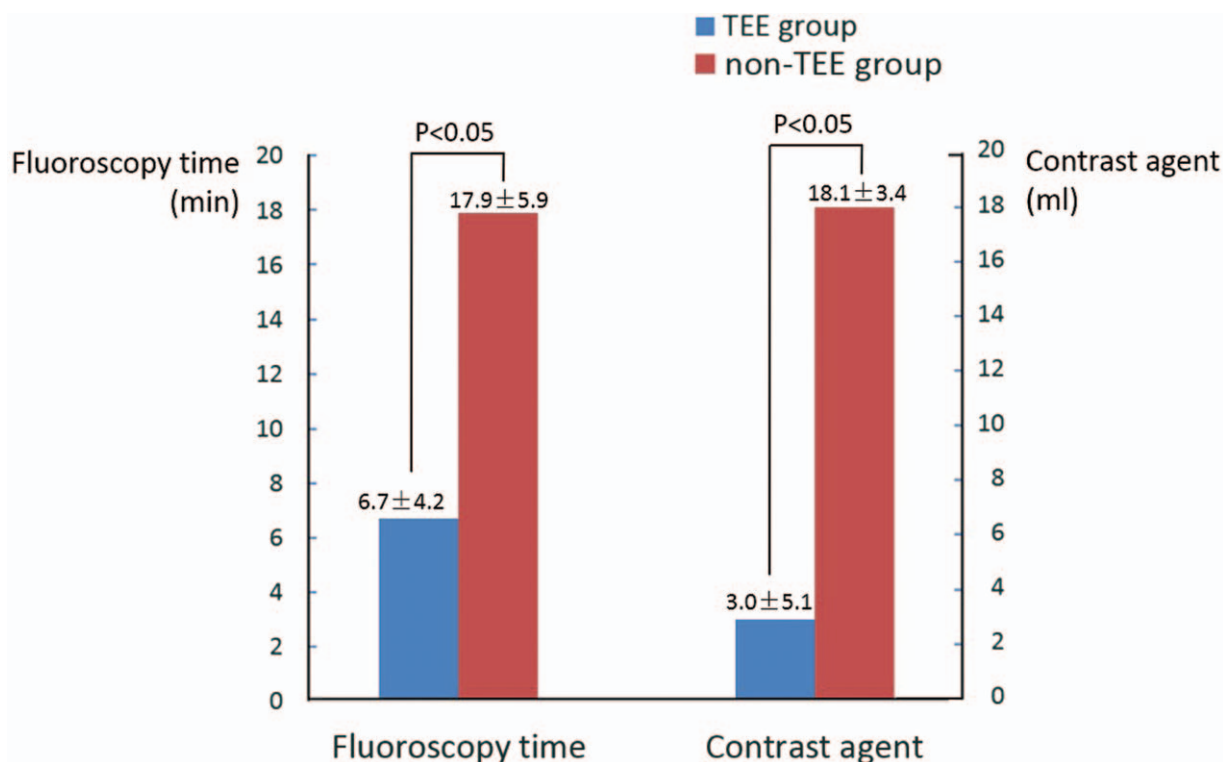


Figure 6: Comparison between the TEE group and non-TEE group with regards to the fluoroscopy time and amount of contrast agent administered. TEE: Transesophageal echocardiography.

Table 2: Pulmonary vein (PV) ostium diameters between transesophageal echocardiography (TEE) group and non-TEE group

Items	Superoinferior diameter (mm)			Transverse diameter (mm)		
	TEE group (n=40)	Non-TEE group (n=40)	P	TEE group (n=40)	Non-TEE group (n=40)	P
LSPV	16.7 ± 0.8	16.8 ± 0.8	0.86	15.1 ± 1.2	15.5 ± 0.9	0.08
LIPV	15.9 ± 1.1	15.1 ± 1.0	0.31	15.4 ± 0.9	15.4 ± 1.0	0.71
RSPV	15.5 ± 1.2	15.9 ± 1.2	0.15	16.0 ± 0.9	15.8 ± 0.8	0.16
RIPV	16.0 ± 0.8	16.1 ± 0.9	0.50	15.5 ± 2.1	15.8 ± 0.7	0.37

LSPV: Left superior PV; LIPV: Left inferior PV; RSPV: Right superior PV; RIPV: Right inferior PV.

Table 3: Distance of the movements of the transesophageal echocardiography (TEE) probe

Position of the esophagus (N, %)	Distance of the probe's movement (cm)	
	LSPV	LIPV
Left (28, 70.0)	2.1 ± 0.2	2.2 ± 0.2
Midline (7, 17.5)	2.1 ± 0.1	2.0 ± 0.1
Right (5, 12.5)	—	—

LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein.

occlusion in a Chinese population. It compared the effect of cryoballoon ablation for AF with TEE *vs.* contrast agent injection only to determine PV occlusion. Acute PVI could be achieved in all targeted PVs with the second-generation cryoballoon in the study. Meanwhile the switch from two-dimensional (2D) to 3D imaging for repositioning the balloon was feasible and useful in a number of cases. We have found that TEE monitoring for PV occlusion in

cryoballoon ablation to be advantageous to that of contrast only injection, with less fluoroscopy time and lower contrast load in the group guided by TEE.

Fluoroscopy exposure in cryoballoon ablation for AF

Radiation protection is of great importance for patients and operators. Occupational radiation exposure is a major concern and a decline in occupational exposure results when patient radiation dose is reduced.^[9] Lickfett *et al*^[10] reported that the lifetime risk of excess fatal malignancies normalized to 60 min of fluoroscopy was 0.07% for women and 0.10% for men. Operators usually involved in several procedures every day are at potentially higher risk than patients. The duration of fluoroscopy for patients undergoing cryoballoon ablation of AF exceeded that of patients undergoing catheter RF ablation primarily due to need for confirmation of PV occlusion with contrast and lack of visualization using 3D mapping systems. The average fluoroscopy time in a previous study from Rubesch-Kütemeyer *et al*^[11] was 18.0 ± 6.0 min and in

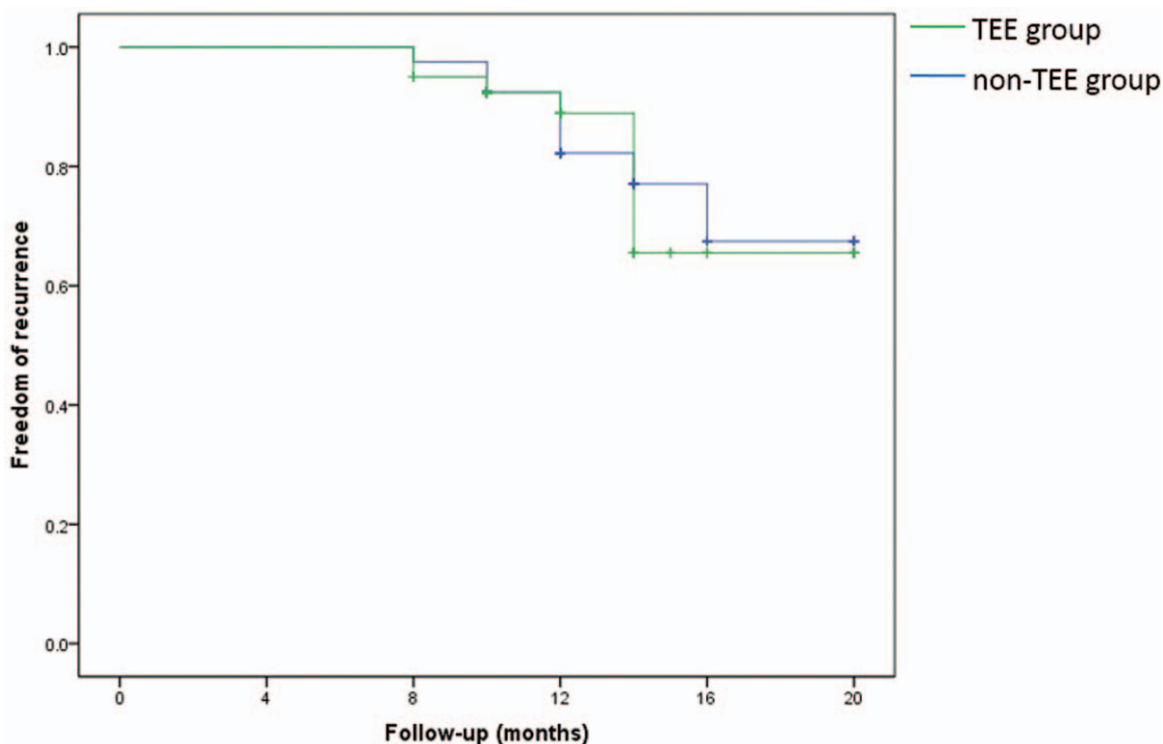


Figure 7: Freedom from recurrence according to TEE an non-TEE group. Kaplan-Meier curve showed that cumulative freedom from recurrence in TEE group and non-TEE group were similar after 13.0 ± 3.3 mon of follow-up (77.5% vs. 80.0%; log-rank test, $P=0.88$). TEE: Transesophageal echocardiography.

another study from Bohó *et al*^[12] was 22.6 ± 8.1 min, similar to our results. Our study showed that we were able to shorten fluoroscopy times significantly from 17.9 ± 5.9 to 6.7 ± 4.2 min with the assistance of real-time 3D TEE imaging during procedures. This reduction in radiation exposure by replacing angiography with Doppler imaging may have benefits for both patients and operators.

Contrast injection in assessing PV occlusion

Traditional cryoballoon ablation for AF requires repetitive contrast agent injection to ensure PV occlusion. The amount of contrast agent differs significantly among different centers. The total amount of contrast used during the procedure was 116 ± 25 mL in a study of cryoballoon ablation for AF,^[13] while in another study the amount of contrast agent was 108 ± 53 mL.^[14] However, in the present study, the amount of contrast administered was 18.1 ± 3.4 mL in the non-TEE group, lower than in other studies. One factor influencing the amount of contrast administered might be the expertise of the operators. Another important reason contributing to our lower contrast load was the method of using the contrast agent. In the procedure, we used the contrast with a 50% concentration, mixed with normal saline in the same volume, for angiography thereby decreasing the absolute amount of contrast given. Furthermore, with the aid of TEE guidance during procedures, we could reduce contrast agent from a mean of 18.1 ± 3.4 mL to 3.0 ± 5.1 mL because only 11 PVs need contrast agent injection for occlusion. This is significant for patients sensitive to higher contrast loads, for instance patients with impaired renal function.

Cryoballoon ablation guided by 3D TEE

Ultrasound imaging technologies have been developed and are used in clinical practice for AF ablation over recent years. Intracardiac echocardiography (ICE) and TEE are the common means of ultrasound imaging for catheter guidance. It has been demonstrated that ICE is a feasible and safe technique for cryoballoon ablation of AF and can help to decrease fluoroscopy exposure.^[14] Similarly, previous studies have reported that TEE has the potential to reduce radiation and facilitate AF cryoballoon ablation procedures. Peyrol *et al*^[15] suggested that TEE is an easily available and effective tool for selecting the size of the cryoballoon for ablation according to evaluated PV diameters and anatomy. Majority of the studies about cryoablation with TEE used 2D image.^[16,17] In the present study, we used 3D TEE monitoring for PV occlusion to replace contrast agent injection when possible and the results suggest that cryoballoon ablation for AF guided by real-time 3D TEE is feasible. Patients who underwent 3D TEE monitoring had similar success rates compared to those in the non-TEE group, and no significant difference in procedure times was noted between the 2 groups. Three-dimensional TEE could display the position relation between the cryoballoon and the orifice of the PVs more clearly, which was more effective than such maneuvers with 2D image.

In addition to guidance for PV occlusion, TEE can also be used to rule out the presence of intracardiac thrombi in the left atrium. Real-time TEE monitoring enables the precise localization of the balloon outside the PVs. When the balloon failed to occlude the PV, the operator could

readjust the balloon accurately to achieve PV occlusion guided by the TEE.^[16] TEE monitoring was also helpful in avoiding catheter tip injury to the left atrial appendage and documenting PV occlusion while freezing.^[17]

Compared to TEE, ICE requires insertion of a large bore venous sheath and may result in a higher rate of complications such as femoral deep venous thrombosis or femoral arteriovenous fistula.^[17] As the ICE catheter is used only once, TEE probes are consistently reusable and more economic. However, we did not compare the efficacy and safety between TEE and ICE, which may be a subject for future studies.

Atrio-esophageal fistula is a severe complication of cryoballoon ablation for AF, and mortality of cryoballoon associated atrio-esophageal fistula was reported to be 63%.^[18,19] The incidence of atrio-esophageal fistula is approximately 0.01% to 0.20%, but an increasing number of reports of atrio-esophageal fistula have been published recently with the use of more 2nd generation cryoballoons.^[20] The esophagus is commonly near the left PVs or midline to the left atrium.^[21] John *et al*^[22] found that atrio-esophageal fistula most commonly occurred near the LIPV likely due to the proximity of the esophagus to the LIPV. In our study, when cryoablation was performed at the orifice of the LIPV, we moved the probe of the TEE rightward to push the esophagus away from the left atrium in order to reduce the risk of cryoinjury to the esophagus. However, there was no difference in incidence rate of atrio-esophageal fistula between the TEE group and non-TEE group (both were 0%) due to the relatively small sample size. The effect of the movement of the probe needs large study population studies to confirm any benefit.

Several limitations exist in the present study. The relatively small study population is a major limitation of this study and the experience of operators might influence the results. We could not analyze the mechanism of atrial tachyarrhythmia inpatients with recurrence and whether PV conduction recovery or other triggers exist in patients with recurrence, and/or whether PV conduction recovery occurred in PVs occluded by TEE *vs.* contrast agent injection. The fluoroscopy time and the amount of contrast largely depended on the operators, and therefore when evaluated the results, the bias from no blinding of operators (blinding was difficult to be achieved) existed. In the present study, we adjusted the probe of the TEE to avoid potential injury to esophagus from hypothermy; however, we did not perform temperature monitoring with a probe positioned in the esophagus. And it is not verified by esophageal endoscopy afterwards.

In summary, the present study suggests that real-time 3D TEE monitoring could be an effective tool for PV occlusion during PVI with cryoballoon ablation in AF. Cryoballoon ablation is safe and feasible under TEE. The use of 3D TEE imaging for repositioning the balloon is both helpful and effective. With the aid of 3D TEE during the procedure, less radiation exposure and lower contrast loads could be achieved. Furthermore, during the procedure, moving the esophagus away from the left atrium by use of the TEE probe is feasible.

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Conflicts of interest

None.

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