

Combined use of cryoballoon and focal open-irrigation radiofrequency ablation for treatment of persistent atrial fibrillation: Results from a pilot study

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BACKGROUND Pulmonary vein isolation (PVI) achieved using a cryoballoon has been shown to be safe and effective. This treatment modality has limited effectiveness for treatment of persistent atrial fibrillation (AF).

OBJECTIVE The purpose of this study was to evaluate a combined approach using a cryoballoon for treatment of PVI and focal radiofrequency (RF) left atrial substrate ablation for treatment of persistent AF.

METHODS Twenty-two consecutive patients with persistent AF were included in the study. PVI initially was performed with a cryoballoon. Left atrial complex fractionated atrial electrograms (CFAEs) then were ablated using an RF catheter. Finally, linear ablations using the RF catheter were performed.

RESULTS Eighty-three PVs, including five with left common ostia, were targeted and isolated (100%). Seventy-seven (94%) of 82 PVs targeted with the cryoballoon were isolated, and 5 (6%) required use of RF energy to complete isolation. A mean of 9.7 ± 2.6 cryoablation applications per patient was needed to achieve

PVI. Median time required for cryoablation per vein was 600 seconds, and mean number of balloon applications per vein was 2.5 ± 1.0 . In 19 (86%) patients in whom AF persisted after PVI, CFAE areas were ablated using the RF catheter. Two cases of transient phrenic nerve paralysis occurred. After a single procedure and mean follow-up of 6.0 ± 2.9 months, 86.4% of patients were AF-free without antiarrhythmic drugs.

CONCLUSION A combined approach of cryoablation and RF ablation for treatment of persistent AF is feasible and is associated with a favorable short-term outcome.

KEYWORDS Atrial fibrillation; Balloon catheter; Catheter ablation; Cryoablation; Pulmonary vein isolation

ABBREVIATIONS AF = atrial fibrillation; CFAE = complex fractionated atrial electrogram; CS = coronary sinus; LA = left atrium; PV = pulmonary vein; PVI = pulmonary vein isolation; RF = radiofrequency

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Introduction

Catheter ablation has become one of the primary treatments of symptomatic drug-refractory atrial fibrillation (AF).¹ Although ablation techniques vary among centers, there is a general trend favoring pulmonary vein isolation (PVI) alone for treatment of

paroxysmal AF^{2–5} and PVI with left atrial (LA) substrate modification for treatment of persistent AF.^{6,7}

Most ablation procedures currently are being performed with closed- or open-irrigation radiofrequency energy (RF) catheters, which are capable only of focal ablations. However, achieving PVI with focal RF catheters is a lengthy process that is technically challenging and requires a high degree of skill. Balloon and coil platforms, using different energy sources, are being tested as potential alternatives for focal RF catheters, with the hope of providing a safer, faster, and more effective technology.^{8–10} Early clinical and pre-clinical studies have suggested that PVI using cryoenergy is associated with a low risk of endothelial disruption, thrombogenicity, and PV stenosis compared with RF ablation.^{11–16} In addition, published studies have suggested that cryothermal balloon ablation for treatment of paroxysmal AF results in a clinical success rate comparable to that of RF ablation.^{17–21} However, clinical success of cryoballoon PVI for treatment of paroxysmal AF has not been

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achieved in patients with persistent AF. In fact, the clinical success rate in one study was only 39% among patients with persistent AF,²⁰ likely because of the need for additional atrial substrate modification in this subgroup. Extensive substrate modification using focal cryoablation catheters is technically feasible but is plagued with a prolonged application time and the inability to create “dragging” ablation lesions due to cryocatheter adherence to tissue, which significantly limits the use of these catheters. In this study, we describe a combined ablation approach for treatment of persistent AF using cryoballoon PVI (Arctic Front, CryoCath, Montreal, Quebec, Canada) and RF ablation for LA substrate modification, including targeting residual triggers and drivers of AF outside the PVs.

Methods

Study population

Twenty-two consecutive patients referred to the St. Camillo-Forlanini Hospital (Rome) for catheter ablation of persistent AF were included in the study. All patients had symptomatic persistent AF of more than 6 months' duration and were refractory to one or more antiarrhythmic medications. Exclusion criteria were as follows: age <18 years or >75 years, ejection fraction <30%, LA size >55 mm, inability to consent, and life expectancy <1 year. Persistent AF was defined according to the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for management of patients with AF.¹

Clinical characteristics of the study subjects are listed in Table 1. All patients gave written informed consent, and data collection was performed in accordance with institutional ethics guidelines.

Electrophysiologic study

All patients had effective anticoagulation for at least 1 month, followed by subcutaneous low-molecular-weight heparin 2 to 4 days before the procedure. Preprocedural cardiac computed tomographic scanning was performed in

all patients. Warfarin was stopped 2 days before ablation. Transesophageal echocardiography was performed within 48 hours before the procedure in all patients to rule out the presence of atrial thrombi. Intraesophageal temperature was monitored continuously using an intraluminal temperature probe. A multipolar mapping catheter was placed into the right atrium and coronary sinus (CS). In addition, an intracardiac echocardiography probe (Acuson, Siemens, Malvern, PA, USA) was placed in the right atrium. Two transseptal punctures were performed, one for the ablation catheter and the other for the multipolar mapping catheter (PentaRay catheter or circular mapping Lasso catheter, Biosense Webster, Diamond Bar, CA, USA). After transseptal puncture, a bolus of 10,000 units heparin was given, followed by intravenous infusion to maintain an activated clotting time of at least 300 seconds. Three-dimensional reconstruction of the LA and PVs was created for all patients using the NavX mapping system (St. Jude Medical, St. Paul, MN, USA). Surface ECGs and multiple intracardiac local electrograms were recorded at a bandpass of 30 to 500 Hz using a computerized electrophysiologic recording system (Bard Electrophysiology, Andover, MA, USA).

LA mapping and ablation

The procedure was performed in a stepwise manner. At the beginning of the procedure, a complex fractionated atrial electrogram (CFAE) map was acquired using a multielectrode catheter (Lasso or PentaRay) and automated software (NavX). CFAEs were defined as areas with an average cycle length <120 ms over a 4-second span. The ablation procedure consisted of three steps. In the first step, PVI was performed using a cryoballoon (28- or 23-mm diameter; CryoCath). The size of the cryoballoon was determined based on measurements of PV diameters on the previously acquired computed tomographic scan. After PV occlusion by the cryoballoon was documented by intracardiac echocardiography, cryoablation applications to the PVs were performed for 5 minutes (Figure 1). An additional application was performed after the PV was isolated. No more than 15 minutes of total cryoapplications was performed per vein. Before the right superior PV was targeted, a quadripolar catheter was positioned in the superior vena cava for phrenic nerve stimulation during cryoablation. If loss of phrenic nerve capture was noted during ablation, the ablation was terminated immediately. After cryoablation, a circular multielectrode mapping catheter positioned at each PV ostium was used to confirm isolation. In the second step, ablation of CFAE sites in the LA, right atrium, and CS (identified by semi-automated electrogram mapping) was performed using an externally irrigated catheter (ThermoCool Celsius, 3.5 mm, Biosense Webster) if AF was still present or inducible. Ablation sites were identified by acquiring a post-PVI CFAE map. RF power was limited to 25 W when ablation was performed in the posterior LA. Ablation was performed until AF terminated or until all CFAE sites were ablated. The third step involved placing linear lesions on the roof, mitral isthmus, and septum. These

Table 1 Baseline characteristics of the study patients (n = 22)

Variable	
Age (years)	56.6 ± 13.6
Male	17 (77.3)
History of AF (months) [median (interquartile range)]	42 (21–67)
Previously ineffective antiarrhythmic drugs	1.8 ± 0.7
Left atrial diameter, long axis (mm)	46.5 ± 4.3
Ejection fraction (%)	50.6 ± 20.3
Follow-up	6.0 ± 2.9
Comorbidity	
Hypertension	12 (60.0)
Lone AF	3 (14.9)
Dilated cardiomyopathy	4 (20)

Values are given as mean ± SD or number (percent) unless otherwise indicated.

AF = atrial fibrillation.

Figure 1 Cryoballoon pulmonary vein isolation. Fluoroscopic appearance (30° left anterior oblique view) of the cryoballoon inflated (*white arrow*) in a left superior pulmonary vein. The guidewire was advanced in a pulmonary vein branch (*black arrow*), and the occlusion is confirmed by the absence of flow during contrast injection in the vein. The circular mapping catheter is placed at the ostium of the right superior pulmonary vein. A 10-pole deflectable mapping catheter is located in the distal coronary sinus.

lesions were performed if AF could not be terminated or if AF changed to an atrial tachycardia or atrial flutter. Of note, block at the LA roof was verified by pacing from the LA appendage with documentation of a change in the activation pattern in the posterior LA, with earlier activation in the low compared to the high posterior LA. Block at the mitral isthmus was verified by pacing the LA appendage with documentation of a change in the activation pattern in the CS (measured proximal to the mitral isthmus ablation), with earlier activation more proximally in the CS. Ablation was continued until block was documented for all lines, including episodes in which AF or atrial flutter terminated during creation of the line. If AF or atrial flutter could not be terminated by ablation, electrical or chemical (ibutilide 1 mg, flecainide 1 mg/kg over 10 minutes) cardioversion was performed.

Postablation management and follow-up

Post procedure, esophagus–gastroduodenal evaluation was performed within 48 hours after ablation. Patients were discharged with the same antiarrhythmic drugs they were taking prior to admission (majority were class IC antiarrhythmic drugs). In eight patients, a loop recorder system (Reveal XT, Medtronic, Minneapolis, MN, USA) was implanted before discharge, and the remaining 14 patients were instructed to send transtelephonic ECG transmissions daily or whenever suspected symptoms occurred. Antiarrhythmic drugs were discontinued at 1 month in patients without structural heart disease and at 3 months in the remaining patients. Subcutaneous heparin was continued after discharge from the hospital until the international nor-

malized ratio reached a value of 2.5. After 6 months and in the absence of AF recurrences, anticoagulant treatment was discontinued unless other major risk factors were present (based on CHADS2 score).

Follow-up outpatient clinic visits were scheduled at 1 and 3 months and every 3 months thereafter or in case of occurrence of any clinical symptom. Because early recurrence of AF may be a transient phenomenon after PVI, a 5-week blanking period was used. Recurrence of AF was defined as AF (or atypical atrial flutter) lasting >30 seconds that occurred more than 5 weeks post-PVI.

Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous data are presented as mean \pm SD or median (interquartile range [IQR]). Continuous variables were analyzed for a normal distribution using the Kolmogorov-Smirnov test. Comparison of continuous variables was performed using the Student's t-test. Comparison of proportions was performed using Chi-square analysis or Fisher exact test. All *P* values were two-sided, and *P* < .05 was considered significant.

Statistical analysis was performed using the Statistical Package for the Social Sciences (version 13.0, SPSS, Inc., Chicago, IL, USA). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 2 Procedural data and outcome (n = 22 patients)

Variable	
Patients with left common ostium	5 (22.7)
PVs isolated with cryoablation	76/82 (92.7)
Cryoablation pulses	9.2 \pm 2.6
28-mm cryoballoon	17 (77.2)
28-mm and 23-mm cryoballoons	4 (18.2)
CFAE ablations in step 2	19 (86.4)
Additional linear lines in step 3	10 (45.5)
Baseline cycle length in coronary sinus, (ms) [median (IQR)]	186 (171–195)
Transient phrenic nerve paralysis	2 (9.1)
Procedural Endpoints	
Atrial flutter during ablation	5 (22.7)
NSR during PV isolation	3 (13.6)
NSR during step 2	4 (18.2)
Successful atrial flutter ablation	3/5 (60.0)
Electrical/pharmacologic cardioversion	12 (54.5)
Ablation Times	
Procedural time (minutes) [median (IQR)]	262 (202–311)
Fluoroscopy time (minutes) [median (IQR)]	84.5 (66.3–94.3)
Total cryoablation time (minutes) [median (IQR)]	47.5 (34.1–62.5)
Outcome	
AF recurrences	3 (13.6)
AF during Blanking	2 (9.1)

Values are given as mean \pm SD or number (percent) unless otherwise indicated.

AF = atrial fibrillation; CFAE = complex fractionated atrial electrogram; IQR = interquartile range; NSR = normal sinus rhythm; PV = pulmonary vein.

Table 3 Cryoablation procedural data by pulmonary vein

Characteristic	LSPV	LIPV	RSPV	RIPV	LCPV
No. of pulmonary veins	17	17	22	21	5
Diameter (mm)	19.6 ± 3.2	17.4 ± 3.1	22.3 ± 4.0	18.2 ± 3.0	28.5 ± 4.0
Successful pulmonary vein isolation	17 (100)	16 (94.1)	21 (95.5)	18 (85.7)	4 (80.0)
Cryoablation pulses	2.6 ± 0.9	2.1 ± 0.5	2.7 ± 1.5	2.4 ± 0.9	2.1 ± 0.5
Cryoablation time (seconds) [median (interquartile range)]	600 (600–900)	600 (600–840)	650 (520–1,044)	640 (570–1,050)	600 (600–840)
Double cryoballoon (23 and 28 mm) to isolation	0	0	1 (4.5)	4 (18.2)	0
Phrenic nerve paralysis	0	0	2 (9.1)	0	0

Values are mean ± SD or number (percent) unless otherwise indicated.

LCPV = left common pulmonary vein; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

Results

Patient population

Twenty-two consecutive patients (17 men; mean age 56.6 ± 13.6 years) with persistent AF referred for ablation were included in the study (Table 1). Three (15%) of the 22 patients had lone AF. Median duration of AF was 42 months (range 21–67 months). Average LA size was 46.5 ± 4.3 mm. In two patients who had previously undergone traditional PVI with RF energy, all the PVs were found to have reconnected. Seventeen patients had typical PV anatomy consisting of four distinct veins, and 5 (22.7%) patients had a left common PV variant. Right middle PVs were treated as early branches and were isolated together with the PVs closest to them.

Acute procedural outcome

Pulmonary vein isolation

A total of 82 PVs were targeted with cryoballoon ablation (Tables 2 and 3): 17 left superior, 17 left inferior, 22 right superior, 21 right inferior, and 5 left common. One right inferior PV was not targeted with cryoablation and was isolated with RF because of phrenic nerve paralysis that occurred during isolation of the right superior PV. Seventy-six (92.1%) of the 82 veins were successfully isolated with the cryoballoon. The remaining six veins were isolated using RF. The reason for switching to RF energy to achieve isolation in the six veins were inability to achieve isolation after three cryoballoon applications in four veins and phrenic nerve paralysis in one vein (phrenic nerve paralysis occurred during isolation of a right superior PV; the right inferior PV in this patient then was isolated with RF rather than with the cryoballoon to reduce the risk of further phrenic nerve injury). Seventy-seven (94%) veins were isolated with the 28-mm diameter balloon. In 5 (6.1%) veins (1 left inferior, 4 right inferior), a balloon with a 23-mm diameter was needed to achieve complete occlusion as noted by intracardiac echocardiography. Mean number of cryolesions per patient was 9.2 ± 2.6. Median time required for cryoablation per vein was 600 seconds (range 180–900 seconds). Mean number of balloon applications per vein was 2.5 ± 1.0. Three (13.6%) patients converted to normal sinus rhythm with PVI.

LA ablation

In 19 (87%) patients in whom AF persisted after PVI, LA and CS substrate modification was performed, including CFAE ablation and linear lesions using RF (Figures 2 and 3). Average number of LA and CS sites sampled for CFAE was 345 ± 140 per patient. Of note, significant CFAE sites were not identified in the right atrium in the patients in this study. After ablation of sites exhibiting CFAE, 4 of 19 patients converted from AF to sinus rhythm. In addition, with this step, five patients converted from AF to atrial flutter, which was successfully ablated to sinus rhythm in three patients. In 10 patients who remained in AF after CFAE ablation, AF persisted despite the creation of linear lesions in the LA.

In the 12 (54%) patients in whom AF (n = 10) or atrial flutter (n = 2) persisted despite PVI and LA/CS substrate modification, electrical or chemical cardioversion was performed at the end of the procedure.

Follow-up

All patients were discharged in sinus rhythm. Patients were followed for 6.0 ± 2.9 months after ablation. At least 3 months of follow-up was completed by all patients. During the blanking period, 2 (9.1%) patients experienced early recurrence, which requiring electrical cardioversion in one patient. Antiarrhythmic drugs were discontinued in all patients within 3 months after the procedure. After mean follow-up of 6.0 ± 2.9 months, 19 (86%) patients remained free from AF recurrences. A repeat procedure is planned for the remaining three patients who had recurrences of AF.

Complications

No thromboembolic events occurred during either the procedure or follow-up. Two (9%) patients had transient phrenic nerve paralysis during cryoablation of the right superior PV. One resolved after cessation of cryotherapy, and the other recovered after 2 days. One occurred with the 28-mm-diameter balloon and the other with the 23 mm-diameter balloon. In one of the two patients, phrenic nerve palsy occurred during the additional consolidation cryolesion. Except for mild hyperemia in two patients, no significant esophageal lesions were revealed by esophagoscopy. A trivial nonhemodynamically significant pericardial effusion occurred in one patient but required no treatment.

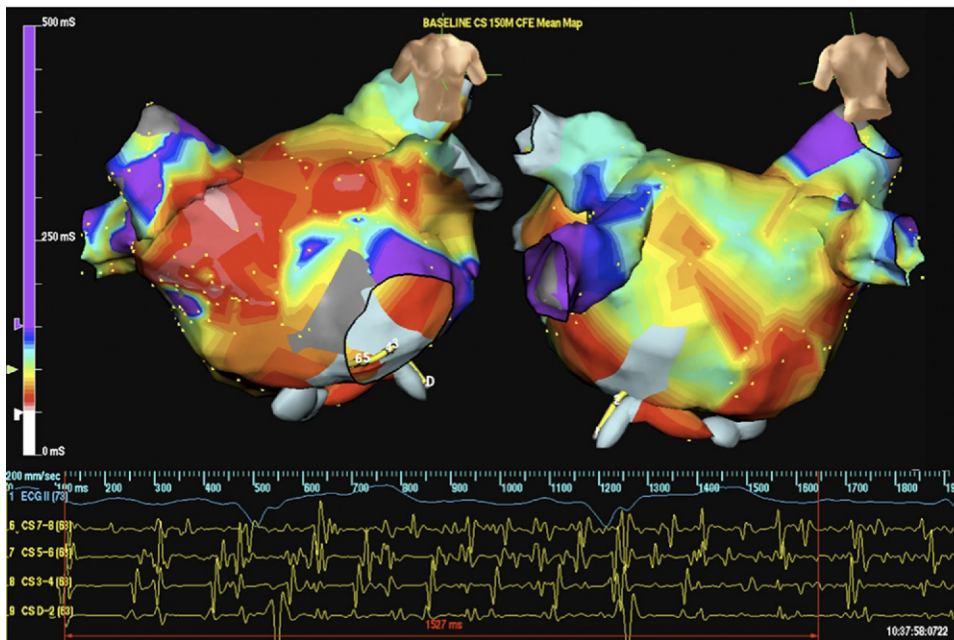


Figure 2 Baseline complex fractionated atrial electrogram map. Anterior and posterior views of an electroanatomic map of the left atrium acquired before pulmonary vein isolation show the locations of complex electrograms. Electrograms with a mean cycle length less than 120 milliseconds were targeted with ablation.

Discussion

This is the first study describing the use of combined cryoenergy and RF energy for ablation of persistent AF. The study revealed the following important findings. (1) A combined approach using a cryoballoon for PVI and focal RF catheter for LA substrate modification is feasible. (2) The majority of the PVs can be isolated using fewer than 10 5-minute cryolesions per patient. (3) This approach improves intraprocedural termination of AF compared with cryoballoon PVI alone. (4) This combined approach is associated with favorable short- and mid-term maintenance of sinus rhythm compared with that in published reports of cryoballoon PVI alone for persistent AF.

Feasibility and potential benefits of a combined cryoablation and RF approach

Despite considerable advances in catheter-based treatment of AF, PVI procedures require a great deal of expertise, and they remain time-consuming and technically challenging. As a result, newer catheter platforms have been developed to optimize efficacy and minimize complications. Cryoballoon has emerged as a promising tool allowing PVI in a safe and effective manner. Results from early preclinical and clinical studies using cryoablation for PVI were encouraging.¹⁷⁻²¹ These studies showed that use of cryoablation is associated with a very low rate of complications, including thrombogenicity, PV stenosis, and esophageal injury. However, PVI is insufficient for eliminating recurrent AF in the vast majority of patients with persistent or permanent AF.^{22,23} Considerable evidence indicates that catheter ablation of persistent/permanent AF, unlike paroxysmal AF, requires ablation of residual triggers or drivers of AF out-

side the PVs.^{6,24} Various adjunctive atrial modifications, such as wider ablation around the veins, linear lines, or ablation of CFAE, have been proposed.⁵ However, exten-

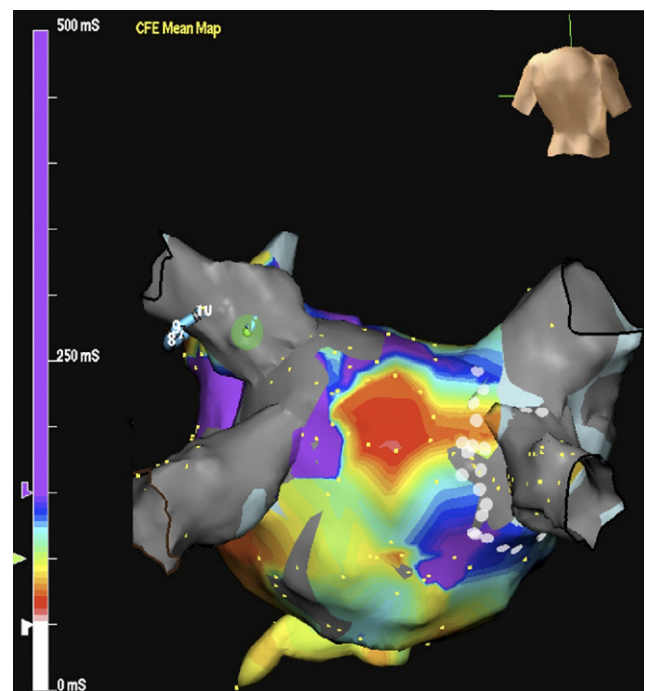


Figure 3 Complex fractionated atrial electrogram map obtained after pulmonary vein isolation. In this patient, the left pulmonary veins and the right superior pulmonary vein were isolated with the cryoballoon. The right inferior pulmonary vein was isolated with radiofrequency because of phrenic paralysis that occurred during the consolidation cryoballoon lesion for the right superior pulmonary vein.

sive substrate modification is extremely difficult to achieve using the focal cryocatheter because of time restraints. As a result, a combined approach combining cryoballoon for PVI and focal RF for substrate modification appears promising and feasible based on this study.

Procedural endpoints and acute success rate

The rate of acute success for PVI using the cryoballoon varies in the published data. Some reports showed that the majority of the PVs can be isolated with this technology.²⁵ However, other studies showed that, in some patients, electrical isolation of all veins could not be achieved using a single size cryoballoon.^{21,26} The current study showed that isolation can be achieved in the majority of the veins with a small number of applications. The decision to switch to a different balloon or to conventional RF ablation was driven in most situations by the delay in achieving isolation. This can be related to multiple factors. In our experience with similar catheters,¹⁰ the most important factor is related to unfavorable angulations of the PV ostia relative to the ablation catheter. In some situations, this can lead to a mismatch between the shaft of the catheter and the axis of the vein, resulting in suboptimal contact. Another anatomic factor is the size of the PV ostia. At the time of our study, the available catheter had a maximum diameter of 28 mm, which was less than the diameter of some PVs, leading to suboptimal contact. A larger-diameter balloon might help to overcome these limitations.

The significance of AF organization and termination during ablation and its relationship to long-term outcome remains controversial. Recent reports demonstrated that AF termination is associated with an improved clinical outcome.²⁷ In our study, AF could not be terminated in 54% of patients, suggesting that not all drivers were ablated. One possible explanation is the level of PVI using cryoballoon. Most balloon- and coil-based technologies create ostial isolation of the PV. The more proximal antra of the PVs typically are spared by the balloon, which may explain the persistence of AF in some of the patients in this study.^{28–30} In contrast, at many centers (including our own), RF-based PVI is performed more proximally, which may help to eliminate CFAE sites that may reside at the vein antra. Additionally, ganglionic plexuses located near the PV antra may not be affected by cryoballoon lesions. Nevertheless, 86% of patients remained arrhythmia-free during follow-up, a success rate comparable to that of published studies on ablation of persistent AF.⁶

Additional substrate modification

Different strategies adjunctive to PVI have been proposed for patients with nonparoxysmal AF. One of the most individualized strategies for elimination of AF is ablation of CFAEs.³¹ Published studies showed that a combined approach of PVI and CFAE ablation in persistent AF leads to excellent long-term outcomes.^{6,32} As shown in these studies, CFAE ablations can lead to AF termination. In our study, CFAE ablation led to organization of AF to atrial

flutter, which was later mapped and ablated. However, the definition and relevance of CFAE remain incompletely understood. Some CFAE areas may represent drivers for AF, but it is conceivable that some are merely nonspecific bystanders with no role in maintaining AF. Tools allowing differentiation between active and passive CFAE sites are crucial for our understanding and treatment of persistent AF.

Complications

One risk of using the cryoballoon for PVI is phrenic nerve paralysis. This is also a major limitation of balloon catheters using other energy sources. In most patients, phrenic nerve function recovers after cryoapplication is stopped. Phrenic nerve injury was the only significant complication seen in our series and resolved without sequelae. It is likely that a small balloon/PV diameter ratio, leading to ablation relatively deep within the PVs, leads to this complication.^{25,33} Chun et al²⁵ showed that distal balloon ablation at the right PVs must be avoided and emphasize the need for a cryoballoon >28 mm for larger veins. At the time of our study, the largest available cryoballoon had a maximum diameter of 28 mm, which is smaller than the diameter of some PVs. Although phrenic nerve paralysis is a potential risk of this technology, cryoballoon PVI has several potential safety advantages compared with standard RF PVI, including a lower risk of PV stenosis.

Atrio-esophageal fistula is an uncommon but devastating complication of RF³⁴ and other energy sources such as focused ultrasound.³⁵ To date, this complication has not been reported with cryoablation. It is important to note, however, that the number of ablations using cryoballoon is very small compared to ablations performed with RF. In our study, esophagus–gastroduodenal evaluation performed the day after ablation showed hyperemia in two patients. This could be related to the use of either cryoablation or RF ablation. No patients had any other evidence of ulcerations or injury to the esophageal mucosa.

Our study supports prior reports of the safety of cryoablation. However, the number of patients in this study is small, and larger studies are needed to evaluate the safety profile of the hybrid approach described in this study.

Follow-up

After a single procedure, short- and mid-term but intensive follow-up aimed at detecting asymptomatic recurrences resulted in maintenance of sinus rhythm without the use of antiarrhythmic drug therapy in 86% of patients. This success rate supports the clinical efficacy of previous studies using PVI and substrate modification for persistent AF using RF ablation.

Study limitations

This study has some limitations. First, the number of patients included in the study is small. However, this was a study intended to demonstrate that a combined approach of cryoablation and RF ablation is feasible and can improve

the rate of intraprocedural termination of AF by ablation compared to cryoballoon PVI alone. Another limitation of this study is the relatively short-term follow-up of 6 months. Longer follow-up is important to demonstrate that this short-term follow-up will translate into a long-term freedom from AF. Finally, randomized studies comparing cryoballoon ablation with conventional RF energy will be necessary to assess efficacy, complications, and cost-efficacy.

Conclusion

Cryoballoon PVI is promising because of its low thrombogenicity and lower risk of PV stenosis but may be inadequate as standalone strategy in most patients with persistent AF. The results of this pilot study demonstrate that a combined approach of cryoablation and RF ablation for persistent AF is feasible and associated with a favorable short- and mid-term outcome. The most frequent complication of this approach is phrenic nerve paralysis, which was transient and reversible in this study. Randomized studies in larger cohorts of patients are required to determine the safety and efficacy of this approach.

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