

Efficacy of pulmonary vein isolation by cryoballoon ablation in patients with paroxysmal atrial fibrillation

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BACKGROUND Radiofrequency ablation of pulmonary veins (PVs) has emerged as an effective treatment for patients with paroxysmal atrial fibrillation (AF). However, serious complications raise concern about an even wider application. In terms of safety, cryoenergy has advantages compared with radiofrequency. A new cryoenergy balloon catheter has been recently developed to make AF ablation shorter and safer.

OBJECTIVE The purpose of this study was to test the 6-month efficacy of this new device for ablation of paroxysmal AF.

METHODS Twenty-one patients with highly symptomatic paroxysmal AF, normal left atrial size, and frequent episodes of AF were included. All PVs were targeted during cryoballoon ablation. Patients received 24-hour Holter electrocardiograms (ECGs) and event recorder during follow-up after 1, 3, and 6 months.

RESULTS A total of 81 (95%) of 85 PVs could be completely isolated with a single-balloon technique. Procedure time was

165 ± 35 minutes, and fluoroscopy time was 39 ± 9 minutes. After 6 months, 86% of the patients were free of symptomatic AF. In two of three patients with recurrence of AF, complete PV isolation has not been achieved initially. After a second procedure (1.04 procedures per patient), 90% of the patients were free of symptomatic AF. Three phrenic nerve palsies occurred during ablation of the right superior PV; two completely resolved after 6 and 9 months, and one is still persisting after 2 months.

CONCLUSION This is the first study that reports the results of the new cryoballoon AF ablation approach showing 86% freedom from AF recurrence after 6 months. Cryoballoon PV ablation promises to be effective for patients with paroxysmal AF and normally sized left atria.

KEYWORDS Ablation; Atrial fibrillation; Cryoablation; Cryoballoon (Heart Rhythm 2008;5:802–806) © 2008 Heart Rhythm Society. All rights reserved.

Introduction

Pulmonary vein (PV) isolation with radiofrequency (RF) has been widely used for the interventional treatment of atrial fibrillation (AF). The success rates of these procedures vary between 65% and 85% in patients with paroxysmal AF depending on technique used, patient selection, and experience of the center.^{1–3} These results lead to a change in the recent guidelines on AF, which recommend AF ablation as a class IIa indication for patients with paroxysmal AF without structural heart disease and refractory to medical antiarrhythmic treatment.⁴ However, the complication rate of RF AF ablation is still high, and complications include PV stenosis, thromboembolic events, pericardial effusion, left atrial flutter, and atrioesophageal fistulae.⁵ Cryoenergy has potential advantages compared with RF with regard to safety aspects. It has been shown that cryoenergy does not lead to PV stenosis, has never been associated with atrioesophageal fistula, and has a lower thrombogenicity.^{6–8} However, cryoablation of PVs by standard steerable cath-

eters would be very time-consuming considering that one single ablation point takes about 4 minutes. A new cryoballoon device now enables us to circumferentially isolate one single vein, which makes cryoablation of PVs faster and feasible. Thus, this new device raises expectations that cryoablation of PVs might be achieved with the same speed as with RF energy but that cryoablation is potentially associated with a better risk profile.

The following study is the first to report the results of this new ablation approach in patients with highly symptomatic paroxysmal AF.

Methods

Patients with documented highly symptomatic paroxysmal AF on two or more occasions and at least one unsuccessful try of medical antiarrhythmic therapy were accepted (patients had symptomatic AF episodes once weekly (Table 1). Exclusion criteria were structural heart disease or enlarged left atria (>45 mm, parasternal long axis by echocardiography), moderate or severe valvular heart disease, and pacemaker implantation.

All patients received transesophageal echocardiography at least 1 day before the procedure to exclude left atrial thrombi. All patients were treated with a double lumen cryoballoon (Arctic Front; CryoCath, Montreal, Quebec, Canada),

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Table 1 Baseline characteristics

Patient characteristics	n
Number	21
Male/female	10/11
Age, years	56 ± 6
History of AF, years	4 ± 2
Mean interval between AF episodes, days	8 ± 5
History of hypertension	14 (67)
Coronary artery disease	3 (14)
Number of unsuccessful antiarrhythmics	2.3 ± 0.7
LA size, mm	38 ± 3
CHADS2 Score	0.6 ± 0.5

Data are mean ± standard deviation or n (%).

either 23 mm (n = 4) or 28 mm in size (n = 17) as appropriate for the size of the PVs. Both femoral veins were used for venous access.

A single posterior transseptal approach (SR0 sheath and BRK-1 needle, St. Jude Medical, Minnetonka, Minnesota)

was used. The SR0 sheath was removed, and the 14-Fr FlexCath sheath was advanced over the wire into the left atrium. Angiography of all PVs was performed via the 14-Fr FlexCath sheath (CryoCath). Either a 23-mm or a 28-mm cryoballoon was selected according to PV angiogram. A decapolar mapping catheter was not used before ablation since ablation of all veins and the associated atrial tissue (junction) was assessed. However, after ablation, a decapolar mapping catheter was used to confirm PV isolation. Optimum position of the cryoballoon in the PV antrum was confirmed by PV angiography and verification of vessel occlusion (Figure 1). Cryoablation was applied for 5 minutes at least 2 times for each vein. When occlusion was not as desired, the wire was changed to a different side branch or position of balloon or the flexion of the sheath was changed to ensure better occlusion. The ablation procedure was always started in the left superior, then left inferior, then right superior, and finally right inferior PV. Before

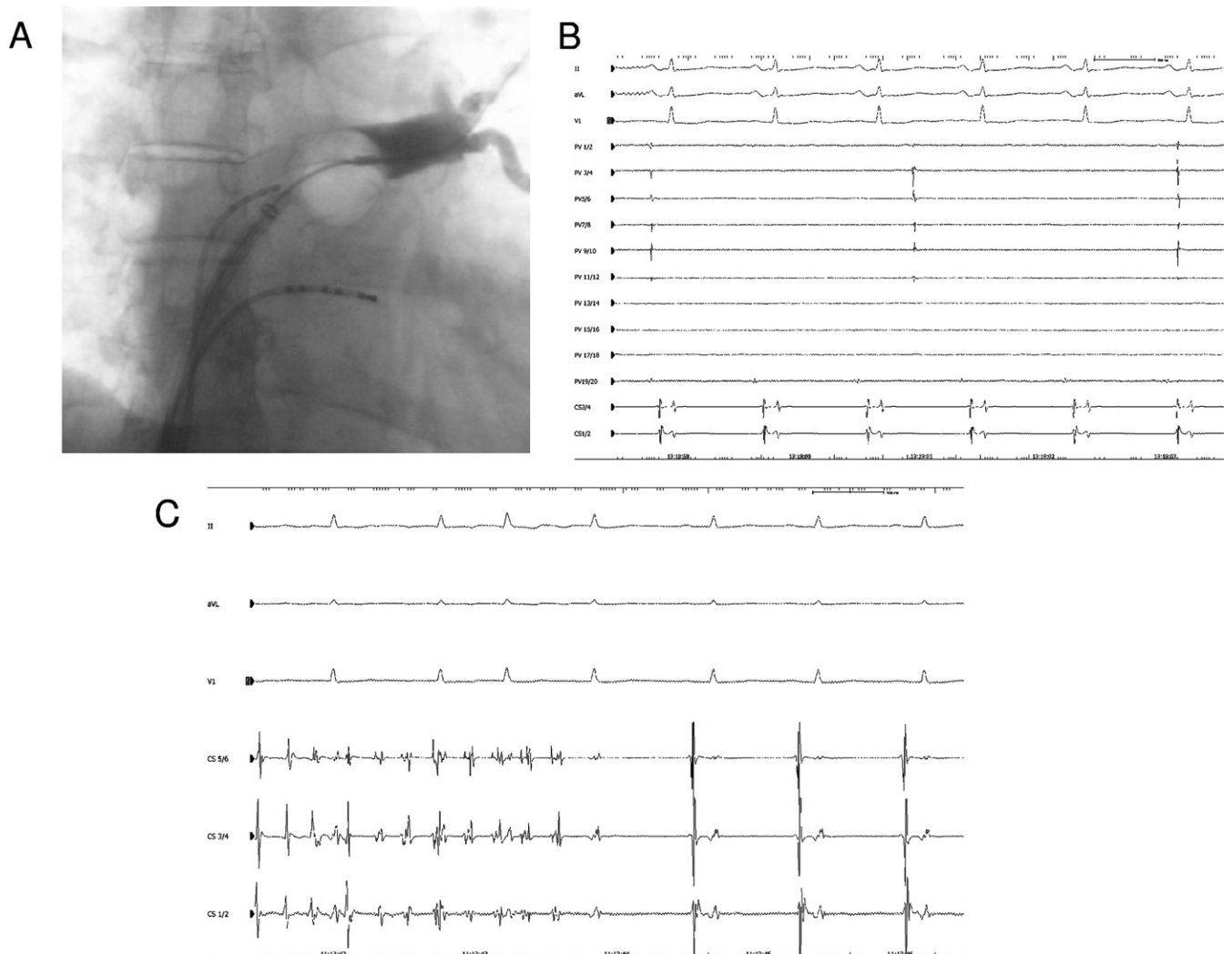


Figure 1 A: X-ray under angiography of the left superior PV occluded by the inflated cryoballoon (AP projection). Quadripolar catheter in the high right atrium and hexapolar catheter at His position. B: Intracardiac electrogram from the left superior PV (PV 1/2 to PV19/20) and the coronary sinus (CS1/2 and CS 3/4) showing dissociated PV potentials on PV 1/2 to PV11/12. C: Conversion of AF to sinus rhythm during cryoballoon ablation in the left superior PV. Surface ECG and intracardiac electrogram from the coronary sinus (CS 1/2, CS 3/4 and CS 5/6).

cryoablation in the right superior vein, a quadripolar catheter was placed in the superior vena cava for stimulation of the right phrenic nerve. When loss of capture occurred, cryoablation was immediately stopped. After all PVs were treated with the cryoballoon, the balloon was exchanged for the decapolar mapping catheter, and entrance block into the veins and exit block from the veins were checked by pacing from the decapolar mapping catheter. It was carefully checked that the catheter was not inserted too deep into the vein. Furthermore, exit block was also defined by the presence of slow dissociated PV rhythms (Figure 1B). Another check-up for PV isolation was performed after waiting 30 minutes. In case of persistent conductance into PV, the balloon was again placed in the antrum of the veins, and contact between balloon and left atrium and vein was optimized. If this did not lead to successful PV isolation, either the smaller sized 23-mm balloon was used, which was easier to be placed in the vein antrum, or a conventional cryocatheter (Freezor max; CryoCath) was used to successfully isolate PVs.

Immediately after the procedure and the next day, patients received transthoracic echocardiography for exclusion of pericardial effusion. During the procedure, the activated clotting time (ACT) was kept at 350 seconds and was checked every 30–60 minutes. After the procedure, patients received intravenous heparin, and oral anticoagulants were started again for at least 3 months at target international normalized ratio (INR) 2.5. During the first 3 months, the patients continued the antiarrhythmic medication, which has been unsuccessful so far. Antiarrhythmic medication and oral anticoagulation were stopped after 3 months when patients were free of symptomatic AF episodes and Holter electrocardiograms (ECGs) showed persistent sinus rhythm. None of the patients received amiodarone immediately before or during follow-up. All patients received either β -blocker or flecainide 100 mg twice daily for the first 3 months. Flecainide was used after ablation in those 11 patients who were already treated with flecainide before ablation but without success (patients had symptomatic AF episodes once weekly; Table 1). Three months after ablation, at the latest, flecainide was stopped in all patients but two, who had early recurrence of AF already 1 week after the initial procedure. In all patients without recurrence of AF, flecainide was stopped 3 months after ablation at the latest. Beta-blocker medication was continued in five patients as part of their antihypertensive therapy or as part of coronary artery disease (CAD) therapy. All patients received 24-hour Holter ECGs during an outpatient follow-up at 1, 3, and 6 months as well as an event recorder for

Table 2 Number of cryoballoon ablations

Vein	Number \pm standard deviation
Right superior PV	2 \pm 1
Left superior PV	3 \pm 1
Right inferior PV	2 \pm 1
Left inferior PV	3 \pm 1

Table 3 Minimum temperature achieved during cryoablation ($^{\circ}$ C)

Vein	Temperature \pm standard deviation
Right superior PV	-54 ± 10
Left superior PV	-54 ± 7
Right inferior PV	-49 ± 10
Left inferior PV	-51 ± 9

documentation of potential symptomatic AF episodes. Since cryoablation has never been shown to induce PV stenosis, transesophageal echocardiography and computed tomography scan were only recommended if PV stenosis was suspected (dyspnea at rest or exercise, cough, hemoptysis, fever). Patients with acute phrenic nerve palsy received chest X-ray 24 hours after the procedure, at 1-, 3-, 6-, 9-, and 12-month intervals.

Statistics

All data are expressed as mean \pm standard deviation. Comparisons between two groups were performed with a *t*-test. For survival curve, a Kaplan-Meier analysis was performed.

Results

Baseline characteristics

Baseline characteristics are reported in Table 1. We studied 21 patients with highly symptomatic paroxysmal AF without structural heart disease and normal left atrial size. Patients had a history of at least two unsuccessful class I or III antiarrhythmics and frequent episodes of AF.

Ablation procedure

The mean duration of ablation procedure was 165 ± 35 minutes, and the fluoroscopy time was 39 ± 9 minutes. When comparing the first six to the last six patients, fluoroscopy time showed a trend to decrease from 45 ± 5 to 36 ± 8 minutes ($P = .055$).

We were able to isolate 81 (95%) of 85 PVs with a single-balloon technique (17 patients with a 28-mm balloon and four patients with a 23-mm balloon), and we had to use a second balloon (smaller 23-mm balloon in two patients and in one patient a conventional Freezor max 6-mm cryocatheter for isolation of the inferior parts of the right inferior PV) in three cases. Nevertheless, we were not able to completely isolate the right superior PV in one patient and the right inferior PV in another patient.

The number of cryoablations for each vein did not differ between left and right PVs or between superior or inferior veins (Table 2). The minimum temperature achieved by cryoballoon ablation was not different in the superior or inferior and right or left PVs (Table 3). However, there was a trend for a higher minimum temperature achieved in the right inferior PV.

Success rate

The efficacy of cryoballoon PV isolation is shown in Figure 2. During a mean follow-up of 172 ± 60 days, we had three patients with recurrence of symptomatic AF episodes (86%

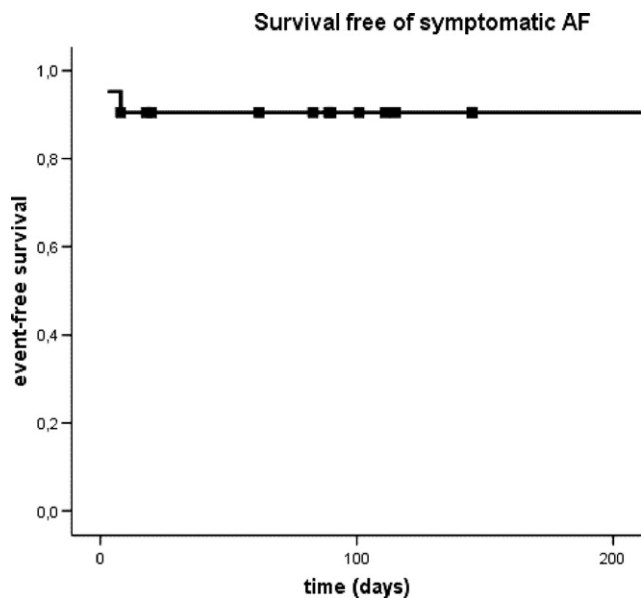


Figure 2 Survival free from symptomatic AF, Kaplan-Meier analysis. After 6 months, 86% of the patients were free of symptomatic AF.

success rate). Most of the recurrences occurred during the first 10 days after ablation, and two of the three patients had incomplete PV isolation during the initial procedure despite touch-up with a conventional cryocatheter or a 23-mm cryoballoon. One patient received a second cryoballoon ablation procedure and was free of AF thereafter. Thus, after 1.04 procedures per patient, we had a 6-month success rate of 90%.

Adverse events

We did not observe any thromboembolic event. However, we observed three phrenic nerve palsies despite pacing the phrenic nerve during ablation of the right superior PV to stop ablation early in case of paralysis. Two of the three patients were asymptomatic, and two palsies completely resolved after 6 and 9 months (Figure 3); one is still persisting after 2 months. Two were observed using a 28-mm balloon and one using a 23-mm balloon. Median time from start of cryoablation in the right superior PV to occurrence of phrenic nerve palsy was 93 seconds.

Discussion

Our study is the first one to report an 86% 6-month success rate of the new cryoballoon AF ablation approach in patients with paroxysmal AF and normally sized left atria.

Although the success rate for RF AF ablation has improved during the last 10 years, a variety of procedure-related complications including thromboembolic events, PV stenosis, left atrial flutter, and atrioesophageal fistula formation still raise concern about an even wider application of this treatment, particularly in low-volume centers.^{5,9–11} With respect to safety, cryoenergy has some potential advantages compared with RF energy.^{6,7,12} First, we have recently shown that lesions created by cryoablation are different from lesions created by RF energy.¹³ Cryoablation lesions appear sharply defined with less endothelial damage and surface thrombosis in contrast to RF lesions, where this is a common phenomenon.⁷ Second, when cryoablation is started, the catheter sticks to the wall because of ice crystal formation and cannot move on the endocardial surface, ensuring a stable catheter position. Third, delivery of RF lesion within venous structures such as the coronary sinus or PV is associated with a risk of venous stenosis, endoluminal thrombosis, and perforation, possibly leading to tamponade or damage to adjacent arterial structures. Cryothermal energy has clearly proven to be less harmful in this respect.¹⁴

However, cryoenergy applied with a conventional cryocatheter is time-consuming since one focal lesion takes about 4 times longer than it takes with RF energy. The new development of a double lumen cryoballoon enables us to cryoablate PVs probably as fast as it takes with RF energy but with the advantages of cryoenergy. Larger studies will have to show if time effectiveness and safety hold true for cryoenergy in a direct randomized comparison.

The new approach is relatively easy to perform. When we started our study, we observed that fluoroscopy times decreased after only five to six procedures to a mean of ~36 minutes. To select the suitable size and achieve an optimum position of the balloon in the antrum of the vein, we considered PV angiography to be mandatory. The most difficult vein to isolate with the new cryoballoon system was the right inferior PV because of its proximity to the transeptal sheath. However, 95% of all veins could be isolated with a single-balloon technique, and in only 5% we had to use a smaller balloon or a conventional cryocatheter. In two patients, the right superior and the right inferior veins in the end were not completely isolated, and both patients showed early recurrence of AF during the first 10 days after ablation.



Figure 3 X-rays at 24 hours (A), 3 months (B), and 6 months (C) after cryoablation with right phrenic nerve palsy. After 6 months phrenic nerve palsy resolved.

Despite the many advantages of this new approach, adverse effects occurred. In three patients, right phrenic nerve palsies occurred, which were completely asymptomatic in two patients; one patient suffered from dyspnea. After 6 and 9 months, two palsies completely resolved; one asymptomatic palsy is still persisting after 2 months. Two of the palsies occurred during the first six procedures and might have been avoided by a more atrial position of the balloon. In this respect, we did not observe the size of the balloon to be relevant because one palsy occurred with a 23-mm balloon and the two others occurred with a 28-mm balloon. We consider that, independent of balloon size, a balloon position deep in the vein should be avoided. However, by this technique, not all palsies will be avoidable, and sometimes complete isolation of the right superior PV might not be achieved. Phrenic nerve palsy is not a complication unique to cryoablation or to the cryoballoon technique, but it has also been described by RF and ultrasound ablation.^{15,16} Fortunately, it has been reported that this complication is only temporary in the majority of the cases.¹⁷ We did not observe any other complications such as symptomatic PV stenosis, pericardial effusion, thromboembolic events, atri-oesophageal fistula, or left atrial tachycardia.

Our study has certain limitations. First, we included a very specific patient population without structural heart disease, with normally sized left atria, and without evidence of moderate tricuspid or mitral regurgitation. Our data might not reflect the situation in patients with more diseased atria and in patients with persistent AF. However, our study population is representative according to the American College of Cardiology/American Heart Association guidelines for AF ablation.⁴ Considering more diseased and larger left atria, it will be increasingly important to achieve substrate modification in the periostial atrium. Since the balloon position is achieved over a wire in the distal PV, periostial ablation with the cryoballoon can only be achieved by changing the angulation of the sheath and retracting the balloon to the antrum, which, however, makes a good venous occlusion angiography more difficult and sometimes impossible. Second, during follow-up, we checked for symptomatic AF episodes by event recorder monitoring, but we did not check intensively for silent episodes of AF beyond 24-hour Holter ECG. However, the main goal in ablation of lone AF is to relieve highly symptomatic patients from symptoms of palpitations. Silent episodes of AF would not have any further therapeutic consequence since all of our patients, who had a mean CHADS2-score of 0.6, did not have any indication for oral anticoagulation.⁴

In summary, our study shows that cryoballoon ablation of paroxysmal AF promises to be an effective approach and

appears to have similar success rates compared with RF ablation after 6 months. Future studies will have to show whether this new device is also cost-effective as first-line treatment of paroxysmal AF without any prior antiarrhythmic medication and whether cryoballoon ablation is also able to achieve a similar substrate modification compared with RF energy in patients with persistent AF.

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