Europace (2008) **10**, 1277–1280
doi:10.1093/europace/eun286

Acute and clinical effects of cryoballoon pulmonary vein isolation in patients with symptomatic paroxysmal and persistent atrial fibrillation

Helena Malmborg*, Stefan Lönnerholm, and Carina Blomström-Lundqvist

Department of Cardiology, Uppsala University Hospital, S-75185 Uppsala, Sweden

Received 27 June 2008; accepted after revision 22 September 2008

KEYWORDS
Atrial fibrillation;
Ablation;
Cryoablation

Aims To assess the acute effects, safety, and clinical outcome of atrial fibrillation (AF) ablation using a cryoballoon catheter.
Methods and results Forty patients with paroxysmal or persistent AF underwent pulmonary vein (PV) isolation with a cryoballoon catheter (Arctic Front, CryoCath). Electrocardiograms were recorded in case of symptomatic AF recurrences, and a 24 h Holter recording was performed at last follow-up. Complete PV isolation was achieved in 39 (91%) of the 43 procedures (56% with the cryoballoon catheter alone, 44% with an additional conventional ryocatheter). The number of balloon applications per procedure was 9.6 ± 1.6. The PV isolation rate was significantly higher (83.9%) if total vessel occlusions were obtained than if intermediate (63.6%, $P = 0.01$) or poor occlusions were achieved (38.1%, $P = 0.0002$). The mean procedure time was 239 ± 48 min. At follow-up (mean 8.9 ± 4.6 months), 52.5% of patients were free from arrhythmia-related symptoms and another 17.5% had reduction of arrhythmia-related symptoms. Two cases each of phrenic nerve paralysis and dysphagia occurred.
Conclusions Cryoballoon PV isolation is a feasible technique with a high acute success rate and comparable clinical outcome to radiofrequency ablation. Although complications were rare, the need for an additional conventional cryocatheter warrants further development of the technique.

Introduction

Atrial fibrillation (AF) is frequently associated with subjective symptoms such as palpitations, shortness of breath, lack of energy during exercise, and fatigue, which all contribute to a decreased quality of life.[1,2] The rather low long-term efficacy rates with antiarrhythmic agents for control of AF[3,4] have urged researchers to develop other treatment alternatives and, since the recognition that rapidly firing foci in the pulmonary veins (PVs) trigger AF,[5,6] AF ablation with PV isolation has steadily been introduced in many centres. Pulmonary vein isolation with radiofrequency (RF) has resulted in variable efficacy rates, ranging from 47 to 70%, partly depending on the type of AF studied.[1,7–9] Although the risk for PV stenosis or left atrioesophageal fistulae formation[10] is low, both are potentially lethal and should be completely avoided. Since both of these complications seem to be attributed to thermal injury,[11] new technologies with other energy sources have been developed to make PV isolation more safe and feasible.

Cryoenergy is a promising energy source related to its low thrombogenicity and absence of PV stenosis, but the technique has been limited by longer procedure times[12] and doubts concerning achieved transmural lesions.[13] The use of a cryoballoon for PV isolation has been demonstrated to be feasible and safe in animal studies.[14] The limited information available on the use of a cryoballoon for PV isolation in humans[15,16] urged us to evaluate and describe our initial experience with cryoballoon ablation (CryoCath) in patients with paroxysmal and persistent AF.

Methods

Patients

Patients with highly symptomatic paroxysmal or persistent AF and who had failed at least two antiarrhythmic drugs were accepted for AF ablation. The arrhythmias were verified on a 12-lead electrocardiogram (ECG) in all patients. Exclusion criteria were valvular heart disease, congestive heart failure, and age >70 years.

* Corresponding author. Tel: +46 18 611 2735; fax: +46 18 510 243.
E-mail address: helena.malmborg@akademiska.se

Ablation procedure

All patients were treated with oral anticoagulation (warfarin) with INR levels kept between 2 and 3 for at least 3 weeks prior to ablation. The oral anticoagulation was withdrawn 3 days before the ablation and replaced by intravenous heparin when the INR level dropped below 2. The heparin, which was stopped 4 h before the procedure, was administered again after the transseptal puncture and then titrated to achieve an active clotting time between 250 and 350 s. All patients underwent transthoracic and a transesophageal echocardiography 1 day before the ablation procedure to exclude underlying heart disease, to assess left ventricular ejection fraction (LVEF), left atrial size (parasternal long-axis view), and to exclude left atrial thrombi. Pulmonary vein anatomy was visualized by a three-dimensional reconstruction from a multi-slice computer tomography (CT) scan.

The procedure was performed under light sedation. A bipolar catheter was positioned in the right ventricular apex for back-up pacing in case of vagal reactions during the procedure. A decapolar catheter was advanced into the coronary sinus (CS). The transseptal puncture was performed with a Brockenbrough needle (St Jude Medical) guided by bi-plane fluoroscopy and intracardiac pressures. The transseptal sheath was exchanged for a 14F steerable sheath (FlexCath, Cryocath, Canada). A circular mapping catheter for recording PV potentials before ablation was used only in patients who had undergone previous PV isolation. A 10.5F double-lumen, 23 or 28 mm cryoballoon catheter (Arctic Front, Cryocath, Canada) was placed in the antrum of the PV. In the early phases, the size of the balloon was selected according to the measured PV diameters. Following the first 16 cases, the 28 mm balloon was the first choice for all procedures. Different cryoballoon positions were evaluated by injecting contrast into the vein distal to the balloon to ensure the most optimal PV occlusion. The degree of vessel occlusion was scored from 4 to 1, with score 4 indicating total occlusion. Two cryoablations for 5 min each were applied for each vein before the presence of conduction block was confirmed. The phrenic nerve function was checked during cryoablation of the right superior PV (RSPV) by observing diaphragmatic movement under fluoroscopy every 20 s. The ablation was immediately stopped if phrenic nerve function was affected. After all veins were treated with the cryoballoon, the balloon was exchanged for a 10- or 20-polar circular mapping catheter to check for persistent PV potentials during sinus rhythm (right-sided veins) and during CS pacing (left-sided veins). If conductance into PV was still present, the balloon was re-inserted and another one or two applications were delivered to that vein. If an acceptable occlusion or position had not been achieved at the first attempt with the balloon catheter, a conventional 9F cryocatheter (Freezor Max, Cryocath) was chosen instead. If the second attempt with the balloon failed, the conventional cryocatheter was used to isolate the PVs. The endpoint of the procedure was complete electrical isolation of all PVs.

Follow-up

All patients were followed for at least 6 months at out patient visits with regard to arrhythmia-related symptoms and complications. A 24 h Holter ECG recording was performed at earliest 6 months after the ablation procedure unless recurrence of AF had already been documented on a 12-lead ECG due to symptoms or from the pacemaker diagnostics in patients with a permanent pacemaker. A recurrence of AF was defined to be present if the duration exceeded 30 s on a Holter recording. Antiarrhythmic drugs were continued for at least 3 months after the ablation procedure and were thereafter withdrawn if the patients were free from arrhythmia-related symptoms.

Statistics

Continuous variables are expressed as mean values $\pm$ one standard deviation, and were, when appropriate, compared with the Student's *t*-test. Categorical variables were compared with the Pearson χ^2 analysis or Fisher's exact test. A *P*-value of <0.05 was considered significant.

Results

Forty consecutive patients (36 men and 4 women) with a mean age of 56.3 years (range 35–68 years) were studied. The mean body mass index (BMI) was 25.5 ± 3.0 kg/m^2. The history of AF was mean 9.2 ± 6.1 years (range 0.8–30 years). Thirty-two (80%) patients had isolated paroxysmal AF, 7 (17.5%) had combined paroxysmal and persistent AF, and 1 (2.5%) patient had persistent AF only. Concomitant cardiovascular diseases included essential hypertension in 13 (32.5%) patients, ischemic heart disease in 3 (7.5%), and sick sinus syndrome with a permanent pacemaker in 3 (7.5%). The LVEF was normal in all but three patients. The left atrial diameter was 44 ± 6 mm (range 35–62 mm). Six patients had either failed one (four patients) or two (two patients) previous attempts of AF ablation with other techniques.

Procedure

Complete PV isolation was achieved in 39 (91%) of the 43 procedures. Three patients thus underwent two procedures with the balloon catheter. Re-conduction was observed in two veins in each of these patients. In two cases, the procedure was terminated prematurely due to complications and in two other cases complete PV isolation could not be achieved. In the six patients who had failed previous attempts of AF ablation recurrence of PV–left atrial conduction was confirmed prior to the cryoablation procedure. Re-conduction was verified in all four PVs in five of these patients and in two veins in one patient.

All targeted PV's were completely isolated with a single cryoballoon catheter in 24 (55.8%) of the 43 procedures, while in the remaining 19 procedures (44.2%) a standard cryoablation catheter (Freezor Max) was also required. The 28 mm size balloon was used in 28 procedures and the 23 mm size balloon was used in 11, while both balloon sizes were used in the remaining 4 procedures. The number of balloon applications per procedure was 9.6 ± 1.6 (range 7–13) among the patients who had all veins ablated. The number of applications with the conventional Freezor Max cryocatheter (combined procedures) was 4.7 ± 1.7 (range 1–11) (*Table 1*). The proportion of successful PV isolations was significantly higher for veins that could be totally occluded during the first two balloon applications (47 of 56 veins, 83.9%), than for those with occlusion score 3 during one or both applications (49 of 77 veins, 63.6%, $P = 0.01$), which in turn was significantly higher than for veins with even lower occlusion scores (8 of 38 veins, 38.1%, $P = 0.0002$).

The procedure time (from first insertion to withdrawal of all catheters) was 239 ± 48 min, the fluoroscopy time 57 ± 21 min, and the cryoablation application time was 3522 ± 920 s for procedures targeting all PVs. An analysis of the learning curve showed that the mean procedure time was reduced by 50 min (from 267 ± 49 to 217 ± 45 min, $P = 0.03$) when the first 10 and the last 10 procedures were compared.

Table 1 Acute results of cryoballoon ablation in the pulmonary veins

	LSPV	LIPV	RSPV	RIPV	*P*-value
Veins treated (no)	39	41	39	40	
Balloon applications/vein (mean)	2.6 ± 0.9	2.6 ± 1.0	2.1 ± 0.6	2.4 ± 0.8	<0.05*
Veins with more than two balloon applications (no)	15	13	5	13	<0.05*
Veins requiring a standard cryoablation catheter (no)	6	8	2	6	0.052#
Mean occlusion score/vein for the first two balloon applications	3.7 ± 0.5	3.1 ± 0.7	3.5 ± 0.6	2.9 ± 0.6	0.09**

no, number; LS, left superior; LI, left inferior; RS, right superior; RI, right inferior; PV, pulmonary vein.
*P-value calculated by comparing RSPV with the other veins. **P-value calculated by comparing RIPV with the other veins, although it did not reach statistical significance when compared with LIPV ($P = 0.09$). #P-value calculated by comparing RSPV with LIPV.

Follow-up

Patients were followed for 8.9 months (range 6–22 months). At follow up, 21 (52.5%) of the 40 patients were free from arrhythmia-related symptoms and 18 (86%) of these were no longer on antiarrhythmic drugs (Vaughan–Williams class I or III). Seven patients (17.5%) experienced a clear reduction of arrhythmia-related symptoms after ablation while the remaining 12 patients reported no effect on clinical symptoms. Recurrence of AF was verified on ECG tracings in all patients who reported arrhythmia-related symptoms. Two of the patients who were free from arrhythmia-related symptoms had asymptomatic sustained AF recorded during the 24 h Holter monitoring. Three of the four patients in whom complete PV isolation was not achieved were still free from symptoms at the time of follow-up.

No significant difference regarding freedom from symptomatic AF was seen between patients with paroxysmal AF alone and those with combined paroxysmal/persistent AF (53.1% compared with 50%, $P = 0.87$) nor between patients in whom the balloon only was used and patients in whom combined procedures were required (60% vs. 45%, $P = 0.34$).

Complications

Complications related to the procedure occurred in 7 (17.5%) of the 43 procedures. There were two (4.7%) right phrenic nerve paralysis, of which one resolved within an hour, while the other persisted for over 6 months. A local haematoma in the left groin resulting in prolonged hospitalization, a minor peroperative haematemesis requiring premature termination of the procedure, and a minor pericardial effusion were each observed in one patient, respectively. The patient with haematemesis had a clinical history of gastroesophageal reflux, and the gastroscopy performed 1 day later showed a mucosal redness. One patient suffered from coughing and minor haemoptysis during the first week after ablation. A CT scan showed a mild oedema surrounding a narrowing of the left inferior PV but without significant stenosis. The CT scan 6 months later showed the same degree of non-significant stenosis but without oedema. There was no PV stenosis among the remaining 17 patients who underwent a post-ablation CT scan.

Two patients suffered from dysphagia, which appeared a few weeks after the ablation procedure. The gastroscopy and oesophageal cinegraphy, performed in one of these patients, were both normal. The other patient, who did not complain until 8 months after ablation, has not yet been evaluated.

Discussion

Our study demonstrates that complete PV isolation can be obtained in 56% of patients with a single cryoballoon catheter. It also shows that two consecutive cryoballoon applications in a vein are not sufficient in a large number of patients, but when additional cryoablations with either the balloon or other cryocatheters are applied, PV isolation can be achieved in over 90% of the patients. The proportion of patients, who had all PVs isolated with a single cryoballoon in our study, is similar to the 54% reported in another study.[15] In that study, a median of two applications were needed per vein for electrical isolation, which in line with our results indicates that an anatomical mismatch between the shape of the balloon and the PV ostium may probably explain why even two applications failed to isolate some of the veins. This is further supported by the divergent PV diameters measured in the frontal and transverse plane, indicating oval-shaped PVs in some cases,[15] and by our finding that total occlusions were associated with a higher success rate of electrical isolation than incomplete occlusions. The higher rate of electrical isolation with a single balloon, reported recently,[16] may be related to their use of PV angiography to select a suitable balloon size and their inclusion of patients with normally sized left atria only.

The smaller (23 mm) sized cryoballoon seemed to be associated with a higher rate of electrical isolation (77% of cases) than the 28 mm cryoballoon catheter (47% of cases) in one study.[15] In our study, the 28 mm cryoballoon was primarily chosen for our later cases due to the reported lower risk of phrenic nerve paralysis, which makes a corresponding comparison difficult. In our study, a significantly lower number of cryoablation applications were required for isolating the RSPV compared with the other three veins. Since the rate of total occlusions did not differ between the veins, differences in wall thickness or other anatomical variations may be of importance for electrical isolation. In two other studies, the number of cryoablations for each vein did not differ between the veins.[15,16]

The follow-up data in our study demonstrate that PV ostium isolation using a cryoballoon in conjunction with standard cryoablation catheters is feasible and results in freedom from symptomatic AF in a majority (52.5%) of patients with paroxysmal and persistent AF. Our results are comparable with the 60% free from AF reported in a recent study.[15] Apart from their shorter follow-up (3 months), patients with only two or more episodes of paroxysmal AF were included, indicating that the patients in their study were treated at an earlier stage of the

disease.[15] The higher rate (86%) of patients free from symptomatic AF reported in another study of 21 patients may be explained by their selection of paroxysmal AF patients only and the exclusion of patients with enlarged left atria.[16]

Although recurrences of asymptomatic AF could not be excluded in our study, 52.5% of patients were free from symptomatic AF and another 17.5% of cases were improved, which is a favourable outcome as the main goal of AF ablation is to relieve the patients from symptoms. Radiofrequency AF ablation has success rates varying between 56 and 88% in randomized studies.[1,7–9] Larger and randomized studies with longer follow-ups are warranted to prove the efficacy of this new cryoballoon procedure.

The most frequently observed complications were phrenic nerve paralysis and dysphagia. Following non-published reports of more frequently occurring phrenic nerve paralyses with the 23 mm balloon in the RSPV, we decided to use primarily the 28 mm balloon. Caution is advised not to ablate inside the RSPV at any time, which may occur accidentally even if a larger sized balloon is used.[16] Dysphagia has only recently been described[17] and occurs in ∼1% of patients undergoing RF AF ablation.[18] Pyloric spasm, gastric hypomobility, and prolonged gastric half emptying time were reported as consequences of RF ablation. It was postulated that peri-oesophageal vagal plexi were damaged while ablating the left atrial posterior wall. If the dysphagia observed in our series is of the same postulated mechanism, it may indicate that similar transmural lesions can be achieved with the cryoballoon. The mechanism of the persistent non-significant PV ostial stenosis observed in one of our patients after cryoablation may be related to a damage of the vein when the balloon was inflated while it was partly inside the vein. The normal CT scans performed after ablation in our study support the previous observations that PV stenoses are rarely seen with cryoablation. On the basis of the low rate of serious complications, cryoballoon ablation seems to be an attractive alternative to RF AF ablation. The learning curve showed that over time the procedure time is reduced, indicating that operator-dependent factors were present. Still, the lengthy cryoapplications and the use of an additional conventional cryoablation catheter increase the cost of the overall procedure. Further development of the cryoballoon technique and randomized studies for comparison with RF ablation are warranted.

Conflict of interest. None declared.

References

1. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F Jr *et al*. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006;**354**:934–41.
2. Lonnerholm S, Blomstrom P, Nilsson L, Oxelbark S, Jideus L, Blomstrom-Lundqvist C. Effects of the maze operation on health-related quality of life in patients with atrial fibrillation. *Circulation* 2000;**101**:2607–11.
3. Crijns H, Van Gelder I, Van Gilst W, Hillege H, Gosselink A, Lie K. Serial antiarrhythmic drug treatment to maintain sinus rhythm after electrical cardioversion for chronic atrial fibrillation or atrial flutter. *Am J Cardiol* 1991;**68**:335–41.
4. Singh BN, Singh SN, Reda DJ, Tang C, Lopez B, Harris CL *et al*. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;**352**:1861–72.
5. Scharf C, Oral H, Chugh A, Hall B, Good E, Cheung P *et al*. Acute effects of left atrial radiofrequency ablation on atrial fibrillation. *J Cardiovasc Electrophysiol* 2004;**15**:515–21.
6. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G *et al*. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66.
7. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G *et al*. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *Eur Heart J* 2006;**27**:216–21.
8. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W *et al*. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *J Am Med Assoc* 2005;**293**:2634–40.
9. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S *et al*. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF study. *J Am Coll Cardiol* 2006;**48**:2340–7.
10. Pappone C, Oral H, Santinelli V, Vicedomini G, Lang CC, Manguso F *et al*. Atrio-esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation. *Circulation* 2004;**109**:2724–6.
11. Benussi S, Nascimbene S, Calvi S, Alfieri O. A tailored anatomical approach to prevent complications during left atrial ablation. *Ann Thorac Surg* 2003;**75**:1979–81.
12. Tse H, Reek S, Timmermans C, Lee K, Geller J, Rodriguez L *et al*. Pulmonary vein isolation using transvenous catheter cryoablation for treatment of atrial fibrillation without risk of pulmonary vein stenosis. *J Am Coll Cardiol* 2003;**42**:752–8.
13. Gaita F, Riccardi R, Caponi D, Shah D, Garberoglio L, Vivalda L *et al*. Linear cryoablation of the left atrium versus pulmonary vein cryoisolation in patients with permanent atrial fibrillation and valvular heart disease: correlation of electroanatomic mapping and long-term clinical results. *Circulation* 2005;**111**:136–42.
14. Garan A, Al-Ahmad A, Mihalik T, Cartier C, Capuano L, Holtan D *et al*. Cryoablation of the pulmonary veins using a novel balloon catheter. *J Interv Card Electrophysiol* 2006;**15**:79–81.
15. Van Belle Y, Janse P, Rivero-Ayerza MJ, Thornton AS, Jessurun ER, Theuns D *et al*. Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. *Eur Heart J* 2007;**28**:2231–7.
16. Klein G, Oswald H, Gardiwal A, Lüsebrink U, Lissel C, Yu H *et al*. Efficacy of pulmonary vein isolation by cryoballoon ablation in patients with paroxysmal atrial fibrillation. *Heart Rhythm* 2008;**5**:802–6.
17. Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D *et al*. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. *Eur Heart J* 2006;**27**:2871–8.
18. Calkins H, Brugada J, Packer DL, Cappato R, Chen S-A, Crijns HJG *et al*.HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up: A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation Developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and Approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace* 2007;**9**:335–79.