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CLINICAL RESEARCH
Ablation for atrial fibrillation

Acute safety, efficacy, and advantages of a novel cryoballoon ablation system for pulmonary vein isolation in patients with paroxysmal atrial fibrillation: initial clinical experience

Ante Anic [1]*, Nigel Lever[2], Andrew Martin[2], Toni Breskovic[1], Matthew S. Sulkin[3], Elizabeth Duffy[3], Walid I. Saliba[4], Mark J. Niebauer[4], Oussama M. Wazni[4], and Niraj Varma[4]

[1]Cardiovascular Diseases, University Hospital Center Split, Spinciceva 1, 21000 Split, Croatia; [2]Cardiovascular Diseases, Green Lane Cardiovascular Services, Auckland City Hospital, Auckland, New Zealand; [3]Electrophysiology, Boston Scientific Corp., St. Paul, MN, USA; and [4]Department for Cardiovascular Diseases, Cleveland Clinic Foundation, Heart and Vascular Institute, Cleveland, OH, USA

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Aims Cryoballoon pulmonary vein isolation (PVI) is a safe and effective treatment for atrial fibrillation (AF). Current limitations include incomplete vein occlusion due to balloon rigidity and inconsistent electrogram recording, which impairs identification of isolation. We aimed to evaluate the acute safety and performance of a novel cryoballoon system.

Methods and results The system includes a steerable sheath, mapping catheter, and a balloon that maintains uniform inflation pressure and size following initiation of ablation. Protocol-directed cryoablation was delivered for 180 s for isolation documented in ≤60 s, otherwise freeze duration was 240 s. Primary endpoints were acute safety and vein isolation. Pulmonary vein isolation was confirmed at ≥30 min post-isolation. Data were compared across vein locations. Thirty patients with paroxysmal AF were enrolled at two centres and underwent PVI. Pulmonary vein isolation was achieved with cryoablation only in 100% of veins (120/120). Nadir temperature was −53.1 ± 5.3°C. The number of applications to achieve PVI was 1.4 ± 0.4 per vein. Of the 120 veins, 89 were isolated with a single cryothermal application (10/30 patients required only 4 total cryoablations). There were no procedural- or device-related serious adverse events at 30 days post-procedure. A subset (24/30) of patients was followed for 1-year and 71% (17/24) remained free of atrial arrhythmias. Six patients with arrhythmia recurrence were remapped and three had durable PVI for all four veins.

Conclusion In this first human experience, the novel cryoballoon platform was safe, efficacious, and demonstrated a high proportion of successful single ablation isolation.

Keywords Novel cryoablation system • Atrial fibrillation • Pulmonary vein isolation

* Corresponding author. Tel: +385 99 233 8009; fax: +385 21 556 872. *E-mail address*: anteanic@gmail.com

What's new?

- Cryoballoon ablation is a safe, effective, and widely used treatment for pulmonary vein isolation (PVI), yet limitations exist, including incomplete vein occlusion and electrogram visualization.
- In the first 30 consecutive patients, acute safety and performance of a novel cryoballoon ablation system was evaluated.
- There were no procedural- or device-related serious adverse events at 30 days post-procedure.
- PVI was achieved with the cryoballoon ablation system alone in 100% of veins and 10 of 30 patients required only four total cryoablations.
- Electrograms were visualized with the cryoablation mapping catheter in all veins permitting accurate identification of acute isolation and tailoring of cryoablation duration.
- Occlusion grade, nadir temperature, and application number were consistent across veins.

Introduction

Cryoballoon ablation for pulmonary vein isolation (PVI) in the treatment of atrial fibrillation (AF)[1,2] is used increasingly due to ease of the 'single-shot' procedure, low complication rates, and high rates of freedom from AF. Nevertheless, significant challenges persist, including ease of vein occlusion and electrogram detection.[3–5]

Incomplete vein occlusion is associated with poor energy transfer and the inability to isolate veins. The right inferior pulmonary vein tends to be the most challenging to successfully manoeuvre a cryoballoon for an antral occlusion. Other challenges are achieving venous occlusion with anatomical irregularities of the ostia and maintaining catheter position during the transition to cryoablation as inflation pressure increases and the balloon becomes more rigid.[6] These can prevent homogenous antral ablation.

The inability to visualize electrogram attenuation during ablation limits the cryothermal dosing strategy which may impact on safety and efficacy. Data on the short-tip cryoballoon (8 mm) have shown improved isolation detection compared to previous versions. With this cryoballoon, detection of isolation has been reported to occur in all veins in ~55–65% of patients.[4,7]

A new cryoablation system was designed with the purpose of improving on these current technical limitations. In this acute safety and efficacy study, we evaluated its ability to occlude veins, detect electrograms, reach clinically relevant balloon temperatures, and achieve PVI consistently in patients with paroxysmal AF.

Methods

This was a non-randomized, single arm, prospective, multicentre study. The study protocol was approved by local institutional review boards. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. All patients consented for 1-month follow-up and a subset of subjects re-consented for 1-year follow-up.

Indication for ablation followed current guidelines and expert consensus statements.[2,8] Patients ages 18–80 years were scheduled for a de novo percutaneous ablation procedure if they had paroxysmal AF refractory to or intolerant of at least 1 antiarrhythmic drug. Key exclusion criteria included left atrial (LA) size >50 mm, left ventricular ejection fraction <40%, or any pulmonary vein (PV) with diameter >30 mm or common long left PV ostium imaged by CT scan, left atrial (LA) venogram, or intracardiac echocardiography.

The primary performance endpoint of the study was the effectiveness at isolating PVs. In addition, the following were evaluated across veins: (i) occlusion grade after balloon inflation, (ii) incidence of recording PV potentials with the cryoablation mapping catheter during freeze, (iii) nadir temperature during freeze, and (iv) success of acute isolation. To further examine biophysical parameters, advanced data export from the cryoablation console was performed for all available cryo procedures, providing temperature traces for the cryoballoon during ablation and the time to isolation if it occurred.

The primary safety endpoint was procedure or device related major adverse events (MAE) at 30 days, including: death, myocardial infarction, cardiac perforation/pericardial tamponade, cerebral infarct or systemic embolism, major bleeding requiring transfusion of blood products, mitral or tricuspid valvular damage, phrenic nerve damage causing permanent diaphragmatic paralysis, symptomatic pulmonary vein stenosis, atrio-oesophageal fistula, and air embolism leading to a life-threatening event, such as a ventricular arrhythmia, stroke, or myocardial infarction. Events were adjudicated by an independent electrophysiologist.

Cryoablation system

The cryoablation system (Boston Scientific Corporation, Marlborough MA, USA) consists of a steerable sheath (POLARSHEATH™), circular mapping catheter (POLARMAP™), cryoballoon catheter (POLARx™), and console (SMARTFREEZE™ Console). POLARMAP™ is a 20 mm circular catheter with 8 electrodes spaced 6 mm apart. The cryoballoon catheter has a 28 mm double layer balloon with a 12 mm tip length. The outer and inner balloon are comprised of a new semi elastic thermoplastic technology, which is designed to maintain uniform pressure and balloon size during inflation, ablation, and thaw phases. The console has direct connections for oesophageal temperature and diaphragm movement monitoring.

Procedure

The cryoablation procedure was performed without OAC interruption, under conscious sedation or general anaesthesia at the discretion of the operator. A single-point oesophageal temperature probe (General Purpose Temperature Probe 9 F Series 400, DeRoyal) was inserted and connected to the cryo console. Throughout the procedure, care was taken to position it adjacent to the cryoballoon during ablation. If oesophageal temperature fell below 25°C, cryoablation was immediately aborted. Prior to transseptal puncture, an intravenous heparin bolus was administered (100 i.u./kg as soon as venous access was obtained and another bolus of 100 i.u./kg immediately after LA access was obtained) with repeat heparin administration as necessary to achieve an activated clotting time greater than 350 s. A steerable sheath (POLARSHEATH™) was used to introduce catheters into the LA. Baseline mapping of the PVs was done using a standard-of-care circular mapping catheter (Lasso® Catheter, Johnson & Johnson, NJ, USA). After baseline electrogram recordings, this circular catheter was removed and the cryoballoon system was advanced through the steerable sheath and positioned at the antrum of each PV.

Balloon position and PV occlusion were verified with fluoroscopy and contrast injection diluted as a 50–50% solution. The quality of PV

occlusion was rated by the operator on a scale of 1–4, where four indicates a complete occlusion with no visible contrast leak into the LA.[5] Once satisfactory PV occlusion was achieved, cryoablation was initiated and operators monitored the mapping catheter electrograms for isolation. A freezing cycle of at least 120 s was required. If PVI was documented in ≤60 s, then a 180 s ablation cycle was completed. If PVI was not documented in ≤60 s, then a 240 s ablation cycle was completed. Cryoapplications were repeated until PVI was confirmed by entrance and exit block testing (those patients in AF following cryoapplications were cardioverted prior to entrance and exit block testing).

Right phrenic nerve pacing was performed during ablation of the right PVs to minimize the risk of phrenic nerve injury. The capture of right phrenic nerve was monitored conventionally (palpation and/or intracardiac echocardiography) and by a movement sensor (Diaphragm Movement Sensor; DMS, Boston Scientific Corporation) positioned on the right upper quadrant of the abdomen. The diaphragmatic movement sensor was connected to the cryoablation console where the amplitude of diaphragmatic movement was displayed.

PVI was confirmed with entrance and exit block using the cryoablation mapping catheter following a 30 min wait period. Afterwards, isolation was reconfirmed in each vein using the standard-of-care circular mapping catheter.

Post-procedure

Post-ablation, all patients had in-office Follow-up visit at discharge (usually the day after the procedure) and at 1 month (± 1 week). A subset of patients reconsented for 3-, 6-, and 12-month follow-up visits. On follow-up visits physical examination was performed, a 12-lead electrocardiogram and 24-h Holter monitor were recorded, and medication changes were documented. If patients had documented episodes of AF, atrial flutter (AFL), or atrial tachycardia (AT), a repeat ablation procedure was offered. At the redo ablation procedure, an electroanatomic map (CARTO 3, Biosense Webster, Inc.) was created and late PV reconnections were ablated (Navistar Thermocool ST-SF, Biosense Webster, Inc.).

Statistics

Continuous variables were reported as mean ± standard deviation. Categorical variables were summarized as count and percentage. Statistically significant differences across PVs [left superior: LS-, left inferior: LI-, right superior: RS-, and right inferior pulmonary veins (RIPV)] were identified using repeated measures analysis of variance, accounting for within subject correlation (SAS Version 9.4, SAS Institute Software Company). A *P*-value <0.05 was considered significant and a *post hoc* paired *t*-test analysis, applying a Bonferroni correction, was performed if significance was reached. Box-and-whisker plots that display data have several key characteristics (Matlab 2017b). The central marker within a box indicates the median, while the bottom and top edges represent the 25th and 75th percentiles, respectively. The whiskers of the boxplot extend to the most extreme values that are not outliers. The + symbols in the boxplot indicate outliers.

Results

A total of 30 patients with paroxysmal AF underwent PVI with the cryoablation system, performed at two centres by three operators. Baseline demographics and clinical data are displayed in *Table 1*.

Table 1 Patient's clinical characteristics

Age	63 ± 11
Male	17/30
CHA_2DS_2-VASc	1.8 ± 7.6
LVEF (%)	63.9 ± 7.6
LA diameter (mm)	43 ± 4
Hypertension	16/30
Stroke/TIA	0/30
MI/PCI/CABG	5/30
Anticoagulation	
Warfarin	2/30
NOAC	28/30
Antiarrhythmic	
Class I	11/30
Class II	0/30
Class III	7/30

CABG, coronary artery bypass graft; LA, left atrium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

Pre-ablation

The cryoballoon demonstrated consistent vein occlusion across pulmonary veins. *Figure 1* shows four RIPV examples of Grade 4 occlusion. A Grade 4 occlusion score was achieved in 94.2% of veins (113 of 120, *Table 2*) and a Grade 3 or above was achieved in 100% of veins (120 of 120). The percentage of Grade 4 occlusion scores for the LSPV, LIPV, RSPV, and RIPV were 96.7%, 96.7%, 90.0%, and 93.3%, respectively. The mapping catheter never had to be exchanged for a stiff wire to achieve better support.

Pulmonary vein isolation

All patients (30 of 30) left the procedure with all veins isolated (120 of 120). Isolation was achieved with a total of 163 cryoballoon ablations and did not require touch-up radiofrequency ablations. For those applications delivered during sinus rhythm (110/163), when pacing manoeuvres or apparent far field component recognition permitted unbiased PV electrogram distinction, electrograms were visualized with the cryoablation mapping catheter in all PVs. Electrograms were visualized during AF, but pulmonary vein electrograms could not always be discerned. The additional insulation layer in circular mapping catheter allowed an increase in recording gain, without jeopardizing quality of the signal (noise to electrogram ratio). There were several cases when PV electrograms became apparent only after cryoenergy induced conduction delay into the PV, thus PV visualization was adjudicated during the lesion delivery. This permitted accurate identification of acute isolation, and therefore tailoring of cryoablation duration for applications during sinus rhythm. A representative example of electrograms in the LSPV pre-ablation (Top) and during ablation (Bottom) are shown in *Figure 2*. In the mapping catheter traces, the early low frequency component is appendage signal, while the late high frequency component is local PV potential. When the LSPV isolates (*Figure 2*—bottom, cross), the local PV potential in the mapping catheter traces disappear and the low frequency far-field signal persists. Representative examples of PV potentials in cryoablation for each PV are included in the Supplementary material online, *Videos S1–S4*.

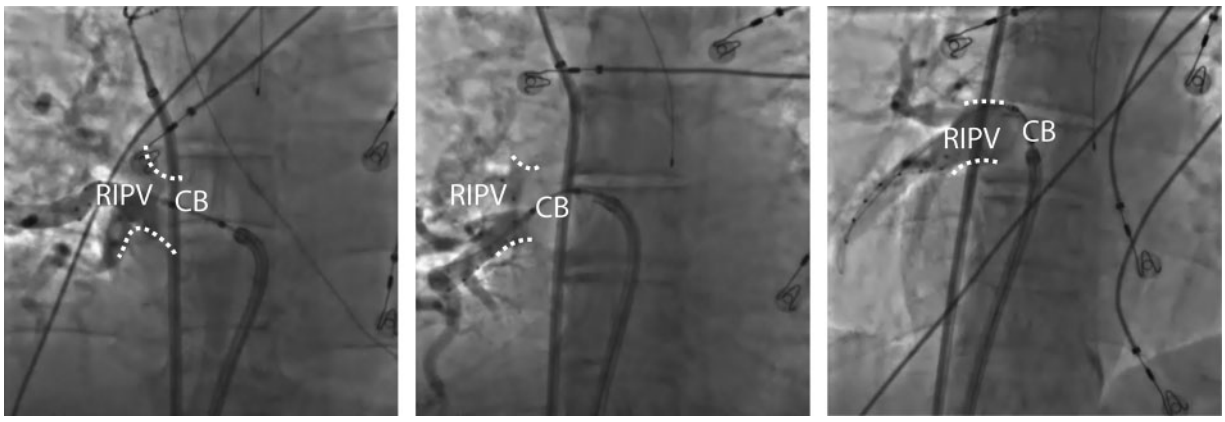

Figure 1 Representative grade 4 occlusions in the RIPV with three different take off angles. CB, cryoballoon; RIPV, right inferior pulmonary vein.

Table 2 Occlusion grade

	All veins	LSPV	LIPV	RSPV	RIPV
Grade 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 3	7 (5.8%)	1 (3.3%)	1 (3.3%)	3 (10.0%)	2 (6.7%)
Grade 4	113 (94.2%)	29 (96.7%)	29 (96.7%)	27 (90.0%)	28 (93.3%)

Data are expressed as total (%).
LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

Isolation was achieved with a total of 163 ablations (1.4 ± 0.4 per vein) using durations of 180 s (92 of 163, 56%) or 240 s (71 of 163, 44%). The number of applications to achieve PVI did not differ among veins (*Table 3*, LSPV: 1.2 ± 0.6, LIPV: 1.4 ± 0.7, RSPV: 1.5 ± 0.9, and RIPV: 1.3 ± 0.6; $P = 0.38$).

In 33% (10 of 30) of patients, PVI was achieved with a total of four cryo-applications (i.e. one application in each of four veins). A total of 74% of veins (89 of 120) were isolated with a single ablation. The LSPV, LIPV, RSPV, and RIPV were successfully isolated with one cryoablation at rates of 83% (25 of 30), 70% (21 of 30), 67% (20 of 30), and 77% (23 of 30), respectively (*Table 3*). In one case, an RSPV reconnected during the 30 min observation period (time to isolation > 90 s, treated with 240 s) and was isolated with an additional cryoablation.

Procedural data

Procedure duration was 135 ± 30 min and calculated as the time from first venous access to last catheter removal from the LA. This duration included the 30 min wait period and standard-of-care mapping catheter validation both prior to ablation and after isolation. LA Dwell time was 124 ± 28 min, including 30 min waiting period. Total fluoroscopy time was 13.4 ± 8.5 min per patient.

Cryoablation biophysics

Nadir temperature was recorded for all cryoablations. The mean nadir temperature for all veins was −53.1 ± 5.3°C (*Table 3*) and was colder than −50.0°C across all veins (LSPV: −53.5 ± 4.0°C, LIPV: −50.1 ± 4.1°C, RSPV: −55.1 ± 4.8°C, and RIPV: −53.3 ± 6.8°C). Cryoablation in the LIPV led to nadir temperatures that were not as cold as the three other veins ($P < 0.05$). Cryoballoon time vs. temperatures traces, from the advanced data export, was available for 100 cryoablations in 16 patients. The freeze profile is shown in *Figure 3A*. The mean time to reach −40°C was 44.7 ± 4.1 s and was consistent across veins (*Figure 3B*). Time to isolation was recorded in 57 out of 64 PVs (89.1%) with a mean time to isolation of 59.0 ± 40.7 s.

Follow-up data

Twenty-four of 30 patients consented for 1-year clinical follow-up. Of these, 17 patients (71%) remained free of AF, atrial flutter (AFL), and atrial tachycardia (AT) 1 year after the ablation procedure. Six patients with arrhythmia recurrence returned for a remap procedure and three patients (50%) had durable PVI for all four veins (*Figure 4*, Left). In each of the three patients with late PV reconnections, there was one late PV reconnection. Late reconnections were found in the right superior ($n = 2$) and left inferior ($n = 1$). Electroanatomic maps showed cryoablation lesions were antral in nature.

Safety

There were no major procedural- or device-related adverse events. One patient experienced transient phrenic nerve injury that recovered intraprocedurally. This was detected by DMS alert and confirmed conventionally. No bonus freeze was applied. In addition, a single cryoablation was stopped early when oesophageal temperature went below 25°C. In this instance, another cryoablation was not performed because sufficient ablation duration (time to isolation plus an additional 120 s) had been reached.

Discussion

This first clinical trial of an advanced cryoablation system permitted complete PV occlusion, consistently recorded PV potentials, and reached target ablation temperatures in all patients. Isolation was successful in all veins without the need of touch-up radiofrequency

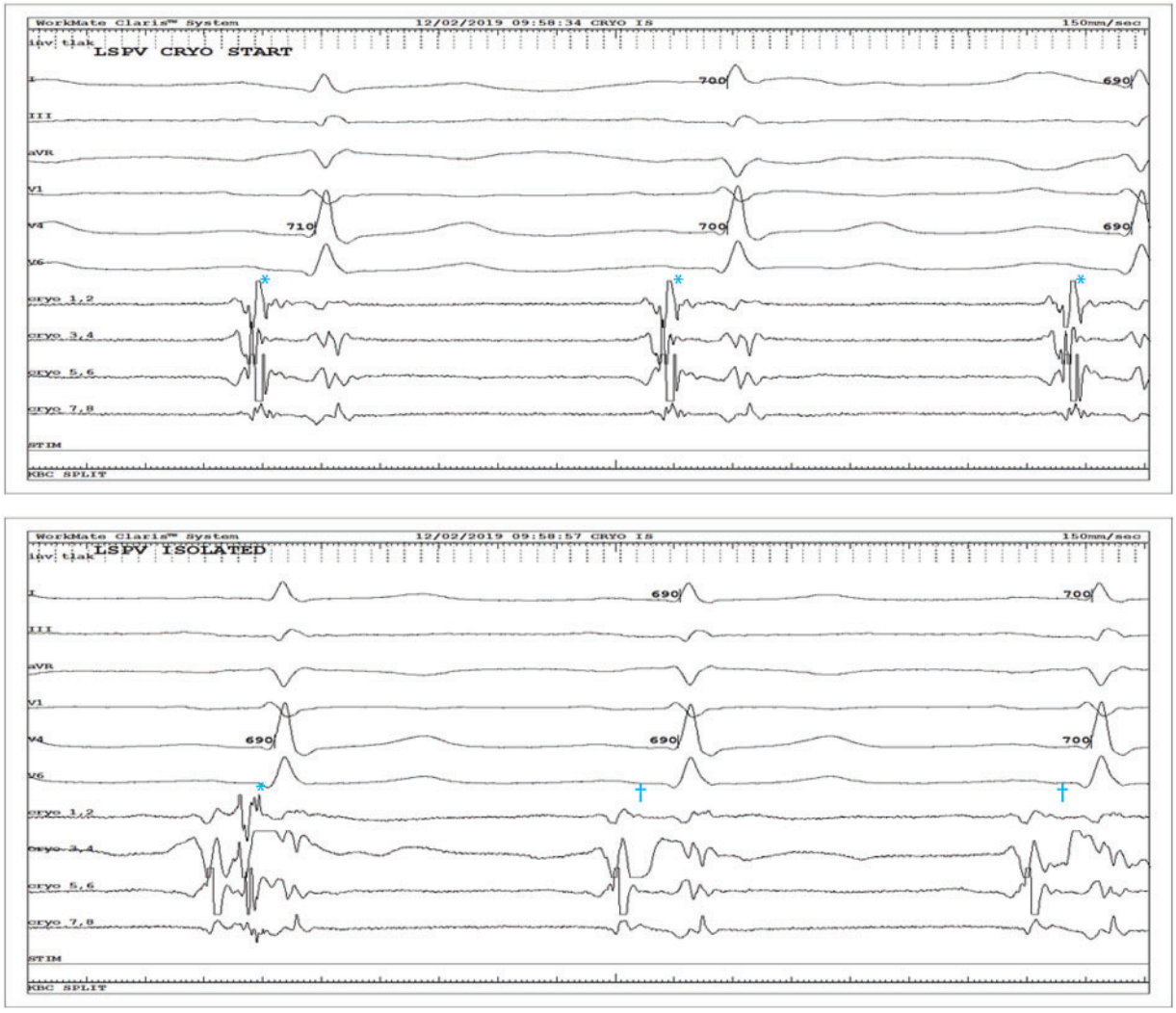

Figure 2 Representative left pulmonary vein potentials from the cryoablation mapping catheter at the start of ablation (top) and at the time of isolation (bottom). [a]Marker for local pulmonary vein potentials. [b]Marker for the disappearance of local pulmonary vein potentials.

Table 3 Cryoballoon performance data

	All veins	LSPV	LIPV	RSPV	RIPV	*P*-value
Applications (*n*)	1.4 ± 0.4	1.2 ± 0.6	1.4 ± 0.7	1.5 ± 0.6	1.3 ± 0.6	0.38
Single ablation (%)	74	83	70	67	77	–
Nadir temperature (°C)	−53.1 ± 5.3	−53.5 ± 4.0	−50.1 ± 4.1	−55.1 ± 4.8	−53.6 ± 6.8	<0.05[a]

Data are expressed as mean ± standard deviation or percentages.
LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.
[a]LIPV is statistically different compared to all other veins.

ablations, and moreover this was achieved with a single freeze application in 74% of veins.

Pulmonary vein isolation is the cornerstone of AF ablation. Compared to radiofrequency ablation, cryoablation is appealing since it offers a 'single-shot' technique that may reduce procedure time while maintaining efficacy rates.[1] These advantages account for the increasing adoption of cryoablation ablation; however, technical limitations exist.

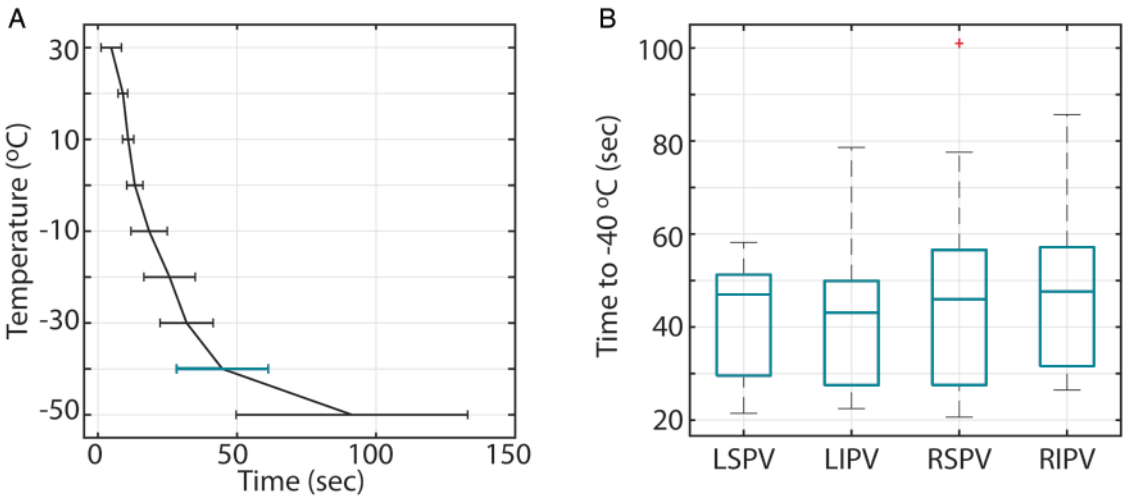

Figure 3 Cryoballoon temperature characteristics in 100 cryo-applications. (*A*) The time required for the cryoballoon to reach 30 to −50°C. All four vein locations are grouped together. Teal bar highlights the data separated out per vein in *B*. (*B*) Box-and-whisker plot of time to −40°C per vein. LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

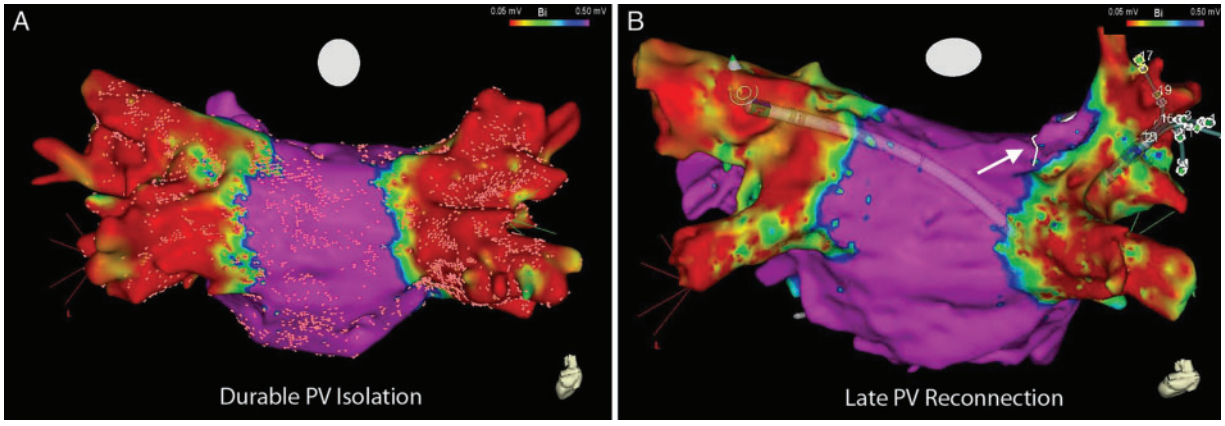

Figure 4 Representative voltage maps of a subject with durable isolation in all four pulmonary veins (left) and a subject with a late reconnection in the right superior pulmonary vein (white arrow, right). PV, pulmonary vein.

Achieving complete venous occlusion can pose a challenge, especially when antral/ostial anatomy is variable. This is further exacerbated during the freeze phase with the current commercially available system due to the increase in inflation pressure that renders the balloon rigid and may alter antral alignment or even displace the original positioning. Together these may reduce the success of complete antral isolation and generate areas of viable tissue that may lead to future AF or flutter recurrence. The right-sided PVs, and in particular the RIPV, are known to be susceptible to this. POLARx^{TM} was designed to maintain the same pressure during inflation for vein occlusion and during the freeze cycle. This may explain the high proportion of complete occlusion (including the RIPV), consistent and deep reduction in balloon temperature, and high isolation rates among veins. All the commonly described maneuvers for cryoablation PVI procedures were used. Since MSCT angiography reconstructions were available for all patients, maneuvers were planned and applied according to size, ostial shape, and take off angles of PVs. 'Hockey-stick' was applied as a first approach to LIPV in most of the patients while 'pull-down' or 'push-up' were planned only if Grade 4 occlusion could not be obtained with reasonable effort. In a single instance, full loop of balloon catheter in LA was required to obtain Grade 4 RIPV occlusion (Supplementary material online, *Video S5*).

Mean nadir temperature of −53.1 ± 5.3°C observed in this series is 3–8°C lower than reported in current practice.[3,5,9–11] Despite cooler temperatures being achieved, no persistent oesophageal cooling was noted when following the study protocol. Further investigation is required to understand potential benefits/drawbacks that colder temperatures have on isolation and AF recurrence rate.

An important development of cryoballoon ablation is the understanding of dosed applications. Fast time-to-isolation within 60 s has been shown to indicate durable isolation.[4,5,10] Conversely, excessive ablation may cause pulmonary or oesophageal lesions. Central to this is the visibility of PV potential recordings. However, most reports to date indicate that these are inconsistently visualized, especially in the inferior veins.[12,13] Hence, the success rate of 100% PV potential monitoring while ablating in sinus rhythm with POLARMAP™ is unprecedented and notably was achieved with a balloon tip length of 12 mm.

The dosing strategy in our protocol mirrored contemporary practice. Applications were 180 s with observed isolation ≤60 s or otherwise 240 s. All PVs were checked for isolation 30 min after the last cryo-application, including independent verification with a standard-of-care circular mapping catheter. POLARMAP™ was congruent to the standard-of-care mapping catheter and did not have any false positive results.

Safety is central to all ablation procedures. In this first in human pilot series, no major adverse events were observed. There was one case of transient phrenic nerve palsy that recovered during the procedure (within couple of minutes after cryo-delivery stopped) and the patient was discharged the day after. In this patient cohort, integration of DMS into the cryoablation system was valuable for managing and avoiding phrenic nerve palsy. Once the sensitivity threshold was appropriately adjusted there were no instances of false alarms while during inadvertent PN capture loss DMS immediately alarmed the operator and PN function would be checked visually (by fluoroscopy or ICE). Reducing procedural time is important to minimize procedural complications. Here, procedure duration of 135 ± 30 min was slightly longer than observed in contemporary series,[1,7,14] but this can be attributed to a study protocol that incorporated a 30 min waiting period and need for the standard-of-care mapping catheter validation prior to and after cryoablation. Given the added protocol driven components, this is an encouraging result for the first clinical experience with POLARx™.

Limitations

There are several limitations to the study, including that this is a dual-centre report of PVI for a small patient cohort. Results demonstrated the biophysical characteristics from the initial clinical experience with a novel cryoballoon; however, further studies with larger patient cohorts are warranted. The procedural results are remarkable for their consistency but whether these translate into improved long-term clinical outcomes require prospective evaluation in a multi-centre study (ClinicalTrials.gov, NCT03723070).

Conclusion

Overall, in this first in human experience, the novel cryoballoon was safe and efficacious in isolating pulmonary veins for the treatment of paroxysmal atrial fibrillation. Specific design elements to the cryoballoon and mapping catheter aiming to resolve several current procedural challenges were successful. These characteristics position this system for improved clinical application of cryoballoon ablation for AF.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: A.A.: consultant to Boston Scientific and Cryterion Medical. M.S.S. and E.D.: salary employee of Boston Scientific. W.I.S. and O.M.W.: consultant to Boston Scientific. N.V.: research grants and consultant to Boston Scientific, consultant to Cryterion Medical. All remaining authors have declared no conflict of interest.

Data availability

The data underlying this article will be shared on a reasonable request to the corresponding author with permission of the study sponsor (Boston Scientific Corp., Electrophysiology, St. Paul, MN, USA).

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