Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy

Z Khoueiry, J-P Albenque, R Providencia, S. Combes, N Combes, F. Jourda, P-A Sousa, C Cardin, Jean Luc Pasquié, T-T Cung, et al.

Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy

Z. Khoueiry[1,2]*, J.-P. Albenque[3], R. Providencia[4], S. Combes[3], N. Combes[3], F. Jourda[5], P.A. Sousa[3], C. Cardin[6], J.-L. Pasquie[1,2], T.T. Cung[1,2], F. Massin[1,2], E. Marijon[7,8], and S. Boveda[3]

[1]INSERM U1046, Université Montpellier1, Université Montpellier 2, Montpellier, France; [2]CHRU Montpellier, Service de Cardiologie, Montpellier 34090, France; [3]Départment de Rhythmologie, Clinique Pasteur, Toulouse, France; [4]Barts Heart Centre, Barts Health NHS Trust, London, UK; [5]Department of Cardiology, Auxerre Hospital, Auxerre, France; [6]Department of Cardiology, University Hospital Rangueil, Toulouse, France; [7]INSERM U970, Paris Cardiovascular Research Centre (PARCC), Paris, France; and [8]Université Paris Descartes, Sorbonne Paris Cité, Paris, France

Aims Pulmonary vein isolation is the mainstay of treatment in catheter ablation of paroxysmal atrial fibrillation (AF). Cryoballoon ablation has been introduced more recently than radiofrequency ablation, the standard technique in most centres. Pulmonary veins frequently display anatomical variants, which may compromise the results of cryoballoon ablation. We aimed to evaluate the mid-term outcomes of cryoballoon ablation in an unselected population with paroxysmal AF from an anatomical viewpoint.

Methods and results Consecutive patients with paroxysmal AF who underwent a first procedure of cryoballoon ablation or radiofrequency were enrolled in this single-centre study. All patients underwent systematic standardized follow-up. Comparisons between radiofrequency and cryoballoon ablation (Arctic Front™ or Arctic Front Advance™) were performed regarding safety and efficacy endpoints, according to pulmonary vein (PV) anatomical variants. A total of 687 patients were enrolled (376 radiofrequency and 311 cryoballoon ablation). Baseline characteristics and distribution of PV anatomical variants were generally similar in the groups. After a mean follow-up of 14 $\pm$ 8 months, there was no difference in the incidence of relapse (17.0% cryoballoon ablation vs. 14.1% radiofrequency, $P = 0.25$). We observed no interaction of PV anatomical variants on mid-term procedural success.

Conclusion Our findings suggest that mid-term outcomes of cryoballoon ablation for paroxysmal AF ablation are similar to those of radiofrequency, regardless of PV anatomy. The presence of anatomical variants of PVs should not discourage the referral of patients with paroxysmal AF for cryoballoon ablation.

Keywords Paroxysmal atrial fibrillation • Cryoballoon ablation • Radiofrequency ablation • Pulmonary vein anatomy

Introduction

Pulmonary vein isolation (PVI) has become the cornerstone of interventional treatment of paroxysmal atrial fibrillation (AF).[1] The success rate with the conventional radiofrequency ablation (RFA) technique is ~70–85% after 1 year of follow-up.[2] However, producing a wide area circumferential ablation using RFA requires a long-learning curve and can be challenging. So-called single-shot techniques such as cryoballoon ablation have been created to circumvent this limitation and simplify the creation of transmural lesions around the pulmonary veins (PVs) through a simplified process and with a limited number of applications.[3]

A circumferential contact of the cryoballoon with the PV ostium—allowing complete vein occlusion to achieve a transmural lesion—is crucial to obtain long-term PVI.[4] This may be easier to achieve in patients with a normal PV anatomy (four separate ostia), which has been observed in >70% of cases.[5] However, the presence of anatomical variants—such a common ostium or

* Corresponding author. Tel: +33 613065544. *E-mail address:* ziad.khoueiry@gmail.com

What's new?

- Cryoballoon ablation for paroxysmal atrial fibrillation displayed the same results as radiofrequency independently of the pulmonary vein distribution pattern.
- Our findings suggest that the presence of a left common ostium or right supernumerary veins is associated with similar outcomes at mid-term follow-up after cryoablation when compared with a control group treated by standard radiofrequency ablation.
- Pulmonary vein anatomical variants should not discourage the use of cryoballoon ablation.

supernumerary PV—can make this occlusion more challenging and impact on procedural outcome results.[6]

To evaluate the efficacy of cryoballoon ablation in an unselected population from an anatomical viewpoint, we compared the mid-term results and freedom from AF with cryoballoon ablation or RFA, according to the different types of PV anatomical variants.

Methods

Setting and patient population

In this single-centre (Clinique Pasteur, Toulouse, France), non-randomized, observational study with prospectively collected data, we compared procedural and mid-term outcomes of patients who underwent a first procedure of PVI for paroxysmal AF with either RFA or cryoballoon ablation, and assessed their interaction with the different PV anatomical variants.

Among all patients undergoing a left atrial ablation procedure from September 2010 to September 2013, the eligibility criterion was the presence of paroxysmal AF refractory to at least one class I or class III antiarrhythmic drug. Patients with persistent AF, previous left atrial ablation procedure, or left atrial thrombus were excluded from the study.

The RFA and cryoballoon ablation procedures were performed by four experienced electrophysiologists (each operator performs >100 AF ablations/year; two operators were fully dedicated to CB ablation and two other operators performing only RFA). Patient assignment to one of the two treatment strategies depended on the electrophysiologist physician they consulted before being referred for the procedure and patient preference. No selection was made according to anatomical criteria for either group.

All patients provided written informed consent prior to the procedure. The study complied with the Declaration of Helsinki and the research protocol was approved by the local ethics committee.

Computed tomography images

Multislice computed tomography (CT) scan imaging of the left atrium was systematically performed 24 h before ablation in all patients. Thoracic acquisition with 0.5-mm section thickness was systematically performed. Left atrial reconstruction served as the baseline for periprocedural anatomical guidance but did not influence the choice of ablation technique. In each patient, we evaluated the PV drainage pattern, the number of PV ostia, left atrial volume, and the presence of left atrial thrombosis. A common ostium was defined as the presence of bifurcated PVs joining the left atrial contour together and with a distance between the left atrial border and their bifurcation of $\geq$5 mm.[7] Three orthogonal planes were used to obtain optimal insight of the ostial insertion. A right supernumerary vein was defined as an additional separate ostium for the middle pulmonary lobe vein.[8]

Procedural details on ablation procedures

The approach to RFA and cryoballoon ablation of paroxysmal AF at our centre has been described.[9] All procedures were performed under general anaesthesia. Venous access was obtained via the femoral vein. A quadripolar catheter was positioned in the coronary sinus in all patients as a reference and for pacing. In the absence of patent *foramen ovale*, a single transseptal puncture was performed under fluoroscopic guidance. Transoesophageal echocardiography was used only in case of failure of the usual fluoroscopic-guided approach. Upon completion of the transseptal puncture, patients received intravenous heparin to maintain an activated clotting time of 300–350 s. The transseptal sheaths throughout were continuously flushed with heparinized saline.

Radiofrequency ablation

A circumferential mapping catheter (Lasso®, Biosense Webster, Inc.) was introduced into the left atrium using an 8.5-F long sheath. The Lasso catheter was used to collect left atrial geometry using a three-dimensional electroanatomical mapping system (Carto 3® Diamond Bar, CA, USA, or Velocity®, SJM, USA). After completion of the left atrial geometry, the lasso catheter was replaced by the ablation catheter.

Initial circumferential PV ablation was performed by systematic radiofrequency application around the PV ostia, consisting of an encirclement of ipsilateral pairs of PV antra (no more than 2 cm from the ostium on the posterior wall on both sides and anterior aspect of right PVs, and guided by the ridge between the left PVs and the appendage) without adjunctive left atrial ablation. When in the presence of a left common *ostium*, a single circle around the PV-atrial junction was produced while delivering RF energy.

The power was limited to 30 W at anterior, superior, and inferior sites (flow rate 17–20 mL/min) and 25 W at the posterior wall (flow rate 17 mL/min) with the temperature limited to 48°C for each lesion. Power was not adjusted according to contact force.

Pulmonary vein isolation was first performed 'anatomically' (i.e. without the Lasso catheter, using an exclusive anatomical approach), the Lasso catheter being used only after completion of anatomical PVI to confirm full PV disconnection. This was done by testing both entrance and exit block (bidirectional block), with a waiting time of 20 min after the last radiofrequency application. In the event that complete disconnection was not achieved (failure of either exit or entrance block), the ablation catheter was reintroduced into the left atrium with the Lasso remaining in place using a double wire technique through the transseptal sheath (Preserving the long sheath in the left atrium, the Lasso catheter is removed and replaced with a long J-wire, advanced to the left upper PV, and a dilator which is used to enlarge the transeptal puncture and make room for a second catheter. Then, keeping the wire in the

left upper PV, the dilator and sheath are withdrawn into the inferior vena cava, allowing access to be gained through the dilated transeptal puncture using the ablation catheter. Once this is achieved, the ablation catheter is deflected and parked in a safe location in the left atrium close to the mitral annulus and the dilator and sheath are again advanced over the wire to gain a second access to the left atrium.). Thereafter, PVI was completed with Lasso guidance to eliminate all points of residual PV connection.

Two types of catheter were used during the study: a new sensor contact catheter (either ThermoCool® SmartTouch™, Biosense Webster, Inc.; or TactiCath™, Endosense, Geneva, Switzerland) or an open irrigated conventional ablation catheter without contact.

Cryoballoon ablation procedure

A 14-F deflectable sheath (FlexCath®, Medtronic, Minneapolis, MN, USA) was advanced through a transseptal puncture (guide wire exchange with the transseptal sheath). The cryoenergy was delivered exclusively using a 28-mm balloon (first-generation Arctic Front™ or second-generation Arctic Front Advance™, Medtronic). The balloon was introduced in the sheath, inflated, and advanced to the ostium of each PV. Ablation of PVs antra was performed with two applications of 240 s per vein. Pulmonary vein occlusion was assessed by venous angiography. Continuous monitoring of the phrenic nerve during ablation of the right PVs was systematically performed by pacing the right phrenic nerve with a quadripolar catheter in the superior vena cava. The freezing cycle was immediately interrupted in case of decreasing or loss of phrenic nerve stimulation.

When in the presence of a common ostium, two 240-s freezes were performed. The Achieve® was inserted in different branches, both an upper and a lower branch, allowing different angulations to increase the chances of freezing around the whole PV-left atrial junction. Occlusion was confirmed under venography, and cryoenergy was only delivered if this was considered adequate. In case of an incomplete occlusion, a pull-down manoeuver could also be performed.[10]

Pulmonary vein isolation was assessed in real time using the circular 20-mm Achieve® catheter (Medtronic) during cryoballoon ablation freezing.[11] If the PV remained connected, additional applications were performed using different angulations. Pulmonary vein isolation was finally checked 20 min after the last cryoballoon application.

Standardized follow-up

A systematic transthoracic echocardiography and 24-h Holter monitoring were performed before discharge. Patients were also evaluated at 1, 3, 6, 9, and 12 months after the procedure. After the first year, follow-up was performed on an annual basis. Information collected during follow-up included a 12-lead electrocardiogram and 24-h Holter monitoring at each visit. Antiarrhythmic drugs were prescribed at discharge only for specific indications (i.e., relapse during the admission or need for cardioversion) and at the operator's discretion. In those instances, antiarrhythmic drugs were stopped after the first 3 months in the absence of recurrence. The first 3 months post-procedure were considered as a blanking period. If there was documented recurrence of symptomatic AF or atrial tachycardia during this time interval and the patient required antiarrhythmic drug therapy, a previously ineffective but well-tolerated class I or class III drug (sotalol) was the preferred option. Anticoagulation strategy after the first 3 months was based on CHA_2DS_2-Vasc (cardiac failure or dysfunction, hypertension, age $\geq$75 years [doubled], diabetes, stroke [doubled]-vascular disease, age 65–74 years, sex category [female]) and HAS-BLED (hypertension, abnormal renal/liver function, stroke—bleeding, labile international normalized ratios, elderly [$\geq$65 years], drug therapy/alcohol intake) scores.[12]

Endpoints and safety concerns

The procedural endpoint was complete PVI in each group. The primary endpoint was freedom from atrial arrhythmias after a blanking period of 3 months and a single atrial ablation procedure. Thereafter, statistical analyses were undertaken to establish whether the presence of anatomical variants of the PVs—particularly left common ostium or right supernumerary vein—were associated with clinical relapses.

Periprocedural safety and efficacy endpoints were assessed using the criteria proposed by Sorgente *et al.*:

(1) All-cause periprocedural death.
(2) Thromboembolism—a composite of stroke, transient ischaemic attack (TIA), and systemic or pulmonary embolism. A stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular aetiology lasting for >24 h not due to another identified cause and confirmed by CT or magnetic resonance imaging of the brain. If symptoms were short lasting (<24 h) and no evidence of necrosis was found on brain imaging, the event was considered to be a TIA. A systemic embolic event was defined as an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism.
(3) Major bleeding—comprising cardiac tamponade, bleeding necessitating intervention (thrombin injection or surgery) or transfusion, massive haemoptysis, haemothorax, retroperitoneal bleeding, or any other life-threatening bleed leading to prolongation of hospitalization.

Recurrence was defined as any symptomatic or asymptomatic atrial arrhythmia lasting >30 s following the 3 months blanking period after catheter ablation. Patients with relapse during the blanking period with no response to pharmacologic or electrical cardioversion were also classified as having a relapse.

Statistical analysis

Comparisons were performed between the two treatment groups. The χ^2 was used for nominal variables and Student's *t*-test for comparison of continuous variables, where appropriate. Levene's test was used to check the homogeneity of variance; equivalent non-parametric tests were used when Kolmogorov–Smirnov was in favour of the absence of normal distribution. Results with $P < 0.05$ were regarded as significant. Variables that differed at baseline between the two treatment groups and their impact on sinus rhythm maintenance were assessed using Cox regression (using the forward stepwise method likelihood ratio; probability for stepwise = 0.05). Cox regression was also performed to assess predictors of relapse. Kaplan–Meier curves were traced for comparing sinus rhythm

maintenance between the two treatment strategies and the log-rank test was used to assess existing differences. PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis.

Results

Study sample

Population baseline characteristics are detailed in *Table 1*. A total of 687 patients undergoing a first procedure of paroxysmal AF ablation in our institution from September 2010 to September 2013 were enrolled in this study, of whom 376 were assigned to RFA and 311 to cryoballoon ablation. Overall, a higher prevalence of heart failure patients and more left PVs were found in patients undergoing cryoballoon ablation. Otherwise, no significant baseline differences were observed between the RFA and cryoballoon ablation groups.

Procedural results

In the RFA group, ThermoCool® SmartTouch™ was used in 159 patients, TactiCath™in 63, and an open irrigated conventional ablation catheter without contact in 154. In the cryoballoon ablation group, the first-generation Arctic Front™ was used in 208 patients and the second-generation Arctic Front Advance™ in 103.

Procedural data are detailed in *Table 2*. The duration of the procedure was significantly shorter in the RFA group than in the cryoballoon ablation group ($P < 0.001$). As a result, the duration of fluoroscopy was also significantly lower in the RFA group.

In both groups, all PVs were disconnected at the end of the procedure. Whilst 156 (41.5%) patients in the RFA group required complementary focal applications, no need for RFA *'touch-up'* was observed in the cryoballoon ablation group.

The rate of procedural complications did not differ between the two groups (*Table 2*) and no periprocedural deaths were observed. We observed two thromboembolic events (one in each group); both patients recovered without residual deficits. Transient phrenic nerve palsy was more frequent with cryoballoon ablation than RFA (*Table 2*). No definitive phrenic nerve palsy was observed in either group after completion of the follow-up.

Relapses during the first 72 h and during the 3-month blanking period were more frequent with cryoballoon ablation than RFA (*Table 2*). The use of antiarrhythmic agents at discharge was similar in both groups.

Anatomical PV variants and their impact in procedural outcomes

A left common ostium was present in 128 (18.6%) patients and 6 (0.9%) patients had a supernumerary left vein. On the right side, 7 (1.0%) patients had a right common ostium, 112 (16.3%) had one supernumerary vein, and 9 (1.3%) had two supernumerary veins. The anatomical distribution of the PVs was similar in the two groups (*Table 3*).

The mean ± SD follow-up duration was 14 ± 8 months (Median = 13 months). Overall, after the initial blanking period of

Table 1 Baseline characteristics of the study population

	Overall (n = 687)	RFA (n = 376)	Cryoballoon ablation (n = 311)	P-value
Age (years)	60.8 ± 10.0	61.0 ± 9.1	60.7 ± 11.1	0.75
Women	204 (29.7%)	102 (27.1%)	102 (32.8%)	0.11
BMI (kg/m^2)	26.9 ± 4.3	26.7 ± 4.1	27.2 ± 4.6	0.11
Paroxysmal AF duration (years)	4.2 ± 4.5	4.4 ± 4.6	4.0 ± 4.3	0.19
Heart failure	28 (4.1%)	10 (2.7%)	18 (5.8%)	0.038
Hypertension	284 (41.3%)	152 (40.4%)	132 (42.4%)	0.59
Diabetes mellitus	48 (7.0%)	22 (5.9%)	26 (8.4%)	0.20
Stroke/TIA	48 (7.0%)	32 (8.5%)	16 (5.1%)	0.09
Vascular disease	69 (10.0%)	37 (9.8%)	32 (10.3%)	0.85
$CHADS_2$ score	0.7 ± 0.9	0.7 ± 0.8	0.8 ± 0.9	0.38
CHA_2DS_2-VASc score	1.5 ± 1.4	1.4 ± 1.3	1.6 ± 1.5	0.17
Sleep apnoea	59 (8.6%)	26 (6.9%)	33 (10.6%)	0.09
Haemoglobin (g/dL)	14.6 ± 1.3	14.7 ± 1.3	14.5 ± 1.3	0.20
CG clearance (mL/min)	70.2 ± 22.3	70.1 ± 19.4	70.3 ± 25.3	0.90
CRP (mg/L)	3.9 ± 8.9	4.2 ± 11.1	3.7 ± 5.3	0.49
Indexed LAV (mL)	40.7 ± 15.4	39.7 ± 13.1	41.8 ± 17.8	0.08
Number of left PVs	1.8 ± 0.4	1.8 ± 0.4	1.9 ± 0.4	0.05
Number of right PVs	2.2 ± 0.4	2.2 ± 0.5	2.1 ± 0.4	0.09
LVEF (%)	64.3 ± 7.7	64.6 ± 6.5	63.9 ± 7.5	0.19

Values are given as mean ± SD or no. (%).
AF, atrial fibrillation; BMI, body mass index; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, TIA, or thromboembolism [doubled]; CHA_2DS_2-VASc, cardiac failure or dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled]—vascular disease, age 65–74 years, sex category [female]; CRP, C-reactive protein; LAV, left atrial volume; LVEF, left ventricular ejection fraction; PV, pulmonary vein; RFA, radiofrequency ablation; SD, standard deviation; TIA, transitory ischaemic attack.

Table 2 Procedural and short-term follow-up data

	Overall (n = 687)	RFA (n = 376)	Cryoballoon ablation (n = 311)	P-value
Duration of procedure (min)	123.0 ± 36.1	114.2 ± 33.3	132.8 ± 37.0	<0.001
Duration of fluoroscopy (min)	24.8 ± 9.9	23.8 ± 10.7	26.1 ± 8.7	0.005
Procedural complications	45 (6.6%)	25 (6.6%)	20 (6.4%)	0.66
Pericarditis/tamponade	7 (1.0%)	6 (1.6%)	1 (0.3%)	0.10
Thromboembolic events	2 (0.3%)	1 (0.3%)	1 (0.3%)	0.89
Transient phrenic palsy	8 (1.2%)	1 (0.3%)	7 (2.3%)	0.016
Vascular complications/major bleeding	19 (2.8%)	12 (3.2%)	7 (2.3%)	0.45
Other complications[a]	9 (1.3%)	5 (1.3%)	4 (1.3%)	0.96
Relapse within 72 h	43 (6.3%)	16 (4.3%)	27 (8.7%)	0.017
Relapse during blanking 3 months	120 (17.5%)	55 (14.6%)	65 (21.1%)	0.037
Class Ic or III antiarrhythmic drug at discharge	53 (7.7%)	28 (7.4%)	25 (8.0%)	0.77

Values are given as mean ± SD or no. (%).
RFA, radiofrequency; TIA, transitory ischaemic attack.
[a]Other complications: RFA: upper digestive bleeding (n = 1), haematuria (n = 1), haemoptysis (n = 1), anaphylactic shock (n = 1); cryoballoon ablation: gastroparesis (n = 1), oesophageal ulcer (n = 1), haemoptysis (n = 1), and haemomediastin (n = 1).

Table 3 Distribution of the different pulmonary vein variants by ablation technique

	RFA (n = 376)	Cryoballoon ablation (n = 311)	P-value
Common left PV ostium	81 (21.5%)	47 (15.1%)	0.08
Two left PVs	291 (77.4%)	262 (84.2%)	
Three left PVs	4 (1.1%)	2 (0.6%)	
Common right PV ostium	3 (0.8%)	4 (1.3%)	0.41
Two right PVs	299 (79.5%)	260 (83.6%)	
Three right PVs	68 (18.1%)	44 (14.1%)	
Four right PVs	6 (1.6%)	3 (1.0%)	

Values are given as no. (%). P refers to PV distribution in RFA vs. CRYO.
PV, pulmonary vein; RFA, radiofrequency ablation.

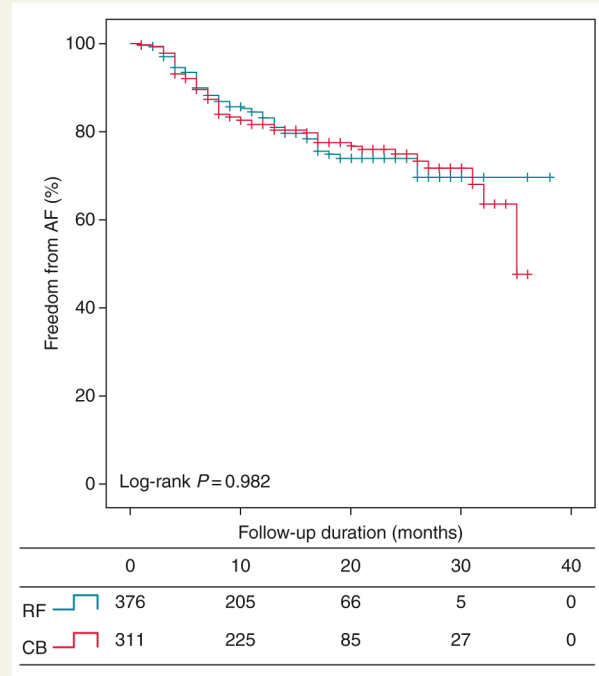

Figure 1 Freedom from atrial arrhythmias during follow-up. CB, cryoballoon ablation; Cum, cumulative; RF, radiofrequency ablation.

3 months, freedom from atrial arrhythmias was 83.0% (258/311) with cryoballoon ablation and 85.9% (323/376) with RFA (P = 0.81) (*Figure 1*). Freedom from atrial arrhythmias at 12 months in relation to the different PV patterns is reported in *Table 4*. *Figure 2* illustrates the course of relapses over time in relation to the most common of the different PV variants.

Predictors of relapse in the whole cohort

On multivariate Cox regression (*Table 5*), only sleep apnoea, indexed left atrial volume, and relapse during the blanking period were independent predictors of arrhythmias relapse (*Table 5*). The presence of anatomical PV variants at baseline was not a predictor of arrhythmias relapse.

Discussion

Our single-centre data suggest that the presence of PV anatomy variants, namely left common ostia, and/or supernumerary PVs, does not adversely impact on the success rate of cryoballoon ablation or RFA. To the best of our knowledge, this is the largest study comparing mid-term outcomes of RFA with those of cryoballoon

Table 4 Freedom from atrial fibrillation according to pulmonary vein anatomy and ablation technique

	RFA	Cryoballoon ablation	*P*-value
Common left PV ostium	74 (91.4%)	44 (93.6%)	0.67
Two left PVs	250 (85.9%)	220 (84.0%)	
Three left PVs	3 (75.0%)	1 (50.0%)	
Common right PV ostium	3 (100%)	4 (100%)	0.57
Two right PVs	260 (87.0%)	222 (85.4%)	
Three right PVs	59 (86.8%)	36 (81.8%)	
Four right PVs	5 (83.3%)	3 (100%)	

Values of AF freedom by PV anatomy are given as absolute no. and %.
AF, atrial fibrillation; PV, pulmonary vein; RFA, radiofrequency ablation.

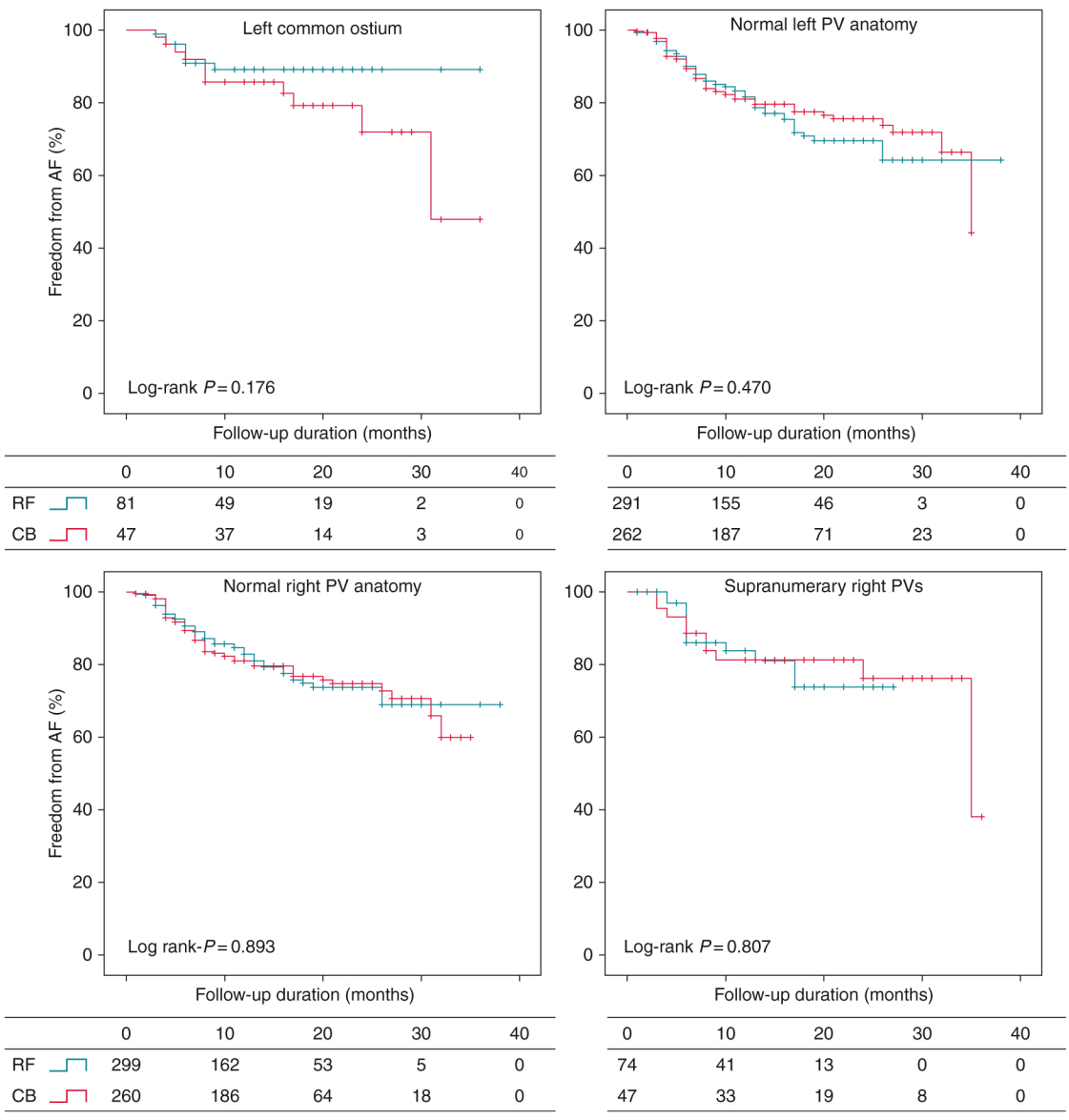

Figure 2 Freedom from atrial arrhythmias during follow-up vs. impact of the different pulmonary vein variants. CB, cryoballoon ablation; RF, radiofrequency ablation.

Table 5 Predictors of relapse after the blanking period for the whole cohort

Variable	Univariate Cox regression		Multivariable Cox regression model A[a]		Multivariable Cox regression model B[b]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (per 1-year increase)	1.01 (0.99–1.03)	0.25	–	–	–	–
BMI (per kg/m^2 increase)	1.02 (0.98–1.06)	0.30	–	–	–	–
AF duration (per 1-year increase)	1.04 (1.00–1.07)	0.035	–	–	–	–
Heart failure	1.07 (0.47–2.43)	0.87	–	–	–	–
Hypertension	1.38 (0.99–1.92)	0.06	–	–	–	–
Diabetes mellitus	1.17 (0.63–2.16)	0.62	–	–	–	–
History of stroke/TIA	1.07 (0.56–2.03)	0.84	–	–	–	–
Vascular disease	1.19 (0.71–2.00)	0.52	–	–	–	–
Sleep apnoea	1.81 (1.13–2.91)	0.014	2.05 (1.27–3.31)	0.003	2.07 (1.28–3.34)	0.003
COPD	0.54 (0.22–1.31)	0.17	–	–	–	–
$CHADS_2$ (per unit increase)	1.12 (0.94–1.34)	0.21	–	–	–	–
CHA_2DS_2-VASc (per unit increase)	1.09 (0.97–1.22)	0.17	–	–	–	–
Left PV variant[c]	0.69 (0.43–1.09)	0.11	–	–	–	–
Right PV variant[c]	0.91 (0.59–1.41)	0.68	–	–	–	–
Indexed LAV	1.01 (1.00–1.03)	0.036	1.02 (1.00–1.03)	0.014	–	–
LVEF (per 1% increase)	1.13 (0.11–11.40)	0.92	–	–	–	–
Haemoglobin (per g/dL increase)	0.88 (0.77–0.99)	0.036	–	–	–	–
CRP (per mg/L increase)	1.00 (0.99–1.02)	0.85	–	–	–	–
GFR (Cockroft-Gault)	1.00 (0.99–1.01)	0.75	–	–	–	–
Cryoballoon ablation	1.00 (0.72–1.40)	0.98	–	–	–	–
Relapse during blanking	4.85 (3.46–6.81)	<0.001	–	–	4.92 (3.44–7.06)	<0.001

AF, atrial fibrillation; BMI, body mass index; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, TIA, or thromboembolism [doubled]; CHA_2DS_2-VASc, cardiac failure or dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled]—vascular disease, age 65–74 years, sex category [female]; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GFR, glomerular filtration rate; HR, hazard ratio; LAV, left atrial volume; LVEF, left ventricular ejection fraction; PV, pulmonary vein; TIA, transient ischaemic attack.

[a]Model A: including only baseline variables.

[b]Model B: including also blanking period relapse.

[c]Common ostium or supernumerary vein (common left ostium, $n = 128$; three left pulmonary veins, $n = 6$; common right ostium, $n = 7$; three right pulmonary veins, $n = 112$; four right pulmonary veins, $n = 9$).

paroxysmal AF ablation in this setting. No differences in mid-term success were found in favour of either of the two approaches in all of the assessed PV distributions. These results suggest that consideration of anatomical criteria is probably not mandatory when selecting paroxysmal AF patients for cryoballoon ablation.

Contradictory results have been published so far regarding the influence of anatomy on outcomes after paroxysmal AF ablation using cryoballoon ablation. Kubala *et al.*[6] have reported a higher proportion of patients free from AF relapse in those with a normal PV pattern. A normal PV pattern was also associated with better mid-term outcomes. However, cryoballoon ablation data in this study were not compared with RFA data, and only first-generation (Arctic Front™) cryoballoons were used. Potential reasons suggested by the authors were: the difficulty of correctly evaluating the isolation compared with normal PVs, the difficulties in manipulating catheters with a conventional fixed size and shape in unusual vein anatomies, and the abnormal localization of AF foci in this population. However, in a letter to the editor, Defaye *et al.* pointed out that the rate of acute successful isolation with cryoballoon ablation was significantly higher in the group with left common ostia, putting the long-term results from Kubala *et al.*[6] into doubt. At around the same time, Defaye *et al.* published data concerning 220 patients and found no difference in mid-term outcomes when in the presence of a common ostium.[13] In a substudy from the Sustained Treatment Of Paroxysmal Atrial Fibrillation trial, the presence of anatomical PV variants was not significantly associated with early or late recurrences in paroxysmal AF patients treated using cryoballoon ablation. Consistent with these findings, Ferrero-de Loma-Osorio *et al.* did not find that the presence of a common left PV ostium was associated with a lower rate of acute PV isolation or worse mid-terms results.[14] Finally, Neumann *et al.*[15] reported no influence of the presence of a left common ostium on long-term results. However, all of these studies had low numbers of abnormal PVs patients and therefore results must be interpreted with caution.

Knecht *et al.*[16] suggested that the presence of a sharp carina between the left superior and left inferior PV and a sharp left lateral ridge between the left appendage and the left superior PV could predict acute and mid-term procedural failure after cryoballoon ablation. They also concluded that the presence of a supernumerary vein did not seem to play a role in mid-term results.

According to our data, a left common ostium should not be considered a contraindication to cryoballoon ablation. Many reasons support this affirmation. First, the use of the largest (28 mm) balloon in all patients is now an accepted policy for the majority of practitioners, resulting in a wider antral lesion. Second, the sheath supporting the balloon and the balloon itself are deflectable, allowing the operator to engage the different branches of the vein separately and thus overcome the difficulties derived from the presence of a large common ostium. This approach—consisting of maneuvering the balloon along the various edges of the left antrum—may be practical and reliable.[17] Third, the use of the second-generation cryoballoon together with the Achieve® catheter also seems to play a determinant role. This balloon improves cooling capabilities by increasing the number of refrigerant injectors, resulting in a bigger and more homogeneous cooling of the balloon surface. In addition, the Achieve® catheter increases the stability of the balloon and allows the real-time assessment of PV disconnection in most cases.[10]

For right supernumerary PVs, data in the literature are scarce. For many operators, the presence of right supernumerary vein(s) is an exclusion criterion for cryoballoon ablation. Preliminary data from a very small sample of patients (without an RF control group) suggest that right upper PV diameter may be an independent predictor of relapse.[18] Our experience in 47 patients with supernumerary right vein(s) shows that the presence of such an anatomical variant does not influence the mid-term results of the procedure. The use of a 28-mm balloon in these patients allows a large antral PVI and probably encompasses supernumerary veins.

We observed longer procedural and fluoroscopy times in the cryoballoon ablation group when compared with RFA. In the literature, cryoballoon ablation procedure duration is usually shorter and more reproducible. As regards procedure duration using RFA, we have to bear in mind that our centre is performing almost 400 RFA ablations of AF per year, which can explain the shorter duration of the procedure with RFA, unlike what is observed in other centres with lower annual caseload. Other centres with strong experience in RFA display comparable results with ours.[19] In addition, two applications of CB were performed in each vein (each application: 240 s). Recent studies on cryoballoon ablation suggested that the application time with the second-generation balloon could probably be reduced to a single 3 min application without affecting the mid-term results.[20] These data should impact on procedure and fluoroscopy durations in the near future. Using such a protocol could have led to a reduction of at least 20 min in total procedural time with CB, making it more comparable with RFA.

Limitations

We acknowledge several limitations of our study. First, this was single-centre non-randomized trial, meaning that even though all variables seem to be balanced between the two treatment groups, we can never exclude that some other may have been unaccounted for. Furthermore, this findings are limited to one high-volume and experienced centre and need to reproduced in other centres, namely with lower annual case load. Second, regarding the cryoballoon ablation group, first- and second-generation balloons were used and this point, as previously mentioned, could have influenced our results. Third, in the RFA group, not all procedures were performed with the same ablation catheter.

Conclusions

Our findings suggest that cryoballoon ablation performed similarly to RFA in paroxysmal AF patients in terms of mid-term results and in all types of PV anatomical subsets. These results suggest that patient selection based on anatomical criteria is not mandatory for patients undergoing cryoballoon ablation for paroxysmal AF.

Acknowledgements

Editorial support on the last version of the manuscript was provided by Medlink Healthcare Communications Ltd and was funded by the authors.

Conflict of interest: S.B. has received fees as a consultant for Medtronic and Boston Scientific. J.P.A. is a consultant for Saint Jude medical and Biosense webster. J.-L.P. has received fees as a consultant for Saint Jude Medical, Biosense Webster, Medtronic, Boston Scientific, and Biotronik.

References

1. Raviele A, Natale A, Calkins H, Camm JA, Cappato R, Ann Chen S *et al.* Venice Chart international consensus document on atrial fibrillation ablation: 2011 update. *J Cardiovasc Electrophysiol* 2012;**23**:890–923.
2. Shah AN, Mittal S, Sichrovsky TC, Cotiga D, Arshad A, Maleki K *et al.* Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence. *J Cardiovasc Electrophysiol* 2008;**19**:661–7.
3. Tse HF, Reek S, Timmermans C, Lee KL, Geller JC, Rodriguez LM *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.
4. Kolasa MW, Okumura Y, Johnson SB, Packer DL. Abstract 2653: Characterization of the pulmonary vein tissue temperature in response to cryo therapy: threshold of irreversible cryothermal injury. *Circulation* 2007;**116**:II 588.
5. Kaseno K, Tada H, Koyama K, Jingu M, Hiramatsu S, Yokokawa M *et al.* Prevalence and characterization of pulmonary vein variants in patients with atrial fibrillation determined using 3-dimensional computed tomography. *Am J Cardiol* 2008;**101**:1638–42.
6. Kubala M, Hermida JS, Nadji G, Quenum S, Traulle S, Jarry G. Normal pulmonary veins anatomy is associated with better AF-free survival after cryoablation as compared to atypical anatomy with common left pulmonary vein. *Pacing Clin Electrophysiol* 2011;**34**:837–43.
7. Scharf C, Sneider M, Case I, Chugh A, Lai SW, Pelosi F *et al.* Anatomy of the pulmonary veins in patients with atrial fibrillation and effects of segmental ostial ablation analyzed by computed tomography. *J Cardiovasc Electrophysiol* 2003;**14**:150–5.
8. Marom EM, Herndon JE, Kim YH, McAdams HP. Variations in pulmonary venous drainage to the left atrium: implications for radiofrequency ablation. *Radiology* 2004;**230**:824–9.
9. Jourda F, Providencia R, Marijon E, Bouzeman A, Hireche H, Khoueiry Z *et al.* Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. *Europace* 2015;**17**:225–31.
10. Chun KR, Schmidt B, Metzner A, Tilz R, Zerm T, Köster I *et al.* The 'single big cryoballoon' technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. *Eur Heart J* 2009;**30**:699–709.
11. Boveda S, Providencia R, Albenque JP, Combes N, Combes S, Hireche H *et al.* Real-time assessment of pulmonary vein disconnection during cryoablation of atrial fibrillation: can it be 'achieved' in almost all cases? *Europace* 2014;**16**:826–33.
12. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH *et al.* ESC Committee for Practice Guidelines-CPG, Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation – developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.

13. Defaye P, Kane A, Chaib A, Jacon P. Efficacy and safety of pulmonary veins isolation by cryoablation for the treatment of paroxysmal and persistent atrial fibrillation. *Europace* 2011;**13**:789–95.
14. Ferrero-de Loma-Osorio A, Izquierdo-de Francisco M, Martinez-Brotons A, Sanchez-Gomez JM, Mascarell-Gregori B, Ruiz-Ros V *et al.* Medium-term results of cryoballoon ablation of the pulmonary veins in patients with paroxysmal and persistent atrial fibrillation. First experience of a Spanish center. *J Interv Card Electrophysiol* 2013;**37**:189–96.
15. Neumann T, Wojcik M, Berkowitsch A, Erkapic D, Zaltsberg S, Greiss H *et al.* Cryoballoon ablation of paroxysmal atrial fibrillation: 5-year outcome after single procedure and predictors of success. *Europace* 2013;**15**:1143–9.
16. Knecht S, Kuhne M, Altmann D, Ammann P, Schaer B, Osswald S *et al.* Anatomical predictors for acute and mid-term success of cryoballoon ablation of atrial fibrillation using the 28 mm balloon. *J Cardiovasc Electrophysiol* 2013;**24**:132–8.
17. Ahmed J, Sohal S, Malchano ZJ, Holmvang G, Ruskin JN, Reddy VY. Three-dimensional analysis of pulmonary venous ostial and antral anatomy: implications for balloon catheter-based pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2006;**17**:251–5.
18. Güler E, Güler GB, Demir GG, Kızılırmak F, Güneş HM, Barutçu İ *et al.* Effect of pulmonary vein anatomy and pulmonary vein diameters on outcome of cryoballoon catheter ablation for atrial fibrillation. *Pacing Clin Electrophysiol* 2015;**38**:989–96.
19. Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kuck KH, Kuniss M *et al.* Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. *J Cardiovasc Electrophysiol* 2014;**25**:1–7.
20. Ciconte G, de Asmundis C, Sieira J, Conte G, Di Giovanni G, Mugnai G *et al.* Single 3-minute freeze for second-generation cryoballoon ablation: One-year follow-up after pulmonary vein isolation. *Heart Rhythm* 2015;**12**:673–80.