Europace (2015) **17**, 379–387
doi:10.1093/europace/euu273

Safety and efficacy outcomes in patients undergoing pulmonary vein isolation with second-generation cryoballoon†

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Received 30 May 2014; accepted after revision 4 September 2014; online publish-ahead-of-print 6 November 2014

Aims The second-generation cryoballoon (Arctic Front Advance™) (Arc-Adv-CB) has a redesigned injection system which distributes the refrigerant homogenously to the frontal balloon surface. The aim of this study was to compare the efficacy and safety of the Arc-Adv-CB and its predecessor (Arctic Front™) (Arc-CB) in patients who underwent pulmonary vein isolation (PVI) for atrial fibrillation (AF).

Methods and results Three hundred and six patients (55.35 ± 10.60 years, 47.05% male) were included in the study. A total of 1205 pulmonary veins were attempted for PVI with either Arc-CB or Arc-Adv-CB. The follow-up durations were 30 (23–38) and 10 (8–13) months in Arc-CB and Arc-Adv-CB groups, respectively ($P < 0.001$). When the blanking period was considered, freedom from AF after a single ablation procedure was 68.53 and 90.83% in patients undergoing PVI with Arc-CB and Arc-Adv-CB, respectively. The most frequent complication was transient phrenic nerve palsy (PNP) which occurred in five(2.54%) and nine(8.26%) of patients undergoing PVI with Arc-CB and Arc-Adv-CB, respectively ($P = 0.040$). Left atrial (LA) diameter (hazard ratio, HR: 3.552, 95% CI: 2.034–6.201, $P < 0.001$), smoking history (HR:1.643, 95% CI: 1.011–2.671, $P = 0.045$), persistent AF (HR:1.725, 95% CI: 1.021–2.915, $P = 0.041$), duration of AF (HR:1.039, 95% CI: 1.000–1.080, $P = 0.047$), and early AF recurrence (HR:2.399, 95% CI: 1.443–3.989, $P < 0.001$) were associated with increased late AF recurrence. On the other hand, intraprocedural vagal reactions (HR: 0.550, 95% CI: 0.331–0.915, $P = 0.021$) and Arc-Adv-CB use (HR: 0.441, 95% CI: 0.225–0.866, $P = 0.017$) were associated with lower late AF recurrence. Left atrial diameter (HR: 3.072, 95% CI: 1.646–5.732, $P < 0.001$), early AF recurrence (HR: 1.906, 95% CI: 1.103–3.291, $P = 0.021$), and Arc-Adv-CB use (HR: 0.472, 95% CI: 0.239–0.931, $P = 0.030$) were independent predictors for late AF recurrence.

Conclusion Our study has shown that Arc-Adv-CB use is associated with lower late AF recurrences at the cost of an increased risk for PNP.

Keywords Atrial fibrillation • Ablation • Cryoballoon • Safety • Efficacy

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia occurring in ∼1–2% of the general population. Its prevalence is estimated to increase by at least 2.5-fold in the next 50 years. It is associated with decreased functional capacity, quality of life and increased prevalence of stroke, thromboembolic events, and mortality rate. Catheter ablation of AF in selected patients is a widely accepted therapeutic approach that is associated with improved symptoms and quality of life.[1]

The first-generation cryoballoon (Arctic Front™, Medtronic) (Arc-CB) has been used as an effective and widely accepted tool

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What's new

- Among studies comparing the first and second-generation cryoballoon, this study has the largest study population, besides identifying the other independent predictors of late atrial fibrillation (AF) recurrence and giving additional information on procedural data, including complications.
- Second-generation cryoballoon use is associated with lower late AF recurrences at the cost of an increased risk for phrenic nerve palsy.
- Second-generation cryoballoon use is also associated with shorter procedural and fluoroscopy times.

for pulmonary vein isolation (PVI). It has recently been redesigned for an injection system aiming to distribute the refrigerant homogenously to the frontal balloon surface, notably the distal pole and the more distally positioned injection ports have been doubled. The newer cryoballoon (Arctic Front Advance™, Medtronic) (Arc-Adv-CB) has been shown to achieve significantly lower temperature and faster isolation time in comparison with Arc-CB.[2]

There are few studies regarding the safety and efficacy of Arc-Adv-CB. Recently, Martins *et al.*[3] and Furnkranz *et al.*[4] have demonstrated that Arc-Adv-CB enabled more efficient ablation of AF in patients undergoing PVI when compared with Arc-CB. Phrenic nerve palsy (PNP), which is known to be the most frequent complication of the procedure, has been suggested to be more frequent with Arc-Adv-CB; however, there are still contradictory results in the literature.[2,3,5,6] It has also been reported that Arc-Adv-CB use was associated with shorter mean time to PV isolation and fluoroscopy time.[3,4]

In this study we aim to compare the efficacy and safety of the first- and second-generation cryoballoon on mid-term clinical follow-up in a larger study population. Predictors of late AF recurrence will also be evaluated thoroughly in the same population.

Methods

Study population

During the period between September 2010 and December 2013, 306 patients with symptomatic paroxysmal or persistent AF despite one or more antiarrhythmic drug(s) who were scheduled for cryoballoon-based AF ablation procedure as per the recent consensus recommendations were enrolled in this prospective observational study.[7]

Atrial fibrillation episodes lasting >7 days were defined as persistent, where AF episodes self-terminating within 7 days were defined as paroxysmal. Patients who had moderate-to-severe valvular disease, thrombus in LA, abnormal thyroid dysfunction, pre-procedural significant coronary artery stenosis, contraindication to anticoagulation, pregnancy, left ventricular ejection fraction (LVEF) < 50%, LA diameter >55 mm, and attempted AF ablation in the past were excluded from the study. Baseline demographic and clinical characteristics, including age, gender, hypertension, diabetes mellitus, hyperlipidaemia, coronary artery disease, smoking history, and alcohol consumption, were recorded for all patients. Data related to the diagnosis of AF including the date of first diagnosis, oral anticoagulation, rate control drugs, and antiarrhythmic medications were also recorded. Symptomatic severity of the patients was recorded according to the European Heart Rhythm Association score.[8] Informed consent was taken from each patient before enrollment. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by the Institutional Ethics Committee. Informed consent has been obtained from each patient.

Pre-procedural management

All patients underwent transthoracic echocardiography (TTE) within 1 week prior to ablation to assess intracavitary dimensions, LVEF, and to exclude valvular heart disease. Transoesophageal echocardiography was performed to rule out the presence of thrombus in the LA appendage, the day before procedure. Furthermore, patients underwent a pre-procedural multidetector computed tomography scan with three-dimensional (3D) construction of the LA to assess detailed LA anatomy, including evaluation of the pulmonary vein (PV) configuration. Anticoagulation was discontinued at least 48–72 h before the procedure and the pre-procedural interval was bridged with enoxaparin 1 mg/kg. Treatment with antiarrhythmic drugs was discontinued for at least 3 days prior to the procedure.

Ablation procedure

Ablation was performed under conscious sedation using boluses of midazolam. Invasive arterial blood pressure, oxygen saturation, and electrocardiogram were monitored throughout the procedure.

Right femoral vein, left femoral vein, and artery punctures were performed with Seldinger technique. A 6 Fr steerable decapolar catheter (Dynamic Deca™, Bard Electrophysiology) was placed in the coronary sinus. Single transseptal puncture by the modified Brockenbrough technique (BRK-1™, St Jude Medical) was performed under fluoroscopy and 8 Fr transseptal sheath (Biosense Webster) placed into the LA. Once LA access was obtained, heparin boluses were repeatedly administered to maintain the activated clotting time between 300 and 350 s. The sheath was then exchanged for a 12 Fr steerable transseptal sheath (FlexCath™, Medtronic CryoCath) over a guidewire (0.032 inch, 180 cm Super Stiff™, St Jude Medical). During PVI with Arc-CB, baseline electrical potentials of all PVs were recorded with a Lasso catheter™ (Biosense Webster, Inc.). In patients who underwent PVI with Arc-Adv-CB, the Achieve mapping catheter™ (Medtronic) was positioned at the PV ostium where baseline PV potentials were documented.

A 28 mm first-generation CB catheter (Arctic Front™, Medtronic CryoCath LP) was used in 197 patients who underwent PVI between September 2010 and December 2012. A 28 mm second-generation CB catheter (Arctic Front Advance™, Medtronic Cryocath LP) was used in 109 patients who underwent PVI between December 2012 and December 2013. The cryoballoon was manoeuvered to all PV ostia by means of the steerable 12 Fr sheath and a guidewire inserted through the lumen of the balloon catheter in the first-generation CB and by Achieve mapping catheter in the second-generation CB. The balloon was inflated in the LA and then directed towards the PV ostia. Assessment of balloon occlusion was performed by injecting 50% diluted contrast through the cryoballoon catheter's central lumen. Optimal vessel occlusion was considered to have been achieved when selective contrast injection showed total contrast retention with no flow back to the LA. Once occlusion was documented, cryothermal energy was started. A minimum of two consecutive freezing cycles were performed for each PV. In cases of incomplete isolation of PV ostia, additional freezing cycles were applied until complete isolation was achieved. The duration of each freezing cycle was 240 and 300 s in patients undergoing PVI with Arc-Adv-CB and Arc-CB, respectively. The procedure systematically began with the left

superior PV (LSPV), followed by the left inferior (LIPV), right superior (RSPV), and right inferior (RIPV) PV's, respectively. During ablation, if PV potentials (PVP) were visible during energy delivery, time to isolation was recorded when PVP's completely disappeared or were dissociated from LA activity. To avoid PNP, the decapolar catheter was inserted into the superior vena cava, and diaphragmatic stimulation was achieved by pacing the ipsilateral phrenic nerve with a 1000 ms cycle and a 20 mA output. Phrenic nerve capture was monitored by intermittent fluoroscopy and tactile feedback obtained following placement of the operator's hand on the patient's abdomen. Refrigerant delivery was immediately stopped if weakening or loss of diaphragmatic movement was noted. No further cryoenergy was delivered if PNP occurred.

Vagal reaction was defined as sinus bradycardia (<40 b.p.m.), asystole, atrioventricular block, or hypotension that occurred during the period of balloon thawing and balloon deflation following thawing at the end of cryoablation. Temporary pacing was performed or atropine was administered intravenously when a symptomatic decrease in heart rate (<40 b.p.m.) or pauses occurred.

Assessment of electrical isolation

At the end of the procedure, PV conduction was re-evaluated with the Lasso and Achieve catheters in PVI with first- and second-generation CB, respectively. Acute procedural success was defined as elimination (or dissociation) of all PVPs.

Post-procedural management

A TTE was performed immediately after the procedure to exclude the presence of pericardial effusion. All patients were followed up for at least 48 h in the telemetry unit. Patients were then discharged provided that their clinical statuses were stable. Oral anticoagulation was initiated in the evening of ablation unless pericardial effusion was detected and continued for at least 3 months after the procedure. Antiarrhythmic drug treatment was also continued for at least 3 months.

Follow-up

Following discharge from the hospital, enrolled patients were scheduled for visits in the outpatient clinics at 1, 3, 6, and 12 months after ablation and every 6 months thereafter, or earlier, if symptoms consistent with recurrent AF developed after the ablation. At each visit, patients were evaluated for the recurrence of arrhythmias with physical examination, questioning for arrhythmia-related symptoms (palpitations, chest discomfort, fatigue, and dizziness), and a 12-lead electrocardiogram. A 24 h Holter recording was conducted in 3, 6, and 12 months and every 6 months thereafter for all patients. The need for further oral anticoagulation was evaluated in the third month based on the CHA_2DS_2-VASc score. Outcome was measured as per the guidelines in the recent consensus document. Any episode of AF, atrial flutter, or atrial tachycardia lasting for at least 30 s was defined as recurrence. A blanking period of 3 months was considered for the study. Any recurrence occurring in the blanking period was classified as an early recurrence; whereas recurrence after the blanking period was considered as late recurrence. Only patients with at least 4 month follow-up were included in the study.

Statistical analysis

Normally distributed continuous parameters are presented as mean ± standard deviation and skewed continuous parameters are expressed as median (interquartile range defined as Q1–3). Categorical data are presented as frequencies and percentages and are compared using the χ^2 test. Comparisons between baseline characteristics are performed by independent Student's *t*, Mann–Whitney rank-sum, Fisher's exact or χ^2 tests where appropriate. To analyse the association of baseline and procedural factors on outcome, the Cox regression model was used. A multivariable model was used to estimate hazard ratios (HRs) for recurrence while controlling for baseline characteristics. Among parameters that are found to be univariately associated with the outcome, but also being in a strong relationship with some others, only the variable showing the strongest univariate association with the outcome is included in the multivariate analysis. Kaplan–Meier analysis is performed to describe AF-free survival. Statistical analyses are performed using SPSS statistical software (version 21.0; SPSS, Inc.). A two-tailed $P < 0.05$ is considered statistically significant.

Results

Baseline population characteristics

Three hundred and six patients (55.35 ± 10.60 years, 47.05% male) were involved in the study. Baseline clinical and demographic characteristics regarding the type of CB are shown in *Table 1*. Age, gender, history of hypertension, diabetes mellitus, CAD, hyperlipidaemia, smoking, and alcohol consumption did not significantly differ

Table 1 Baseline clinical and echocardiographic characteristics of patients regarding the type of cryoballoon (*n* = 306)

	Arc-CB (*n* = 197)	Arc-Adv-CB (*n* = 109)	*P* value
Demographic variables			
Age (years)	54.65 ± 10.07	56.77 ± 11.53	NS
Gender: male *n* (%)	95 (48.22)	49 (44.95)	NS
Medical history			
History of AF (years)	5 (3–12)	5 (3–12)	NS
Hypertension *n* (%)	82 (41.62)	46 (42.20)	NS
Diabetes mellitus *n* (%)	25 (12.69)	16 (14.68)	NS
CAD *n* (%)	21 (10.66)	13 (11.93)	NS
Hyperlipidaemia *n* (%)	45 (22.84)	29 (26.61)	NS
Smoking *n* (%)	53 (26.90)	31 (28.44)	NS
Alcohol consumption *n* (%)	9 (4.57)	6 (5.50)	NS
Type of AF *n* (%)			
Persistent AF	42 (21.31)	17 (15.59)	
Paroxysmal AF	155 (78.69)	92 (84.41)	NS
Laboratory data			
Serum creatinine (mg/dL)	0.84 (0.70–1.01)	0.84 (0.72–0.96)	NS
White blood cell count ($\times 10^3/\mu L$)	7.81 ± 2.32	7.58 ± 2.31	NS
Echocardiographic parameters			
LA diameter (cm)	3.85 ± 0.41	3.88 ± 0.34	NS
LVEF (%)	64.4 ± 5.10	64.2 ± 4.50	NS

AF, atrial fibrillation; Arc-Adv-CB, Arctic Front Advance™ cryoballoon; Arc-CB, Arctic Front™ cryoballoon; CAD, coronary artery disease; LA, left atrial; LVEF, left ventricular ejection fraction; NS, non-significant.

between two groups. Also, there was no difference between type and duration of AF, LA diameter, and LVEF among groups.

A total of 1205 PV's were attempted for PVI. No patient was excluded due to anatomical reasons based on the CT scan. A four distinct PV pattern was present in 188 patients (61.40%) [120 (61.00%) and 68 (62.40%) patients undergoing PVI with Arc-CB and Arc-Adv-CB, respectively].

Procedural characteristics

Pulmonary vein isolation was performed by using either Arc-CB (197, 64.38%) or Arc-Adv-CB (109, 35.62%). Detailed procedural characteristics are shown in *Table 2*. Cumulative time of procedure and fluoroscopy were shorter in patients treated with Arc-Adv-CB when compared with Arc-CB [(66.67 ± 9.52 vs.75.61 ± 12.64 min, $P < 0.001$) and (12.96 ± 2.69 vs. 16.22 ± 1.62 min, $P < 0.001$) respectively]. CB applications on RSPV (519.58 ± 89.87 vs. 645.00 ± 101.00 s, $P < 0.001$), RIPV (462.64 ± 158.44 vs. 512.14 ± 133.29 s, $P = 0.010$), LSPV (536.40 ± 87.88 vs. 659.77 ± 120.02 s, $P < 0.001$), LIPV (545.00 ± 93.28 vs. 627.29 ± 164.06 s, $P < 0.001$) lasted shorter in the Arc-Adv-CB group. Median temperature (−°C) reached during CB applications were 51(45–56) and 52(46–55) in the LSPV, 46 (42–51) and 48(45–52) in the LIPV, 42(39–45) and 44(42–45) in the RIPV, 46(44–49) and 48 (47–49) in the RSPV with Arc-CB and Arc-Adv-CB, respectively ($P > 0.05$). Number of CB applications per PV did not differ between both groups [2 (2–5) vs. 2 (2–4), $P > 0.05$)]. Intra-procedural vagal reactions were more common in patients treated with Arc-Adv-CB compared with Arc-CB [(50.45% and 38.07% respectively ($P = 0.036$)]. Acute procedural success rates were similar in patients treated with Arc-CB and Arc-Adv-CB [766/770 (99.50%) and 433/435 (99.50%) respectively, $P > 0.05$].

Complications

Despite continuous PN stimulation, the most frequent complication was phrenic nerve palsy (PNP) which occurred in 5 (2.54%) and 9 (8.26%) patients undergoing PVI with Arc-CB and Arc-Adv-CB,

Table 2 Procedural and follow-up characteristics ($n = 306$)

	Arc-CB ($n = 197$)	Arc-Adv-CB ($n = 109$)	*P* value
Anatomical features			
Number of pulmonary veins, median (range)	4.0 (3–6)	4.0 (3–7)	NS
Pulmonary vein abnormality, *n* (%)	17 (15.60)	29 (14.70)	NS
Left common PV, *n* (%)	70 (35.50)	37 (34.00)	NS
Right common PV, *n* (%)	7 (3.50)	4 (3.60)	NS
Procedural details			
Acute procedural success *n* (%)	766/770 (99.50)	433/435 (99.50)	NS
Cumulative time of procedure (minutes)	75.61 ± 12.64	66.67 ± 9.52	<0.001*
Fluoroscopy time (minutes)	16.22 ± 1.62	12.96 ± 2.69	<0.001*
Median temperature reached during cryoballoon applications (°C)			
RSPV	46 (44–49)	48 (47–49)	NS
RIPV	42 (39–45)	44 (42–45)	
LSPV	51 (45–56)	52 (46–55)	
LIPV	46 (42–51)	48 (45–52)	
Cumulative time of cryoballoon applications (s)			
RSPV	645.00 ± 101.00	519.58 ± 89.87	<0.001*
RIPV	512.14 ± 133.29	462.64 ± 158.44	0.010*
LSPV	659.77 ± 120.02	536.40 ± 87.88	<0.001*
LIPV	627.29 ± 164.06	545.00 ± 93.28	<0.001*
Cryoballoon application/PV, median (range)	2 (2–5)	2 (2–4)	NS
Vagal reactions *n* (%)	75 (38.07)	55 (50.45)	0.036*
Procedure-related complications *n* (%)			
Tamponade requiring percutaneous drainage	1 (0.50)	0 (0)	NS
Femoral AV fistula requiring surgical/interventional repair	2 (1.00)	1 (0.90)	NS
Phrenic nerve palsy	5 (2.54)	9 (8.26)	0.040*
Haematoma/pseudoaneurysm	4 (2.00)	2 (1.80)	NS
Post-procedural pericardial effusion *n* (%)	14 (7.1)	8 (7.3)	NS
Follow-up parameters			
Follow-up time (months)	30 (23–38)	10 (8–13)	<0.001*
Early recurrence *n* (%)	36 (18.27)	12 (11.01)	NS

Arc-Adv-CB, Arctic Front Advance™ cryoballoon; Arc-CB, Arctic Front™ cryoballoon; AV, arteriovenous; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; NS, non-significant; PV, pulmonary vein; PVI, pulmonary vein isolation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

respectively ($P = 0.040$). In the follow-up, recovery from PNP was observed in all patients who underwent PVI with Arc-CB and six of nine patients (66.67%) who underwent PVI with Arc-Adv-CB. Data regarding the follow-up characteristics for patients with PNP following cryoablation is shown in Supplementary material online, *Table S1*.

Six patients (1.96%) experienced a pseudoaneurysm or haematoma in the femoral access site. Three (0.98%) patients had femoral arteriovenous (AV) fistula requiring surgical or interventional repair. Twenty-two (7.19%) patients had post-procedural mild pericardial effusion and one (0.33%) patient developed pericardial tamponade requiring percutaneous drainage. None of the complications differed between CB types, except PNP (*Table 2*).

Follow-up

Three hundred and six patients were followed up at a median time of 22 (13–34) months. Forty-eight patients had early AF recurrence within the first 3 months of follow-up after the index cryoballoon ablation procedure [36 (18.27%) and 12 (11.01%) patients undergoing PVI with Arc-CB and Arc-Adv-CB, respectively, $P > 0.05$] (*Table 2*). When the blanking period was considered, freedom from AF after a single ablation procedure was 68.53 and 90.83% at median follow-ups of 30 (23–38) and 10 (8–13) months in patients undergoing PVI with Arc-CB and Arc-Adv-CB, respectively and this was statistically significant in the log-rank analysis ($P = 0.012$) (*Figure 1*). Baseline demographic, clinical, procedural, and follow-up characteristics regarding the outcome following cryoablation are shown in *Table 3*. Patients developing early AF recurrence had higher incidence of late AF recurrence in the follow-up compared with those who had no early AF recurrence (43.75 vs. 19.76%, $P = 0.001$).

Regarding the baseline demographic and clinical parameters, body mass index (BMI) was found to be higher in patients with late AF recurrence (25.34 ± 3.20 vs. 24.50 ± 2.99 kg/m^2, $P = 0.042$). Duration of AF was also longer in these patients [(7 (5–12) vs. 5 (3–8) years, $P = 0.002$]. Late AF recurrence was also more common in patients with persistent AF (38.98 vs. 20.00%, $P = 0.028$) and larger LA diameter (4.14 ± 0.38 vs. 3.81 ± 0.36 cm, $P < 0.001$). Patients developing intra-procedural vagal reactions had significantly less late AF recurrence in the follow-up (16.20% vs. 29.00%, $P = 0.009$) (*Table 3*).

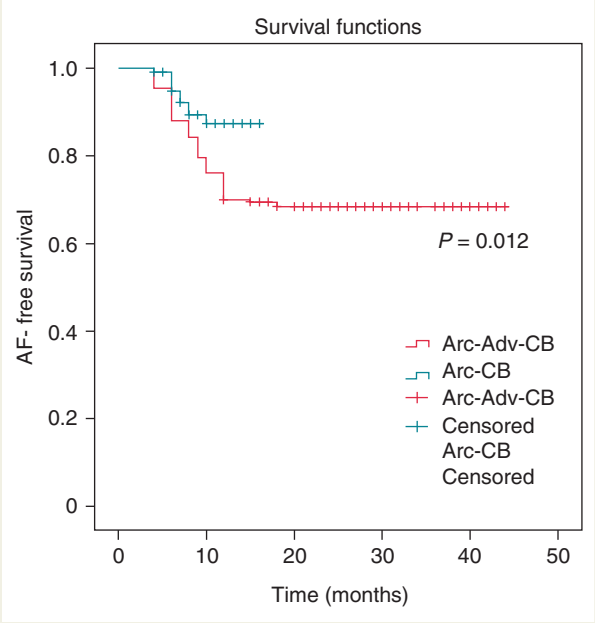

Figure 1 Type of cryoballoon and AF-free survival: Kaplan–Meier curve showing freedom from AF during the follow-up.

Univariate Cox proportional hazard modelling of the late AF recurrence showed that LA diameter (HR: 3.552, 95% CI: 2.034–6.201, $P < 0.001$), smoking history (HR: 1.643, 95% CI: 1.011–2.671, $P = 0.045$), persistent AF (HR: 1.725, 95% CI: 1.021–2.915, $P = 0.041$), duration of AF (HR: 1.039, 95% CI: 1.000–1.080, $P = 0.047$), and early AF recurrence (HR:2.399, 95% CI: 1.443–3.989, $P < 0.001$) were associated with increased late AF recurrence in the follow-up. On the other hand, intra-procedural vagal reactions (HR: 0.550, 95% CI: 0.331–0.915, $P = 0.021$) and Arc-Adv-CB use (HR: 0.441, 95% CI: 0.225–0.866, $P = 0.017$) were found to be associated with decreased late AF recurrence (*Table 4*).

Multivariate Cox proportional hazard regression analysis showed that LA diameter (HR: 3.072, 95% CI: 1.646–5.732, $P < 0.001$), early AF recurrence (HR: 1.906, 95% CI: 1.103–3.291, $P = 0.021$), and Arc-Adv-CB use (HR: 0.472, 95% CI: 0.239–0.931, $P = 0.030$) were independent predictors for late AF recurrence (*Table 5*) (*Figure 2*).

Discussion

To the best of our knowledge, this is one of the largest series comparing the efficacy and safety outcomes in patients undergoing PVI with first- and second-generation cryoballoon. Our study has shown that although the acute procedural success rates were similar, second-generation cryoballoon use was associated with lower late AF recurrence rate. Cumulative time of procedure and fluoroscopy were also shorter in patients treated with Arc-Adv-CB when compared with Arc-CB. PNP was the most frequent complication of the procedure in both groups and was more common in the Arc-Adv-CB group. LA diameter, early AF recurrence, and Arc-Adv-CB use were independent predictors for late AF recurrence in the multivariate Cox proportional hazard regression analysis.

Efficacy outcomes

van Belle *et al.*[9] have reported an event-free survival rate of 44% on 1-year follow-up in patients who underwent PVI with Arc-CB. The event-free survival rate was 73% when the blanking period was considered.[9] Neumann *et al.* have described 74 and 42% freedom from AF at 1-year follow-up in patients with paroxysmal AF and persistent AF, respectively, where patients underwent PVI with Arc-CB with either or both balloon sizes (23 or 28 mm) depending on the diameters of the PVs determined by computed tomography/magnetic resonance imaging scan.[10] The same group has also reported the 5-year success rate after single CB ablation procedure with Arc-CB as 53%.[11] On the other hand, Chierchia *et al.*[5] have reported that freedom from AF could be achieved in 78% of patients undergoing PVI with Arc-Adv-CB on a 1-year follow-up. Freedom from AF was achieved in 83% of the same group of patients when the blanking

Table 3 Demographic, clinical, procedural and follow-up characteristics regarding the late recurrence following single cryoablation ($n = 265$)

	Late AF recurrence ($n = 234$)	Late AF recurrence + ($n = 72$)	*P* value
Demographic variables			
Age (years)	55.05 ± 10.70	56.28 ± 10.30	NS
Gender: male, *n* (%)	103 (44.01)	41 (56.94)	NS
Medical history			
BMI (kg/m^2)	24.50 ± 2.99	25.34 ± 3.20	0.042*
Hypertension, *n* (%)	97 (41.45)	31 (43.05)	NS
Diabetes mellitus, *n* (%)	32 (13.67)	9 (12.50)	NS
CAD, *n* (%)	23 (9.80)	11 (15.27)	NS
Hyperlipidaemia, *n* (%)	60 (25.64)	14 (19.44)	NS
Smoking, *n* (%)	57 (24.35)	27 (37.50)	0.047*
Alcohol consumption, *n* (%)	9 (3.84)	6 (8.33)	NS
Duration of AF (years)	5 (3–8)	7 (5–12)	0.002*
Type of AF, *n* (%)			
Paroxysmal AF	196 (84.62)	49 (68.06)	0.028*
Persistent AF	36 (15.38)	23 (31.94)	
EHRA score (1–4)	2.92 ± 0.62	2.91 ± 0.56	NS
Laboratory data			
Serum creatinine (mg/dL)	0.86 ± 0.22	0.88 ± 0.20	NS
White blood cell count ($\times 10^3/\mu L$)	7.44 ± 1.89	7.82 ± 2.43	NS
Echocardiographic parameters			
LA diameter(cm)	3.81 ± 0.36	4.14 ± 0.38	<0.001*
LVEF (%)	64.62 ± 5.17	64.02 ± 4.60	NS
Procedural characteristics			
Type of CB, *n* (%)			
Arc-CB	135 (57.69)	62 (86.11)	<0.001*
Arc-Adv-CB	99 (42.31)	10 (13.89)	
Vagal reactions, *n* (%)	109 (46.58)	21 (29.16)	0.009*
Follow-up characteristics			
Early recurrence, *n* (%)	27 (11.53)	21 (29.16)	<0.001*

AF, atrial fibrillation; Arc-Adv-CB, Arctic Front Advance™ cryoballoon; Arc-CB, Arctic Front™ cryoballoon; BMI, body mass index; CAD, coronary artery disease; CB, cryoballoon; EHRA, European Heart Rhythm Association; LA, left atrial; LVEF, left ventricular ejection fraction; NS, non-significant.

period was considered.[5] Metzner *et al.*[12] have shown that the use of Arc-Adv-CB resulted in an 80% 1-year success rate. In our study, freedom from AF was achieved in 68.53% of patients undergoing PVI with Arc-CB on a median 30-month follow-up and 90.83% of patients undergoing PVI with Arc-Adv-CB on a median 10-month follow-up when the blanking period was considered.

Shortening of the procedure and fluoroscopy time in patients undergoing PVI is regarded as one of the most important advantages of Arc-Adv-CB use.[2–4] This is an important advantage of the second-generation cryoballoon when the operator and patient's safety is concerned. Findings in our study are compatible with the previous data. As the learning curve gets overcome, further shortening of the cumulative procedural time is expected.

Complications

Acute procedural complications related with cryoballoon ablation have been reported as <3–5% in the literature.[13] In the meta-analysis of cryoballoon-based ablation studies, Andrade *et al.* have reported the complication rates as 0.3% for ischaemic stroke or transient ischaemic stroke (TIA), 0.3% for cardiac tamponade, 0.17% for PV stenosis, and 1.8% for access-site complications.[14] Otherwise, the most common complication of the procedure is known to be PNP. Several studies have investigated the incidence of PNP following CB. The use of Arc-CB was found to be associated with PNP incidence of 11.2% in a study by Guiot *et al.*,[15] where van Belle *et al.*[9] reported the incidence as 4%. A systematic review of studies on the outcome of PVI using Arc-CB demonstrated an overall incidence of PNP as 6.38%.[14] There is inconsistency in the literature regarding PNP incidence with Arc-Adv-CB use. Chierchia *et al.*[5] have reported that transient PNP incidence was 19%, where Metzner *et al.*[6] have reported a lower incidence of 3.5% in patients who underwent PVI with Arc-Adv-CB. In a study comparing first- and second-generation CB, PNP was found to be significantly higher in patients treated with Arc-Adv-CB with an incidence of

Table 4 Univariate Cox proportional hazard modelling results of the late AF recurrence after cryoablation

Univariate Cox regression model	HR	95% confidence interval (CI) (lower–upper)	*P* value
Age (years)	1.012	0.990–1.034	0.293
BMI (kg/m^2)	1.066	0.997–1.140	0.061
LA diameter (cm)	3.552	2.034–6.201	<0.001*
Gender: male	1.490	0.934–2.376	0.094
Hypertension	1.020	0.633–1.645	0.934
Diabetes mellitus	0.933	0.463–1.882	0.846
CAD	1.608	0.843–3.068	0.150
Dyslipidaemia	0.754	0.419–1.358	0.347
Smoking	1.643	1.011–2.671	0.045*
Alcohol consumption	1.775	0.769–4.095	0.178
AF type: Persistent AF	1.725	1.021–2.915	0.041*
Duration of AF (years)	1.039	1.000–1.080	0.047*
EHRA score	0.992	0.676–1.456	0.967
Early recurrence	2.399	1.443–3.989	0.001*
Vagal reactions	0.550	0.331–0.915	0.021*
CB type: Arc-Adv-CB	0.441	0.225–0.866	0.017*

AF, atrial fibrillation; Arc-Adv-CB, Arctic Front Advance™ cryoballoon; BMI, body mass index; CAD, coronary artery disease; CB, cryoballoon; EHRA, European Heart Rhythm Association; LA, left atrial.

Table 5 Multivariate Cox proportional hazard regression analysis regarding the late AF recurrence following single cryoablation

Multivariate Cox regression model	HR	95% Confidence interval (CI) (lower-upper)	*P* value
LA diameter (cm)	3.072	1.646–5.732	<0.001*
Smoking	1.513	0.927–2.472	0.098
AF type: persistent AF	1.020	0.582–1.773	0.948
Duration of AF (years)	1.024	0.983–1.066	0.263
Early recurrence	1.906	1.103–3.291	0.021*
BMI (kg/m^2)	1.033	0.969–1.102	0.327
Vagal reactions	0.574	0.335–1.002	0.055
CB type: Arc-Adv-CB	0.472	0.239–0.931	0.030*

AF, atrial fibrillation; Arc-Adv-CB, Arctic Front Advance™ cryoballoon; BMI, body mass index; CB, cryoballoon; LA, left atrial.

19.5% compared with 6.25% in the Arc-CB group.[2] In that study, PNP persisted in one (2.5%) patient in the Arc-Adv-CB group at 7 months.[2] In our study, the most frequent complication was PNP, similar with previous studies. It occurred in five (2.54%) and nine (8.26%) patients undergoing PVI with Arc-CB and Arc-Adv-CB, respectively. Phrenic nerve palsy resolved in all patients undergoing PVI with Arc-CB, but was persistent in three patients undergoing PVI with Arc-Adv-CB during follow-up.

Predictors of outcome

Predictors of AF recurrence following PVI have been investigated previously. Type of AF, age, LA size, diabetes mellitus, valvular heart disease, and non-ischaemic dilated cardiomyopathy have been proposed to be predictors of outcome.[7,16,17] In our study, LA diameter, early AF recurrence, and Arc-Adv-CB use were independent predictors of late AF recurrence.

Several studies have demonstrated that LA volume is one of the strongest predictors of outcome following PVI.[18,19] Neumann *et al.*[11] have reported that normalized LA are was an independent predictor for outcome following PVI with Arc-CB. The predictive role of LA size in the outcome following PVI is compatible with its known association with LA remodeling, since PVI may reverse electrical remodelling by eliminating focal triggers, but may not be expected to stop or reverse structural remodelling.[11]

Andrade *et al.*[20] have recently reported that early AF recurrence occurred after CB ablation in 51.5% of patients and was strongly associated with late AF recurrence. Compatible with this, early AF recurrence was found to be an independent predictor of outcome following PVI and was more common in patients undergoing PVI with Arc-CB in our study.

Similar to our findings, di Giovanni *et al.*[21] have reported improved outcomes with the use of Arc-Adv-CB, despite the lack of statistically significant difference between minimal temperature values reached during the ablation procedure in both types of CB. Therefore, the predictive role of Arc-Adv-CB use for late AF recurrence following PVI may be explained with increased area of balloon-tissue contact and resultant greater and more proximal antral lesions.[2–4,21] di Giovanni *et al.*[21] have hypothesized that aforementioned antral lesions may target non-PV triggers, such as rotors located in the antrum. In addition to these, Arc-Adv-CB use may have an impact on the modification of ganglinated plexi. Intra-procedural vagal reactions, which were attributed to the possible concomitant ablation of ganglionated plexi during antral PVI, were found to be independent predictors of late AF recurrence following PVI with Arc-CB.[22] In our study, vagal reactions were more common in patients undergoing PVI with Arc-Adv-CB and patients experiencing vagal reactions also had less late AF recurrence during the follow-up.

Study limitations

This study has several limitations. First, this was a single-center study. Secondly, none of the patients involved in the study were implanted with an internal loop recorder. Therefore, asymptomatic episodes might have occurred unnoticed and success rate may have been overestimated. Thirdly, follow-up periods differ in a statistically significant way between types of CB. However, possible misleading effects on interpretation have been minimized by statistical methods including log-rank and Cox regression analysis.

Conclusion

Our study has shown that Arc-Adv-CB use is an independent predictor of lower late AF recurrences following cryoablation. It also enables shorter procedural and fluoroscopy time when compared with its predecessor and is associated with lower early AF recurrence

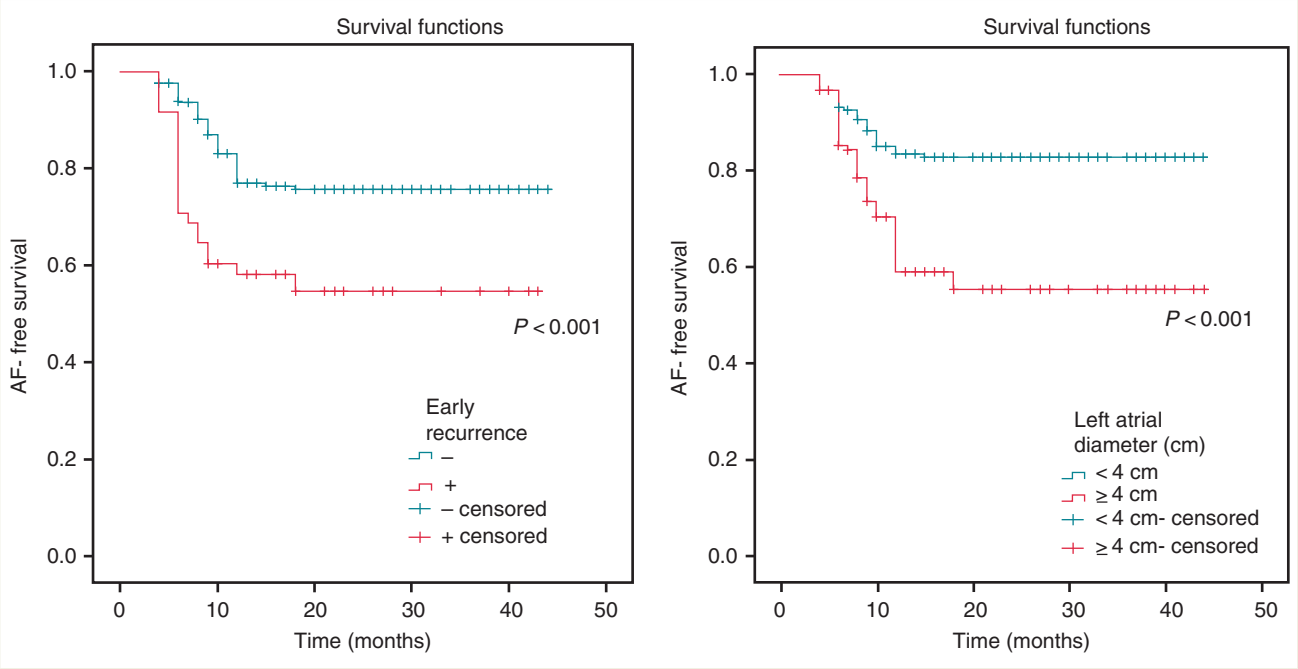

Figure 2 Other independent predictors of late AF recurrence: Kaplan–Meier curves showing freedom from AF during the follow-up.

which is a predictor of better outcome following cryoablation. However, it has been found to be associated with higher incidence of PNP. Further studies with larger study population and longer follow-up are needed to clarify the safety and efficacy outcomes in patients undergoing PVI for AF with the Arc-Adv-CB.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

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EP CASE EXPRESS

doi:10.1093/europace/euu399

Respiratory cycle-dependent left atrial tachycardia in a former Tour de France cyclist

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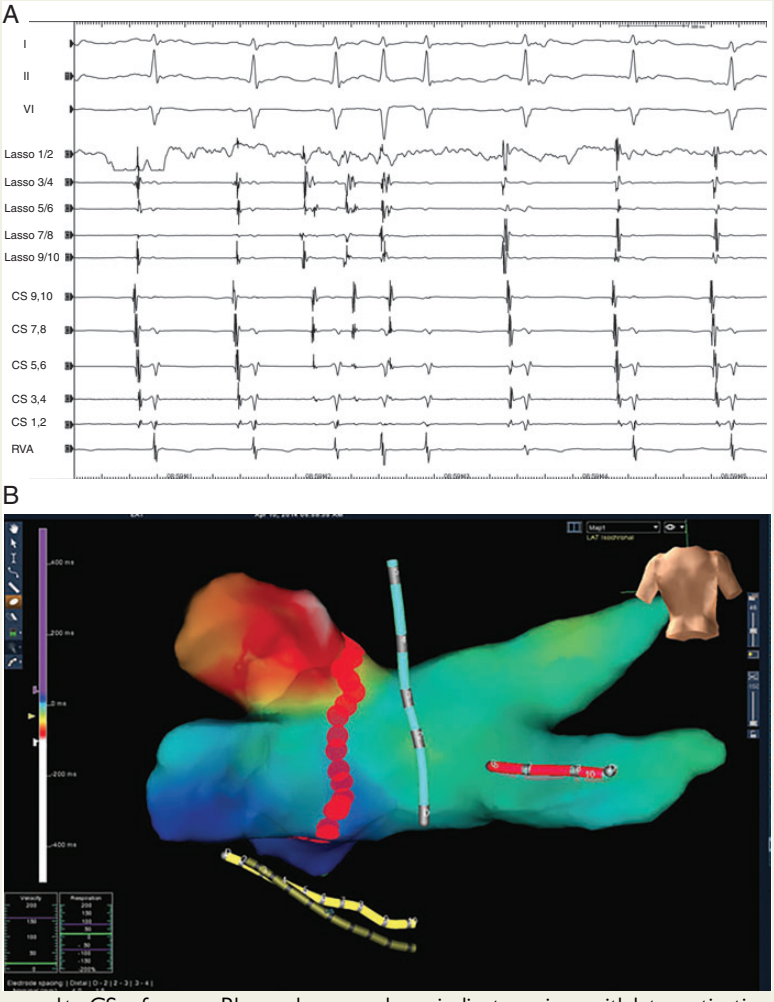
A former elite cyclist presented with palpitations, often induced by exercise. Electrophysiological study revealed an atrial tachycardia of 280–420 ms cycle length (*Panel A*). Activation mapping revealed an origin from LSPV (*Panel B*). Deep inspiration triggered 'firing' of the ectopic atrial focus. The patient underwent isolation of the LSPV by radiofrequency ablation (RFA) and remained symptom-free during the follow-up.

Respiratory cycle-dependent atrial tachycardia infrequently occurs in patients with symptomatic supraventricular tachycardia and can be effectively treated with RFA. As shown with this example, they do also occur in athletes. Whether respiratory cycle-dependent left atrial tachycardia play a role as a trigger for AF in athletes warrants further investigations.



Panel A. The first two and last three beats are sinus beats, and the other three beats are ectopic beats; surface ECG: I, II, V1; intracardiac electrograms from circular decapolar catheter (Lasso) in left superior pulmonary vein (LSPV), coronary sinus (CS 9/10 proximal, 1/2 distal), right ventricular apex (RVa); paper speed 50 mm/s. Artefacts and baseline shifts in the surface ECG leads I, II and V1 are due to deep respiration.

Panel B. Posterior–anterior view of the left atrium (LA) with a colour-coded activation map, using the Ensite NAVx three-dimensional mapping system (St Jude Medical, St Paul, MN, USA). Red colour indicates the origin of the AT from the left superior pulmonary vein (PV) with the earliest signals compared to CS reference. Blue and green colours indicate regions with later activation of the atrium. The red dots around the left PV indicate radiofrequency catheter ablation (RFCA) lesions, using an irrigated tip catheter (Therapy Coolflex, St Jude Medical, St Paul, MN, USA).

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/Respiratory-cycle-dependent-left-atrial-tachycardia.pdf.