Acute outcome after a single cryoballoon ablation: Comparison between Arctic Front Advance and Arctic Front Advance PRO

Short Title: Comparison of second- and fourth-generation cryoballoons

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Abstract

Background

The novel fourth-generation cryoballoon (CB4) potentially allows for enhanced catheter maneuverability and more frequent capture of pulmonary vein (PV) potentials which can be used to monitor real-time PV isolation. Aim of our study is to compare the acute procedural endpoints between the CB4 and second-generation cryoballoon (CB2).

Methods

A single-center retrospective chart review was used to examine 50 consecutive patients with drug-refractory atrial fibrillation undergoing CB4-based pulmonary vein isolation (PVI). Procedural data and acute success of these patients were compared to 50 propensity- matched controls who underwent cryoballoon ablation procedure using CB2.

Results

Procedures performed with the CB4 showed significant shorter fluoroscopy time (14.8 ± 5.5 vs 18.0 ± 6.5 min, p = 0.04), shorter procedure time (58.3 ± 15.7 vs 65.3 ± 21 min, p = 0.13), and shorter total ablation time (10.8 ± 1.5 vs 13.8 ± 1.9 min, p = 0.42). The real –time PVI visualization rate was 33.3% in CB2 group and 74.7% in CB4 group (p <0.001). CB4 was correlated to significant increase of acute real- time recordings with regard to all the single PV (left superior PV: 58% vs 84%, p= 0.02; left inferior PV: 26% vs 71%, p= 0.001; right superior PV 29% vs 61%, p= 0.01; and right inferior PV 19% vs 58%, p= 0.002).

Conclusion

The CB4 was more often able to capture real-time recordings of PV potentials and the subsequent acute PV isolation.

Keywords: Atrial fibrillation; Pulmonary vein isolation; Catheter ablation; Cryoablation; Cryoballoon catheter

1. Introduction

As a cornerstone technique, pulmonary vein isolation (PVI) is the primary target for catheter ablation in patients with drug-refractory symptomatic paroxysmal and persistent atrial fibrillation (AF)(1). Furthermore, the cryoballoon (CB) catheter is a well-described tool that has achieved good procedural results with a freedom from AF recurrence that is similar to radiofrequency ablation catheters (2). Particularly, since 2012, the second-generation CB (CB2, Artic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) has been described as a catheter with a high procedural success rate and durability of clinical outcomes in the treatment of patients with AF(3-7). Recent technical changes were completed to improve the CB catheter in terms of maneuverability and pulmonary vein (PV) signal recordings during PVI. The resulting fourth-generation CB (CB4, Artic Front Advance PRO, Medtronic, Inc., Minneapolis, MN, USA) is characterized by a shorter tip (8 mm distal tip versus 13.5 mm tip of the traditional balloon; a 40% reduction) that can potentially facilitate better visualization of PV signals (**Figure 1).**

The real-time visualization of PV potentials allows for a patient-tailored ablation strategy. Specifically, the visualization of time-to-effect (TTE; defined as the duration of freeze until acute circumferential cellular electrical dormancy is achieved) can be utilized to define a freeze duration at each individual PV. In practice, TTE is the time from the beginning of the freeze application until the moment the PV is electrically isolated. Consequently, the routine usage of TTE can potentially avoid

extra freeze-cycle(s) and predict longer-term clinical outcome such as AF recurrence (as a predictive clinical parameter of outcomes) (7-11). Here, the objective of the current study is to assess and compare the first acute procedural data using the novel CB4 compared to the CB2.

2. Material and methods

2.1 Patient population.

Consecutive patients with drug-refractory paroxysmal or persistent AF scheduled for an index CB-base ablation by PVI method at our Institution (from November 2017 to February 2019) were retrospectively analyzed. Procedures performed between November 2017 and September 2018 were done with the CB2 catheter; whereas, those ablations between October 2018 and February 2019 were performed using the CB4 catheter. The procedural data of 50 patients treated with the CB4 technology (CB4-group) were collected and compared to propensity-matched patients treated with the second-generation CB (CB2-group) technology. The data collection and study design complied with the Declaration of Helsinki.

2.2 Procedural management.

Before the procedure, transesophageal echocardiography was performed to rule out intracardiac thrombi (if clinically indicated). Novel oral anticoagulants were stopped at most 12 hours prior the procedure; whereas, vitamin-K antagonists were continued with an INR around two.

All patients provided informed consent before the procedure, and all procedures were performed by experienced operators (beyond the well-established learning curve).

At the start of the catheter ablation procedure, deep sedation was established using a bolus of fentanyl and a continuous infusion of propofol. The cryoablation procedure has been described in detail in previous studies (3, 6). Briefly, a single transseptal puncture was performed using a transseptal needle system (BRK, Abbott, Minneapolis, MN, USA) and a standard sheath (SL0 8-Fr, Abbott, MN, USA). The transseptal sheath was exchanged over a guidewire for a 12-Fr steerable sheath (FlexCath Advance, Medtronic, Minneapolis, MN, USA). Thereafter, the balloon was advanced into the left atrium (LA) guided by the inner-lumen diagnostic mapping catheter (Achieve Advance, 20 mm diameter, Medtronic, Inc., Minneapolis, MN, USA). Heparin was administered intravenously as a bolus followed by a continuous infusion. An esophageal temperature probe was used in all patients (Esotherm, FIAB) to monitor luminal temperature.

After the CB was inflated and maneuvered to the antra surface of the PV; a contrast injection was completed to assess the PV occlusion. The Achieve catheter was positioned proximally to visualize PV potential recordings. TTE was recorded and defined as the time from cryoablation initiation until the last recorded PV potential signal. All procedures were guided by TTE, and under the TTE guidance protocol, four individualized dosing methodologies were defined. Initially, if PVI was obtained within the first-freeze application and TTE was <40 sec; then a “short-freeze” protocol was performed (which continued the freeze-cycle until a total ablation time of 180 sec). If TTE was between 40 and 120 sec, then a “no-bonus- freeze” protocol was used (which entailed a standard freeze-cycle duration of 240 sec without an additional bonus-freeze-cycle). In a third option, if TTE

was >120 sec, a "bonus- freeze" protocol was selected (which continued the freeze-cycle for 240 sec and followed the freeze with an additional bonus-freeze-cycle of 180 sec or 240 sec duration, depending on the operator preference). Finally, if the TTE could not be visualized, then the freeze-cycle duration was set to a standard freeze-cycle of 240 sec, and an extra freeze was done according to physician's opinion.

As usual in our Center, during right-sided PV cryoablations, continuous phrenic nerve (PN) pacing (1200 msec cycle; 10mA, 2 ms) was performed using a diagnostic catheter to electrically pace the PN at a level above the superior vena cava. Freeze energy delivery was interrupted immediately if weakening or loss of diaphragmatic contraction was noted by tactile feedback or was observed under fluoroscopic imaging. Acute PVI was confirmed by demonstrating entry and exit block with the Achieve mapping catheter placed in each vein, and another freeze was performed if acute PV reconnection occurred.

2.3 Statistical Analysis

This was an observational, single-center study, and to reduce bias due to patient baseline clinical characteristics, a propensity-score matching analysis was performed to account for critical differentiating patient variables, including: gender, age, hypertension, body mass index (BMI), LA volume, previous antiarrhythmic drug(s) usage, and type of AF. During statistical analyses, continuous variables were reported as mean ± standard deviation, and comparisons of continuous variables were performed using the independent sample Student's *t*-test. Categorial variables were

presented as frequency or percentage and were compared by Fisher's exact test. The ANOVA test was performed to assess the differences between continuous, normally distributed data for two groups, and the Mann-Whitney test was used otherwise. Statistical significance was considered with a p-value of <0.05. Lastly, SPSS v.19.0 statistical software (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

3. Results

In our study, 50 patients underwent CB4 catheter PVI (CB4-group). Previously, 545 patients underwent PVI ablation with CB2 catheter, and a propensity-score matching with the CB2 group left 50 patients for analysis with the CB4 group. In total, 100 patients underwent CB ablation at Centro Cardiologico Monzino IRCCS, in Milan, Italy, and these patients were evaluated in our retrospective study. As the two groups were propensity-score matched, the baseline clinical characteristics in terms of age, gender, type of AF, BMI, LA volume were all similar. Also, no significant differences were found between the two study groups regarding CHA_2DS_2-VASc score and other baseline medical recordings. Baseline patient characteristic data for both CB2 and CB4 groups are provided in **Table 1.**

3.1 Procedural results of CB2 and CB4 groups

Acute success and procedural data are reported in **Table 2.** Compared to CB2 ablations, procedures performed with the CB4 showed significant shorter fluoroscopy time (14.8 ± 5.5 vs 18.0 ±

6.5 min, p = 0.04), shorter procedure time (58.3 ± 15.7 vs 65.3 ± 21 min, p = 0.13), and shorter total ablation time (10.8 ± 1.5 vs 13.8 ± 1.9 min, p = 0.42). A total of 389 of 389 PVs (100%) were identified and successfully isolated (195 PVs in CB2 group and 194 in CB4 group). Balloon nadir temperature was significantly higher in the CB4 group only for the left superior PV (-49.8 ± 5.6 vs -45.6 ± 6.7 °C, p = 0.01) and the left inferior PV (- 47.7 ± 5.2 vs -43.2 ± 5.6 °C, p = 0.002). Real-time PVI was visualized in 33.3% of the PVs in CB2 group and 74.7% of PVs in CB4 group (p < 0.001), using the Achieve Advance catheter in both groups. As shown in **Figure 2**, there was a significant difference with regard to all the single PV acute TTE recordings between the two groups (left superior PV: 58% vs 84%, p= 0.02; left inferior PV: 26% vs 71%, p= 0.001; right superior PV 29% vs 61%, p= 0.01; and right inferior PV 19% vs 58%, p= 0.002). In addition, the frequency of recording TTE in Left Common PV was greater using CB4 than using CB2, without reaching statistical significance (75% vs 33%, p=0.37). Significant difference in total cryo-applications number were founded between the two groups (1.2 ± 0.43 in CB2 vs 1.1 ± 0.31 in CB4; p= 0.01). Transient PN palsy occurred in 3 (6%) patients in CB2 group and in 2 (4%) patients in CB4 group (p=0.50) with full recovery of nerve function before the hospital discharge. No severe complications occurred in both groups as reported in **Table 2.**

4. Discussion

To the best of our knowledge, this study is the first comparison of acute clinical outcomes of CB2 and CB4 in patients underwent first PVI for AF. A case report from our group described the first

case of the CB4 PVI, reporting the feasibility of the procedure, the acute success, and the TTE visualization for all 4 PVIs(12).

Our findings suggest that CB2 and CB4 have similar acute success in obtaining PVI. Peri-procedural complication rates were low and equivalent in both groups. Mean procedure and fluoroscopy times were shorter in the CB4 group. Moreover, total cryo-applications number was significantly reduced in CB4 procedures. Finally, CB4 significantly increased the possibility of reading the TTE, regardless the different PV anatomy.

4.1 Acute Procedural outcomes.

In recent times, the cryoablation is increasingly used in the electrophysiology laboratories for the treatment of patients with AF. Technological developments have allowed an easier maneuverability of the cryoballoon inside the LA and a greater possibility of reading the electrical signals of the pulmonary veins due to a proximal position of the Achieve catheter. Mainly, AF cryoablation procedures performed with CB4 showed a better visualization of real-time vein signals (74.7% vs 33.3%), providing evidence for acute PVI. The significant improvement in TTE detection was observed in all veins. These results confirm previously published data regarding the third-generation cryoballoon (CB3, Arctic Front Advance ST, Medtronic, Inc., Minneapolis, MN, USA) that was withdrawn from the commercial market due to higher balloon nadir temperatures probably caused by a more proximal positioning of the intra-balloon thermocouple (13-15). In our population, the main reason for failure to obtain TTE recordings was the distal placement of the Achieve in order

to guarantee balloon stability especially in right inferior pulmonary veins (TTE displayed CB2 vs CB4, 19% vs 58% respectively, p= 0.002). This result could be also explained by the typically shorter PV sleeves extension around the inferior pulmonary veins (16).

Moreover, the possibility to measure TTE allows the physician to significantly reduce fluoroscopy time, probably because the PV signals confirm the correct position of the balloon during the initial freeze cycle and led to a lesser use of fluoroscopy to guide the operators. More importantly, TTE enables the user to tailor the PVI procedure personalizing the number of freeze(s). In our study total cryo-applications number was significantly lower in CB4 group, probably because the TTE visualization allowed to avoid extra freeze cycles. Ferrero-de-Loma-Osorio *et al.* proposed a new individualized protocol, based on TTE plus 60- and a 120-sec bonus freezes, which led to shorter procedure times and similar AF recurrence at 1-year follow-up (17, 18).

In our current study, procedure and total ablation time were also decreased by the use of the CB4 catheter probably due to a greater ability to record PV electrograms and real time TTE that enhance the procedural efficacy by reducing the number of total cryo-applications and as a consequence the total procedure and ablation time. From previous reports, procedural times in cryoablation PVI largely ranged from 60 to 160 minutes (7, 17-20) and depended on several factors, including: the experience of the operator, the volume of caseloads of the center, the choose PVI protocol in terms of number and durations of freezes, and the method of verification of PV reconnections.

Despite the internal cryoballoon structure has not been modified, the nadir temperature resulted to be significantly higher in CB4 group during cryoenergy delivery, especially for the

superior and inferior left PVs. It is important to know that the temperature was measured by the thermocouple located on the proximal part of the balloon and provided information about balloon-tissue contact. Then, our finding could be explained by several independent variables such as the balloon position within the PV ostium (proximal/distal), balloon to PV diameter ratio and balloon manipulation by the operator.

Finally, in our experience the CB4 provided a similar rate of acute PVI in comparison to previous CB2. However, larger and multicenter studies are needed to better evaluate if the CB4 could improve both acute- and longer-term clinical outcomes.

5. Limitations

Our study has some limitations. First, it is not a prospective randomized trial. Although the two groups were propensity-score matched so that the baseline characteristics were similar, a possible confounding effect of unknown variables cannot be excluded.

Secondly, it is a single-center study and the number of enrolled patients was relatively small. These findings have to be confirmed by larger multicenter experiences and randomized studies.

Thirdly, it cannot be a blind study due to structural differences between the two cryo-catheters.

Lastly, only acute efficacy and safety data are provided while long term clinical outcome will need future assessment.

6. Conclusions

The novel CB4 has been designed to improve the recording of real-time PV signals during balloon PVI. The availability of a shorter tip leads to a significant increase in the observation rate of TTE. An increase in TTE observation rate permits a tailored procedure approach and a reduction in fluoroscopy time and procedure duration.

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FIGURE LEGENDS

Figure 1.

Primary changes of the fourth-generation cryoballoon catheter compared to the second- generation. Panel A) Second-generation Arctic Front Advance cryoballoon with longer distal tip (13 mm). Panel B) Fourth-generation Arctic Front Advance PRO was designed to have a shorter tip (8mm) in order to allow more proximal placement of the spiral mapping catheter in the pulmonary vein and increase in the ability to visualize real-time pulmonary vein recording(s) during ablation**.**

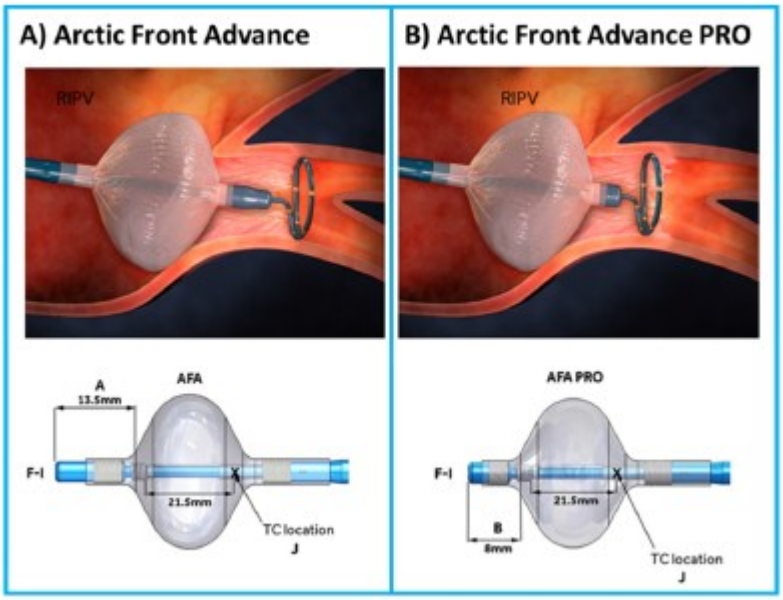

Figure 2.

The percentage of real time pulmonary vein recording(s) during the procedure per vein according to the cryoballoon generation that was utilized.

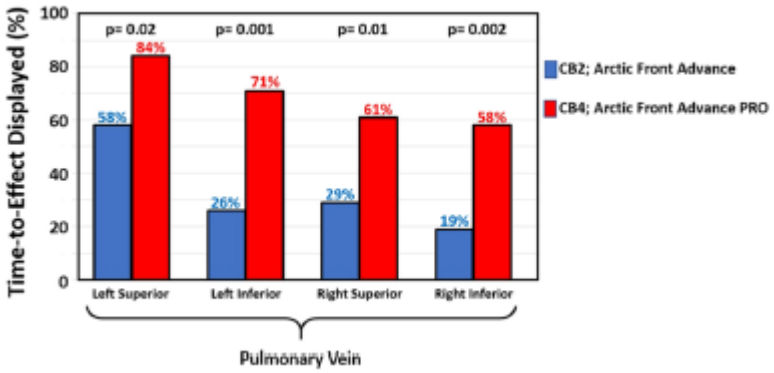

Table 1. Clinical baseline characteristics of the study population. Continuous data presented as mean and standard deviation. Categorical data given as number count and percentage.

	Overall (N=100)	**CB2 (N=50)**	**CB4 (N=50)**	***p-Value***
Baseline Variables				
Age (years)	59.7 ± 12.1	59.4 ± 13.2	60.0 ± 11.2	0.84
Female gender	28 (28)	16 (32)	12 (24)	0.25
Hypertension	58 (58)	32 (64)	26 (52)	0.15
Diabetes mellitus	7 (7)	2 (4)	5 (10)	0.22
Body Mass Index (Kg/m^2)	26.2 ± 5.7	27.3 ± 7.4	25.1 ± 2.9	0.56
Prior TIA/Stroke	6 (6)	3 (6)	3 (6)	0.66
Obstructive sleep apnea	14 (14)	5 (10)	9 (18)	0.19
Chronic renal failure	0 (0)	0 (0)	0 (0)	-
CHA2DS2-VASc	1.5 ± 1.2	1.6 ± 1.3	1.3 ± 1.2	0.36
EHRA Classification	2.1 ± 0.6	2.2 ± 0.6	2.1 ± 0.5	0.41
Persistent AF status	20 (20)	12 (24)	8 (16)	0.23
Coronary artery disease	9 (9)	6 (12)	3 (6)	0.24
Echocardiographic Variables				
Left Atrial volume (ml/mq)	38.8 ± 11.7	39.1 ± 11.9	38.6 ± 11.7	0.86
Left Ventricular EF (%)	60.5 ± 8.4	59.5 ± 9.5	61.5 ± 7.1	0.34
Baseline medical therapy				
Amiodarone	16 (16)	7 (14)	9 (18)	0.39
Antiarrhythmic drugs (Class I)	84 (84)	42 (84)	42 (84)	0.61
Beta blockers	38 (38)	19 (38)	19 (38)	0.61

Abbreviations: TIA= transient ischemic attack, EHRA= European heart rhythm association, EF= ejection fraction, AF= atrial fibrillation.

Table 2. Procedural data, acute success, and complications. Intra-procedural cryoballoon ablation data in all population and according to the second- and fourth-generation cryoballoon usage. Continuous data presented as mean and standard deviation. Categorical data given as number count and percentage.

	Overall (N=100)	CB2 (N=50)	CB4 (N=50)	*p-Value*
Procedural data				
Procedure time (min)	61.8 ± 18.7	65.3 ± 21.0	58.3 ± 15.7	0.13
Fluoroscopy time (min)	16.4 ± 6.2	18.0 ± 6.5	14.8 ± 5.5	**0.04**
Total ablation time (min)	12.3 ± 2.3	13.8 ± 1.9	10.8 ± 1.5	0.42
Left Atrial dwell time (min)	44.7 ± 11.3	46.6 ± 11.9	42.9 ± 10.5	0.20
Number of PVs	389/389 (100)	195/195 (100)	194/194 (100)	-
Number of PVs isolated	389/389 (100)	195/195 (100)	194/194 (100)	-
Number of Left Common PV	7/7 (100)	3/3 (100)	4/4 (100)	-
Rate of PVI recordings	210/389 (54.0)	65/195 (33.3)	145/194 (74.7)	**< 0.001**
Total freeze cycles until PVI	1.2 ± 0.38	1.2 ± 0.43	1.1 ± 0.31	**0.01**
Time-to-effect				
Left Common PV (sec)	47.4 ± 21.2	44.3 ± 22.5	49.7 ± 23.4	0.62
Left Superior PV (sec)	47.8 ± 24.5	49.3 ± 28.5	46.1 ± 21.4	0.67
Left Inferior PV (sec)	42.8 ± 24.7	43.5 ± 31.1	42.5 ± 22.5	0.32
Right Superior PV (sec)	36.9 ± 30.6	39.3 ± 46.7	35.7 ± 20.7	0.77
Right Inferior PV (sec)	40.6 ± 24.2	36.5 ± 19.4	42.1 ± 25.9	0.56
Temperature at isolation				
Left Common PV (°C)	-37.1 ± 2.8	-37.3 ± 3.0	-37.0 ± 3.2	0.80
Left Superior PV (°C)	-36.2 ± 7.9	-33.0 ± 9.1	-37.5 ± 6.6	0.07
Left Inferior PV (°C)	-32.6 ± 9.6	-28.8 ± 8.8	-33.7 ± 9.2	0.18
Right Superior PV (°C)	-33.3 ± 8.4	-31.2 ± 8.8	-34.3 ± 8.2	0.37
Right Inferior PV (°C)	-32.2 ± 8.1	-30.3 ± 5.9	-32.8 ± 8.7	0.51
Nadir balloon temperature				
Left Common PV (°C)	-45.8 ± 1.8	-46.0 ± 1.7	45.7 ± 2.2	0.52
Left Superior PV (°C)	-47.8 ± 6.5	-45.6 ± 6.7	-49.8 ± 5.6	**0.01**
Left Inferior PV (°C)	-45.6 ± 5.8	-43.2 ± 5.6	- 47.7 ± 5.2	**0.002**
Right Superior PV (°C)	-48.1 ± 6.4	-47.4 ± 7.4	-48.8 ± 5.2	0.37
Right Inferior PV (°C)	-45.7 ± 5.9	-45.0 ± 6.3	-46.4 ± 5.6	0.36
Procedure-related complications				
Acute PNP	5 (5)	3 (6)	2 (4)	0.50

Pericardial effusion	1 (1)	1(2)	0 (0)	0.50
Cardiac tamponade	0 (0)	0 (0)	0 (0)	-
Cerebral embolization	0 (0)	0 (0)	0 (0)	-
Vascular injury	1 (1)	0 (0)	1 (2)	0.50

Abbreviations: PV= pulmonary vein, PVI= pulmonary vein isolation, PNP= phrenic nerve palsy