1. Introduction

Catheter ablation is an established therapy in patients with drug-refractory symptomatic atrial fibrillation (AF) [1,2]. Even if multiple ablative strategies have been proposed, pulmonary veins isolation (PVI) is a cornerstone of any AF ablation procedure [3–6]. Electrical PVI can be obtained through radiofrequency either point-by-point or single shot technique or by means of cryoenergy delivered by “single-shot” devices such as cryoballoon [7,8]. It has been observed that cryoballoon and radiofrequency AF ablation are associated with a similar reported AF freedom, as confirmed in some meta-analysis [9] or recently in a randomized trial (Fire and ICE trial) [10]. Significant improvement of ablative results have been achieved with the second generation Cryoballoon Artic Front Advance (CB2), that was designed with technical modifications mainly focused to a better application of the cryoenergy over the balloon surface [11–13]. However, some procedural predictors, in order to improve the ablative efficacy became popular. The time to achieve the PV de-connection defined as time-to-effect (TTE), appeared to be important in order to increase ablative efficacy and

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Impact of the third generation cryoballoon on atrial fibrillation ablation: An useful tool?

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ABSTRACT

Background: Third-generation cryoballoon (CB3) is characterized by a 40% shorter distal tip designed to increase the rate of pulmonary veins real-time signal recording in order to measure time necessary to isolate veins, the “Time to effect” (TTE). Few data are currently available on clinical follow up of CB3 treated patients.

Methods: Sixtyeight consecutive patients (mean age 57.8 ± 9.6 years, 48 male) with paroxysmal or persistent atrial fibrillation (AF) were enrolled. Thirthyfour (25 paroxysmal AF) underwent to a 28 mmCB3 pulmonary veins isolation and were compared to 34 treated (21 paroxymal AF) with 28 mmCB2.

Results: CB3 use was correlated to significant increase of the possibility to measure TTE in every treated veins (left superior 82.35% vs 23.53%, left inferior 70.59% vs 38.24%, right superior 58.82% vs 14.71%, right inferior 52.94% vs 17.65%). When it is measured, TTE wasn’t different between two groups. Higher nadir temperature was observed in CB3 patients (−39.4 ± 5.2°C vs −43.0 ± 7.2°C, p = 0.03). CB3 procedures were shorter (91.4 ± 21.7 vs 110.9 ± 31.8 min, p = 0.018), with a significant reduction in cryoenergy delivery time (24.2 ± 8.5 vs 20.3 ± 6.7 min, p < 0.05), and a significant reduction in left atrium dwell time (59.3 ± 9.8 vs 69.3 ± 10.8 min, p = 0.02, p < 0.05). At one year follow up period the Kaplan-Meier curve didn’t show any significant difference in AF-free survival (Log p = 0.49).

Conclusions: Novel CB3 is a useful tool in order to simplify AF cryoballoon ablation when compared to second generation cryoballoon, as observed in our experience. Follow up data seem confirm a clinical CB3 efficacy at least comparable CB2.

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to reduce useless cryo application time [14–17]. Recently, a new third-generation cryoballoon ablative catheter, the Artic Front Advance ST (CB3), has been produced, with a 40% shorter distal tip (Fig. 1). Such a feature could theoretically facilitate catheter manoeuvrability, and could increase the possibility of veins signal recording during ablation. The catheter is still not available in the market, but early published experiences by centres testing the balloon in pre-market release seem to be encouraging [18, 19]. Only one recent report from Koekruk et al. described a not significant increasing in the ratio of PV signal recordings obtained during the PVI using CB3 [21]. Cryo-DOSING Investigators confirmed in a large multicentre experience the CB3 ability to improve PV signal recordings during PVI with similar AF-freedom at a 12 months mean follow up [22].

1.1. Aim of the study

To compare in our experience the acute efficacy of second-generation and third generation cryoballoon ablative catheters for ablation of AF, in a prospective cohort study.

To compare early clinical follow-up data of patients with AF, treated with the second and third generation cryoballoon catheters.

2. Material and methods

2.1. Study population

Sixtyeight consecutive patients with symptomatic, drug-refractory, paroxysmal or persistent atrial fibrillation were enrolled. A prospective not randomized cohort study was planned. Patients underwent to 68 consecutive AF ablation first procedure with PVI performed by means of cryoballoon technology. Thirtyfour patients were consecutively treated with CB2 technology and 34 were treated consecutively with third generation cryoballoon (CB3) technology.

Exclusion criteria were: extracardiac causes of atrial fibrillation (hyperthyroidism, rheumatic diseases, electrolyte imbalance, etc), age under 18 y.o. or over 80 y.o., prior left atrium ablation attempts, severe valvular heart disease, presence of contraindication to oral anticoagulation, severe left atrial dilation (left atrial anteroposterior diameters > 60 mm), recent percutaneous coronary intervention or cardiac surgery.

In every patients a transesophageal echocardiography was performed in order to rule out intracardiac clots. In novel oral anticoagulants treated patients, the drug was stopped at least 24 h prior the procedure and continued 6 h after ablation. In patient on vitamin k antagonists the procedure was performed with an INR around 2. All patients gave written informed consent to the procedure.

In order to allow a better view of vein potential, antiarrhythmic drugs wash-out (at least 5 times the drug half life) was performed. Amiodarone was interrupted at least one months before ablation.

2.2. Intraprocedural management

Procedure was performed in a fasting state under mild sedation, using low dose midazolam ev. One decapolar diagnostic catheter was introduced via left femoral vein and positionated within the coronary sinus (6F, Boston Scientific Dynamic XT Diagnostic Catheter). Single, pressure and fluoroscopic guided transseptal puncture was performed (Biosense Webster Heartspan transseptal needle) and an 8.5 F transseptal sheath (Biosense Webster Preface Sheath) was introduced in left atrium. With an exchange guidewire a 12 F steerable sheath (Flexcath Advance, Medtronic) was introduced in LA. Activated clotting time (ACT) was maintained between 250 and 350 s administering heparin boluses.

A 28 mm CB was advanced into the LA via steerable sheath using the ACHIEVE catheter (20 mm diameter, Medtronic, Inc.) for guidance. The ACHIEVE catheter was advanced into PVs and the CB was inflated proximal PV ostium and pushed on the venous antrum. Contrast injections were performed to verify complete occlusion. Standard freeze-cycle duration was 240 s, but it was reduced to 180 s when TTE was <60 s. A bonus freeze-cycle was applied when TTE was >120 s. The procedural endpoint was defined as persistent PV isolation verified by ACHIEVE catheter 30 min after the last CB application. While right PVs cryoenergy delivery, continuous phrenic nerve stimulation pacing was performed into the superior vena cava using the diagnostic catheter previously positionated within the coronary sinus. Phrenic nerve capture was monitored by tactile feedback; energy delivery was interrupted if weakening or loss of diaphragmatic contraction.

2.3. Postprocedural care

Post procedural echo scan was performed in order to rule out pericardial effusion. Novel oral anticoagulants were restarted 6h post ablation. In vitamin K antagonist treated patients supplemental dose of low molecular-weight heparin was administered when the INR was lower than 2. In persistent AF patients the antiarrhythmic drug was continued for at least 3 months and then discontinued. In paroxysmal AF patients no antiarrhythmic drug was administered. Patients were discharged 48 h after the ablation.

![Fig. 1. Shorter tip in CB3 (right panel) technology than CB2 (left panel).](image-url)
2.4. Follow up management

Every patient joined an outpatient follow up plan (3; 6; 9 and 12 months post ablation) with clinical assessment, ECG, and 24-h Holter ECG. Additional follow ups were planned in case of symptoms. Clinical success was defined as absence of arrhythmic documented recurrence (>30 s), no prescription of antiarrhythmic drug (AAD) and no need of re-ablation after the blanking period (3 months) [23].

2.5. Statistical analysis

Analysis was performed using SPSS v. 11.5 (IBM, Chicago, IL, USA). Continuous variables were expressed as the mean value ± standard deviation. Differences of metric variables were analyzed with t-test if the data were normally distributed. A X² test was used for categorical variables. Non-parametric tests were used when appropriate. Kaplan-Meier univariate analysis were used to estimate AF-free survival.

3. Results

3.1. Patients characteristics

Sixtyeight consecutive patients were treated with circumferential antral PVI using CB2 technology and the new cryoballoon catheter (CB3). Persistent AF patients were represented in both group (9 in CB2 group and 11 in CB3 group). Clinical characteristics of patients population are summarized in Table 1.

3.2. Procedural characteristics

A total of 270 of 270 PVS (100%) were identified and all the veins (100%) were successfully isolated. The mean total procedural time was 101 ± 28.8 min. Ablation procedure performed with CB3 resulted to be shorter when compared to CB2 procedure (91.4 ± 21.7 vs 110.9 ± 31.9 min, p < 0.05). Total cryoenergy delivery was significant reduced in CB3 group (24.2 ± 8.5 vs 20.3 ± 6.7 min, p < 0.05). No significant difference in total cryoapplications number were founded between the two groups (6.4 ± 1.8 vs 6.0 ± 2.8, p = ns).

Nadir balloon temperature was significant higher in CB3 group (−39.4 ± 5.2 °C vs −43.0 ± 7.2 °C, p = 0.03). A significant reduction in left atrium dwell time (59.3 ± 9.8 vs 69.3 ± 10.8 min, p = 0.02). A mild groin subcutaneous haematoma occurred in the CB2 group and it did not require any treatment. No severe complications occurred in both groups.

Procedural characteristics are presented in Table 1.

3.3. Time to effect

Significant advantage using CB3 in measuring TTE in every treated PV was observed (in every treated vein p < 0.01) (Fig. 2).

When it was measured, no statistically significant difference of TTE values were observed in the two groups (Fig. 3).

3.4. Follow up

Freedom from documented paroxysmal and persistent AF-free survival is given in Fig. 4. We found that circumferential PVI with the cryoballoon technique resulted in maintenance of sinus rhythm and no AAD prescription in 49 (72%) patients. At one year follow up (Fig. 4) the Kaplan-Meier univariate analysis didn’t show any significant difference between CB2 or CB3 treated patients in AF-free survival (Log Rank Test p = 0.49).

4. Discussion

In a very early stage cryoballoon ablation of AF was considered a sort of "anatomical procedure", without the possibility to measure electrophysiological signals during cryoenergy delivery. A significant technical improvement of the cryoballoon technique was the possibility to associate to the single shot balloon ablation technology, the possibility to record electrophysiological signals.

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Table 1

| Baseline Characteristics                  | Total (CB2+CB3, 68pts) | CB2 (34pts) | CB3 (34pts) | CB2 vs CB3 p-value |
|-------------------------------------------|------------------------|-------------|-------------|---------------------|
| Male Gender (%)                           | 48 (70%)               | 25 (73.5%)  | 23 (67.6%)  | ns                  |
| Age (years)                               | 57.8 ± 9.6             | 57.3 ± 9.9  | 58.3 ± 9.5  | ns                  |
| Paroxysmal AF (%)                         | 46 (67.6%)             | 25 (73.5%)  | 21 (61.7%)  | ns                  |
| AF history (months)                       | 50.2 ± 52.1            | 58.0 ± 60.1 | 41.5 ± 40.9 | ns                  |
| LA size (mm)                              | 42.2 ± 4.9             | 41.6 ± 5.2  | 42.8 ± 4.6  | ns                  |
| LVEF (%)                                  | 57.9 ± 4.9             | 59.6 ± 3.4  | 56.1 ± 5.6  | ns                  |
| Absence of heart disease                  | 46 (67.6%)             | 23 (67.6%)  | 27 (79.4%)  | ns                  |
| Hypertension                              | 18 (26.3%)             | 11 (32.3%)  | 14 (41.1%)  | ns                  |
| Diabetes mellitus type 2                  | 1 (1.5%)               | 1 (3%)      | 0           | ns                  |
| Antiarrhythmic drugs tested per patient   | 1.7 ± 0.9              | 1.6 ± 0.7   | 1.8 ± 1.0   | ns                  |
| CHA2DS2-Vasc                              | 1.8 ± 0.5              | 1.6 ± 0.5   | 1.9 ± 0.6   | ns                  |
| EHRA-Classification                       | 1.9 ± 0.5              | 2 ± 0.6     | 2.1 ± 0.4   | ns                  |

| Procedural data                           | Total (CB2+CB3, 68pts) | CB2 (34pts) | CB3 (34pts) | CB2 vs CB3 p-value |
|-------------------------------------------|------------------------|-------------|-------------|---------------------|
| Procedure time (min)                      | 101.1 ± 28.8           | 110.9 ± 31.8| 91.4 ± 21.7 | 0.018               |
| Fluoroscopy time (min)                    | 26.3 ± 9.3             | 26.6 ± 9.5  | 26.1 ± 9.0  | ns                  |
| Pulmonary veins isolated (count)          | 270 (100%)             | 135 (100%)  | 135 (100%)  | ns                  |
| Total ablation time (min)                 | 22.9 ± 7.7             | 24.2 ± 8.5  | 20.3 ± 6.7  | 0.04                |
| Total balloon applications per patient (count) | 6.2 ± 2.4        | 6.4 ± 1.8   | 6.0 ± 2.8   | ns                  |
| Nadir balloon temperature (°C)            | −41.2 ± 3.8            | −43.0 ± 7.2 | −39.4 ± 5.2 | 0.03                |
| LA dwell time (min)                       | 64.3 ± 10.3 min        | 69.3 ± 10.8 | 59.3 ± 9.8 min | 0.02                |
| Severe complications                      | None                   | None        | None        | None                |

Values expressed as n (%), mean ± standard deviation.
AF = Atrial fibrillation; LA = Left atrium; LVEF = Left ventricle ejection fraction.
obtained by means of the ACHIEVE mapping catheter [15–17]. However, CB2’s distal tip design could allow vein signals recording only in a minority of treated veins [16–18]. In order to overcome such a problem, the CB3 was produced with a shorter tip favouring a more proximal location of the ACHIEVE inside the veins.

Our study demonstrates that CB3 is able to facilitate the real-time disappearance of vein signals, providing evidence for PV isolation. In fact, the use of CB3 in our experience was correlated to a significant increase of the possibility to measure TTE in every PVs. These results further confirm similar recent observations in literature [18–20,22]. To date only Koekturk and coll. [21] found a not significant increase in the ratio PV signal recordings obtained during PVI using the novel technology, except for the right inferior PV. In our experience the significant improvement in TTE detection was confirmed even in the right inferior PV, that is known to be sometimes difficult to map for anatomical reasons. Because of the

Fig. 2. % Interpretable electrograms: the figure presents the rate of real-time pulmonary vein isolation for individual veins using the CB2 and CB3 respectively. LSPV left superior pulmonary vein, LIPV left inferior pulmonary vein, RPSV right superior pulmonary vein, RIPV inferior pulmonary vein. Values expressed as %. P < 0.01 in every treated vein.

Fig. 3. Time to PVI: the figure presents time to effect in PVI for individual veins using the CB2 and CB3 respectively, when it was measured. Values expressed as seconds. P: ns in every treated vein.
acute angle created between the right inferior PV inlet and trans-septal puncture site, in order to guarantee balloon stability while ablating, a distal placement of the ACHIEVE is sometimes needed, beyond the muscular sleeves inside the vein ostium. This can prevent vein signals recording. The special design of CB3 allowed us to improve PVs signal recording even in the right inferior PVs.

When TTE was measured, the time needed to isolate PVs resulted to be not different between CB2 and CB3. This may be explained by the concept that the freezing technology is the same for both balloons, with a consequent equal freezing effect of both technologies.

During cryoenergy delivery the minimum temperature achieved (nadir temperature) resulted to be slightly but significantly higher in CB3 group. Such a feature was also reported by Heeger et al. [18,20], but not confirmed in other experience [21,22]. The higher nadir temperature recorded with CB3 could be explained by the different balloon design. In CB3 technology the thermocouple is located more proximally, thus it could be less influenced by the cooling effect. Such observation should be taken in count by electrophysiologist when CB3 is used, tolerating slightly higher temperature.

The increased possibility to measure the TTE with CB3 was correlated to a significant reduction of the total time of cryoenergy application, without any difference in total cryoapplications number. This finding is different from Heeger [18] experience, in which this phenomenon was observed only in right pulmonary veins, without demonstration of a significant reduction of the total cryoenergy application time. This difference may be explained by the higher rates of TTE observation in our CB3 group. A favourable TTE, known to be a good predictor of PV deconnection [14–17], allows to reduce the time of erogation. In fact, it’s been demonstrated that TTE could be a good parameter to predict an optimal PV deconnection. [16–18] Utilizing a TTE-guided protocol, a higher TTE recordings could translate into a total cycle freeze application time reduction and in a total procedure time reduction.

The shorter tip of CB3 could be associated to a better maneuverability of such device. These feature, combined with better an improved TTE detection, contributes to a significant reduction in left atrium dwell time with CB3. However it could be questioned if the balloon stability over the veins ostia could be affected by the shorter tip. In our experience we did not have such an impression and no early dislodgment were observed neither during “hockey stick” maneuver. This observation is confirmed in Aryana et al. [22] experience, but not in Furnkranz [19] work that reported balloon dislodgement in 6% when using CB3. To date, few follow up data of AF patients treated with CB3 are available in literature. In our preliminary experience, in spite an important proportion of persistent AF patients, follow up data are encouraging and no significant differences were observed between CB2 and CB3 technology in terms of AF recurrences as noted in Cryo INVESTIGATORS study [22].

To date CB3 technology are not available on the market and the company are working on a new release. After diffusion on the market, multicenter studies are required to confirm our preliminary results in a larger population.

5. Conclusions

Our study confirms that the new CB3 is a useful tool in order to simplify the cryoballoon ablation of AF.
Early follow-up data in a limited population of paroxysmal or persistent AF patients seems to confirm a clinical CB3 efficacy at least comparable to previous technology.

The new 40% shorter distal tip could allow to perform an easier procedure, faster and more comfortable for physician and patient, without losing effectiveness in cryoenergy delivery and lesions durability around the pulmonary veins.

Compliance with ethical standards

α) The authors report no relationships that could be construed as a conflict of interest

β) No funding received.

γ) Research involving Human Participants and/or Animals: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this study we collect ethical approval from our internal review board.

δ) Informed consent: “Informed consent was obtained from all individual participants included in the study.” All data have been anonymized before data collection.

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