Circumferential pulmonary vein isolation as index procedure for persistent atrial fibrillation: a comparison between radiofrequency catheter ablation and second-generation cryoballoon ablation

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Aims
To assess the 1 year efficacy of pulmonary vein isolation (PVI) as index procedure for persistent atrial fibrillation (PersAF) comparing conventional radiofrequency irrigated-tip catheter ablation (RFCA) using contact-force technology and ablation using the second-generation cryoballoon (CB-AdvA).

Methods and results
One hundred consecutive patients (74 male, 74%; mean age 62.4 ± 9.6 years) with drug-refractory PersAF undergoing PVI using RFCA and CB-AdvA were enrolled. Follow-up was based on outpatient clinic visits including Holter-electrocardiograms. Recurrence of atrial tachyarrhythmias (ATAs) was defined as a symptomatic or documented episode >30 s. Among 100 patients, 50 underwent RFCA whereas 50 CB-AdvA. Mean procedure and fluoroscopy times were 90.5 ± 41.7 vs. 140.2 ± 46.9 min and 14.5 ± 6.6 vs. 19.8 ± 6.8 min in the CB-Adv and in the RFCA group, respectively (P < 0.01). At 1 year follow-up, after a 3 months blanking period (BP), freedom from ATAs after a single procedure was 60% (28/50 patients) in the CB-Adv and 56% (27/50 patients) in the RFCA group (P = 0.71). Multivariate analysis demonstrated that PersAF duration (P = 0.01) and relapses during BP (P = 0.02) were independent predictors of ATa recurrences following the index procedure.

Conclusion
Freedom from ATAs following PersAF ablation with RFCA and CB-Adv is comparable at 1 year follow-up after a single procedure. Ablation with the CB-Adv is associated with shorter procedure time and radiation exposure as compared with RFCA. Atrial tachyarrhythmias occurrence during BP and longer time of PersAF seem to be significant predictors of arrhythmia recurrences after the index procedure.

Keywords
Radiofrequency catheter ablation; Cryoballoon ablation; Second generation cryoballoon; Persistent atrial fibrillation; Pulmonary vein isolation; One year follow-up

Introduction
Circumferential pulmonary vein isolation (CPVI) is an established and effective treatment for drug-resistant atrial fibrillation (AF). Data available in the literature indicate that patients initially affected by persistent AF (PersAF) might maintain stable sinus rhythm (SR) on a mid-term follow-up after CPVI using an irrigated-tip radiofrequency (RF) catheter guided by a 3D-mapping system.†
What’s new?

- One year clinical outcome of patients undergoing pulmonary vein isolation (PVI) as index procedure for persistent atrial fibrillation (PersAF) ablation with the novel second-generation cryoballoon.
- One year clinical outcome of patients undergoing PVI as index procedure for PersAF ablation with radiofrequency catheter using contact-force technology.
- Prospective clinical comparison of these two technologies.
- Predictors of atrial tacharythmia recurrences following the index procedure.

Recently, the second-generation cryoballoon (CB-Adv; Arctic Front Advance, Medtronic) has been released with technical developments resulting in a larger and more homogeneous zone of freezing on the balloon surface, translating into significant improvements in procedural and clinical outcomes as compared with its predecessor.\(^2,3\) Recent data seem to indicate that cryoballoon ablation offers similar rates of acute PVI and mid-term freedom from AF to conventional RF catheter ablation (RFCA) in patients affected by PAF.\(^4–6\)

To date, however, no data are available about efficacy and clinical outcome on a mid-term follow-up period of 1 year of CPVI for PersAF comparing conventional RFCA using an irrigated-tip catheter guided by 3D mapping and ablation using the novel CB-Adv (CB-AdvA).

Methods

Study population

All patients having undergone PVI as index procedure from March 2012 to September 2013 for symptomatic PersAF (≥7 or <7 days requiring electrical or pharmacological cardioversion) refractory to at least one class I or class III antiarrhythmic drug (AAD) was consecutively included in this single-centre, non-randomized study and clinically followed. All RFCA procedures were carried out from March to September 2012, while CB-AdvA procedures were performed from October 2012. Exclusion criteria were long-standing persistent AF, presence of an intracavitary thrombus, uncontrolled heart failure, moderate or severe valvular disease, previous PVI procedure, left atrium (LA) diameter ≥60 mm, and contraindications to general anaesthesia. All patients provided written informed consent to the procedure.

Aim of the study

The aim of the study was to compare the single procedural outcome on a 1 year follow-up period between RFCA guided by 3D mapping and CB-AdvA, in a series of consecutive patients undergoing PVI for PersAF. Potential predictors of arrhythmia recurrence were also considered as secondary objective.

Pre-procedural management

Structural heart disease was defined as coronary artery disease, impaired left ventricular ejection fraction <40%, left ventricular hypertrophy >15 mm, valvular insufficiency >2/4, significant valvular stenosis, and prior valve replacements. All AADs were discontinued at least 3 days before ablation. For patients under novel anticoagulant agents our practice is to stop anti-coagulation as follows: (i) the last dose of dabigatran was given the morning 1 day prior to the procedure; (ii) and the last dose of rivaroxaban was given the evening 2 days prior. For warfarin uninterrupted administration is performed. A transthoracic echocardiogram (TTE) was performed within 1 week prior to ablation. To exclude the presence of thrombi in the LA appendage, all patients underwent trans-oesophageal echocardiography the day before the procedure. All patients underwent a pre-procedural computed tomographic (CT) scan to assess detailed LA and PV anatomy.


Cryoballoon ablation procedure

Our standard ablation procedure has been previously reported in detail.\(^7\) In brief, after obtaining LA access, through a steerable 15 Fr sheath (FlexCath Advance\(^8\), Medtronic\(^8\)), inner lumen mapping catheter (MC; Achieve\(^9\), Medtronic\(^9\)) was advanced in each PV ostium. A 28 mm CB-Adv (Arctic Front Advance\(^8\), Medtronic\(^8\)) was advanced inflated and positioned in each PV ostium. Ostial vessel occlusion was considered to have been achieved when selective contrast injection showed total contrast retention with no backflow to the atrium. Once occlusion was documented, cryothermal energy was started. Cryo-energy applications lasted at least 240 s. Pulmonary vein activity was recorded with the MC at a proximal site in the ostium prior to ablation in each vein. During ablation, if PV potentials (PVPs) were visible during energy delivery, time to isolation was recorded when PVPs completely disappeared or were dissociated from LA activity. If PVPs were not visible during ablation, the MC was immediately retracted after completion of the freeze-thaw cycle to a more proximal position in which PVPs had been recorded prior to ablation. In order to avoid phrenic nerve palsy (PNP) a decapolar catheter was inserted in the superior vena cava, and diaphragmatic stimulation was achieved by pacing the ipsilateral phrenic nerve with a 1200 ms cycle and a 20 mA output. The reason of pacing at such a slow rate was to prevent catheter displacement, due to diaphragmatic contraction, in the early phases of application. If after isolation, AF did not convert to SR, external electrical cardioversion (ECv) was performed. During the whole procedure, activated clotting time was maintained over 250 s by supplementing heparin infusion as required.

Radiofrequency catheter ablation procedure

After having accessed the LA with a double transseptal puncture, a 70 U/kg heparin intravenous bolus was given then. A circumferential MC (Lasso\(^10\), Biosense Webster\(^10\)) was positioned into the LA. Left atrial geometry was reconstructed with either CARTO\(^11\) (Biosense-Webster\(^11\)) or EnSite\(^12\) (NavX, St. Jude Medical\(^12\)) with image integration was used for each procedure. Radiofrequency applications were performed with an open irrigated tip catheter with contact-force (CF) monitoring (Thermocoool\(^13\), SmartTouch\(^13\), Biosense Webster\(^13\); Tacti cath\(^13\), Endosense, St. Jude Medical\(^13\)) in a power-controlled mode with a power limit of 35 W and at a maximum temperature of 48°C. A 25 W power was limited to the posterior sites. Contact-force data were continuously monitored throughout the entire procedure, with the aim to achieve at least 10 g (mean) with a vector perpendicular to the tissue and with an upper limit of 50 g. The ablation strategy consisted in creating contiguous focal lesions at a distance of ≥5 mm from the ostia of the PVs resulting in circumferential lines around ipsilateral PVs. The endpoint of PVI was defined as the absence of any PV spike potential recorded on either Lasso catheter after PVI and confirmation of bidirectional block with a waiting time of 20 min after last application. If after isolation, AF did not convert to SR, ECv was performed. During the whole procedure, activated clotting time was maintained over 300 s by supplementing heparin infusion.
Repeat procedures were performed with RF irrigated-tip CF catheter. Every patient was evaluated to undergo a second ablation. All catheter ablation; CB-Adv, second-generation cryoballoon.

Statistical analysis
Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as mean ± SD or median and range as appropriate. Comparisons of continuous variables were done with a Student’s t-test and binomial variables with χ² or Fisher’s test as appropriate. Event-free survival were estimated by Kaplan–Meier method and compared by log-rank test. Predictors of arrhythmia recurrence were performed using Cox proportional hazards regression models. The multivariate prediction models for time to recurrence were performed by stepwise regression based on likelihood ratios. For each variable, hazard ratio (HR), 95% confidence interval (CI), and P values of the final model are displayed. A 2-tailed probability value of < 0.05 was deemed significant. Statistical analyses were conducted using the SPSS software (SPSS v22).

Results
Study population
A total of 100 consecutive patients (74 male, 74%; mean age 62.4 ± 9.6 years) undergoing ablation because of symptomatic drug refractory PersAF were included. Fifty patients underwent RFCA, whereas 50 CB-Adv ablation. All patients failed ≥ 1 class I or III AAD. All patients had undergone at least one ECv in the year prior to ablation. No difference in terms of baseline population characteristics was observed between both groups. At pre-procedural CT scan, a 4 distinct PV pattern was present in 88/100 (88%) patients, while discrete left common ostium could be observed in 7 patients (7%), 3 patients in RFCA group and 4 in CB-Adv group. Four patients (4%) exhibited a right-sided accessory vein, two in each group. Mean AAD duration was 29.6 ± 31.2 months (median 15 months, ranging from 6 to 240 months), mean AF persistency was 7.4 ± 2.0 (median 8 months, ranging from 4 to 11 months).

Procedural characteristics
Mean procedure times were 90.5 ± 41.7 min in the CB-Adv group and 140.2 ± 46.9 min in the RFCA group (P < 0.01) (Table 1). Mean fluoroscopy times were 14.5 ± 6.6 min in the CB-Adv group and 19.8 ± 6.8 min in the RFCA group (P < 0.01) (Table 1). At the beginning of the procedure 58/100 patients (58%) presented AF; 26 (44.8%) belonged to CB-Adv group and 32 (55.2%) to RFCA group (P = 0.31). Conversion to SR occurred during ablation in 11/58 (19%) patients. It was achieved in seven patients (14%) in the CB-Adv group and in four patients (8%) in the RFCA group (P = 0.52). Following PVI, no patient experienced atrial tachycardia (AT) in the CB-Adv group. In the RFCA group, two ATs could be observed from the beginning of the procedure 58/100 patients (58%) presented AF; 26 (44.8%) belonged to CB-Adv group and 32 (55.2%) to RFCA group (P = 0.31). Conversion to SR occurred during ablation in 11/58 (19%) patients. It was achieved in seven patients (14%) in the CB-Adv group and in four patients (8%) in the RFCA group (P = 0.52). Following PVI, no patient experienced atrial tachycardia (AT) in the CB-Adv group. In the RFCA group, two ATs could be observed during the procedure: in one patient, AF changed to typical atrial flutter and subsequent cavotricuspid isthmus ablation resulted in SR restoration; in the other one, AF changed into a left-AT. In the latter, 3D mapping confirmed a roof-dependent left-AT, which has been successfully ablated. In the remaining 47/58 patients (81%),

Table 1: Clinical and procedural characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>CB-Adv (n = 50)</th>
<th>RFCA (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62.4 ± 9.8</td>
<td>62.4 ± 9.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Male, n</td>
<td>36 (72%)</td>
<td>38 (76%)</td>
<td>0.82</td>
</tr>
<tr>
<td>BMI</td>
<td>27.5 ± 3.4</td>
<td>28.7 ± 4.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>26 (52%)</td>
<td>34 (68%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dyslipidemia, n</td>
<td>9 (18.8%)</td>
<td>14 (28%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>4 (8%)</td>
<td>7 (14%)</td>
<td>0.52</td>
</tr>
<tr>
<td>HF, n</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>0.62</td>
</tr>
<tr>
<td>CAD, n</td>
<td>2 (4%)</td>
<td>5 (10%)</td>
<td>0.44</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>57.5 ± 3.7</td>
<td>56.3 ± 4.1</td>
<td>0.21</td>
</tr>
<tr>
<td>LA size, mm</td>
<td>46.0 ± 7.2</td>
<td>47.2 ± 6.2</td>
<td>0.36</td>
</tr>
<tr>
<td>CHA2DS2-Vasc score, n</td>
<td>1.4 ± 1.3</td>
<td>1.8 ± 1.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Total AF duration, months</td>
<td>32.7 ± 37.6</td>
<td>26.7 ± 23.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Persistent AF duration, months</td>
<td>7.2 ± 2.2</td>
<td>7.6 ± 1.8</td>
<td>0.33</td>
</tr>
<tr>
<td>Procedure duration, minutes</td>
<td>90.5 ± 41.7</td>
<td>140.2 ± 46.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fluoroscopy duration, minutes</td>
<td>14.5 ± 6.6</td>
<td>19.8 ± 6.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Post-ablation management
Patients were discharged the day following ablation if the clinical status was stable. After the intervention, the patients were continuously monitored with electrocardiogram (ECG) telemetry for at least 18 h. Before hospital discharge, all patients underwent TTE in order to exclude pericardial effusion and chest X-ray. Oral antiarrhythmic was started the same evening of ablation and continued for at least 3 months. Previously ineffective AADs were continued for 3 months and after that time their discontinuation was recommended. Decision to restart AADs after the blanking period (BP) was usually made in case of first episode of atrial tachyarrhythmia (ATs) recurrence.

Follow-up
After discharge, patients were scheduled for follow-up visits with baseline ECG and 24 h Holter recordings at 1, 3, 6, and 12 months. Any symptoms following ablation were deemed as deserving a Holter monitoring. All reports of Holter or ECG recordings having been performed in referring centres were sent to our centre for confirmation of the diagnosis of AT recurrence. Furthermore, telephone calls were performed during the follow-up. All documented ATs episodes > 30 s after the index procedure, with standard ECG or 24 h ECG Holter monitoring and during both planned and symptom driven consultation, were considered as a recurrence. A BP of 3 months was applied. Follow-up period was truncated at 1 year. In case of highly symptomatic drug-refractory ATs recurrences, every patient was evaluated to undergo a second ablation. All repeat procedures were performed with RF irrigated-tip CF catheter guided by electroanatomical-mapping system.
an ECv was performed to restore SR: 19 in the CB-Adv group and 28 in the RFCA group ($P = 0.10$). All CB-Adv procedures were performed with a large 28 mm balloon and PVI was successfully achieved in all veins without the need of additional focal catheter applications. In the RFCA group, PVI could be documented in all veins at the end of the procedure. Mean RF energy application time was $41.2 \pm 8.4$ min per patient, and the mean CF observed $18.5 \pm 25$ g. In one patient (2%) an adjunctive RF ablation line on the left-sided interpulmonary carina was needed in order to achieve isolation in these ipsilateral PVs.

**Procedural complications**

Cardiac tamponade occurred in one patient (1%) in the RFCA group. In this case, immediate pericardiocentesis was successfully performed. Two patients experienced femoral pseudoaneurysm (2%) requiring surgical treatment, one in both groups. Transient PNP occurred in two cases (4%) only in the CB-Adv group, during RSPV ablation, with complete resolution before the end of the procedure. At the time of palsy occurrence, PVI was already achieved and no further applications were applied. None of patients died or experienced cerebrovascular events in the peri-procedural period and during the entire follow-up.

**Outcome after the index procedure**

All patients completed the 1 year follow-up. Figure 1 shows clinical outcome of patients according to the ablation strategy (RFCA and CB-AdvA). Overall freedom from ATas off-AADs after a single procedure was achieved in 55/100 patients (55%). At 1 year of follow-up, freedom from ATAs after a single procedure was achieved in 56% patients (28/50) in the CB-Adv group and in 54% of patients (27/50) in the RFCA group ($P = 0.78$) (Figure 2, left panel). If a 3 months BP was taken into consideration, freedom from ATAs off-AADs after a single procedure was 58% (58/100) in the total study population, 60% (30/50 patients) in the CB-Adv group and 56% (28/50 patients) in the RFCA group ($P = 0.71$) (Figure 2, right panel).

**Atrial arrhythmias recurrences**

During the BP, 27/100 patients (27%) had arrhythmia recurrences: 13/27 (48.1%) in the RFCA group, 14 (51.9%) in the CB-Adv group ($P = 1.00$). Of them, only 4/21 patients did not show further arrhythmia episodes (2/4 RFCA group, 2/4 CB-Adv group). During the follow-up, after the BP, a total of 42/100 patients (42%) experienced arrhythmia recurrences after the index procedure: 22/42 patients (52.4%) in the RFCA group and 20/42 patients (47.6%) in the CB-Adv group ($P = 0.84$) (Figure 1). Mean time to first ECG documented recurrence was $3.9 \pm 2.6$ months in RFCA group and $3.3 \pm 2.2$ months in CB-Adv ($P = 0.22$). In the RFCA group ATAs recurred as PAF in 5/22 (22.7%), PersAF in 13/22 (59.1%) and AT in 4/22 (18.2%) patients (Figure 1). AT presented as typical isthmus-dependent flutter in two patients, while as left AT in two individuals. In the CB-Adv group, ATAs recurred as PAF in 9/20 (45%), PersAF in 10/20 (50%), and AT in 1/20 (5%) (Figure 1). AT presented as right isthmus-dependent flutter. Paroxysmal and PersAF recurrences did not differ between both groups (5/14, 35.7% vs. 9/14, 64.3%, $P = 0.10$; 13/23, 56.5% vs. 10/23, 43.5% $P = 0.63$; in the RFCA and in the CB-Adv group, respectively). Moreover, new onset left AT occurred only in two patients having undergone RFCA ($P = 0.49$).

After the BP, 17/42 patients (40.5%) experiencing arrhythmia recurrences underwent successful electrical external cardioversion. The remaining 25/42 (59.5%) decided to pursue medical treatment: 15 continued drug therapy because of symptom amelioration or maintenance of SR with previously ineffective AADs, while 10 underwent a second procedure because of recurrent drug-refractory ATAs. Among those receiving electrical cardioversion, 8/17 underwent a second procedure because of symptomatic recurrences (4/8 RFCA group, 4/8 CB-Adv group). Following the BP, among patients experiencing ATa recurrences, 18/42 patients (42.8%) underwent a repeat procedure, 11 in the RFCA group and 7 in the CB-Adv group ($P = 0.36$) (Figure 1). The repeat procedure was due to PAF in three patients in the CB-Adv group, to PersAF in 10 patients (three in the CB-Adv group and seven in the RFCA group), and in five patients for AT (four in the RFCA group and one in CB-Adv group). AT presented as typical isthmus-dependent flutter in 3/5 patients, 1/5 showed PV reconnection in the RIPV, and 1/5 a roof-dependent left atrial flutter. During the redo procedure with RFCA, LA to PV reconnection was found in 8/18 patients (44.4%) in at least one vein. Among those undergoing the second ablation, late PV recovery could be documented in 3/7 patients (42.9%) of the CB-Adv group, whereas in 5/11 patients (45.5%) of the RFCA group ($P = 1.00$). In two patients undergoing AT ablation, a roof-dependent LA flutter was confirmed by electroanatomical mapping, while a RIPV reconnection could be documented only in one of them. Both patients underwent successful ablation. Arrhythmic recurrences following the second procedure are shown in Figure 1.

**Predictors of arrhythmia recurrence**

After single procedure, univariate predictors of recurrence were LA dimension, AF persistency and arrhythmia recurrences during the BP (Table 2). For each additional month of persistent AF, the risk of arrhythmia recurrence increased by 1.6 times (HR 1.60, 95% CI 1.35–1.90; $P < 0.01$), while having a recurrence during the BP the risk increased by 6.3 times (HR 6.31, 95% CI 3.37–11.83; $P < 0.01$) (Table 2). However, in multivariate analysis, only persistent AF duration and relapses during the BP independently predicted arrhythmia recurrences (Table 2).

**Discussion**

To the best of our knowledge, this is the first study comparing RFCA and second-generation CB-AdvA for the treatment of PersAF after 1 year follow-up. The main findings of our study are: (i) success rate at 12 months follow-up with a single-procedure is comparable between the two strategies (RFCA 56% vs. CB-AdvA 60%); (ii) mean procedure and fluoroscopy times are shorter in CB-AdvA group; and (iii) persistent AF duration and relapses during the BP independently predict arrhythmia recurrences.

**Pulmonary vein isolation in persistent atrial fibrillation: radiofrequency irrigated-tip catheter ablation vs. ablation using the second-generation cryoballoon**

Similarly to previously described experience, in our study, PVI alone achieved by RFCA successfully maintained SR after 12 months
follow-up in 56% in patients undergoing the index procedure. Moreover, we observed that CB-AdvA success rate was comparable to RFCA, since 60% of patients were in stable SR at the end of follow-up. According to recent publications, both techniques achieved similar success rate in treating PAF, underlining that PVI is essential to attain a successful clinical outcome in this group of patients, irrespective of the energy source applied or the device used to achieve this goal. On the other hand, data comparing the abovementioned approaches in the treatment of PersAF are lacking in the literature.

Pulmonary vein ostia and neighbouring areas are important for the

Figure 1 Flow chart demonstrating arrhythmia outcome of patients according to the ablation strategy.

Figure 2 Freedom from ATa recurrences after 1 year follow-up according to ablation strategy (RFCA turquoise line; CB-AdvA red line) off drugs, considering (right panel) or not (left panel) a 3 months blanking period.
initiation and maintenance of AF, since most triggers are located in these regions.8,9 For these reasons, nowadays, wide antral PVI might lead to better outcome following AF ablation. In fact, a wide, antral set of lesions performed around the PVs might affect the areas of slow conduction, wave collision and/or anchor points for re-entrant circuits which are basically involved in the persistency of the arrhythmia. So far, while PVI represents the first step in the any ablative treatment of AF, the role of adjunctive lesions at the time of index procedure is still controversial and poorly standardized. This might explain why clinical success following RFCA in PersAF varies substantially among previous studies.8–11

In the setting of cryoballoon ablation for PersAF, the clinical outcome could be affected by the catheter used.12,13 In our study only the 28 mm second-generation device was used. The novel catheter design results in increased refrigerant flow producing more uniform zone of freezing on the balloon surface, and the large 28-mm balloon allows a larger area of ablation involving the PV antrum. Therefore, due to the wider ablation surface of this novel catheter, it could be hypothesized that the latter could lead to more proximal lesions in the antrum similarly to wide circumferential lesions with RF. Thus, the clinical outcome might also be due to the modification of atrial substrate by potentially targeting rotors and non-PV triggers located in the antrum or alter the influence of the intrinsic cardiac autonomic nervous system. All the above-mentioned mechanisms are involved in the perpetuation and maintenance of AF.14,15 These results highlight the importance of PVI attainment in PersAF ablation regardless the strategy and the source of energy adopted. In our study population, freedom from arrhythmic recurrence could be documented after a single procedure in 56% and 60% of patients in the RFCA and CB-Adv group, respectively. Therefore, in this patient population, further substrate modification with linear lesions and/or CAFEs ablation performed at the time of the index procedure might be considered in order to ameliorate the long-term clinical outcome. In this setting, a more versatile focal RF catheter might be preferred in order to achieve additional lesions outside the PV antrum and potentially obtain higher rates of freedom from AF in this patient population. However, further randomized studies with longer follow-up are needed to finally confirm this preliminary data.

### Shorter procedural and fluoroscopy times

In our study, CB-AdvA was associated with significantly shorter ablation procedure duration compared with the RFCA approach. Data available in the literature vary among published reports considering both PAF and PersAF.16–18 However, they mainly refer to the first-generation cryoballoon. According to recent experiences, CB-Adv allows faster procedures with lower exposition to fluoroscopy as compared with its predecessor.3 In line with these results, this study highlighted this advantage carried by the CB-Adv over the conventional RFCA. In addition, it should be underlined that these lower times are not associated with different outcome in terms of arrhythmia-free survival, as observed in our series. Procedural and fluoroscopy times in the RFCA group are in line with previous observations;18 however, in the CB-Adv cohort tended to be lower than that in previously published trials. These findings might be explained by the different cumulative experiences with either technique at individual centres.

### Predictors of tachyarrhythmia recurrences after the index procedure

In this study, univariate analysis showed that LA dimensions, arrhythmia recurrences during the BP and the duration of persistent AF affect the outcome after the procedure. However, multivariate analysis demonstrated that only recurrences in the BP and duration of arrhythmia persistency predict the freedom from ATAs after a 1 year follow-up. This study is in agreement with previous observations underlining factors impacting clinical outcome after AF ablation.19–21 In fact, occurrence of arrhythmias within the first 3 months after the procedure and longer duration of PersAF were relevant predictors of the likelihood of 1-year success after the index procedure.

### Limitations

The study was a non-prospective, non-randomized trial conducted in a relatively limited number of patients. Future randomized, larger studies with longer follow-up are needed to confirm these data. Furthermore, in a recently published study, the MC proved slightly less reliable than the classical circular MC. Therefore, the PVI rate might have been overestimated in CB-Adv group. Second-generation 28 mm cryoballoon is associated with significant oesophageal lesions in 19% of the patients.22 Luminal oesophageal temperature (LET) measurement might accurately predict lesion formation potentially enhancing the safety of this novel device.22 However, no LET monitoring nor systematical oesophagastroduodenoscopy was performed in this study, thus underestimating the incidence of oesophageal lesions. Finally, no long-term monitoring has been performed (internal loop-recorder or 7 day Holter), therefore the arrhythmia recurrence rate and asymptomatic episodes might have been underestimated.

**Table 2 Univariate and multivariate Cox regression analysis among patients experiencing arrhythmia recurrences after a single procedure**

<table>
<thead>
<tr>
<th>Variables</th>
<th>β coefficient</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>0.02</td>
<td>1.01 (0.98–1.05)</td>
<td>0.41</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.45</td>
<td>1.89 (0.79–4.52)</td>
<td>0.15</td>
</tr>
<tr>
<td>AF duration</td>
<td>0.01</td>
<td>1.01 (0.99–1.01)</td>
<td>0.29</td>
</tr>
<tr>
<td>LA dimension</td>
<td>0.02</td>
<td>1.09 (1.04–1.14)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BP recurrences</td>
<td>0.32</td>
<td>6.31 (3.37–11.83)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>0.09</td>
<td>1.60 (1.35–1.90)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LA dimension</td>
<td>0.02</td>
<td>1.03 (0.98–1.08)</td>
<td>0.17</td>
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<tr>
<td>BP recurrences</td>
<td>0.41</td>
<td>2.58 (1.15–5.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>0.11</td>
<td>1.31 (1.05–1.63)</td>
<td>0.01</td>
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</tbody>
</table>

The hazard ratio for persistent AF duration considers every month increase.
The hazard ratio for LA dimension considers every millimeter increase.
AF, atrial fibrillation; BP, blanking period; CI, confidence interval; LA, left atrium.
Conclusions

Freedom from ATas following PersAF ablation with RFCA and CB-Adv is comparable at 1 year follow-up after the index procedure. Second-generation cryoballoon ablation is associated with shorter procedure time and radiation exposure as compared with RF point-by-point catheter ablation in achieving PVI. ATas occurrence during the BP and longer time of PersAF seem to be significant predictors of arrhythmia recurrence after the index procedure.

Conflict of interest: G.B.C. and C.d.A. receive compensation for teaching and proctoring purposes from AF solutions Medtronic.

References


