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Efficacy and safety of the second generation cryoballoon ablation for the treatment of paroxysmal atrial fibrillation in patients over 75 years: a comparison with a younger cohort

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Aims In this double centre, retrospective study, we aimed to analyse the 1-year efficacy and safety of cryoballoon ablation (CB-A) in patients older than 75 years compared with those younger than 75-years old.

Methods and results Fifty-three consecutive patients aged 75 years or older with drug-resistant paroxysmal AF (PAF) who underwent pulmonary vein isolation (PVI) by the means of second generation CB-A, were compared with 106 patients aged <75 years. The mean age in the study group (>75 years) was 78.19 ± 2.7 years and 58.97 ± 8.5 in the control group. At 1-year follow-up the global success rate was 83.6% and did not significantly differ between older (10/53) and younger patients (16/106) (81.1 vs. 84.9%, $P = 0.54$). Transient phrenic nerve palsy was the most common complication which occurred in eight patients in the younger group and in three in the older group (7.5 vs. 5.7%, respectively, $P = 0.66$).

Conclusions The results of our study showed that CB-A for the treatment of PAF is a feasible and safe procedure in elderly patients, with similar success and complications rates when compared with a younger population.

Keywords Cryoballoon • Second-generation cryoballoon • Atrial fibrillation • Elderly

Introduction

Second generation cryoballoon ablation (CB-A) (Arctic Front Advance, Medtronic), has proven to be very effective in the treatment of patients affected by drug-refractory atrial fibrillation (AF).[1–3] Several nonrandomized clinical studies have addressed the issue of catheter ablation in the elderly and have shown favorable rates of success,[4] but little is known about the results of CB-A in the elderly population. In this double centre, retrospective study, we aim to analyse the 1-year efficacy and safety of CB-A in patients older than 75 years compared with those younger than 75-years old.

Methods

Patient characteristics

Consecutive patients aged 75 years or older, with drug-resistant paroxysmal AF (PAF) who underwent pulmonary vein isolation (PVI) by the

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What's new?

- This is the first study comparing the efficacy and safety of pulmonary vein isolation by means of second generation cryoballoon between patient younger and older than 75 years.
- Pulmonary vein isolation with CB-A is an effective treatment for atrial fibrillation in patients aged over 75 years.
- The complication rate of PVI by means of CB-A is no different between patients older and younger than 75 years.

means of CB-A as the index procedure from June 2012 to February 2016 in two centres were retrospectively included in our analysis. A second group of patients, aged <75 years, who underwent PVI by the means of CB-A as the index procedure during the same period of time, were randomly selected in a 1:2 ratio as a control group. The exclusion criteria were any contraindications for the procedure, including the presence of an intracavitary thrombus, uncontrolled heart failure, contraindications to general anaesthesia and inability to provide informed consent. The study was approved by our local Ethical Committee and was carried out in accordance with the ethical principles for medical research involving human subjects established by Helsinki's Declaration, protecting the privacy of all the participants as well as the confidentiality of their personal information.

Preprocedural management

All patients provided written informed consent to the procedure. All antiarrhythmic drugs (AADs) were discontinued at least 3 days before ablation, apart from amiodarone which was stopped 1 month before. A transthoracic echocardiogram (TTE) was performed within 1 week prior to ablation. To exclude the presence of intracavitary thrombi, all patients underwent transesophageal echocardiography the day before the procedure. All patients underwent a preprocedural computed tomography (CT)-scan to assess detailed left atrium (LA) and pulmonary vein (PV) anatomy.

Ablation procedure

Our standard ablation procedure has been previously reported in detail. Briefly, after obtaining LA access, through a steerable 15 Fr sheath (FlexCath Advance, Medtronic), an inner lumen mapping catheter (ILMC) (Achieve, Medtronic) was advanced to each PV ostium. A 28-mm Cryoballoon Advance (Arctic Front Advance, Medtronic) was advanced, inflated and positioned at each PV ostium. Optimal vessel occlusion was considered as achieved upon selective contrast injection showing total contrast retention with no backflow into the atrium. Once occlusion was documented, cryothermal energy was commenced. Standard cryoenergy applications lasted at least 180 s. Usually, the left superior PV (LSPV) was treated first, followed by the left inferior (LIPV), right inferior (RIPV), and right superior (RSPV). PV activity was recorded with the ILMC at a proximal site within 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. In cases of phrenic nerve palsy (PNP), recovery of diaphragmatic contraction was carefully monitored for 30 min. Further additional cryoenergy applications were not applied if the veins were isolated following the initial freeze. If needed, pacing from the distal and/or proximal coronary sinus was performed to distinguish far field atrial signals from PVPs recorded on the mapping catheter, for left- and right-sided PVs, respectively. During the entire procedure, activated clotting time was maintained over 250 s by supplementing heparin infusion as required.

Phrenic nerve monitoring

Phrenic nerve (PN) monitoring was performed during ablation of both right sided veins. Prior to ablation of the right-sided PVs, a standard decapolar catheter was placed in the superior vena cava or in the right subclavian vein in order to pace the right PN (20–24 mA at 1.0–2.0 ms pulse width at a cycle length of 1200 ms) during ablation. PN capture was achieved when contraction of the right hemidiaphragm could be observed both by fluoroscopic imaging and with manual palpation of the abdomen. The exact position of optimal PN stimulation was then captured in two fluoroscopic projections in order to memorize it. PN pacing started once the temperature reached –20 °C in order to avoid balloon dislodgement due to diaphragmatic contraction in the first phase of cryoenergy application. Pacing was continued throughout the entire duration of cryoenergy delivery. Of note, as the procedure was performed under general anaesthesia, it is important to underline that only short acting paralytic agents were used to facilitate intubation. In cases of PN injury, the freeze was immediately aborted and observed for recovery. Moreover, as from December 2013, an immediate deflation technique was performed in cases of PNP as described by Ghosh *et al.*[5]

Post-ablation management

Patients were discharged the day after ablation if clinical status was stable. Following the intervention, the patients were continuously monitored with ECG telemetry for at least 18 h. Prior to hospital discharge, all patients underwent TTE in order to exclude pericardial effusion, and a chest X-ray was also performed. Oral anticoagulation was commenced the evening of the procedure and continued for at least 2 months. The decision to continue AADs after the blanking period (BP) or to perform a repeat procedure was taken in cases of a first episode of recurrence of AF.

Follow-up

All patients who were included in the survival analysis underwent physical examination and a 24-h Holter recordings at 1, 3, 6, and 12 months after the procedure. Additional Holter monitoring was performed if arrhythmic symptoms occurred. We considered a post-ablation BP of 3 months. AADs were continued during the BP.

Statistical analysis

Continuous variables are expressed as mean ± SD or median and percentile 25 and 75 in case of abnormal dispersion tendencies. Categorical variables are expressed as percentages. Cox regression analysis was applied in order to evaluate potential predictors of AF recurrence. Event-free survival rates were estimated by the method of Kaplan–Meier. All analyses were performed with SPSS Statistics for Windows, Version 24.0.

Results

Baseline population characteristics

A total of 159 patients were included in the analysis. Fifty-three patients with drug-resistant PAF older than 75 years constitute the study group and 106 patients younger than 75 years who were included as the control group.

The baseline characteristics are presented in *Table 1*. In brief, the mean age in the study group (>75 years) was 78.19 ± 2.7 years and 58.97 ± 8.5 in the control group. The prevalence of arterial hypertension (AHT) (79.2 vs. 41.3%, $P < 0.05$), coronary artery disease (CAD)

Table 1 Baseline characteristics of the study population

	Younger than 75 years (n = 106)	Older than 75 years (n = 53)	P value
Age (years)	58.97 ± 8.5	78.19 ± 2.7	<0.05
Male gender	62 (58.5%)	24 (45.3%)	0.12
Hypertension	43 (41.3%)	42 (79.2%)	<0.05
Dyslipidemia	32 (30.8%)	25 (47.2%)	<0.05
Diabetes mellitus	9 (8.7%)	6 (11.3%)	0.59
CAD	8 (7.5%)	10 (18.9%)	<0.05
Chronic heart failure	3 (2.9%)	3 (5.7%)	0.39
Previous TIA/stroke	2 (1.9%)	(15.1%)	<0.05
CHA_2DS_2-VASc score	1.3 ± 1.2	4.0 ± 1.3	<0.05
CHA_2DS_2-VASc score > 3	5 (4.7%)	35 (66%)	<0.05
CIEDs (Pacemaker/ICD/ILR)	7 (6.6%)	6 (11.3%)	0.36
Body mass index	25.8 ± 4.7	26.0 ± 4.0	0.78
Left ventricular ejection fraction (%)	59.9 ± 6.4	59.2 ± 5.2	0.51
Left atrial diameter (mm)	40.9 ± 6.6	41.4 ± 7.2	0.72
Left ventricule filling pressure (E/e')	8.8 ± 2.9	12.3 ± 3.8	<0.05

Categorical variables are expressed as absolute and percentage (in brackets). Continuous variables are expressed as mean ± SD. TIA, transient ischaemic attack; CAD, Coronary artery disease; CIEDs, Cardiac implantable electronic devices.

Table 2 Procedural characteristics and follow-up

	Younger than 75 years	Older than 75 years	P value
Procedural time (min)	64.7 ± 20.7	70.9 ± 29.2	0.13
Fluoroscopy time (min)	14.6 ± 6.4	13.2 ± 5.2	0.21
Freezes in LSPV	1.3 ± 0.5	1.3 ± 0.4	0.52
Freezes in LIPV	1.2 ± 0.4	1.3 ± 0.5	0.89
Freezes in RSPV	1.3 ± 0.5	1.3 ± 0.5	0.62
Freezes in RIPV	1.2 ± 0.4	1.1 ± 0.3	0.13
LSPV freeze duration (s)	239.4 ± 96.2	224.2 ± 78.2	0.32
LIPV freeze duration (s)	227.3 ± 91.4	224.2 ± 85.8	0.84
RSPV freeze duration (s)	237.1 ± 96.5	227.5 ± 87.5	0.55
RIPV freeze duration (s)	228.5 ± 89.7	212.8 ± 61.8	0.25
Min temp in LSPV (°C)	-52.3 ± 4.9	-50.7 ± 5.5	0.06
Min temp in LIPV (°C)	-48.5 ± 6.0	-47.6 ± 4.4	0.32
Min temp in RSPV (°C)	-51.7 ± 5.1	-51.5 ± 6.2	0.81
Min temp in RIPV (°C)	-49.8 ± 6.7	-50.5 ± 5.6	0.55
Follow-up (months)	13.8 ± 2.4	14.2 ± 6.4	0.56

Continuous variables are expressed as mean ± SD. Min temp, minimal temperature; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

(20 vs. 8%, $P < 0.05$), previous stroke or transitory ischaemic attack (TIA) (15.1 vs. 1.9%, $P < 0.05$), CHA2DS2VASC score (4.0 ± 1.3 vs. 1.3 ± 1.2, $P < 0.05$) and the Left ventricle filling pressure (E/e') (12.3 ± 3.8 vs. 8.8 2.9, $P < 0.05$) were significantly higher in the older vs. younger patients respectively.

All patients had failed treatment with at least a class I or III AAD or needed to stop them due to poor tolerability. At the time of the procedure, 92.5% of the patients in the study group and 85.8% in the control group were on AADs ($P = 0.23$).

Anatomical characteristics

No patient was excluded due to anatomical reasons based on the pre-procedural CT scan. A left common ostium was observed in three patients (5.7%) in the older group and in six (5.7%) in the younger group ($P = 1.0$). A right-sided middle vein could be observed in three patients (5.7%) in the older group and in four (3.8%) of the younger group ($P = 0.59$). In case of a common ostium, the standard approach was to address, sequentially, the superior and the inferior branches delivering a single cryoenergy application for each one.

Procedure characteristics

All the patients underwent the procedure with the large 28-mm CB-A. At the beginning of the procedure, all patients were in sinus rhythm (SR). In two patients of the older group, AF was induced during the procedure; one of these patients returned to SR during ablation of the LSPV, the other patient required electrical cardioversion at the end of the procedure. There were no significant differences in the mean procedural (70.9 ± 329.2 vs. 64.7 ± 20.7, $P = 0.13$) and fluoroscopic (13.2 ± 5.2 vs. 14.6 ± 6.4, $P = 0.21$) times in the older vs. younger groups, respectively. Procedural time was considered from groin puncture to extraction of all catheters from the patient. Procedural details are shown in *Table 2*.

Outcomes

Efficacy

After a mean follow-up period of 13.97 ± 4.2 months, a total 133 out of 159 patients (83.6%) were free of any atrial arrhythmic event (AAE) after the BP. Freedom from recurrences at 1-year follow-up, was not significantly different in older patients (10/53) compared with the younger group (16/106) (81.1 vs. 84.9%, $P = 0.54$). During the BP, older patients had more recurrences than the younger group (eight patients: 15.1% vs. five patients: 4.7%; $P = 0.03$). Most of the patients that suffered a recurrence in the BP, presented also a recurrence then after. This happened in six out of the eight patients in the older group and in three out of the five patients of the younger group.

As above mentioned, 16 patients presented a PV abnormality, of these, 13 (81.3%) (Younger group: 9; Older group: 4), where free of any AAE after the BP. The recurrence rate was not significantly different among patients with a PV abnormality compared with those with a normal PV anatomy (18.8 vs. 16.1; $P = 0.73$). A cardiac implantable electronic device was present in 13 patients. Five patients (38.5%) in this subgroup (younger group: two; older group: three) experienced a recurrence after the BP. Interestingly, four out of five did not complain about palpitations and the recurrence was only detected on the device.

Finally, after the BP, four patients in the younger group and nine in the older group, were on AADs (3.8 vs. 17%, $P < 0.05$). Of note, most of the patients who were advised to continue AADs (except for one patient of the older group), suffered a recurrence during the BP.

Table 3 Redo procedures

	Age		PV reconnections				ML	RL	PB	CFAE	Recurrence after second procedure
			LS	LI	RS	RI					
PATIENT 1	75	PAF	-	-	-	+	–	-	-	-	No
PATIENT 2	76	PAF	-	-	-	+	–	-	-	-	No
PATIENT 3	35	PAF	-	-	+	-	-	-	-	-	Yes
PATIENT 4	49	PAF	+	+	-	+	-	-	-	-	No
PATIENT 5	66	PAF	-	-	+	–	+	+	+	+	Yes
PATIENT 6	63	LA Roof depended Flutter	+	-	-	+	+	+	-	-	No
PATIENT 7	75	LA Roof depended Flutter	-	-	-	-	-	+	-	+	No

PAF, paroxysmal AF; LS, left superior; LI, left inferior; RS, right superior; RI, right inferior; ML, mitral line; RL, roof line; CFAE, complex fractionated atrial electrograms; PB, Posterior box; LA, Left Atrium.

Redo procedures

Seven out of the 25 patients with recurrences after the BP (3 in the elderly group and 4 in the younger branch) underwent open irrigated focal tip RF ablation guided by electroanatomical mapping as a redo-procedure. In the older group three patients underwent repeat procedures. Two patients recurred with PAF and re-isolation was performed in RIPV in both. The third patient presented with a roof dependent left atrial flutter. Ablation of the critical isthmus led to conversion to SR. Further pacing maneuvers proved bidirectional block across the line. The main data of the redo-procedures is summarized in *Table 3*.

Predictors of recurrences

In the univariate Cox regression analysis, the LA diameter (HR: 1.0, 95% CI: 1.01–1.13, $P < 0.05$), the presence of AHT (HR: 2.52, 95% CI: 1.05–6.04) and the LV filling pressure (E/e' ratio) (HR: 1.27, 95% CI: 1.11–1.50, $P < 0.05$) were found as predictors of recurrence. In the multivariate analysis, only the E/e' ratio was an independent predictor of recurrence (HR: 1.26, 95% CI: 1.03–1.54, $P < 0.05$).

Complications

The most frequent complication consisted of PNP, which presented in eight patients of the younger group and in three of the older group (7.5 vs. 5.7%, respectively, $P = 0.66$). In one patient of the younger group, the PN function did not recovered, and at the time of follow-up, there was a persistent elevation of the right hemidiaphragm in the chest X-ray. In all the other cases the PN function recovered before the end of the procedure. One patient in the elderly group presented a groin haematoma that did not require further intervention, and one patient of the younger group presented a femoral pseudoaneurysm that required thrombin injection. No major complications occurred (*Table 4*).

Table 4 Adverse events in the study population

	Younger than 75 years	Older than 75 years	*P* value
Death related to the procedure	0	0	1.0
Atrial-esophageal fistula	0	0	1.0
Thromboembolic complications			
Stroke	0	0	1.0
Transient ischaemic attack	0	0	1.0
Cardiac tamponade	0	0	1.0
Severe PV stenosis	0	0	1.0
Retroperitoneal haematoma	0	0	1.0
Femoral pseudoaneurysm	1 (1%)	0	0.48
Transient PNP	7 (6.6%)	3 (5.7%)	0.82
Persistent PNP	1 (1%)	0	0.48

PV, pulmonary vein; PNP, phrenic nerve palsy.

Discussion

This is the only study comparing the efficacy and safety of CB-A for the treatment of AF in patients older than 75 years with a cohort younger than 75 years. The main findings are that: (i) CB-A is an effective procedure for the treatment of AF in patients older than 75 years, granting freedom from AF/AT in 81.1% of patients, (ii) CB-A is safe in this patient population, and (iii) high LV filling pressures predicted arrhythmic recurrence.

Efficacy

A well-known limitation of the previously published randomized controlled trials of PVI for the treatment of AF, such as the ThermoCool AF,[6] RAAFT-2,[7] STOP-AF,[2] and 'Fire and ice' trial[1] is that the elderly has been largely excluded from the study cohorts.[4,8] This is probably due to the common belief that given the fact that the fibrosis and atrial remodeling increase with aging, it is likely that simple PVI will result in a lower success rate in older patients compared with younger individuals. Several non-randomized, retrospective studies have explored this issue in the field of RF ablation and have shown promising results. Corrado *et al.*[9] evaluated the efficacy and safety of catheter ablation for AF in patients over the age of 75. Freedom of AF after a single procedure was observed in 127 patients (73%), with a mean follow-up of 20 ± 14 months. Of the 47 patients with recurrent

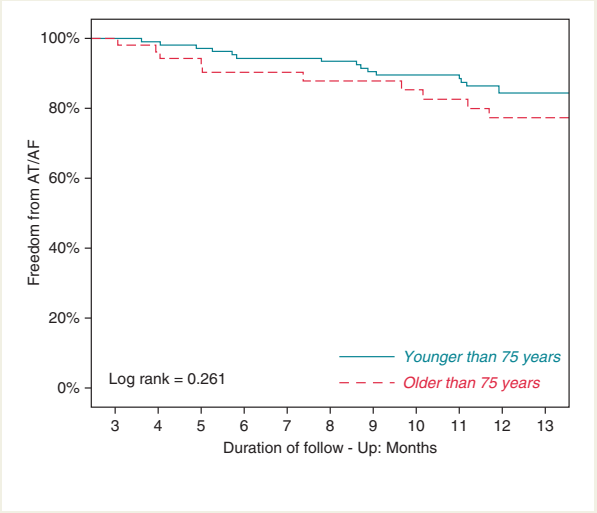

Figure 1 Kaplan-Meier curve for freedom from AF/AT recurrence.

AF, 20 underwent a second ablation. Freedom from AF was achieved in 16(80%) of the 20 patients. Zado *et al.*[10] performed a single centre, long-term study that reviewed 1165 patients, having undergone 1506 AF ablation procedures over the course of 7 years. The above mentioned article included 32 patients aged 75 or older and reported a success rate of 86% in this specific group of individuals. More recently, Metzner *et al.*[11] reported the long-term results of RF ablation in 93 patients over 75 years. Following a single procedure, 35/93 (38%) patients were in stable SR after a mean FU of 37 ± 20 months. After more than one procedure, 55/93 (59%) patients were ultimately in stable SR (76% PAF, 41% persAF, and 20% long-standing persAF). Also, they reported 8(5.8%) major (2 pericardial tamponades, 1 severe bleeding and 2 haemothorax) and 26 minor (19%) complications.

In 2010 our group published a prospective study analyzing the results of first generation CB in septuagenarians with paroxysmal AF (PAF).[12] Although the study cohort comprised a limited number of patients, the results were promising, with success rate of 62% at a mean follow-up of 11.5 ± 4.7 months. In this study, we observed a significantly higher rate of freedom from AF in patients initially affected by PAF (81.1%) if compared with the abovementioned article. This might be the result of the technical improvements characterizing the CB-A if compared with its predecessor. In fact the number of injection ports has been doubled, from four to eight, and these have been positioned more distally on the catheters shaft resulting in a larger and more uniform zone of freezing on the balloons surface if compared with the previous version.

Recently, Potts *et al.*[13] performed a single centre study describing the outcomes of CB-A in 40 patients (9 with persistent AF) over 75 years. After a mean follow-up of 15.1 ± 8.2 months (range 3–35 months) 31/40 patients (77.5%) were free of any AAE, and in the Kaplan-Meir analysis, the freedom from AAE at 12 months was 86%. He also reported one major complication in a patient presenting a late pericardial tamponade and three temporary PNPs. The two main handicaps of the study are the lack of a control group and the small number of patients.

The results of this study are in line with previously published data in other observational studies, in which the authors report a success rate of CB-A ablation on a 12 months follow-up period around 82–86% in patients presenting with PAF.[3,14,15] When comparing both groups in our study, there was no significant difference in the success rate. Importantly, when interpreting this result, one must take into account that patients with persistent AF were excluded from the analysis and that the follow-up is limited to 1 year, and even there is no significant difference in the rate of recurrence, there is a slight trend toward a higher recurrence in the elderly population. Longer follow-up in the elderly population undergoing CB-A needs to be addressed in further studies.

Interestingly, we found that older patients had more recurrences during the BP (15.1 vs. 4.7%; $P = 0.03$) and that virtually all the patients presenting a recurrence during the BP in the elderly group, suffered from relapses of AF also after the first 3 months. This issue had recently been addressed in a article by Mugnai *et al.*,[16] in which the authors divided a predefined 3-month BP into an early BP of 1.5 months and a late BP of the next 1.5 months. The authors found that AAEs during the BP were strongly associated with late recurrences (hazard ratio 6.79; 95% CI 3.52–10.14; $P < 0.0001$) and that when AAEs occurred later than 1.5 months, patients systematically experienced a late recurrence. In accordance, the mean time to recurrence in the BP in the elderly group was 44.8 ± 26.2 days, almost all of these patients presented a recurrence thereafter. This might reflect a higher degree of fibrosis of the LA in the older population.

Safety

Importantly, our results show that CB-A is a safe procedure in elderly patients. This is in line with previous reports suggesting that PVI with RF in elderly patients was not associated with an increased number of complications if compared with younger patients. Of the 194 ablation procedures reported by Corrado *et al.*,[9] (2.6%) major complications were observed. Similarly Zado *et al.*,[10] reported that there was no significant difference in the incidence of major (3.3 vs. 2.9%; P = NS) or other (4.8 vs. 5.9%; P = NS) complications among the young and elderly groups.

There were no cases of cardiac tamponade, stroke or retroperitoneal haematoma. The most frequent adverse event was transient PNP, which was not different between groups. Except in one patient, the PN recovered during the procedure. In this patient, a permanent phrenic palsy was reported and at the time of follow-up, he was been followed by the pneumology department without any further therapy. Despite the high CHA_2DS_2VASC score there were no cerebral embolic events related to the procedure in neither group, possibly reflecting the low thrombogenicity of cryothermal energy as well as the effectiveness of the current anticoagulation recommendations.

Predictors of recurrence

At the multivariate analysis high LV filling pressures, reflected by a high E/E' ratio was the only independent predictor of risk of recurrence. This is consistent with previously reported findings.[17]

Limitations

Our study has some limitations. First, the study was retrospective, which may restrict our ability to draw substantial conclusions. We did not systematically monitor possible procedural complications (e.g. heart CT scan for PV stenosis) therefore the complication rate may have been underestimated. Not all the patients have a CIED and therefore, asymptomatic episodes may have occurred unnoticed and our success rate may have been overestimated. In addition we did not perform voltage mapping during repeat procedures in the older patients group. This probably would have led to the documentation of a more advanced atrial disease which might have benefitted from a more extensive ablation strategy

Conclusion

The results of our study showed that CB-A for the treatment of PAF is a feasible and safe procedure in elderly patients, with similar rates of success (Older vs. younger: 81.1 vs. 84.9%, $P = 0.54$) and complications when compared with a younger population.

Conflict of interest: Dr. G.-B.C. and Dr. C.d.A. have received compensation for teaching purposes and proctoring from AF Solutions and Medtronic. Dr. P.B. has received research grants on behalf of the center from Biotronik, Medtronic, St. Jude Medical, Sorin, and Boston Scientific and speaker's fees from Biosense Webster, Biotronik, and Medtronic. Dr. C.d.A. is a consultant for Daiichi Sankyo. Dr. G.M. has received an educational grant for the Postgraduate in Cardiac Electrophysiology and Pacing academic course from Medtronic. Dr. J.-P.A. is currently receiving an educational grant from St. Jude medical for the Postgraduate in Cardiac Electrophysiology and Pacing academic course.

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