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Impact of an additional right pulmonary vein on second-generation cryoballoon ablation for atrial fibrillation: a propensity matched score study

Ken Takarada[1] · Erwin Ströker[1] · Juan-Pablo Abugattas[1] · Valentina de Regibus[1] · Hugo-Enrique Coutiño[1] · Ian Lusoc[1] · Lucio Capulzini[1] · Juan Sieira[1] · Giacomo Mugnai[1] · Francesca Salghetti[1] · Rajin Choudhury[1] · Saverio Iacopino[2] · Carlo de Asmundis[1] · Pedro Brugada[1] · Gian-Battista Chierchia[1]

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Abstract

Purpose Cryoballoon (CB) technology in the context of anatomical pulmonary vein (PV) variants might hypothetically hamper successful PV isolation (PVI). Our aim was to assess the impact of a right middle PV (RMPV) in the setting of second-generation cryoballoon (CB advance—CB-A), on procedural parameters and on mid-term follow-up.

Methods Consecutive patients with AF presenting RMPV (RMPV+) at the pre-procedural computed tomography who underwent PVI by CB-A were enrolled. Comparison with propensity score-matched patients without RMPV (RMPV−) was performed. Acute procedural parameters and clinical follow-up were assessed.

Results A total of 240 patients (80 RMPV+) were included in the analysis. Twelve of 80 (15%) RMPV+ patients underwent a direct cryo-application in this variant and accomplished the isolation without phrenic nerve palsy, whereas in 25 of 80 (31%) RMPV+ patients, the RMPVs were not targeted directly nor indirectly (by co-occlusion during application at a major PV). At a median follow-up of 17.3 [interquartile range 11.3–26.5] months, there was no significant difference in AF-free survival between RMPV+ and RMPV− patients (78.8 vs 78.1%, $P = 1.00$), and the recurrence of atrial arrhythmias among patients with versus without an intentional or indirect cryo-application to the RMPV was not different (22 vs 20%, $P = 1.00$).

Conclusions Mid-term outcome after CB-A ablation did not differ between RMPV+ and RMPV− patients. Within RMPV+ patients, outcome was similar between those with versus without a cryo-application (either direct or indirect) to the additional vein.

Keywords Additional pulmonary vein · Second-generation cryoballoon · Atrial fibrillation · Pulmonary vein isolation

1 Introduction

Second-generation cryoballoon (CB-A, Arctic Front Advance, Medtronic, Minnesota, USA) enhanced procedural efficacy of pulmonary vein isolation (PVI) compared to the first-generation device [1–5], and demonstrated similar efficacy and safety to RF ablation with contact force-sensing [6, 7]. Although the CB-A can create a large circumferential lesion around the pulmonary vein (PV) ostium in a single application, anatomical variants of the PV drainage pattern might hypothetically hamper successful PVI when using this tool.

Additional PVs can be observed in up to 17–23% of patients undergoing AF ablation. In this setting, the right middle pulmonary vein (RMPV) is the most frequently observed additional vessel. The latter can be identified in up to 8–20% of patients [8, 9]. In the current study, we analyzed the impact of the presence of an RMPV on the procedural outcomes, mid-term efficacy, and safety of CB-A in patients undergoing PVI for drug resistant AF.

Ken Takarada and Erwin Ströker contributed equally to this work.

✉ Gian-Battista Chierchia
gbchier@yahoo.it

[1] Heart Rhythm Management Center, Postgraduate Program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, 101 Laarbeeklaan, 1090 Brussels, Belgium

[2] Villa Maria Cecilia Hospital, Gruppo Villa Maria, Cotignola, Italy

2 Methods

2.1 Study population

This single-center, retrospective observational study consisted of consecutive patients with drug-resistant atrial fibrillation presenting an RMPV at the pre-procedural CT scan who underwent PVI by means of CB-A as the index procedure at our center from June 2012 to May 2015. Consecutive patients with RMPV (RMPV+) were compared with a cohort of propensity score-matched patients without RMPV (RMPV−). Only patients having undergone the index procedure at least 6 months before were included in order to facilitate follow-up. The protocol 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.

2.2 Pre-procedural management

All patients provided written informed consent prior to the procedure. To exclude the presence of thrombi in the left atrial appendage, all patients underwent trans-esophageal echocardiography (TEE) the day before the procedure, along with trans-thoracic examination (TTE) enabling assessment of left atrial (LA), LV, and valvular function. Also, patients underwent a pre-procedural computed tomography (CT) scan to assess LA and PV anatomy. Exclusion criteria: Patients in whom CB ablation was not the index modality of PVI and those with contraindications for the procedure including the presence of a left atrial thrombus, uncontrolled heart failure, and contraindications to general anesthesia. Our local ethics committee approved the study.

2.3 Computed tomography image analysis

Additional PV was defined as an extra vein with an independent atrio-pulmonary venous junction completely separate from the superior and inferior veins. RMPV was defined as an additional pulmonary vein between the right superior and inferior PVs. CT images were first viewed in the axial, coronal, and coronal oblique plane. The ostium was defined as the point of inflection between the LA wall and PV wall. The strictly perpendicular plane to the ostium was determined on a reformatted adaptive plane and was used to measure the maximal and minimal diameters, and the cross-sectional area, as previously described (Fig. 1a–c) [10]. Images in the axial/coronal plane were used to measure the distance from the upper edge of the right superior pulmonary vein (RSPV) to the lower edge of the RMPV, and from the lower edge of the right inferior pulmonary vein (RIPV) to the upper edge of the RMPV respectively (Fig. 1d). Quantitative assessment of the LA was rendered by the 3D threshold-based method. CT images were retrospectively analyzed by two observers in consensus. Any inconsistencies related to anatomical variants and measurements between the observers were resolved by discussion.

2.4 Ablation procedure

The CB ablation procedure was carried out as previously described in detail [11]. Ablation was performed under general anesthesia. Briefly, after gaining LA access, through a steerable 15 Fr sheath (FlexCath Advance®, Medtronic), an inner lumen-mapping catheter (ILMC) (Achieve®, Medtronic) was advanced into each PV ostium. Then, a 28-mm CB-A (Arctic Front Advance™, Medtronic) was advanced inflated and positioned sequentially in the PV ostium of each vein. Optimal vessel occlusion was considered as achieved upon selective contrast injection. Cryothermal applications lasted at least 3 min [12]. A single application per vein was delivered. A second freeze was delivered in case of failure to isolate the PV after the first cycle, in case of nadir temperature greater than − 3 5 °C, and in the occurrence of early PV reconnection. In order to avoid right-sided phrenic nerve palsy (PNP) during cryoablation, the ipsilateral nerve was paced and monitoring was performed by evaluation of diaphragmatic stimulation and measurement of the venous pressure waveform as previously described [13]. During the whole procedure, activated clotting time was maintained > 250 s with boluses of heparin as required.

2.5 Ablation of the right middle pulmonary vein

The RMPV was targeted after having accomplished PVI of the RSPV and the RIPV (Fig. 2). The additional vein was not targeted if (1) the ILMC could not be advanced into the vessel or (2) in the case of simultaneous occlusion of the RMPV with the superior or inferior right-sided PV. All efforts were made to gather electrical information before and after ablation at the RMPV ostium.

2.6 Assessment of pulmonary vein isolation

PV activity was recorded with the ILMC at a proximal site in the ostium prior to ablation in each vein. If needed, pacing from the distal and/or proximal coronary sinus was performed to distinguish far-field atrial signals from PV potentials recorded on the mapping catheter. Moreover, after having retrieved the 15-Fr sheath to the right atrium while keeping the ILMC in the LSPV, a bipolar catheter was introduced through the trans-septal access into the left atrial appendage (LAA), and pacing was performed to distinguish potential far-field left atrial electrical activity from PV potentials. In order to memorize the location of the PVs, positions of the

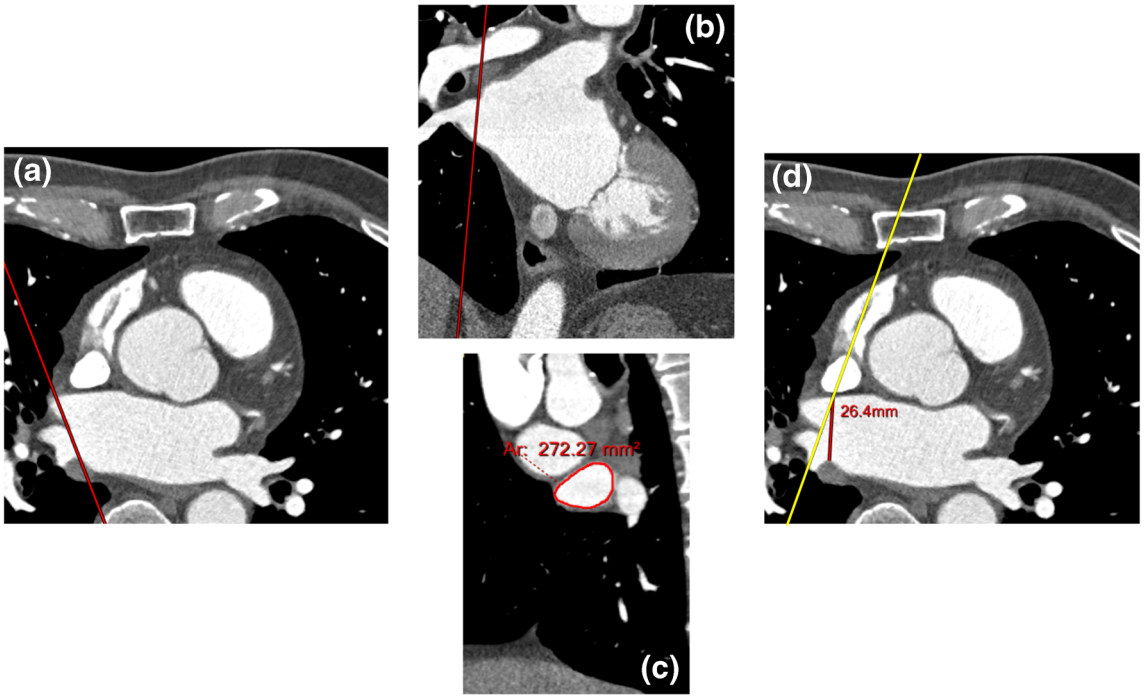

Fig. 1 Measurements at the RMPV. **a**, **b** To assess RMPV diameters, 2 orthogonal planes (axial, coronal) were placed parallel to the course of the vein. **c** A third orthogonal plane, oriented perpendicular to the vein course, was then used to measure the maximal and the minimal diameters, and calculate trans-sectional area at the junction between the RMPV and LA. **d** Example of distance measurement between outer venoatrial junctions of RSPV and RMPV (red line). In yellow, the ostial intersection line at RSPV. LA left atrium, RMPV right middle pulmonary vein, RSPV right superior pulmonary vein

ILMC were fluoroscopically saved in each ostium before ablation in order to guide the operator in PV isolation assessment after ablation. Successful PVI was defined as the absence of all PV potentials (PVPs) or their dissociation from atrial activity, verified immediately after ablation in case of no real-time PVPs visualization and 20 min after the last cryo-energy application.

2.7 Post-procedural management

All patients were discharged the day following ablation. Oral anticoagulation was started the same evening of ablation and continued for at least 3 months. Anti-arrhythmic therapy was administered for 3 months following the procedure and discontinued if the patient was free of AF relapse.

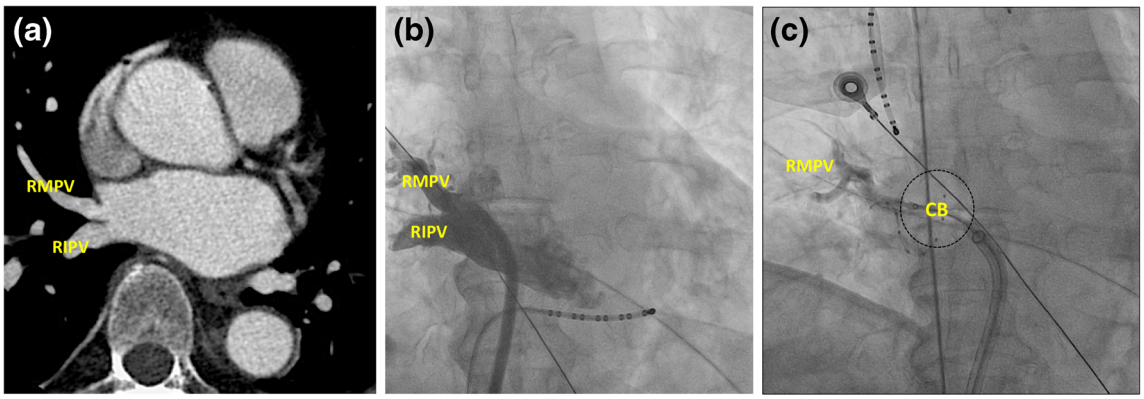

Fig. 2 Example of a selective cryoballoon application to the RMPV. **a** Axial CT image of LA: the RMPV drainage is shown as a completely separated vessel from RSPV and RIPV. **b** AP fluoroscopic view with angiogram of the RMPV. **c** AP fluoroscopic view during a direct occlusion of the RMPV with the balloon. AP antero-posterior, LA left atrium, RIPV right inferior pulmonary vein, RMPV right middle pulmonary vein, RSPV right superior pulmonary vein

2.8 Follow-up

After the procedure, all patients underwent clinical evaluation, an ECG and a 24-h holter recording at 1, 3, 6, and 12 months. All individuals completed at least 6-month follow-up. Recurrence of AF was defined as any ECG documented episode lasting > 30 s as per recent guidelines [14]. A blanking period of 3 months was considered for the study. Atrial fibrillation recurrence during the blanking period was not taken into consideration for final analysis. In order to evaluate the impact of the RMPV on clinical outcome, we compared the patients in our study group with a similar group of patients affected by AF without additional veins having undergone CB-A in the same study period. Finally, we also compared the clinical outcomes between patients in which the RMPV was targeted versus patients in which direct or indirect ablation of the RMPV was not carried out.

2.9 Statistical analysis

Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as mean ± SD or median and interquartile range [IQR] as appropriate. Comparison of continuous variables was performed with a Student's *t* test or the Mann-Whitney *U* test as appropriate. The chi-square test or the Fisher exact test was used to compare categorical variables as appropriate. Event-free survival was estimated by the method of Kaplan–Meier and compared by the log-rank test. A two-tailed probability value of 0.05 was deemed significant. Propensity score matching was performed in order to compare the findings in our study cohort of RMPV+ patients with a similar group of RMPV− patients. Patients were matched in a 1:2 ratio on the basis of propensity scores. Propensity scores were calculated for each patient using multivariable logistic regression with covariates: age, persistent AF (PersAF), gender and LA volume, and using calipers of width equal to 0.2 of the SD of the logit of the propensity score. SPSS version 24 and PS Match 3.33 R extension for SPSS were used for the calculations (Armonk, NY: IBM Corp).

3 Results

3.1 Baseline characteristics and CT image analysis

A total number of 240 patients (74% male, mean age 58.9 ± 12.5 years) were included in the analysis. Seventy-nine percent of the total cohort presented paroxysmal AF (PAF). The baseline characteristics of the matched patients are presented in Table 1. The anatomical characteristics of RMPVs are shown in Table 2. Although most RMPVs are small, larger vessels were noted with a cross-sectional area > 100 mm^2 in 11/80 (14%) of RMPV+ patients. In sub-analysis, a comparison of these anatomical measurements was performed in RMPV+ patients between those presenting with PAF and PersAF, as shown in Table 3. In PersAF patients, distances between RSPV and RMPV were significantly longer than PAF patients, whereas distances from RIPV did not differ.

3.2 Procedural data

Mean procedural time (from groin puncture to removal of catheters from the LA) was 66.8 ± 19.3 min, while the mean fluoroscopy time was 14.9 ± 8.3 min. After cryo-applications, isolation could be demonstrated in all PVs. In 12 of 80 RMPV+ patients (15%), ILMC could be advanced inside the vein and a cryo-application of the RMPV was performed (direct RMPV occlusion). Six of abovementioned patients (6/12, 50%) presented pulmonary vein potentials (PVP) in the RMPVs. In patients in whom the ILMC could not be advanced into the RMPV, the trans-sectional area was significantly smaller compared to patients having got ILMC insertion to that PV (a median ostium area 57.6 [IQR 46.5–72.0] mm^2 vs 128.2 [55.8–160.5] mm^2, $P = 0.004$).

In 43 RMPV+ patients (54%), the RMPV was occluded during the freezing of one of the other major right-sided veins as demonstrated by contrast injection (indirect RMPV co-occlusion), during ablation of RSPV and RIPV in 30 and 13 patients, respectively. In the remaining 25 of 80 (31%) patients, the RMPV could not be occluded, either directly or indirectly during the occlusion of one of the 2 major right-sided PVs. Sub-analysis of the distances from the major PVs to the RMPV in patients with versus without an RMPV co-occlusion, is shown in Table 4.

In the group of patients in whom an application was performed directly into the RMPV, the minimal achieved temperature was significantly warmer than the major PVs (− 42.5 ± 3.6 vs − 49.3 ± 6.2 °C, $P < 0.001$); furthermore, mean procedure time and fluoroscopy time did not differ from those patients without a direct application, respectively (procedure time: 75.3 ± 36.4 vs 66.4 ± 18.0 min, $P = 0.42$; fluoroscopy time: 16.4 ± 9.9 vs 14.9 ± 8.2 min, $P = 0.63$).

3.3 Follow-up

At a median follow-up of 17.3 [IQR 11.3–26.5] months, 188/240 (78%) patients were free from any AF recurrence off AADs. Success rate did not differ significantly among RMPV+ and RMPV− patients (78.8 vs 78.1%, respectively, $P = 1.00$). Recurrence rate among RMPV+ patients with (either direct or indirect) versus without an RMPV application was not statistically different (12/55 [22%] vs 5/25 [20%], $P = 1.00$).

Table 1 Baseline characteristics of patients included ($n = 240$)

	RMPV+ ($n = 80$)	RMPV− ($n = 160$)	P value
Age (years)	58.7 ± 13.0	58.8 ± 12.3	0.79
Male gender	60 (75)	118 (74)	0.88
Body mass index (kg/m^2)	26.4 ± 4.5	26.5 ± 4.5	0.99
Persistent AF	15 (19)	36 (23)	0.62
AF duration (months)†	24 [10–60]	20.5 [6–46]	0.20
Failed class I or III AADs‡	1.2 ± 0.2	1.1 ± 0.2	0.47
Hypertension	45 (56)	72 (45)	0.10
Diabetes mellitus	8 (10)	12 (8)	0.62
Heart failure	4 (5)	8 (5)	1.00
Coronary artery disease	5 (6)	15 (9)	0.47
LVEF (%)	57.1 ± 7.4	57.7 ± 7.2	0.55
Follow-up period (months)	20.8 ± 10.9	19.3 ± 11.1	0.33
LA volume (ml)	104.9 ± 32.6	103.9 ± 35.2	0.83
LA volume index (ml/m^2)	53.7 ± 14.2	52.8 ± 16.0	0.68
Left common PV	25 (31)	57 (36)	0.57
Right common PV	1 (1)	4 (3)	0.67
Left middle PV	1 (1)	0 (0)	0.33

Values are given as mean ± SD, median [interquartile range], or number (%)

AADs anti-arrhythmic drugs, *AF* atrial fibrillation, *CT* computed tomography, *LA* left atrium, *LVEF* left ventricular ejection fraction, *RMPV* right middle pulmonary vein, *PV* pulmonary vein

†From first diagnosis to the index procedure

‡Total number of failed anti-arrhythmic agents

3.4 Complications

The most frequent complication observed was phrenic nerve palsy (PNP) which occurred in 25 (10%) of 240 cases. In 96% (24/25) of those cases, PNP resolved completely during the procedure. In the remaining 1 case, the palsy persisted after discharge for less than 1 month. At the end of follow-up, no patient exhibited phrenic nerve palsy. There was no PNP occurrence in patients who underwent additional direct cryo-application of the RMPV.

4 Discussion

The main findings of our study are (1) mid-term clinical outcome after CB-A ablation was similar between RMPV+ and RMPV− patients, (2) the absence of targeting (by direct or indirect CB occlusion) was observed in 31% of RMPV+ patients without repercussion on clinical outcome, (3) RMPV+ patients without an indirect RMPV co-occlusion with a major PV showed significantly longer distance from RSPV or RIPV to RMPV compared to patients having an indirect RMPV co-occlusion, and (4) direct freeze to RMPV showed no right-sided PNP.

4.1 CB-A ablation in the presence of RMPV

An additional RMPV is one of the most common variations in PV drainage together with a left common PV (LCPV) [8, 15, 16]. Although data on the clinical outcome following PVI with the CB-A in the context of an RMPV is sparse in today's literature, recent articles have analyzed the influence of a LCPV on the success rate of this procedure. Interestingly, there seems to be conflicting evidence on this issue. On the one hand, Shigeta

Table 2 Measurement of RMPV ostium and distance from RSPV/RIPV

Max diameter (mm)	Min diameter (mm)	Trans-sectional area (mm^2)	Distance from RSPV Axial (mm)	Distance from RSPV Coronal (mm)	Distance from RIPV Axial (mm)	Distance from RIPV Coronal (mm)
10.8 ± 3.0 [5.5–21.3]	7.9 ± 2.0 [3.1–14.6]	69.1 ± 37.4 [12.3–272.3]	19.6 ± 3.6 [13.4–32.3]	21.0 ± 3.6 [15.4–32.7]	21.4 ± 3.2 [13.2–30.5]	22.3 ± 4.0 [12.2–31.5]

Values are given as mean ± SD and [minimum–maximum]

Max maximal, *min* minimal, *RIPV* right inferior pulmonary vein, *RMPV* right middle pulmonary vein, *RSPV* right superior pulmonary vein

Table 3 Measurement of RMPV ostium and distance from RSPV/RIPV ($n = 80$)

	PAF ($n = 65$)	PersAF ($n = 15$)	*P* value
Trans-sectional area (mm^2)	85.9 ± 58.5	66.2 ± 35.1	0.09
Axial view			
Distance from RSPV (mm)	19.1 ± 3.3	21.7 ± 4.2	0.01
Distance from RIPV (mm)	21.1 ± 3.3	22.9 ± 3.5	0.44
Coronal view			
Distance from RSPV (mm)	20.4 ± 3.2	23.3 ± 4.4	0.03
Distance from RIPV (mm)	22.0 ± 3.9	23.7 ± 4.0	0.13

Values are given as mean ± SD

PAF paroxysmal atrial fibrillation, *PersAF* persistent atrial fibrillation, *RIPV* right inferior pulmonary vein, *RMPV* right middle pulmonary vein, *RSPV* right superior pulmonary vein

et al. reported worse outcomes in the presence of LCPV; on the other, both Heeger et al. and Ströker et al. showed no difference in outcomes between patients exhibiting a normal PV drainage pattern versus patients with LCPV. Of note of all the abovementioned papers, the article by Heeger et al. was the only multicenter study. Therefore, the results of this article might bare an additional value. Nevertheless, future randomized trials might be needed to elucidate the real value of CB-A in comparison to traditional point-by-point ablation [17–19]. Previous findings seem to indicate that patients with separate ostia for the right middle lobe pulmonary vein(s) tend to have a higher frequency of atrial arrhythmias including AF than those with other PV drainage patterns [20]. In our study, we considered an additional RMPV as a vessel completely separated from the venoatrial junction of major PVs and carefully discriminated the latter from early branching defined as an origin of the first PV branch within 10 mm of the PV ostium [21]. Most RMPVs were small, with maximal and minimal diameters of 10.8 ± 3.0 mm and 7.9 ± 2.0 mm, respectively, and a trans-sectional area of 69.1 ± 37.4 mm^2. This is in line with previous articles focusing on the anatomy of PV drainage patterns [8, 9, 22]. Eleven (14%) of 80 RMPVs were larger than 100 mm^2 in trans-sectional area, which is comparable to major PV dimensions [23].

In our study, among the 12 patients who underwent the cryo-application directly targeting the RMPV, 6 out of 12 of the latter exhibited real-time recordings during cryo-energy delivery. In the other 6 patients, isolation was verified after retrieving the ILMC to a more proximal position in the ostium. In the latter, distal positioning of the ILMC proved crucial in guaranteeing occlusion and stability in the PV ostium of the RMPV. In more than half the proportion of RMPV patients (69%, 55/80), direct or indirect occlusion (co-occlusion of the RMPV during ablation in 1 major PV) could be demonstrated by dye injection. It is contemplated that the distance from the major PV to the accessory PV can be related to the possibility of an accidental RMPV co-occlusion during cryo-applications at the major PVs based on our study results (Table 4). In fact, when using the large 28 mm CB-A, the shaft length covered by the balloon is around 29.9 mm, and the tip diameter is 3.5 mm. As shown in Fig. 3, if the distance between the outer venoatrial junctions of a major PV and the RMPV is less than 21.7 mm, which is calculated from the abovementioned values, the accessory PV should theoretically be covered by the CB-A during cryo-energy delivery in a major PV. Finally, the remaining 31% of RMPV, being small in diameter and without documentation of a direct or indirect CB occlusion, might have been isolated by a "piece meal" approach by targeting the upper and lower rims of the ostia when ablating at the RSPV and RIPV antrum respectively (Fig. 4).

4.2 Freedom from AF recurrence

Our study reported no significant difference in freedom from AF recurrence between patients with versus without RMPV following CB-A ablation. In 31% (25/80) of RMPV patients, the RMPV was not targeted considering that no balloon occlusion (either directly or indirectly) was obtained. Moreover, no electrical information by the ILMC could be retrieved. The small dimensions of these RMPVs might explain why in the

Table 4 The distance from the major PVs to the RMPV between patients with and without co-occlusion with the major right PVs

	Co-occlusion + with RSPV ($n = 30$)	Co-occlusion + with RIPV ($n = 13$)	Co-occlusion− ($n = 37$)	*P* value*	*P* value†
Distance from RSPV axial	18.2 ± 2.7	18.6 ± 2.8	21.1 ± 3.9	0.001	0.04
Distance from RSPV coronal	19.6 ± 3.2	21.0 ± 3.2	22.1 ± 3.8	0.01	0.36
Distance from RIPV axial	21.0 ± 3.0	20.8 ± 4.2	22.0 ± 3.1	0.19	0.31
Distance from RIPV coronal	22.0 ± 3.5	20.3 ± 5.1	23.3 ± 3.7	0.13	0.03

Values are given as mean ± SD

PV pulmonary vein, *RIPV* right inferior pulmonary vein, *RMPV* right middle pulmonary vein, *RSPV* right superior pulmonary vein

**P* value, co-occlusion+ with RSPV versus co-occlusion−

†*P* value, co-occlusion+ with RIPV versus co-occlusion−

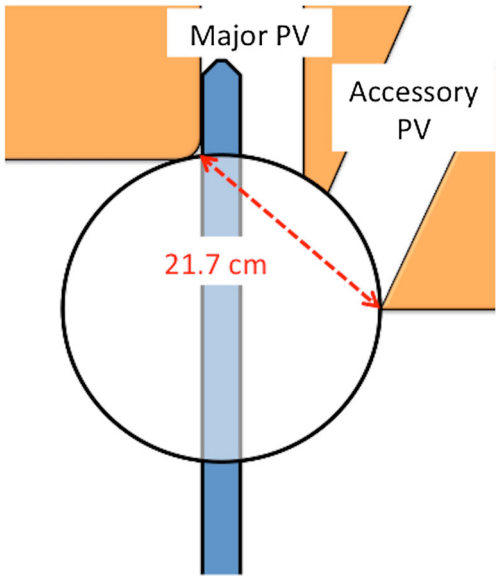

Fig. 3 Schematic drawing showing the contact zone of the cryoballoon against a major PV and a RMPV. The minimal distance is displayed between the outer venoatrial junctions of both vessels, within which the accessary PV can be covered by the balloon at the occlusion of the major PV

latter it proved challenging to insert the ILMC. In addition, forceful insertion of these small vessels was not attempted to avoid unwanted damage to the vessel wall. Hypothetically though, as mentioned above, these small veins might have been indirectly isolated by a "piece meal" approach therefore contributing to clinical success. Finally, one might not exclude that a proportion of the RMPVs in our study might not have played an active role (culprit veins) in triggering AF. Therefore, AF would not have recurred in these patients, even in the absence of RMPV isolation.

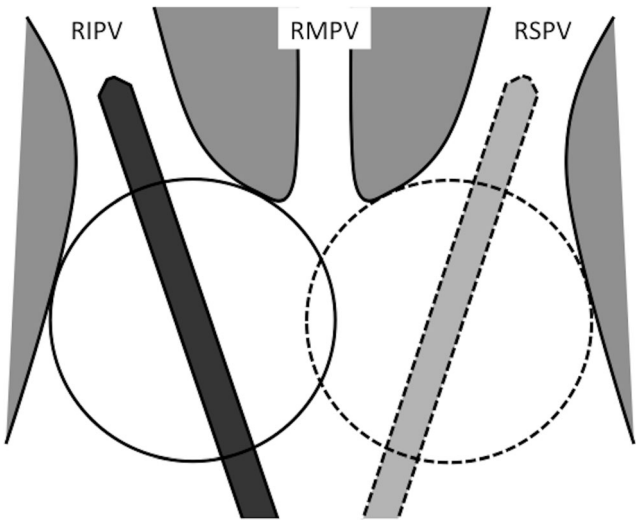

Fig. 4 Schematic drawing showing the hypothesis that an adventitious isolation of RMPV is achieved by creation of a cryo-lesion in the upper and lower rims of the ostia when ablating in the RSPV and RIPV. RIPV right inferior pulmonary vein, RMPV right middle pulmonary vein, RSPV right superior pulmonary vein

5 Limitations

The study was limited by its retrospective single-center design. Our results might not be applicable for persAF patients, considering the relatively low total number of patients in which persAF patients occupied only 21%. Further larger studies are necessary to confirm our findings. We did not systematically monitor possible procedural complications (for example cardiac CT scan for PV stenosis, esophagoscopy in order to verify the presence of esophageal damage or brain MRI for silent cerebral infarctions), that could have caused underestimation of the complication rate. Most importantly, only 10% of patients had implanted devices such as PM, loop recorders, or ICD; therefore, although all patients suffered from symptomatic AF prior to ablation, asymptomatic episodes might have gone undiagnosed and the success rate overrated.

6 Conclusion

CB-A ablation in the settings of AF showed no difference in recurrence rate between RMPV+ and RMPV− patients. In up to one third of RMPV+ patients, the additional vein was not directly targeted due to the size of the vein nor given indirect cryo-application due to the distance from RMPV to RSPV or RIPV. Direct or indirect cryo-application in RMPV did not provide advantageous influence to a mid-term outcome after CB-A ablation for AF recurrences, compared to individuals without CB-A around the RMPV.

Compliance with ethical standards

Conflict of interest Ken Takarada is currently receiving an educational grant from Japanese Heart Rhythm Society. Juan-Pablo Abugattas is currently receiving an educational grant from St. Jude medical for the Postgraduate in Cardiac electrophysiology and Pacing academic course. Carlo de Asmundis receive compensation for teaching purposes and proctoring from AF solutions, Medtronic, member steering committee ETNA-AF Europe Daiichi Sankyo Europe and research grants on behalf of the center from Biotronik, Medtronic, St Jude Medical Abbot, Livanova, Boston Scientific. Pedro Brugada receives speakers' fees from Biotronik, Medtronic. Gian-Battista Chierchia receives compensation for teaching purposes and proctoring from AF solutions, Medtronic.

Ethical approval 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.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Fürnkranz A, Bordignon S, Schmidt B, Gunawardene M, Schulte-Hahn B, Urban V, et al. Improved procedural efficacy of pulmonary vein isolation using the novel second-generation cryoballoon. J Cardiovasc Electrophysiol. 2013;24:492–7.
2. Martins RP, Hamon D, Césari O, Behaghel A, Behar N, Sellal JM, et al. Safety and efficacy of a second-generation cryoballoon in the ablation of paroxysmal atrial fibrillation. Heart Rhythm. 2014;11:386–93.
3. Straube F, Dorwarth U, Vogt J, Kuniss M, Heinz Kuck K, Tebbenjohanns J, et al. Differences of two cryoballoon generations: insights from the prospective multicentre, multinational FREEZE cohort substudy. Europace. 2014;16:1434–42.
4. Aytemir K, Gurses KM, Yalcin MU, Kocyigit D, Dural M, Evranos B, et al. Safety and efficacy outcomes in patients undergoing pulmonary vein isolation with second-generation cryoballoon. Europace. 2015;17:379–87.
5. Di Giovanni G, Wauters K, Chierchia GB, Sieira J, Levinstein M, Conte G, et al. One-year follow-up after single procedure cryoballoon ablation: a comparison between the first and second generation balloon. J Cardiovasc Electrophysiol. 2014;25:834–9.
6. Brugada P, Jourda F, Providencia R, Marijon E, Bouzeman A, Hireche H, et al. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation—a prospective evaluation. Europace. 2015;17:225–31.
7. Squara F, Zhao A, Marijon E, Latcu DG, Providencia R, Di Giovanni G, et al. Comparison between radiofrequency with contact force-sensing and second-generation cryoballoon for paroxysmal atrial fibrillation catheter ablation: a multicentre European evaluation. Europace. 2015;17:718–24.
8. Chen J, Yang ZG, Xu HY, Shi K, Long QH, Guo YK. Assessments of pulmonary vein and left atrial anatomical variants in atrial fibrillation patients for catheter ablation with cardiac CT. Eur Radiol. 2017;27:660–70.
9. McLellan AJ, Ling LH, Ruggiero D, Wong MC, Walters TE, Nisbet A, et al. Pulmonary vein isolation: the impact of pulmonary venous anatomy on long-term outcome of catheter ablation for paroxysmal atrial fibrillation. Heart Rhythm. 2014;11:549–56.
10. Ströker E, de Asmundis C, Saitoh Y, Velagić V, Mugnai G, Irfan G, et al. Anatomic predictors of phrenic nerve injury in the setting of pulmonary vein isolation using the 28-mm second-generation cryoballoon. Heart Rhythm. 2016;13:342–51.
11. Irfan G, de Asmundis C, Mugnai G, Poelaert J, Verborgh C, Umbrain V, et al. One-year follow-up after second-generation cryoballoon ablation for atrial fibrillation in a large cohort of patients: a single-centre experience. Europace. 2016;18:987–93.
12. Ciconte G, Sieira-Moret J, Hacioglu E, Mugnai G, DI Giovanni G, Velagic V, et al. Single 3-minute versus double 4-minute freeze strategy for second-generation cryoballoon ablation: a single-center experience. J Cardiovasc Electrophysiol. 2016;27:796–803.
13. Ghosh J, Singarayar S, Kabunga P, McGuire MA. Subclavian vein pacing and venous pressure waveform measurement for phrenic nerve monitoring during cryoballoon ablation of atrial fibrillation. Europace. 2015;17:884–90.
14. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.
15. Anselmino M, Blandino A, Beninati S, Rovera C, Boffano C, Belletti M, et al. Morphologic analysis of left atrial anatomy by magnetic resonance angiography in patients with atrial fibrillation: a large single center experience. J Cardiovasc Electrophysiol. 2011;22:1–7.
16. Thorning C, Hamady M, Liaw JV, Juli C, Lim PB, Dhawan R, et al. CT evaluation of pulmonary venous anatomy variation in patients undergoing catheter ablation for atrial fibrillation. Clin Imaging. 2011;35:1–9.
17. Shigeta T, Okishige K, Yamauchi Y, Aoyagi H, Nakamura T, Yamashita M, et al. Clinical assessment of cryoballoon ablation in cases with atrial fibrillation and a left common pulmonary vein. J Cardiovasc Electrophysiol. 2017;28:1021–7. https://doi.org/10.1111/jce.13267.
18. Ströker E, Takarada K, de Asmundis C, Abugattas JP, Mugnai G, Velagić V, et al. Second-generation cryoballoon ablation in the setting of left common pulmonary veins: procedural findings and clinical outcome. Heart Rhythm. 2017;14:1311–8. https://doi.org/10.1016/j.hrthm.2017.06.019.
19. Heeger CH, Tscholl V, Wissner E, Fink T, Rottner L, Wohlmuth P, et al. Acute efficacy, safety, and long-term clinical outcomes using the second-generation cryoballoon for pulmonary vein isolation in patients with a left common pulmonary vein: a multicenter study. Heart Rhythm. 2017;14:1111–8.
20. Marom EM, Herndon JE, Kim YH, McAdams HP. Variations in pulmonary venous drainage to the left atrium: implications for radiofrequency ablation. Radiology. 2004;230:824–9.
21. Cabrera JA, Ho SY, Climent V, Sánchez-Quintana D. The architecture of the left lateral atrial wall: a particular anatomic region with implications for ablation of atrial fibrillation. Eur Heart J. 2008;29:356–62.
22. Knecht S, Kühne M, Altmann D, Ammann P, Schaer B, Osswald S, et al. Anatomical predictors for acute and mid-term success of cryoballoon ablation of atrial fibrillation using the 28 mm balloon. J Cardiovasc Electrophysiol. 2013;24:132–8.
23. Kim YH, Marom EM, Herndon JE 2nd, McAdams HP. Pulmonary vein diameter, cross-sectional area, and shape: CT analysis. Radiology. 2005;235:43–9.