



HAL
open science

Cryoballoon ablation of atrial fibrillation in patients with atypical right pulmonary vein anatomy

Camille Pichard, Amélie Nicolas, Vincent Galand, C Coquard, Nathalie Behar, Céline Chérel, J.-C. Daubert, Philippe Mabo, Christophe Leclercq, Dominique Pavin, et al.

► **To cite this version:**

Camille Pichard, Amélie Nicolas, Vincent Galand, C Coquard, Nathalie Behar, et al.. Cryoballoon ablation of atrial fibrillation in patients with atypical right pulmonary vein anatomy. *Archives of cardiovascular diseases*, 2020, 113 (11), pp.690-700. 10.1016/j.acvd.2020.05.008 . hal-02958981

HAL Id: hal-02958981

<https://hal.science/hal-02958981v1>

Submitted on 15 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Cryoballoon ablation of atrial fibrillation in patients with atypical right pulmonary vein anatomy

Abbreviated title: Cryoablation in patients with atypical PV anatomy

Camille Pichard^{a,b,c}, Amélie Nicolas^d, Vincent Galand^{a,b,c}, Charlène Coquard^{a,b,c}, Nathalie Behar^{a,b,c}, Celine Chérel^{a,b,c}, Jean-Claude Daubert^{a,b,c}, Philippe Mabo^{a,b,c}, Christophe Leclercq^{a,b,c}, Dominique Pavin^{a,b,c}, Mathieu Lederlin^d, Raphaël P. Martins^{a,b,c,*}

^a *Service de Cardiologie et Maladies Vasculaires, CHU de Rennes, 35000 Rennes, France*

^b *CIC-IT 1414, Université de Rennes 1, 35000 Rennes, France*

^c *INSERM U1099, 35000 Rennes, France*

^d *Service de Radiologie et d'Imagerie Médicale, CHU de Rennes, 35000 Rennes, France*

* Corresponding author at: Service de Cardiologie et Maladies Vasculaires, CHU de Rennes, 2 rue Henri Le Guilloux, 35000 Rennes, France.

E-mail address: raphael.martins@chu-rennes.fr (R. P. Martins).

Summary

Background. – Cryoballoon ablation is widely used for pulmonary vein isolation in patients with atrial fibrillation. There are no data regarding the clinical efficacy of cryoballoon ablation in patients with atypical right pulmonary vein anatomy.

Aim. – We aimed to evaluate the impact of right pulmonary vein anatomy on the safety and efficacy of cryoballoon ablation.

Methods. – Patients referred for cryoballoon ablation of paroxysmal atrial fibrillation were enrolled prospectively. Left atrial computed tomography was performed before cryoballoon ablation to determine whether the right pulmonary vein anatomy was “normal” or “atypical”. For patients with atypical anatomy, cryoballoon ablation was only performed for right superior and right inferior pulmonary veins, neglecting accessory pulmonary veins.

Results. – Overall, 303 patients were included: 254 (83.8%) with normal and 49 (16.2%) with atypical right pulmonary vein anatomy. First freeze isolation for right superior and right inferior pulmonary veins occurred in 44 (89.8%) and 37 (75.5%) patients with atypical pulmonary vein anatomy, and in 218 (85.8%) and 217 (85.4%) patients with typical pulmonary vein anatomy, respectively (*P* not significant). Phrenic nerve palsies were only observed in patients with normal anatomy (0 vs 26 [8.6%]; *P* = 0.039). Mid-term survival free from atrial arrhythmia was similar, regardless of right pulmonary vein anatomy.

Conclusions. – A significant proportion of patients have atypical right pulmonary vein anatomy. Procedural characteristics, acute pulmonary vein isolation success and mid-term procedural efficacy were similar, regardless of right pulmonary vein anatomy. In addition to left-side pulmonary vein isolation, cryoballoon ablation of right superior and right inferior pulmonary veins only, neglecting accessory pulmonary veins, is sufficient to obtain acute right-side pulmonary vein isolation and mid-term sinus rhythm maintenance in patients with atypical anatomy.

KEYWORDS

Arrhythmias;

Atrial fibrillation;

Catheter ablation;

Electrophysiology;

Cryoablation

Abbreviations: 3D, three-dimensional; AF, atrial fibrillation; CT, computed tomography; LA, left atrium/atrial; PNP, phrenic nerve palsy; PV, pulmonary vein; RIPV, right inferior pulmonary vein; RMPV, right middle pulmonary vein; RSPV, right superior pulmonary vein.

Background

Cryoballoon ablation has become a widely used technique to achieve pulmonary vein (PV) isolation in patients with symptomatic atrial fibrillation (AF). Similar mid- and long-term results compared with radiofrequency ablation have been reported [1, 2]. However, PV isolation using the cryoballoon is critically dependent on circumferential and homogeneous freezing all around the PV ostia, and anatomical factors may affect catheter stability, ablation efficacy and long-term sinus rhythm maintenance. Thus, PV anatomy is an important factor influencing cryoballoon ablation. Indeed, the efficacy of cryoballoon ablation in patients with a left common trunk has been analysed in a few studies, which reported either similar [3, 4] or lower [5, 6] long-term efficacy compared with patients with normal left PV drainage.

A considerably more variable anatomy has been described for right PV drainage, as up to 26% of patients may present a middle lobe vein directly connected to the left atrium (LA) [7]. However, to the best of our knowledge, there are no studies analysing the efficacy of cryoballoon ablation in such patients. Thus, in this study, we prospectively evaluated mid-term efficacy and procedural characteristics of cryoballoon ablation in patients with typical and atypical PV anatomy, and hypothesize that ablation of the right superior PV (RSPV) and the right inferior PV (RIPV), neglecting accessory PVs, is sufficient to obtain acute right-side PV isolation and maintenance of mid-term sinus rhythm.

Methods

Patients and design

Consecutive patients referred to our tertiary centre from 01 January 2015 to 31 October 2018 for cryoballoon ablation of paroxysmal AF were enrolled prospectively. Patients were included if they presented symptomatic drug-refractory AF with at least one recurrence on antiarrhythmic drug therapy. Patients were not included if a left atrial (LA) computed tomography (CT) scan could not be realized before the procedure. This study was approved by the institutional ethics committee, and all patients provided informed consent.

Cardiac CT acquisition and analysis of right PV anatomy

A left atrial CT scan was performed on the day before cryoballoon ablation to analyse PV anatomy.

Image acquisition was performed on a 64-row multidetector CT scanner (Discovery™ CT750 HD; GE Healthcare, Milwaukee, WI, USA) during a single breath-hold, without electrocardiogram gating. Typical acquisition parameters were: field of view 20–25 cm; tube voltage 100–120 kV; tube current 350 mAs with a dose modulation protocol; slice thickness 0.625 mm; and pitch 0.984. Z-axis coverage was limited to the cardiac volume, from the carina to the caudal part of the LA. A bolus of 60–100 mL of iobiditridol (Xenetix® 350; Guerbet, Roissy, France) was injected at 4 mL/s, followed by a 40 mL saline chaser bolus. An automated bolus tracking system was used to synchronize the arrival of the contrast material with the initiation of the scan, with a threshold set at 150 Hounsfield units in the LA. A blind analysis of right PV anatomy was performed by two independent observers (one thoracic radiologist and one cardiologist) using Telemis PACS software, version 4.7 (Telemis SA, Louvain-la-Neuve, Belgium) and through a postprocessing three-dimensional (3D) reconstruction using CARTO-Merge software (Biosense Webster, Diamond Bard, CA, USA). Discordance between readers was adjudicated by a third reader to determine the exact type of anatomy. Ostial architecture (using both external and endoluminal projections) was analysed, identifying PV drainage pattern. For each patient, PV drainage pattern, number of PV ostia and maximal and minimal right PV ostial diameters were assessed. The classification proposed by Marom et al. [7] was used to classify right PV anatomy (Fig. 1); thus, R1, R2, R3, R4 and R5 patterns of right PV anatomy were used to describe patients with one, two, three, four or five right PV ostia draining to the LA, respectively. Then, each pattern was differentiated depending on the draining pattern of the middle pulmonary lobe (e.g. R2a, R2b or R2c, as shown in Fig. 1). In our study, “normal” PV anatomy was defined as patients having two PV ostia (i.e. R2a, R2b and R2c patterns), while “atypical” PV anatomy was defined as those having one, three, four or five PV ostia (i.e. R1, R3a, R3b, R3c, R4a, R4b and R5 patterns).

Cryoballoon ablation procedural characteristics

Before the procedure, transoesophageal echocardiography was performed to exclude the presence of LA thrombus. Vitamin K antagonists were continued (international normalized ratio of 2–3) if prescribed, while non-vitamin K antagonist oral anticoagulation was discontinued and replaced with intravenous heparin before ablation. Procedures were performed under conscious sedation using midazolam and fentanyl as necessary.

Venous access was obtained via the femoral vein. A 6F Xtrem® quadripolar catheter (Sorin SPA,

Milan, Italy) was placed in the coronary sinus via the right femoral vein. A single transseptal puncture was performed under fluoroscopic and pressure guidance, without the use of periprocedural transoesophageal or intracardiac echocardiography. A “single big cryoballoon” approach, using a 28 mm balloon (Medtronic, Minneapolis, MN, USA) was performed, as described previously [8].

The cryoballoon catheter was introduced into the LA through a steerable, 12F inner diameter FlexCath® sheath (Medtronic, Minneapolis, MN, USA) constantly flushed with heparinized saline. An Achieve™ mapping catheter (Medtronic, Minneapolis, MN, USA) was advanced over the cryoballoon to the PV orifice and positioned inside the PV. The cryoballoon was inflated and advanced to the ostium of each PV. The quality of vein occlusion was assessed by the injection of diluted iodinated contrast agent into the PV using a semiquantitative grading, as previously described, from grade 4 (excellent with full retention of contrast medium) to grade 1 (very poor occlusion leading to rapid leakage from the PV) [9]. Ablation duration was decided upon depending on the time to PV isolation: 180 or 240 seconds if PV isolation was documented before or after 30 seconds of freezing, respectively; if the Achieve™ catheter was pushed into the PV to obtain a better stability of the cryoballoon, leading to the inability to observe real-time PV isolation, a 240-second freezing was performed.

Ablation was first performed for the left superior PV and then for the left inferior PV. Before ablation of the right-sided PVs, the quadripolar catheter was relocated to the superior vena cava to constantly pace the right phrenic nerve at a 1500–2000 ms cycle length and a 10 mA/2 ms output during freezing. The pacing was started 30 seconds after the initiation of freezing to avoid cryoballoon dislodgment as a result of the intense right hemidiaphragmatic contractions. In case of cessation or weakening of the contraction, freezing was immediately discontinued and the cryoballoon was deflated.

For patients with atypical right PV anatomies, cryoballoon ablation was only performed for the RSPV and the RIPV. Indeed, because a 28 mm cryoballoon was used, and to avoid increasing the risk of phrenic nerve palsy (PNP), we assumed that the RSPV and RIPV applications would isolate these supplementary PVs.

Finally, the accessory right PVs were eventually catheterized with the Achieve™ catheter to assess PV isolation before cryoballoon removal.

Postablation management and follow-up

After the procedure, all antiarrhythmic drugs were stopped, and patients underwent continuous in-hospital electrocardiogram monitoring for 48 hours. The first out-patient clinic visit was 4–6 weeks after the procedure. Subsequent follow-up visits consisted of a clinical interview, surface electrocardiogram and 24-hour Holter monitoring, at 3, 6 and 12 months. Recurrence of atrial arrhythmia was defined as any AF, atrial tachycardia or flutter lasting longer than 30 seconds, recorded, after a 3-month blanking period, according to the latest guidelines [10]. Procedural success was defined as freedom from any documented arrhythmia recurrence without administration of any antiarrhythmic drugs.

Endpoints

The primary endpoint was survival free from any documented atrial arrhythmia. The secondary endpoints were procedural characteristics during the first freezing application (minimal temperature, time to PV isolation, number of pulmonary vein potentials recorded during freezing) in both groups (normal and atypical right PV anatomy) and the occurrence of PNP.

Statistical analysis

Normally distributed variables are expressed as means \pm standard deviations, and were compared using Student's *t* test. Non-normally distributed variables are expressed as medians (interquartile ranges), and were compared using the Mann-Whitney U test. Categorical variables are expressed as counts and percentages, and were compared using the χ^2 test or Fisher's exact test when needed. A *P* value < 0.05 was considered statistically significant. The analyses were performed with the SPSS statistical package, version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Population characteristics

From 01 January 2015 to 31 October 2018, 303 consecutive patients had cryoballoon ablation of symptomatic paroxysmal AF, and were included prospectively. Clinical characteristics are described in [Table 1](#). Patients were mainly men, the median age was 61.0 (53.8–67.9) years and co-morbidities were rare, reflected by the low CHA₂DS₂-VASc score of the overall population (66.0% of all patients

had a score of 0 or 1). The median left ventricular ejection fraction was 62.0% (60.0–65.0%). A median of 2.0 (1.0–2.0) antiarrhythmic drugs were tested before the ablation was scheduled.

Anatomical considerations

Right PV drainage pattern were classified as stated above (Fig. 1). As shown in Table 2, most patients ($n = 254$, 83.8%) had the expected normal right PV anatomy, consisting of two right atrial ostia for upper and lower lobe veins, respectively, with the middle lobe vein joining the superior lobe vein. The remaining 49 (16.2%) patients had an atypical right PV anatomy. The most common atypical drainage was an R3a pattern ($n = 40$, 81.6%) i.e. three atrial ostia for the superior, middle and lower lobe veins, respectively. R3b and R4 anatomies were each found in three patients, R3c anatomy was found in two patients and one patient had an R5 anatomy. None of the patients presented an R1 anatomy.

Examples of atypical right PV anatomies are depicted in Fig. 2.

RSPV short- and long-axis diameters of patients with “atypical” right PV anatomy were significantly smaller than those with the R2 pattern ($P < 0.001$). For patients with an R3 anatomy, the right middle PV (RMPV) long and short axes were 10.3 ± 2.3 mm and 7.9 ± 2.2 mm respectively, and its distances to the RSPV and the RIPV were 3.7 ± 2.1 and 5.3 ± 2.7 mm, respectively.

Procedural characteristics

After ablating left-side PVs, cryoballoon applications were performed in the RSPV and RIPV only, neglecting accessory right PVs. First-freeze isolation for RSPV occurred in 44 (89.8%) and 218 (85.8%) patients with atypical and typical right PV anatomy, respectively ($P = 0.61$; Table 3). Similar results were observed for the RIPV, with first-freeze isolation occurring in 37 (75.5%) and 217 (85.4%) patients with atypical and typical right PV anatomy, respectively ($P = 0.13$). There was no difference in terms of occlusion degree during freezing. Minimal temperature was lower in both the RSPV and RIPV in the group with normal anatomy (-47.6 ± 5.7 vs -49.5 ± 9.5 [$P = 0.006$] and -46.2 ± 7.2 vs -47.7 ± 8.1 [$P = 0.046$]), and more real-time recordings of PV potentials were observed in the RSPV for patients with normal anatomy. Lastly, there was no difference in procedural duration between the two groups.

Of note, once RSPV and RIPV isolation were performed, accessory right PV isolation was assessed, and was found to be isolated in all patients with an R3 anatomy pattern. Catheterization of

accessory PVs in patients with R4 and R5 anatomies could not be obtained because of their small diameter.

Complications

Twenty-nine transient PNPs occurred in 26 (8.6%) patients, including 20 PNPs during RSPV isolation, three PNPs during RIPV isolation and three PNPs during both superior and inferior cryoballoon isolation. Interestingly, all PNPs occurred in patients with normal right PV anatomy, whereas none of the patients with atypical anatomy had this complication ($P = 0.039$). Of note, all the PNPs resolved before the end of the procedure. No other major complication occurred.

Follow-up

After a follow-up of 12.6 ± 0.2 months, 42 (13.9%) patients had symptomatic documented recurrences of atrial arrhythmias, including 37 (14.6%) and five (10.2%) patients with normal and atypical right PV anatomy, respectively ($P = 0.560$). Kaplan-Meier curves of survival free from atrial arrhythmias are shown in [Fig. 3](#). No difference was observed between groups (log-rank $P = 0.43$). Among these patients, 22 and four patients were referred for a redo ablation, respectively. The localization of gaps encountered during redo cases are detailed in [Table 4](#). Among the four patients with atypical anatomy, only one had a gap in the RSPV, in its posterosuperior region (i.e. not close to the accessory PV).

Discussion

Main results

The main findings of our study are as follows: (1) a significant proportion of patients have atypical right PV anatomy (16.2% in our study); (2) procedural characteristics and acute PV isolation success are similar in all patients, regardless of their right PV anatomy, although a less negative temperature was observed in patients with atypical anatomy; (3) the isolation of the RSPV and RIPV, neglecting the accessory PVs, is sufficient to obtain acute right-side PV isolation and maintenance of mid-term sinus rhythm in patients with atypical anatomy; and (4) PNPs were only observed in patients with normal anatomy.

Variations in PV anatomy

Normal PV anatomy is defined as the presence of four PVs presenting well-defined ostia. The RSPV usually drains the right upper and middle pulmonary lobes, whereas the left superior PV drains the left upper lobe, including the lingula. Inferior PVs drain their respective lower lobes. This configuration is observed in 57–82% of the population [7, 11-16]. Anatomical variants of this typical drainage have been described in 18–53% of patients [11, 13, 16-18], the most common being the presence of a left common trunk (8–59%) [3, 4, 6, 7, 16-19]. Anatomical variants of the right PVs are less common (6–32%) [7, 11, 12, 14, 16-18], but tend to be more complex because of the presence of a third PV coming from the middle pulmonary lobe, draining either into the superior or inferior PV, or directly into the LA through a separated ostium. The presence of an RMPV has been described in 11–26% of individuals [7, 11, 12, 14, 17, 20]. Tsao et al. [21] reported that the RMPV might drain directly into the LA in 23% of patients. In our study, 16.2% of the patients had an atypical right PV drainage, mainly an R3a pattern, consisting of a separate PV coming from the middle lobe and draining directly into the LA. Other types of atypical right PV anatomy were less common, and only four patients had four or five PV ostia.

Cryoballoon ablation in patients with atypical PV anatomy

Data regarding the efficacy of cryoballoon ablation in patients with a left common trunk are controversial. Some studies have demonstrated a similar AF-free survival rate compared with patients with normal left PV anatomy [3, 4], whereas others have reported a worse arrhythmia-free survival rate [5, 6]. Shigeta et al. [6] demonstrated that the presence of a left common trunk was an independent predictor of atrial tachyarrhythmia recurrence after a follow up of 454 ± 195 days (hazard ratio 3.0, 95% confidence interval 1.32–6.83; $P < 0.01$). Further studies will be needed to investigate whether a critical size of common trunk impairs cryoballoon ablation efficacy.

However, to the best of our knowledge, there are currently no reports specifically on the efficacy of cryoballoon ablation in patients with atypical right PV anatomy. In our study, we did not find any difference in terms of mid-term arrhythmia-free survival, although some procedural variables differed between groups. Indeed, there was no difference in terms of degree of PV occlusion, successful first freeze and total number of applications per PV. However, the nadir temperature was significantly more negative in those patients with normal PV anatomy, probably explained by their larger short- and long-axis diameters compared with patients with atypical drainage. Indeed, the middle lobe vein is usually

connected to the RSPV, which drains the blood coming from the upper and the middle pulmonary lobes. In patients with a middle lobe vein directly connected to the LA, the RSPV only drains the upper pulmonary lobe, explaining its smaller size and, subsequently, the less negative nadir temperatures. Surprisingly, more applications with PV potentials were recorded in patients with normal right PV drainage during RSPV isolation compared with in those with atypical PV anatomy ($P = 0.005$). This observation can possibly be explained by a difference in terms of myocardial PV sleeve anatomy or a more distal positioning of the Achieve™ catheter during ablation.

Interestingly, as previously stated, because a 28 mm cryoballoon was used, and to avoid increasing the risk of PNP, we decided to not perform a freezing application specifically for the accessory PVs, assuming that the proximity to RSPV and RIPV ostia (3.7 ± 2.1 and 5.3 ± 2.7 mm, respectively) would lead to isolation of these supplementary PVs. Despite their smaller size (10.3 ± 2.3 mm x 7.9 ± 2.2 mm for the RMPV in patients with an R3 pattern), accessory PVs could be catheterized in patients with an R3 pattern to prove PV isolation, demonstrating that a specific freezing application is unnecessary for these PVs, and that they can be neglected without compromising ablation outcome. Indeed, the similar mid-term efficacy observed in our study, regardless of the right PV pattern, is a plea to avoid performing supplemental freezing applications in patients with atypical PV drainage. As described, none of the two patients requiring a redo ablation had conduction gaps in the region close to the supplemental PV.

Clinical impact of preprocedural imaging

The aim of this study was to show whether a difference in clinical outcomes after cryoballoon ablation of paroxysmal AF was observed between patients with normal and atypical right PV anatomy, ablating the RSPV and the RIPV only, and neglecting ablation of accessory PVs. Indeed, some studies [22] have shown cryoballoon ablation efficacy to be critically dependent on the degree of venous occlusion, suggesting that it would be more difficult to obtain perfect occlusion in patients with atypical PV drainage. Conversely, in this study, we did not show any difference in terms of clinical outcomes depending on PV anatomy, and patients with atypical right PV drainage should not be denied a cryoballoon ablation based only on this anatomical pattern. However, we believe that this finding should not weaken the value of preprocedural 3D imaging of the PV anatomy. Indeed, many studies have demonstrated the benefit of cardiac CT scans or magnetic resonance imaging before AF ablation

[13, 14, 23], allowing recognition of anatomical variants, and providing an indication about PV orientation, shape and size. Furthermore, as described above, the efficacy of cryoballoon ablation in patients with a left common trunk is still a matter of debate [3-6]. Thus, we believe that 3D reconstruction is essential for procedural planning, and may help to decide whether cryoballoon- or radiofrequency-based ablation should be performed in a given patient.

Lastly, although treatment efficacy was similar, regardless of right PV anatomy, the safety profile was different. Indeed, patients with normal anatomy seemed to be at higher risk of PNP. Knowing a patient's anatomy before the procedure may lead to more careful evaluation of phrenic nerve contraction during cryoballoon ablation of right PVs in patients with a typical right PV drainage.

Impact of PV anatomy on PNP

PNP is one of the most common complications during cryoballoon ablation, occurring in 1.5–13.6% of patients [24-29]. A similar rate of PNP occurrence (8.6%) was observed in our study. Several predictors of PNP occurrence have been described, including the presence of a right common ostium, large PV dimensions, early branching pattern originating from the same ostium or shorter distance from the PV to the superior vena cava [24, 28]. More precisely, these studies described predictors of PNP occurrence for RSPV freeze (RSPV area, RSPV-LA angle) and RIPV freeze (temperature drop velocity from basal to $-20\text{ }^{\circ}\text{C}$). Saitoh et al. [30] found that the strongest predictor of phrenic nerve injury at the RSPV was the position of the balloon at least one third outside the cardiac shadow (odds ratio 119.9, 95% CI 11.6–1234.7; $P = 0.001$). Interestingly, in our study, all PNPs occurred in patients with normal PV anatomy, and none of the patients with atypical right PV drainage had this complication. Different hypotheses may explain such a finding. First, one may postulate that an atypical right PV anatomy may be associated with an atypical phrenic nerve position, located further from the PV ostia, making it less prone to freezing. This hypothesis was not specifically analysed in this study, and would require further investigation. Second, as demonstrated in our study, patients with normal PV anatomy have larger RSPVs, and cryoenergy may be delivered further inside the PV ostium, closer to the phrenic nerve position. Indeed, Casado-Arroyo et al. [31] showed that a less vigorous wedging manoeuvre in the RSPV ostia might reduce the occurrence of PNP. The authors recommended slightly retrieving the inflated cryoballoon until a small leak is observed, before repositioning it at the beginning of the cryoenergy application to create a more proximal lesion, without

compromising the quality of the occlusion. Patients with atypical anatomy, having smaller RSPVs, are probably at less risk because the lesion created by a big 28 mm cryoballoon is possibly more proximal. Lastly, the nadir temperature was less negative in patients with atypical anatomy, a variable that may explain why no PNPs were observed in this group. Further studies will be needed to analyse the effect of PV shape, orientation and anatomy on PNP occurrence.

Study limitations

This study had several limitations that must be considered. First, it was a single-centre study. The clinical endpoint of sinus rhythm maintenance evaluated the global efficacy of cryoballoon ablation for both right and left PVs, and AF recurrence in a given patient with typical or atypical right PV anatomy may be the result of a reconnection of left PVs while right PVs remain disconnected. Most of the patients with atypical anatomy had an R3 pattern, only a limited number of patients had an R4/R5 pattern and none had an R1 pattern, somewhat limiting the results observed to patients with this type of anatomy. Lastly, PV reconnection was only assessed in those patients referred for a redo ablation, and one may argue that the reconnection rate could differ between asymptomatic and symptomatic patients not referred for a second procedure. However, Miyazaki et al. proved that, regardless of clinical recurrences, the incidence and characteristics of PV reconnections were similar in both groups [32].

We focused our study on CT scans. However, PV angiography or rotational angiography may also be helpful in delineating PV anatomy. The impact of such imaging modalities in patients with atypical PV anatomies would require further studies.

Conclusions

To the best of our knowledge, this is the first study specifically reporting the safety and efficacy of cryoballoon ablation in patients with atypical right PV drainage. In addition to the isolation of left-side PVs, the isolation of the RSPV and the RIPV, neglecting accessory PVs, is sufficient to obtain acute right-side PV isolation and maintenance of mid-term sinus rhythm in patients with atypical anatomy. To note, the risk of PNP seems to be negligible in these patients, and further studies will be needed to determine whether anatomical or procedural characteristics can explain such a finding.

Sources of funding

None.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

- [1] Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* 2016;374:2235-45.
- [2] Mugnai G, Chierchia GB, de Asmundis C, et al. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. *Am J Cardiol* 2014;113:1509-13.
- [3] Heeger CH, Tscholl V, Wissner E, 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.
- [4] Stroker E, Takarada K, de Asmundis C, 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.
- [5] Beiert T, Lodde PC, Linneborn LPT, et al. Outcome in patients with left common pulmonary vein after cryoablation with second-generation cryoballoon. *Pacing Clin Electrophysiol* 2018;41:22-7.
- [6] Shigeta T, Okishige K, Yamauchi Y, 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.
- [7] 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.
- [8] Chun KR, Schmidt B, Metzner A, et al. The 'single big cryoballoon' technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. *Eur Heart J* 2009;30:699-709.
- [9] Chierchia GB, Sorgente A, Sarkozy A, de Asmundis C, Brugada P. The Use of Cryoballoon Ablation in Atrial Fibrillation: Simplifying Pulmonary Vein Isolation? *J Atr Fibrillation* 2010;3:294.
- [10] Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. *Europace* 2018;20:157-208.
- [11] Cronin P, Kelly AM, Desjardins B, et al. Normative analysis of pulmonary vein drainage

- patterns on multidetector CT with measurements of pulmonary vein ostial diameter and distance to first bifurcation. *Acad Radiol* 2007;14:178-88.
- [12] Hof I, Chilukuri K, Arbab-Zadeh A, et al. Does left atrial volume and pulmonary venous anatomy predict the outcome of catheter ablation of atrial fibrillation? *J Cardiovasc Electrophysiol* 2009;20:1005-10.
- [13] Kato R, Lickfett L, Meininger G, et al. Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging. *Circulation* 2003;107:2004-10.
- [14] Mansour M, Holmvang G, Sosnovik D, et al. Assessment of pulmonary vein anatomic variability by magnetic resonance imaging: implications for catheter ablation techniques for atrial fibrillation. *J Cardiovasc Electrophysiol* 2004;15:387-93.
- [15] Scharf C, Sneider M, Case I, et al. Anatomy of the pulmonary veins in patients with atrial fibrillation and effects of segmental ostial ablation analyzed by computed tomography. *J Cardiovasc Electrophysiol* 2003;14:150-5.
- [16] Sohns C, Sohns JM, Bergau L, et al. Pulmonary vein anatomy predicts freedom from atrial fibrillation using remote magnetic navigation for circumferential pulmonary vein ablation. *Europace* 2013;15:1136-42.
- [17] McLellan AJ, Ling LH, Ruggiero D, 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.
- [18] Wannasopha Y, Oilmungmool N, Euathrongchit J. Anatomical variations of pulmonary venous drainage in Thai people: multidetector CT study. *Biomed Imaging Interv J* 2012;8:e4.
- [19] Kubala M, Hermida JS, Nadji G, Quenum S, Traulle S, Jarry G. Normal pulmonary veins anatomy is associated with better AF-free survival after cryoablation as compared to atypical anatomy with common left pulmonary vein. *Pacing Clin Electrophysiol* 2011;34:837-43.
- [20] Mulder AA, Wijffels MC, Wever EF, Boersma LV. Pulmonary vein anatomy and long-term outcome after multi-electrode pulmonary vein isolation with phased radiofrequency energy for paroxysmal atrial fibrillation. *Europace* 2011;13:1557-61.
- [21] Tsao HM, Wu MH, Yu WC, et al. Role of right middle pulmonary vein in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2001;12:1353-7.

- [22] Sorgente A, Chierchia GB, de Asmundis C, et al. Pulmonary vein ostium shape and orientation as possible predictors of occlusion in patients with drug-refractory paroxysmal atrial fibrillation undergoing cryoballoon ablation. *Europace* 2011;13:205-12.
- [23] Mlcochova H, Tintera J, Porod V, Peichl P, Cihak R, Kautzner J. Magnetic resonance angiography of pulmonary veins: implications for catheter ablation of atrial fibrillation. *Pacing Clin Electrophysiol* 2005;28:1073-80.
- [24] Abugattas JP, de Asmundis C, Iacopino S, et al. Phrenic nerve injury during right inferior pulmonary vein ablation with the second-generation cryoballoon: clinical, procedural, and anatomical characteristics. *Europace* 2018;20:e156-e63.
- [25] Furnkranz A, Bordignon S, Schmidt B, et al. Incidence and characteristics of phrenic nerve palsy following pulmonary vein isolation with the second-generation as compared with the first-generation cryoballoon in 360 consecutive patients. *Europace* 2015;17:574-8.
- [26] Martins RP, Hamon D, Cesari O, et al. Safety and efficacy of a second-generation cryoballoon in the ablation of paroxysmal atrial fibrillation. *Heart Rhythm* 2014;11:386-93.
- [27] Mugnai G, de Asmundis C, Ciconte G, et al. Incidence and characteristics of complications in the setting of second-generation cryoballoon ablation: A large single-center study of 500 consecutive patients. *Heart Rhythm* 2015;12:1476-82.
- [28] Stroker E, de Asmundis C, Saitoh Y, 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.
- [29] Su W, Orme GJ, Hoyt R, et al. Retrospective review of Arctic Front Advance Cryoballoon Ablation: a multicenter examination of second-generation cryoballoon (RADICOL trial). *J Interv Card Electrophysiol* 2018;51:199-204.
- [30] Saitoh Y, Stroker E, Irfan G, et al. Fluoroscopic position of the second-generation cryoballoon during ablation in the right superior pulmonary vein as a predictor of phrenic nerve injury. *Europace* 2016;18:1179-86.
- [31] Casado-Arroyo R, Chierchia GB, Conte G, et al. Phrenic nerve paralysis during cryoballoon ablation for atrial fibrillation: a comparison between the first- and second-generation balloon. *Heart Rhythm* 2013;10:1318-24.
- [32] Miyazaki S, Taniguchi H, Hachiya H, et al. Clinical recurrence and electrical pulmonary vein

reconnections after second-generation cryoballoon ablation. *Heart Rhythm* 2016;13:1852-7.

Figure legends

Figure 1. Right pulmonary drainage pattern; adapted from Marom et al. [7]. RLL: right lower lobe; RML: right middle lobe; RUL: right upper lobe; SSRLL: superior segment right lower lobe; BSRL: basilar segment right lower lobe.

Figure 2. Cardiac computed tomography scan reconstructions of left atrium (posteroanterior view and endoluminal view). A. R3a pattern. B. R3b pattern. C. R3c pattern. D. R4 pattern. E. R5 pattern.

Figure 3. Kaplan-Meier curves for cumulative survival free of atrial arrhythmias in patients with normal and atypical right pulmonary vein (PV) anatomy.

Table 1 Patient characteristics.

	All patients (<i>n</i> = 303)	Atypical right PV anatomy (<i>n</i> = 49)	Normal right PV anatomy (<i>n</i> = 254)	<i>P</i>
Age (years)	61.0 (53.8–67.9)	56.9 (50.7–66.8)	61.5 (54.5–68.3)	0.09
Male/female sex (<i>n/n</i>)	212/91	36/13	176/78	0.68
Hypertension	94 (31.0)	11 (22.4)	83 (32.7)	0.21
Diabetes mellitus	9 (3.0)	2 (4.1)	7 (2.7)	0.97
Current smoker	33 (10.9)	10 (20.4)	23 (9.05)	0.037
Dyslipidaemia	49 (16.2)	7 (14.3)	42 (16.5)	0.87
History of stroke	20 (6.6)	5 (10.2)	15 (5.9)	0.43
Body mass index (kg/m ²)	25.9 (23.5–28.7)	25.8 (22.8–27.8)	26.0 (23.5–28.7)	0.24
CHA ₂ DS ₂ -VASc score				
0	128 (42.2)	20 (40.8)	108 (42.5)	
1	72 (23.8)	13 (26.5)	59 (23.2)	
2	67 (22.1)	11 (22.5)	56 (22.0)	
3	23 (7.6)	4 (8.2)	19 (7.5)	0.97
4	7 (2.3)	1 (2)	6 (2.4)	
5	5 (1.7)	0 (0)	5 (2.0)	
6–9	1 (0.3)	0 (0)	1 (0.4)	
AF episode duration				
< 12 hours	196 (64.7)	27 (55.1)	169 (66.5)	
12–24 hours	51 (16.8)	10 (20.5)	41 (16.1)	0.47
24–48 hours	26 (8.6)	6 (12.2)	20 (7.9)	
> 48 hours	30 (9.9)	6 (12.2)	24 (9.5)	
Number of antiarrhythmic drugs tested before ablation	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.75
LVEF (%)	62.0 (60.0–65.0)	62.0 (55.7–65.0)	62.0 (60.0–65.0)	0.59

Data are expressed as median (interquartile range) or number (%), unless otherwise indicated. AF: atrial fibrillation;

CHA₂DS₂-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years (Doubled), Diabetes, Stroke/transient

ischaemic attack/thromboembolism (Doubled) – Vascular disease, Age 65–74 years and Sex category [Female]);

LVEF: left ventricular ejection fraction; PV: pulmonary vein.

Table 2 Anatomical considerations.

	Atypical right PV anatomy (<i>n</i> = 49)	Normal right PV anatomy (<i>n</i> = 254)	<i>P</i>
Right PV size, mm			
RSPV long axis	17.6 ± 3.3	20.3 ± 3.0	< 0.001
RSPV short axis	14.2 ± 3.2	17.2 ± 3.2	< 0.001
RIPV long axis	17.5 ± 3.3	18.1 ± 3.1	0.23
RIPV short axis	15.0 ± 3.1	15.8 ± 2.9	0.09
RMPV anatomy			
R1	0 (0)	NA	
R2a	NA	182 (71.6)	
R2b	NA	53 (20.9)	
R2c	NA	19 (7.5)	
R3a	40 (81.6)	NA	NA
R3b	3 (6.1)	NA	
R3c	2 (4.1)	NA	
R4a	3 (6.1)	NA	
R4b	0 (0)	NA	
R5	1 (2.1)	NA	
For R3 (<i>n</i> = 28)			
RMPV long axis (mm)	10.3 ± 2.3	NA	NA
RMPV short axis (mm)	7.9 ± 2.2	NA	
Distance to RSPV (mm)	3.7 ± 2.1	NA	
Distance to RIPV (mm)	5.3 ± 2.7	NA	

Data are expressed as mean ± standard deviation or number (%). NA: not applicable; PV:

pulmonary vein; RIPV: right inferior pulmonary vein; RMPV: right middle pulmonary vein; RSPV: right superior pulmonary vein.

Table 3 Procedural characteristics.

	Atypical right PV anatomy (<i>n</i> = 49)	Normal right PV anatomy (<i>n</i> = 254)	<i>P</i>
RSPV			
Occlusion 4/4	48 (98.0)	248 (97.6)	0.70
Applications with PVP recording	34 (69.4)	220 (86.6)	0.005
Minimal temperature (°C)	-47.6 ± 5.7	-49.5 ± 9.5	0.006
PNP	0 (0)	23 (9.05)	0.06
Successful first freeze	44 (89.8)	218 (85.8)	0.61
Total number of applications	1.2 ± 0.5	1 ± .20.5	0.94
RIPV			
Occlusion 4/4	43 (87.7)	232 (91.3)	0.60
Applications with PVP recording	13 (26.5)	74 (29.1)	0.84
Minimal temperature (°C)	-46.2 ± 7.2	-47.7 ± 8.1	0.046
PNP	0 (0)	6 (2.4)	0.60
Successful first freeze	37 (75.5)	217 (85.4)	0.13
Total number of applications	1.2 ± 0.5	1.2 ± 0.5	0.42
Procedure duration (minutes)	75.0 (67.5–87.5)	75.0 (70.0–90.0)	0.74
Fluoroscopy time (minutes)	16.3 (12.0–22.0)	16.9 (13.1–22.7)	0.35

Data are expressed as number (%), mean ± standard deviation or median (interquartile range). PNP:

phrenic nerve palsy; PV: pulmonary vein; PVP: pulmonary vein potential; RIPV: right inferior pulmonary vein;

RSPV: right superior pulmonary vein.

Table 4 Localization of conduction gaps during redo procedures.

	LSPV	LIPV	RSPV	RIPV
Normal anatomy				
Patient 1	0	Posteroinferior	0	Posteroinferior
Patient 2	Anterosuperior	Posterosuperior	Anterosuperior	0
Patient 3	0	0	Anteroinferior	0
Patient 4	Superior	0	0	0
Patient 5	0	0	Anterosuperior	0
Patient 6	0	Anterior & inferior	0	0
Patient 7	Anterior	0	Anteroinferior	0
Patient 8	0	Posteromedian	Anteroinferior	0
Patient 9	Posterior & anterosuperior	0	Anteroinferior	Posteromedian
Patient 10	0	0	0	Posterior & inferior
Patient 11	Posterior	0	0	0
Patient 12	0	0	0	0
Patient 13	0	0	Anteroinferior	0
Patient 14	Posterosuperior & posteroinferior	Posterosuperior & posteroinferior	Anteroinferior	0
Patient 15	0	0	Inferior	Posteroinferior
Patient 16	0	0	Anteroinferior, anterosuperior & superior	0
Patient 17	0	0	Anteroinferior	0
Patient 18	0	0	Anteroinferior	0
Patient 19	0	0	0	0
Patient 20	0	0	0	0
Patient 21	0	0	Anteroinferior	0
Patient 22	0	0	0	0

Atypical anatomy

Patient 1	0	0	Posterosuperior	0
Patient 2	Superior & posterior	Posterior	0	0
Patient 3	0	0	0	0
Patient 4	0	0	0	0

LIPV: left inferior pulmonary vein; LSPV: left superior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.





