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The impact of left common pulmonary vein on cryoballoon ablation of atrial fibrillation. A meta-analysis

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ABSTRACT

Introduction: Conflicting results regarding the impact of left common pulmonary vein (LCPV) on clinical outcome of atrial fibrillation (AF) ablation with cryoballoon technology have been reported.

Methods: We systematically searched PubMed and Cochrane library for articles that compared the arrhythmia recurrence rate after cryoballoon ablation between patients with normal pattern PVs and patients with LCPV. Studies of first ablation for persistent and paroxysmal AF using the 28 mm Arctic Front Advance, Medtronic cryoballoon (CB-A) reporting clinical success rates at a mean follow-up of ≥ 12 months were included. Data were analyzed by applying a random effects model.

Results: A total of 5 studies with a total of 1178 patients met our predefined inclusion criteria. After a mean follow-up of 18.4 months, the overall success rate of CB-A ablation among patients with persistent and paroxysmal AF was 57%; in the LCPV group the success rate was 46% and in the normal anatomical pattern group it was 61%. No significant heterogeneity was noted among the studies ($I^2 = 35.8\%$; Q ($df = 3$) = 6.23 p -value = 0.18). Arrhythmia recurrence after CB-A ablation was not statistically significant between the two groups (LogOR 0.24; 95% CI [-0.16-0.63]; p -value = 0.23). No significant difference in PNI was observed between the two groups (p -value = 0.693).

Conclusion: The presence of LCPV does not affect the long-term outcome of paroxysmal and persistent atrial fibrillation ablation with 28 mm CB-A compared to normal left PVs pattern.

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1. Introduction

The PV is confirmed to be the most important and critical trigger for AF, and PV isolation (PVI) using catheter ablation is the cornerstone therapy for symptomatic AF refractory to antiarrhythmic drugs [1]. Cryoballoon ablation, which achieves PVI by a single-shot technique, has become a valid alternative to traditional point-by-point radiofrequency ablation [2,3]. The significant variability of PV anatomy might explain in part the occurrences of PV reconnection after catheter ablation, but conflicting results

Abbreviations: LCPV, left common pulmonary vein; AF, atrial fibrillation; CB-A, second-generation cryoballoon; PNI, phrenic nerve injury; PVI, pulmonary vein isolation; FU, follow-up; CB, cryoballoon; LogOR, Log Odds Ratio; CI, confidence interval; Newcastle-Ottawa Scale, NOS; MOSE, Meta-analysis of Observational Studies in Epidemiology; PRISMA, Systematic Reviews and Meta-Analysis.

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regarding the impact on clinical outcome have been reported. A LCPV is present from 9% to 20% of patients, depending on the population analyzed and the definition used [4,5] and it is the most frequent PV variation, followed by right accessory middle vein. Size and shape of the PVs ostia have been reported to have an influence on the efficacy of CB ablation [6]. Previous experience with the first-generation CB reported a worse AF-free survival for paroxysmal AF in patients with LCPV compared to patients with normal left PVs [7]. The 28 mm CB-A (Arctic Front Advance, Medtronic®) offers a more antral and more homogeneous freezing area on the balloon surface, resulting in significantly better procedural and clinical long-term outcomes compared with its predecessor [8]. However, the efficacy of the 28 mm CB-A in the setting of LCPV is still debated. In theory, cryoablation of a LCPV might be suboptimal since left atrial ablation of the common ostium is not always possible. Often the left-sided PV branches have to be targeted individually with isolation operated inside the veins. In the present study, we sought to investigate the performance of the 28 mm CB-A

ablation in terms of procedural outcome in patients with LCPV.

2. Material and methods

Our systematic literature search was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOSE) guidelines [9] and conducted using a predetermined protocol by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [10].

In this meta-analysis, all published studies in which 28 mm CB-A ablation was performed for paroxysmal and persistent AF with pre-procedural computed tomography scan were considered eligible.

2.1. Search strategy

Scientific database such as PubMed, EMBASE and Cochrane library were searched for studies comparing ablation for AF with 28 mm CB-A in normal pattern PV versus LCPV until August 2, 2019. The search terms were as follows: “second generation cryoballoon ablation” OR “cryoballoon pulmonary vein isolation” AND “atrial fibrillation” OR “pulmonary vein abnormality” OR “left common pulmonary vein” OR “left common trunk”. No restriction was applied on languages. We also searched the reference lists of relevant review articles to identify other relevant studies.

2.2. Study selection and outcomes of interest

Studies that were included in our meta-analysis should meet the following criteria: (1) prospective randomized studies and retrospective studies enrolling consecutive patients; (2) studies comparing the outcome of patients with paroxysmal and persistent AF undergoing first PVI using 28 mm CB-A after a mean follow-up (FU) ≥ 12 months. Abstract only articles, case reports and reviews as well as studies containing non adequate outcomes of interest were excluded from this study. All studies were reviewed twice and disagreements were discussed. We extracted the following data from the included studies: publication year, first author, number of patients, baseline characteristics of the study population, features of the study design and the data we need in our meta-analysis. We defined the primary outcome criterion as recurrence of any atrial arrhythmia lasting longer than 30 s without administration of anti-arrhythmic drugs 3 months after a first ablation procedure using 28 mm CB-A. Furthermore, the incidence of persistent phrenic nerve injury (PNI) was analyzed. Whenever the data of interest were not available in the literature, the investigators tried to contact the authors by email to obtain the data. We used the Newcastle-Ottawa Scale (NOS) to further evaluate the quality of the observational studies, and a NOS score ≥ 7 was considered good quality [11].

2.3. Cryoballoon ablation strategy of included studies

All the included studies performed PV isolation using 28-mm CB-A inserted through a 15-Fr steerable sheath (FlexCath Advance; Medtronic Inc, Minneapolis, MN) over a 20-mm diameter inner lumen mapping catheter (Achieve; Medtronic Inc). Optimal PV occlusion was achieved by “proximal-seal” technique. The CB-A was inflated and advanced toward the ostium of each PV. When the balloon nadir temperature exceeded -60 °C, the ablation was terminated. During CB ablation of the right-sided PVs, high output right phrenic stimulation (1500 ms, 20 mA) was performed using a quadripolar catheter within the superior vena cava. If loss of phrenic capture occurred, the cryoapplication was immediately terminated. For LCPVs the following ablation strategies were

applied: if an antral occlusion of the LCPV, determined by contrast injection and fluoroscopy, was achieved, the freeze cycle was initiated. If an antral LCPV occlusion could not be obtained, the operators adapted a sequential ablation approach. At first the first superior branch of the LCPV was targeted, followed by ablation of the first inferior branch. In all the studies an antral freezing cycle was applied as much as possible to LCPV.

2.4. Statistical analysis

Statistical analysis was performed using the R software (version 3.5.0). Data were pooled using random effects models, according to Mantel-Haenszel model. The results are reported as Log odds ratio (Log OR) with 95% confidence intervals (CI) for dichotomous outcomes. Heterogeneity was assessed using the I^2 index, Cochran's Q statistic. I^2 values of 25%, 25–50%, or 50% indicated low, moderate, or high heterogeneity, respectively [12]. Funnel plot analysis was used to evaluate potential publication bias. In all analyses, a p -value < 0.05 was considered statistically significant.

3. Results

3.1. Study selection and characteristics

The selection procedure with flow diagram for the included studies is shown in Fig. 1. Initially, 60 potentially relevant articles were identified in the preliminary literature search until December 2019, 48 of them were excluded after reviewing the abstracts. Of the 12 trials that were retrieved for further examination, 7 articles were excluded on the basis of full-text detailed review. Ultimately, 5 qualified retrospective studies involving 1178 patients who underwent catheter ablation with 28 mm CB-A for AF were included for analysis [13–17].

The characteristics of the included studies are described in Table 1. All of the included studies had at least 1-year mean FU. The included studies mean FU was 18.4 months. During FU all studies used 24-h Holter recordings. In all studies symptom-driven consultations were planned in case of symptoms occurring outside the scheduled FU, to record a 12-lead ECG, or if needed, to plan additional 24-h Holter.

All the included studies were slightly asymmetrical on visual inspection of the funnel plot (regression test for funnel plot asymmetry $t = 3.8715$, $df = 3$, p -value = 0.03) (Fig. 2).

3.2. Ablation strategy, complication procedure-related and primary outcomes

Three studies performed 3 min single freezing cycle for each PVs with a second application in case of not achieved PVI [13,16,17] and the other 2 studies performed 4 min with bonus freeze or different ablation protocol [14,15] Table 1.

After a mean FU of 18.4 months in the patients with persistent (14%) and paroxysmal (86%) AF the success rate after CB-A ablation was 61% in the group with PVs normal pattern and 46% in the LCPV group, this difference did not reach the statistically significant difference (p -value 0.05). No significant heterogeneity was noted among studies ($I^2 = 35.8\%$; Q ($df = 3$) = 6.23 p -value = 0.18), Fig. 3. The overall effect is not statistically significant (Log OR 0.24 95% CI [-0.16-0.63], p -value 0.23), Fig. 3. No significant difference was noted in both groups about PNI (Log OR -0.3 95% CI [-1.36-0.70], p -value 0.53, test for heterogeneity Q ($df = 2$) = 0.53, p -value 0.76, $I^2 = 0.0\%$), Fig. 4.

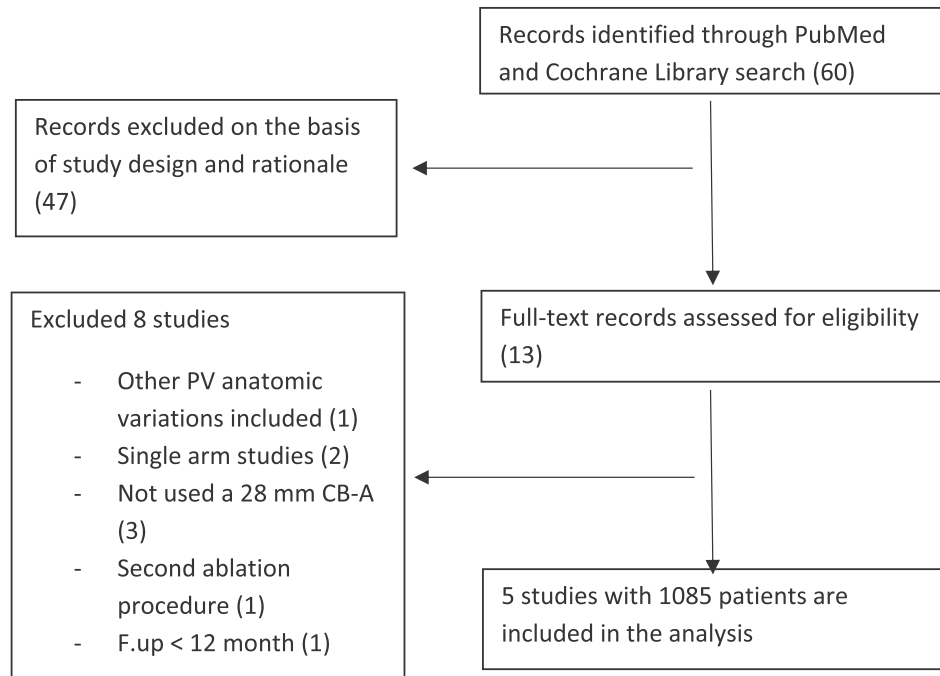


Fig. 1. Flow chart of studies selection procedure.

Table 1

Table with clinical, procedural and FU characteristics of the included studies.

Ref	Nr of patients	AF paroxysmal (%)	Class of Studies	Catheter	Ablation Strategy	PVI	PNI (%)	Age (years)	Male (%)	F Up method	F Up (months)
Ströker et al. [13] 2017	290	229 (78)	single-center retrospective	28 mm CB-A	Single 3 min	100%	22 (7)	55	200 (68)	24 h Holter, implanted device, symptom-driven consultations	19
Heeger et al. [14] 2017	147	108 (73)	multi-center retrospective	28 mm CB-A	Different ablation protocols*	99%	3 (2)	65	77 (52)	24 h Holter, symptom-driven consultations	23
Beiert et al. [15] 2017	68	29 (43)	single-center retrospective	28 mm CB-A	4 min with bonus freeze	100%	1 (1)	66	41 (60)	24 h Holter, symptom-driven consultations	19
Shigeta et al. [16] 2017	324	324 (100)	single-center retrospective	28 mm CB-A	Single 3 min	100%	26 (8)	65	217 (67)	24 h Holter, symptom-driven consultations	15
Wei et al. [17] 2019	424	327 (77)	single-center retrospective	28 mm CB-A	Single 3 min	100%	3 (1)	55	303 (71)	24 h Holter, symptom-driven consultations	16

Table with clinical, procedural and FU characteristics. * 29 patients were treated by a “bonus freeze” protocol (freeze cycle duration of 240 s followed by 1 additional bonus freeze cycle of 240 s duration after PVI). Another 26 patients were treated with a “no bonus freeze” protocol (freeze cycle duration of 240 s without an additional bonus freeze cycle following PVI). The last 19 consecutive patients were treated based on a “time-to-effect” guided ablation protocol (after real-time PVI another 120 s was applied without an additional freeze cycle). PVI: pulmonary vein isolation; PNI: phrenic nerve injury; CB-A: second generation cryoballoon. Min: minute; mm: millimetres.

4. Discussion

To the best of our knowledge this is the first meta-analysis on the impact of the LCPV in AF ablation with cryoballoon technology.

4.1. Cryoballoon ablation in the setting of PVs anatomic variations

The PVI are currently among the most effective therapeutic option for the AF treatment. The ablation effect might be attributed to various mechanisms, including the elimination of trigger, modification of substrates and atrial denervation. It is well known that the sleeves of cardiac tissue originating from the left atrium extend onto and around the PVs, forming fascicles of myocardial fibers running peripherally [18]. In comparison to left atrial myocytes, PV and atrial-pulmonary venous junction myocytes are more prone to arrhythmogenesis due to their shorter refractoriness and

increased triggered activity [19]. Since Haissaguerre et al. [1] reported that AF most often began in the PVs, PVI via catheter ablation has been the cornerstone of non-pharmacological treatment of AF. The two most frequently energy sources used are radio-frequency and cryo-thermal, although other energy sources are being actively investigated for their efficacy and safety. In 2012 the FDA approved a multicenter examination of CB-A which can deliver via cryo-thermal energy a continuous and wide encircling lesion to the left atrial tissue surrounding the ostia of the PVs, thus being more consistent in ablation lesion and being less prone to gaps. On the other hand, the adaptability of the catheter to anatomic variations of the PVs is limited due to the fixed balloon size and geometrical shape. The shape and the size of PV ostia have been reported to influence the outcomes of CB ablation. Theoretically the difficulty to achieve a complete occlusion and/or an antral lesion leads to worsening of outcomes. Therefore, the use of the CB in the

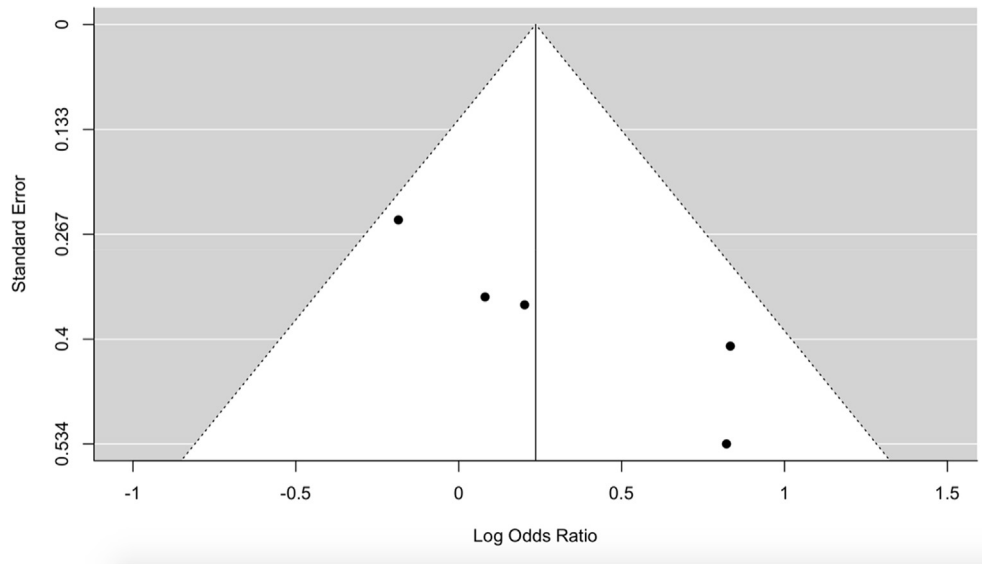


Fig. 2. Funnel plot to evaluate the publication bias of the included studies. Funnel plot of the publication bias of the selected studies in this meta-analysis.

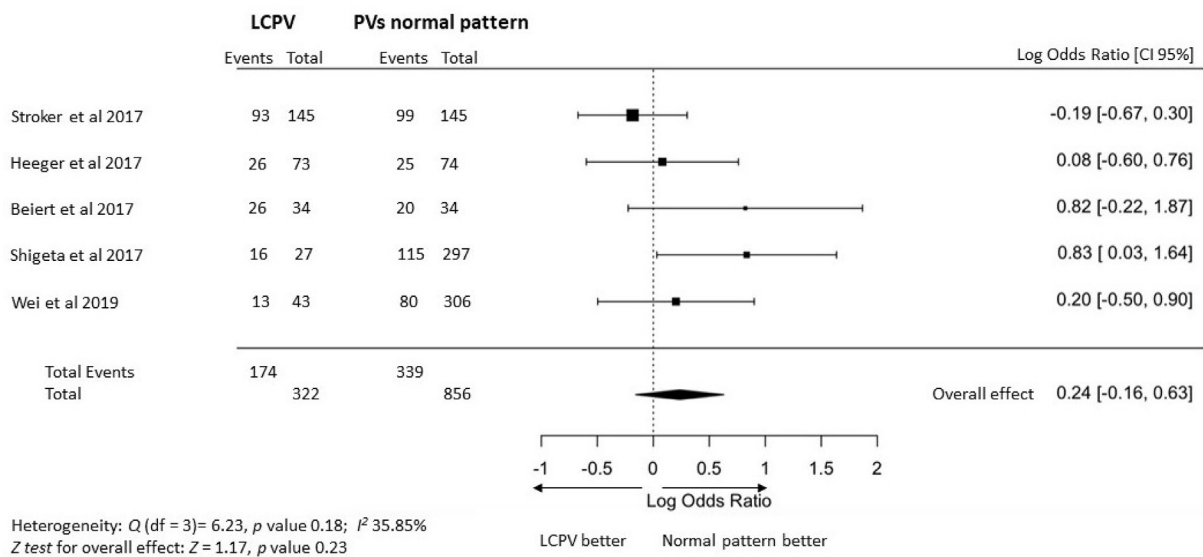


Fig. 3. Forest plot of the procedural results of the included studies. Forest plot of the clinical outcomes results, single studies results and the overall effect. LCPV: left common pulmonary vein, PVs: pulmonary veins.

setting of anatomic PVs variations is not widely accepted, conversely in the point by point radio-frequency ablation the operator is more flexible in handling the ablation catheter and he can adjust the lesion line on the basis of PV anatomy. The most common variant anatomy is a LCPV, followed by a right middle pulmonary vein [4]. Chierchia et al. showed the efficacy of a segmental superior and inferior approach with CB technology in the setting of LCPV [20]. Some recent studies compared the clinical outcome after a CB-A ablation in patients with and without a LCPV, however the results were conflicting. Ströker et al. [13], Heeger et al. [14] and Wei et al. [17] showed that the clinical outcome after the CB PVI was similar in patients with and without a LCPV. On the contrary, Beiert et al. [15] and Shigeta et al. [16] demonstrated that the clinical outcome after the CB ablation was worse in patients with a LCPV than in those without.

4.2. Procedural characteristics during LCPV ablation in selected studies

We think that a wide antral lesion, as well as a correct PVI without gaps, impact on the clinical efficacy of AF ablation. Applying this strategy, we might spare the potentially arrhythmogenic tissue of the PVs and of the antral region and the reduction of left atrium critical mass. Therefore, we have ensured that in all studies, included in this meta-analysis, an antral freezing cycle was applied as much as possible to LCPV as well as $\geq 99\%$ of PVI was achieved. The probability of obtaining these ablation features increases with CB-A and with a large balloon diameter. Therefore, we included in the analysis all studies that used a 28 mm CB-A to perform AF ablation. In all the studies the LCPV was isolated with one-shot technique, if sufficient antral occlusion could be achieved.

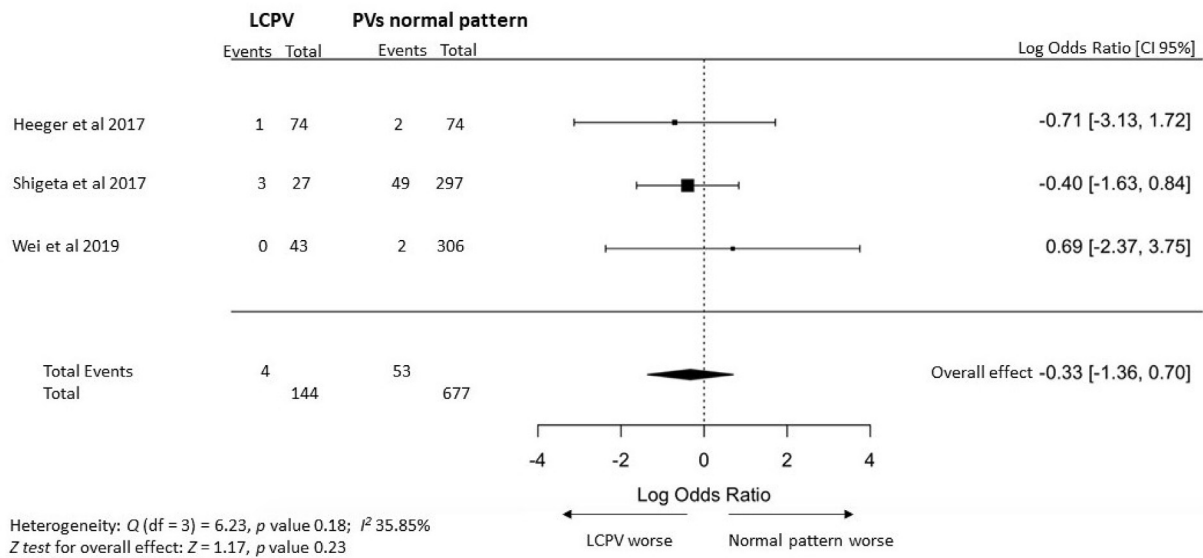


Fig. 4. Forest plot of the incidence of PNI of the included studies.

Forest plot of the PNI incidence, single studies results and the overall effect. LCPV: left common pulmonary vein, PVs: pulmonary veins.

Otherwise, the left superior and inferior branches of the LCPV were targeted individually with an antral sequential ablation approach. The two different ablation approaches used for electrical isolation in LCPVs revealed equal findings with regard to clinical outcomes. Unfortunately, the prevalence of single shot electrical isolation LCPV is about 20%. The short trunk LCPVs are characterized by wider ostium that required frequently an antral or distal sequential ablation approach to achieve electrical isolation. In our opinion the sequential ablation approach must be as antral as possible. This strategy leads to elimination of arrhythmogenic tissue near PVs and to reduction of critical mass. The studies included patients with both the morphology of LCPV. The results of the meta-analysis suggest that the cryoballoon technology could be a valid therapeutic approach in the setting of LCPV with a wider ostium. Three studies performed 3 min single freezing cycle for each PVs with a second application in case of not achieved PVI [13,16,17] and the other 2 studies performed 4 min with bonus freeze or different ablation protocol [14,15]. We think that 3 min single freezing cycle for each PVs with a second application in case of not achieved PVI is a reasonable approach to achieve PVI with CB-A.

4.3. CB-A in the setting of LCPV

As mentioned above the second-generation balloon with a diameter of 28 mm in this context seems to be an important choice. The second-generation balloon improves cooling capabilities by increasing the number of refrigerant injectors, resulting in a wider and more homogeneous cooling surface and the 28 mm diameter balloon increases the probability of electrical isolation of LCPV. Kubala et al. [21] compared the ablation outcomes with first generation CB between the normal pattern PVs and LCPV. At the end of the 13 months FU, patients with normal PVs had significantly better AF-free survival compared to patients with LCPV (67% vs 50%, p -value = 0.02). In this meta-analysis, the success rate of ablation with CB-A in the setting of LCPV is slightly better, as expected, although the mean FU of the studies included is much longer.

4.4. What are the difficulties in the setting of LCPV?

The ostium size, the angle of the branches and the ovality index

of LCPV are the elements that make it difficult to achieve an electrical isolation of LCPV [22,23]. The dimension of some LCPV ostium allows one shot electrical isolation. In case of wider LCPV ostium, a combined antral ablation of superior and inferior portion leads to electrical isolation. In addition, excessive angulation on the frontal plane between the LCPV ostium and its lower branch could induce difficulty in occluding in a stable manner the common trunk irrespectively from the ostium size. However, the sheath supporting the balloon and the balloon itself are deflectable, allowing the operator to try to achieve a correct occlusion. The overall high acute success rates in the studies analyzed may reflect that the operator can partially overcome the anatomical difficulty by specific handling maneuvers. The main finding of this meta-analysis is that the PVI with cryoballoon technology in patients with LCPV had no statistically different clinical outcome compared to patients with normal PVs pattern. There is a trend of better outcome in the group of patients with PVs normal pattern, although it does not reach statistical significance. It is interesting to compare radio-frequency and cryo-thermal in this group of patients: Khouery, Yamaguchi and Coutiño et al. [24–26] compared these two groups and they didn't show statistical difference in the outcomes.

4.5. PNI in the setting of LCPV cryoballoon ablation

Although the PNI is a prevalent complication of right PVs ablation, in line with all studies included we tested this complication in the two groups and as expected the incidence of PNI in both groups was similar.

5. Conclusion

This meta-analysis of patients undergoing a first ablation for persistent or paroxysmal AF shows a similar efficacy for PVI using the 28 mm CB-A regardless of the presence of a LCPV.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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