

# Cryoballoon Versus Radiofrequency Ablation for Atrial Fibrillation – Is There a Role for Individualised Patient Selection?



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## Introduction

Cryoballoon and radiofrequency have emerged as the two most frequently used approaches for catheter ablation of atrial fibrillation (AF). Some centres have adopted cryoballoon (CB) ablation as their universal ablation modality for the index AF ablation procedure, citing shorter procedural times and a shorter learning curve. Other operators still prefer the more “flexible” tool of radiofrequency ablation (RFA) as their “universal strategy”.

Fundamentally, the cryoballoon was designed in two sizes to achieve one goal: isolation of the pulmonary veins. The question can be asked—does a two-size balloon adequately accommodate for the heterogeneity in patient characteristics, cardiac substrate, and specific left atrial and pulmonary vein anatomy that we observe in our AF patient population? It is quite feasible that careful evaluation of such factors may “select” the optimal technology for ablation in individual patients and potentially improve outcomes, in terms of efficiency, efficacy or safety. To date, the approach of individualised patient selection for mode of AF ablation has not been systemically studied.

## Randomised Controlled Trials of Cryoballoon Versus Radiofrequency Ablation

The seminal Fire and Ice study [1], a randomised trial of over 700 patients with drug-refractory paroxysmal atrial fibrillation to CB or RFA, is often used to justify the non-inferiority of either approach. Indeed, clinical efficacy and safety outcomes were similar between the two groups, albeit with a

higher incidence of transient phrenic nerve palsy (PNP) in the CB arm. Procedural duration and left atrial dwell time were shorter in the CB group, whilst fluoroscopy time was shorter with RFA. Closer examination of the patient characteristics reveals that the patients were relatively young (mean age being 60 yrs) and most had structurally normal hearts (mean left atrial diameter was 40 mm). In addition, specific patient groups were excluded, such as those with prosthetic valves, previous left atrial ablation or surgery, New York Heart Association (NYHA) class III/IV heart failure, ejection fraction <35%, left atrial diameter >55 mm, right pulmonary vein diameter >26 mm, or hypertrophic cardiomyopathy. Freeze AF [2], a smaller randomised trial comparing CB and RFA, reported similar efficacy and safety outcomes, and it used similar exclusion criteria. It is, therefore, possible that CB or RFA may be associated with better clinical outcomes in patient populations not well represented by these randomised trials (Figure 1).

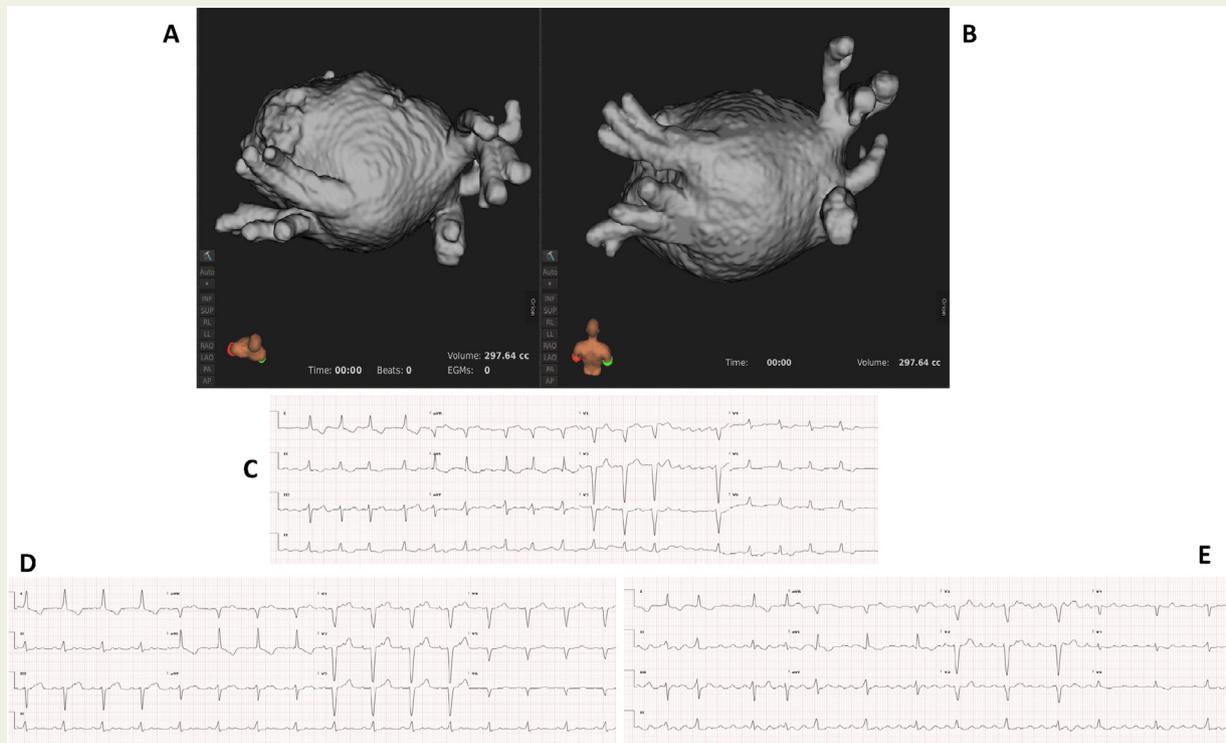
The remainder of this review will highlight patient characteristics, cardiac substrate, and specific left atrial and pulmonary vein anatomy which have the potential to influence the modality of ablation (summarised in Table 1).

## Non-Pulmonary Vein Substrate

The presence of non-PV triggers in initiating AF may limit the efficacy of CB ablation. The therapeutic value of targeting non-PV triggers routinely, however, is still controversial. Santangeli et al. [3] rigorously evaluated the frequency of focal AF triggers in over 2,000 patients, and found that non-pulmonary vein triggers were only elicited in ~11% of patients. Interestingly,

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**Figure 1** Example of an AF substrate where cryoballoon ablation may not be suitable.

A 45-year-old female with drug-refractory long-standing persistent AF and hypertrophic cardiomyopathy. The left atrium was severely dilated (297 mL) on pre-procedural CT imaging, as seen in the superior view (A) and postero-anterior view (B). Review of ECGs over the previous 12 months revealed AF (C), as well as two types of atrial flutter (D, E). This is an extreme example of a patient in whom radiofrequency ablation would likely be favourable.

Abbreviations: CT, computed tomography; ECG, electrocardiograph; AF, atrial fibrillation.

this proportion appeared unchanged whether AF was paroxysmal, persistent or long-standing persistent in duration. Their results support current recommendations for PV isolation (PVI) as the cornerstone of catheter ablation for AF. However, the frequency of non-pulmonary vein triggers may be higher in certain populations. For example, studies of patients with Asian ethnicity have consistently shown an increased prevalence of non-PV triggers, of up to 20–35% [4,5], with the most common non-PV trigger site being the superior vena cava (SVC). Outside of Asian populations, a single study has suggested empirical SVC isolation using RFA, in addition to PVI, may reduce paroxysmal AF recurrence [6]. Other factors associated with non-PV triggers include female gender [4,5], younger age [5], persistent AF [5], or left atrial enlargement (the latter specifically for posterior left atrial triggers) [4]. Recurrence of AF may be significantly reduced with ablation of non-PV triggers in such populations [4,5,7]. Zhao et al. [8] also demonstrated 69% of their patients with impaired ejection fraction ( $EF < 35\%$ ) had non-PV triggers, with reduced recurrence of AF if these were ablated.

Cryoballoon has been applied to non-PV substrates. Small series or case reports have reported the feasibility of ablation of the SVC, left and right atrial appendages or left atrial substrate using the cryoballoon [9–14] (Figure 2). However, it is important to acknowledge that the cryoballoon was

never designed to address such substrates, and neither long-term efficacy or complications have been adequately characterised with such “off-label use”.

Similarly, cryoballoon was not designed for linear ablation of macro-reentrant arrhythmias. As an example, concomitant cavo-tricuspid isthmus ablation was performed in 19% of patients in the Freeze AF study despite exclusion of patients with prior surgery/ablation, severely enlarged atria, or significant left ventricular dysfunction. Radiofrequency ablation may have intuitive advantages, in patients with documented atrial flutter (in addition to atrial fibrillation), or in those with atrial substrates prone to macro-reentry such as prior ablation, or surgery.

## Duration and Type of Atrial Fibrillation

Ablation outcomes in persistent AF are known to be less favourable than in paroxysmal AF [15]. Although additional substrate ablation (such as linear ablation, ablation of complex fractionated atrial electrograms (CFAEs), and/or rotors) in persistent AF may improve outcomes, this assumption was called into question by the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF II) study

**Table 1** Potential factors influencing choice of ablation modality.

Factor	Evidence/implications
<b>Significant structural heart disease</b> (eg. severe systolic dysfunction, severe left atrial dilatation, HCM, previous atrial surgery or ablation).	<ul style="list-style-type: none"> <li>Excluded from major CB PVI trials</li> <li>May have more non-PV substrates for AF</li> </ul>
<b>Suspected non-PV AF substrate</b>	
Documented flutter/AT on ECG	<ul style="list-style-type: none"> <li>Consider RFA, or hybrid approach</li> </ul>
Potential non-PV trigger	<ul style="list-style-type: none"> <li>Asian ethnicity, female</li> <li>Reduced ejection fraction</li> <li>Severe left atrial dilatation</li> </ul>
Long-standing persistent AF	<ul style="list-style-type: none"> <li>Evidence for CB PVI lacking</li> <li>Evidence for benefit of additional substrate ablation (with RFA) lacking</li> </ul>
<b>Anatomical challenges</b>	
LCPV	<ul style="list-style-type: none"> <li>Conflicting evidence regarding efficacy with CB PVI</li> <li>More venous ablation and increased recurrence if long trunk (&gt;10–20 mm)</li> </ul>
RMPV and rare variants	<ul style="list-style-type: none"> <li>Evidence lacking</li> </ul>
Early branching or sharp angulation of PV	<ul style="list-style-type: none"> <li>May impair alignment, occlusion and effective ablation</li> </ul>
Sharp ridge left PVs/LAA	<ul style="list-style-type: none"> <li>May impair alignment, occlusion and effective ablation</li> </ul>
Very large vein (>26 mm)	<ul style="list-style-type: none"> <li>Increased risk of PNP, PV stenosis, particularly on right side</li> <li>Reduced antral ablation</li> </ul>
Oval or funnel-shaped vein	<ul style="list-style-type: none"> <li>Reduced antral ablation, possibly increased recurrence of AF</li> </ul>

Abbreviations: HCM, hypertrophic cardiomyopathy; CB, cryoballoon; PVI, pulmonary vein isolation; PV, pulmonary vein; AF, atrial fibrillation; AT, atrial tachycardia; RFA, radiofrequency ablation; LCPV, left common pulmonary vein; RMPV, right middle pulmonary vein; LAA, left atrial appendage; PNP, phrenic nerve palsy.

[15]. In this randomised trial, no additional benefit (at the index procedure) was seen by adding linear ablation or targeting of CFAEs to antral PVI with RFA for persistent AF. These results may not necessarily be applicable to CB however, which may deliver a more ostial (rather than antral) ablation, compared to RFA [16,17], especially in the setting of large calibre funnel shaped PVs or left common PVs.

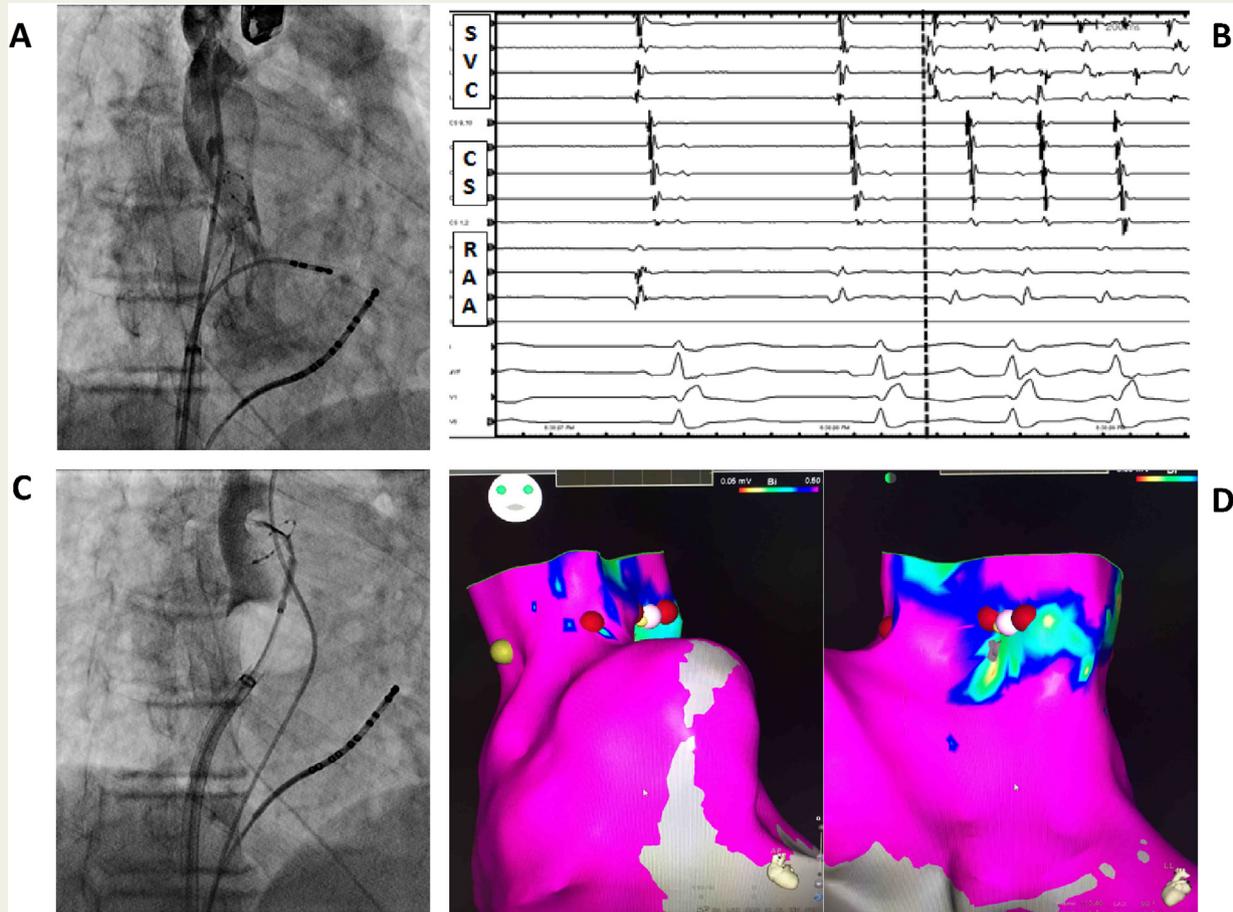
Limited non-randomised data suggests similar short to mid-term outcomes in persistent AF when comparing the second-generation CB (CB2) with RFA [18–20]. In a propensity-matched study of 118 patients undergoing either CB PVI only or RFA PVI plus substrate ablation for persistent AF, Boveda et al. [21] did not find any difference in outcomes between groups. The literature was summarised in a systematic review and meta-analysis by Voskoboinik et al. [22], analysing 14 studies of PVI only for persistent AF, with 45% of patients receiving RFA and 55% CB2. Long-term outcomes were similar between ablation strategies, with 67% single procedure freedom from arrhythmia at 12 months and a 0.9% persistent PNP rate in the CB group. Importantly, the overall prevalence of structural heart disease in these studies was low, and few patients had severe left ventricular systolic dysfunction or severe left atrial dilatation. In addition, only a minority had *long-standing* persistent AF. Currently, evidence for CB PVI in long-standing persistent AF is lacking. Some operators have reported the use of the CB to successfully ablate CFAEs or create linear lesions (roof or mitral lines) [10,23], suggesting that additional substrate ablation is technically feasible. More recently, a randomised trial of 390 persistent AF patients suggested CB posterior wall isolation in addition to PVI reduced arrhythmia recurrence compared to CB PVI alone [24]. Notably, a mean of 13.7 CB applications was required to isolate the posterior wall, “touch-up” RFA was required in nearly one third and significant oesophageal cooling was observed in several cases. For now, such use of the CB remains “off-label” with insufficient data to support mainstream adoption, and RFA remains the modality of choice for ablation beyond the pulmonary veins.

In redo ablation procedures, RFA is preferable to CBA because it addresses focal pulmonary vein reconnections as well as allowing additional non-PV trigger or substrate ablation when it is required.

## Variations in Pulmonary Vein Anatomy

Adequate contact between the cryoballoon and the PV antrum is critical to ensure transfer of heat energy and effective lesion formation. A mismatch between the PV and the two-size CB, due to variations in size, shape or configuration of pulmonary veins, may theoretically impede ablation efficacy; and, extreme variations in such factors may favour the flexibility of RFA (Figure 3).

Nevertheless, CB users may be reassured that the original “single big balloon” study [25] did not mandate screening of PV anatomy for inclusion. In addition, large randomised trials [1,2,26] did not exclude PV anatomical variants, *except* for large right sided veins in the “Fire and Ice” trial. Acute isolation of anomalous PV variants was successfully achieved by CB in nearly all cases in the “Fire and Ice” trial (28/28 left common PVs and 12/13 right middle PVs).



**Figure 2** “Off-label” superior vena cava (SVC) isolation using cryoballoon.

A 74-year-old male with drug-refractory paroxysmal AF. Cryoballoon ablation successfully isolated all 4 pulmonary veins, with AF subsequently organising into atrial tachycardia. The circular mapping catheter was placed in the SVC (A), where a rapidly firing focus was identified (B). The SVC was successfully isolated using cryoballoon (C), with tachycardia termination during ablation. AF recurred at 6 months, with reconnection of the SVC; this was then isolated using radiofrequency energy (D – antero-posterior and left lateral views).

Abbreviations: AF, atrial fibrillation; SVC, superior vena cava; CS, coronary sinus; RAA, right atrial appendage.

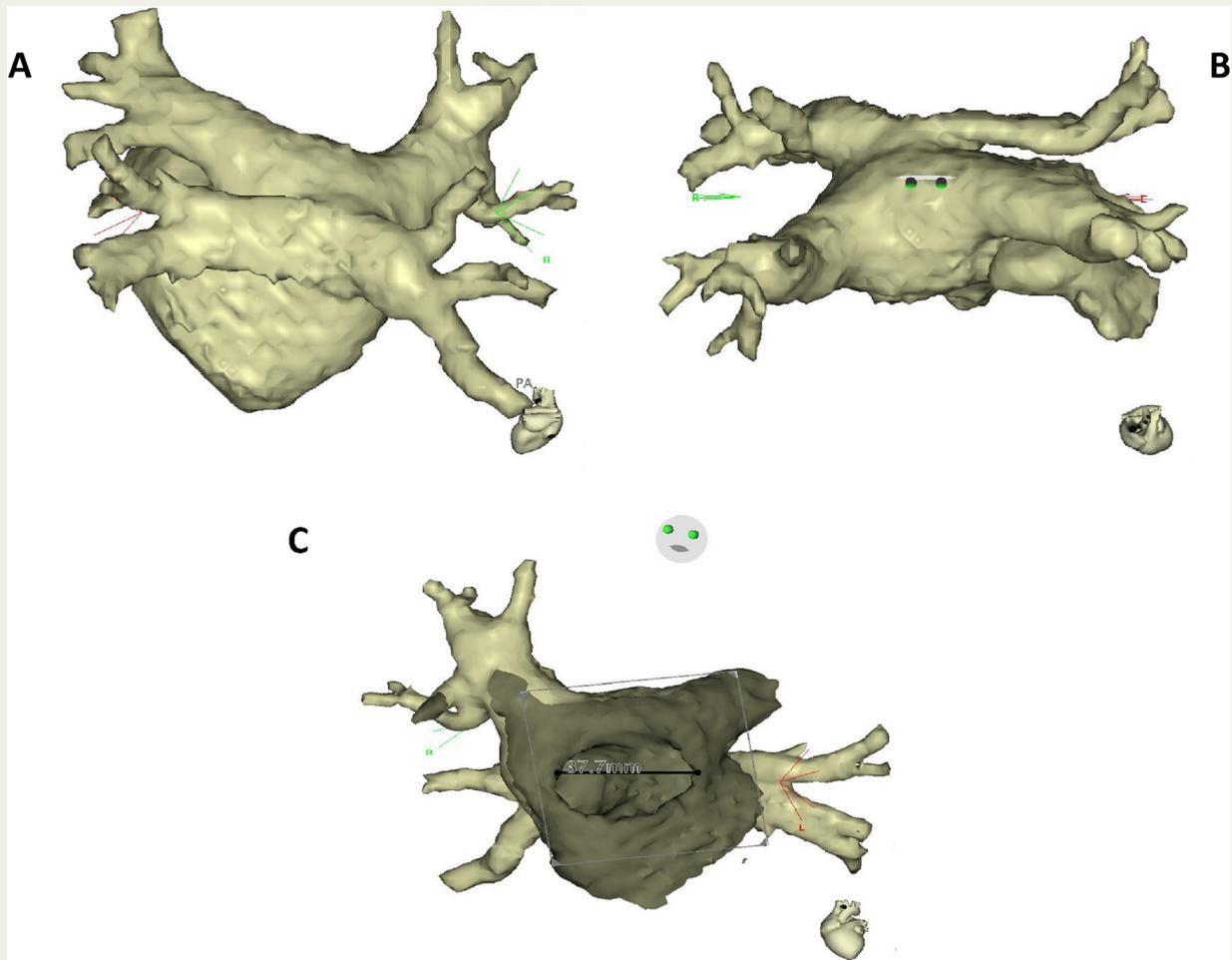
However, the results have been more heterogeneous in the wider literature examining the impact of PV anatomy on CBA efficacy.

### Anomalous Pulmonary Vein Anatomy

Magnetic resonance imaging (MRI) and computed tomography (CT) imaging studies examining PV anatomy have established that anomalous anatomy is common; a “normal” four PV ostia configuration may be present in only 50–70% of patients [27–29]. A left common PV (LCPV) is seen in 9–17% of patients and a right middle PV (RMPV) in 13–29% of patients [27,29–32]. Less commonly, a left supernumerary vein may be present in up to 2% and a right common ostium in 0.5–2%.

The mean diameter of LCPVs may range from 26 to 31 mm [27,33], potentially providing a challenge to satisfactory CB occlusion and the delivery of effective antral ablation, even with the 28 mm balloon. Indeed, early experience with the

first-generation CB (CB1) found increased rates of AF recurrence with LCPVs [34], particularly in those patients with a long common trunk (>20 mm) prior to branching. Results with the more conformable CB2, however, have been more optimistic, with several studies showing similar long-term freedom from atrial arrhythmia in the setting of normal PV anatomy or a LCPV [35–37]. Variably, isolation can be achieved with either a single antral freeze, or sequential freezes with the spiral catheter in upper and lower branches [35,36]. Recording PV potentials may be more challenging with distal positioning of the recording catheter. No increased risk of clinically significant PV stenosis was detected in these studies. However, it is notable that Shigeta et al. [38] recently reported an increased risk of AF recurrence with CB2 in LCPVs, defining LCPV as a trunk >10 mm. Recurrence only occurred in those with a more distal (venous) ablation, rather than antral ablation. In the four patients who underwent a repeat ablation, the distal LCPV



**Figure 3** Example of rare anomalous PV variant – common inferior pulmonary vein ostium.

A 60-year-old male with drug-refractory persistent AF and tachycardia-mediated cardiomyopathy. The preoperative CT revealed a common inferior pulmonary vein ostium, seen in the postero-anterior (A) and superior (B) views. Maximal dimension of the common os was 38 mm (C). All pulmonary veins were successfully isolated using radiofrequency energy. Abbreviations: AF, atrial fibrillation; CT, computed tomography.

remained isolated, prompting the authors to hypothesise that the lack of antral ablation was causative of AF recurrence.

Patients with a RMPV have been historically excluded from older CB studies [39], and some operators remain reluctant to use CB in these typically small diameter veins. Technically, overlapping ablations of the right superior and inferior veins may be sufficient to isolate a small RMPV. Data specific to RMPVs is scarce; although no increased risk of AF recurrence was seen with CB1 [35,40], a small study of CB2 ablations found increased AF recurrence in this group [41].

### Pulmonary Vein Branching, Angulation, Size and Shape

Early branching of a pulmonary vein has been defined as branching within 5 mm of the PV ostium; this may be present (in at least one vein) in up to 40% of patients [27]. If the early PV branch is directed with an acute angle relative to the main PV trunk, optimal alignment of the CB with the ostium may be impaired. Knecht et al. [40], using CB1, found that early

branching of the right inferior PV was particularly associated with increased failure of isolation. A study of early PV reconstructions in CB PVI (with adenosine challenge at 30 mins post-isolation) supported this observation, as early branching of right sided veins was associated with reconnection [42]. Sharp angulation of the main PV trunk, relative to the frontal plane of the atrium, may similarly impair optimal alignment and therefore occlusion with the CB. Sharp angulation in CB1 studies was predictive of conduction recovery, particularly at the inferior aspect of the inferior veins [39,43]. CB1 studies have also reported increased recurrence in patients with a sharply angled ridge between the left PVs and the left atrial appendage, or a sharp carina between the left PVs [40,43].

A very large vein may potentially increase the risk of PNP and PV stenosis, whilst reducing antral ablation and rendering the recording of PV potentials technically difficult. In Fire and Ice [1], right sided veins >26 mm were excluded for these reasons. Mansour et al. observed that 14% of patients had at

least one vein with a maximal ostial diameter exceeding 25 mm, and 30% of patients had >10 mm variability between PVs [27]. Indeed, all cases of PNP in Chun et al.'s [25] original CB study occurred when the PV to CB ratio exceeded 0.93. The smaller 23 mm CB has been associated with an increased risk of PNP in several studies [44,45], although a signal towards more *permanent* PNP with the larger 28 mm balloon should be noted with caution [46,47]. With respect to reduced antral ablation, limited data with CB has reported an increased AF recurrence with a large right superior PV [41] or large left inferior PV [48].

Not only size but shape of PVs may impact cryoablation efficacy. Increased ovality of PVs (quantified by the ratio of maximal to minimal diameters of the vein) has been shown to impede occlusion and lead to unfavourable outcomes [39,49]. Funnel-shaped veins, although not studied systematically, may potentially have the same effect. These were defined as a 60% decrease in diameter over 10 mm by Mansour et al. [27], and were present in at least one vein in 47% of patients.

## Ganglionic Plexus Ablation

The ganglionic plexi, located at the antral aspect of the PV ostia, may play a role in the pathogenesis of AF via cardiac parasympathetic innervation [50]. Some have argued that CB potentially modulates these plexi (the concept of “bystander ablation”), more so than RFA [51,52]. Intra-procedural vagal reactions to cryoablation, requiring atropine or temporary pacing, were associated with reduced AF recurrence in a study by Yorgun et al.'s [51]. Conversely, the reproducibility of vagal reactions with “bonus” cryoapplications prompted Peyrol et al. [53] to suggest that the phenomenon may reflect autonomic stimulation, rather than modulation or denervation. The effect on the autonomic nervous system appears to be temporary, as assessed by analysis of heart rate variability with gradual recovery by 3 months post CB ablation [52].

## Cryoballoon Design Enhancements

The first-generation CB produced a band of maximal cooling immediately distal to the equator of the balloon. Eccentric positioning of the CB1 in a PV could, therefore, result in suboptimal alignment of this band with the PV antrum. The second-generation balloon redesigned the position and number of refrigerant injector ports, to produce more homogeneous cooling of the distal hemisphere; thereby alignment was less critical to achieve isolation [54]. New CB designs have already been described in small series [55]. These enhancements may further improve the flexibility and conformability of the cryoballoon, such that it can more reliably accommodate PV anatomical variants and non-PV substrates.

## Conclusions

The question of individualised patient selection for cryoballoon or radiofrequency ablation of AF has not been systematically studied. The results of recent randomised trials such as “Fire and Ice” and “Freeze AF” suggests that CBA and RFA may deliver equivalent efficiency, efficacy and safety in the majority of patients undergoing ablation for AF. However, these trials excluded certain types of structural heart disease or PV anatomical variants. Cryoablation may be less favourable when a non-PV substrate is documented or suspected (for example, significant structural heart disease, specific ethnicity or potentially long-standing persistent AF). Cryoablation may also be less favourable when anatomical challenges are detected on pre-procedural imaging, such as anomalous PV anatomy, large, angulated or ovoid veins. Future research should aim to address the potential benefit of patient selection for mode of AF ablation in these subgroups. From a practical perspective, it is important for contemporary electrophysiology Fellowship programs to continue training in both modalities of ablation.

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## Declarations of Interest

Nil.

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## References

- [1] Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016;374(23):2235–45.
- [2] Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hormann P, et al. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation: the prospective, randomized, controlled, noninferiority freeze AF study. *Circulation* 2015;132(14):1311–9.
- [3] Santangeli P, Zado ES, Hutchinson MD, Riley MP, Lin D, Frankel DS, et al. Prevalence and distribution of focal triggers in persistent and long-standing persistent atrial fibrillation. *Heart Rhythm* 2016;13(2):374–82.
- [4] Lee SH, Tai CT, Hsieh MH, Tsao HM, Lin YJ, Chang SL, et al. Predictors of non-pulmonary vein ectopic beats initiating paroxysmal atrial fibrillation: implication for catheter ablation. *J Am Coll Cardiol* 2005;46(6):1054–9.
- [5] Chang HY, Lo LW, Lin YJ, Chang SL, Hu YF, Li CH, et al. Long-term outcome of catheter ablation in patients with atrial fibrillation originating from nonpulmonary vein ectopy. *J Cardiovasc Electrophysiol* 2013;24(3):250–8.
- [6] Corrado A, Bonso A, Madalosso M, Rossillo A, Themistoclakis S, Di Biase L, et al. Impact of systematic isolation of superior vena cava in addition to pulmonary vein antrum isolation on the outcome of paroxysmal, persistent, and permanent atrial fibrillation ablation: results from a randomized study. *J Cardiovasc Electrophysiol* 2010;21(1):1–5.

- [7] Hayashi K, An Y, Nagashima M, Hiroshima K, Ohe M, Makihara Y, et al. Importance of nonpulmonary vein foci in catheter ablation for paroxysmal atrial fibrillation. *Heart Rhythm* 2015;12(9):1918–24.
- [8] Zhao Y, Di Biase L, Trivedi C, Mohanty S, Bai R, Mohanty P, et al. Importance of non-pulmonary vein triggers ablation to achieve long-term freedom from paroxysmal atrial fibrillation in patients with low ejection fraction. *Heart Rhythm* 2016;13(1):141–9.
- [9] Yorgun H, Canpolat U, Kocyigit D, Coteli C, Evranos B, Aytemir K. Left atrial appendage isolation in addition to pulmonary vein isolation in persistent atrial fibrillation: one-year clinical outcome after cryoballoon-based ablation. *Europace* 2017;19(5):758–68.
- [10] Su WW, Alzubaidi M, Tseng R, Jebaily N, Lin YJ, Wang PJ. Novel usage of the cryoballoon catheter to achieve large area atrial substrate modification in persistent and long-standing persistent atrial fibrillation. *J Interv Card Electrophysiol* 2016;46(3):275–85.
- [11] Canpolat U, Evranos B, Kocyigit M, Yorgun H, Aytemir K. Case images: electrical isolation of superior vena cava as well as pulmonary vein isolation with cryoballoon technique in a young patient with persistent atrial fibrillation. *Turk Kardiyol Dern Ars* 2017;45(2):208.
- [12] Schneider MA, Schade A, Koller ML, Schumacher B. Cryoballoon ablation of paroxysmal atrial fibrillation within the dilated coronary sinus in a case of persistent left superior vena cava. *Europace* 2009;11(10):1387–9.
- [13] Chun KJ, Ouyang F, Schmidt B, Kuck KH. Focal atrial tachycardia originating from the right atrial appendage: first successful cryoballoon isolation. *J Cardiovasc Electrophysiol* 2009;20(3):338–41.
- [14] Ng B, Ilisar R, McGuire M, Singarayar S. Atrial fibrillation resulting from superior vena cava drivers addressed with cryoballoon ablation: late reconnection at the site of phrenic nerve pacing catheter. *Heart Rhythm* 2018.
- [15] Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372(19):1812–22.
- [16] Arentz T, Weber R, Burkle G, Herrera C, Blum T, Stockinger J, et al. Small or large isolation areas around the pulmonary veins for the treatment of atrial fibrillation? Results from a prospective randomized study. *Circulation* 2007;115(24):3057–63.
- [17] Miyazaki S, Taniguchi H, Hachiya H, Nakamura H, Takagi T, Iwasawa J, et al. Quantitative analysis of the isolation area during the chronic phase after a 28-mm second-generation cryoballoon ablation demarcated by high-resolution electroanatomic mapping. *Circ Arrhythm Electrophysiol* 2016;9(5):e003879.
- [18] Ciconte G, Ottaviano L, de Asmundis C, Baltogiannis G, Conte G, Sieira J, et al. Pulmonary vein isolation as index procedure for persistent atrial fibrillation: one-year clinical outcome after ablation using the second-generation cryoballoon. *Heart Rhythm* 2015;12(1):60–6.
- [19] Tscholl V, Lsharaf AK, Lin T, Bellmann B, Biewener S, Nagel P, et al. Two years outcome in patients with persistent atrial fibrillation after pulmonary vein isolation using the second-generation 28-mm cryoballoon. *Heart Rhythm* 2016;13(9):1817–22.
- [20] Koektuerk B, Yorgun H, Koektuerk O, Turan CH, Aksoy MN, Turan RG, et al. Cryoballoon ablation for pulmonary vein isolation in patients with atrial fibrillation: preliminary results using novel short-tip cryoballoon. *J Interv Card Electrophysiol* 2016;47(1):91–8.
- [21] Boveda S, Providencia R, Defaye P, Pavin D, Cebon JP, Anselme F, et al. Outcomes after cryoballoon or radiofrequency ablation for persistent atrial fibrillation: a multicentric propensity-score matched study. *J Interv Card Electrophysiol* 2016;47(2):133–42.
- [22] Voskoboinik A, Moskovitch JT, Harel N, Sanders P, Kistler PM, Kalman JM. Revisiting pulmonary vein isolation alone for persistent atrial fibrillation: a systematic review and meta-analysis. *Heart Rhythm* 2017;14(5):661–7.
- [23] Kuniss M, Greiss H, Pajitnev D, Akkaya E, Deubner N, Hain A, et al. Cryoballoon ablation of persistent atrial fibrillation: feasibility and safety of left atrial roof ablation with generation of conduction block in addition to atrial pulmonary vein isolation. *Europace* 2017;19(7):1109–15.
- [24] Aryana A, Baker JH, Espinosa Ginic MA, Pujara DK, Bowers MR, O'Neill PG, et al. Posterior wall isolation using the cryoballoon in conjunction with pulmonary vein ablation is superior to pulmonary vein isolation alone in patients with persistent atrial fibrillation: a multicenter experience. *Heart Rhythm* 2018;15(8):1121–9.
- [25] Chun KR, Schmidt B, Metzner A, Tilz R, Zerm T, Koster I, 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(6):699–709.
- [26] Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;61(16):1713–23.
- [27] Mansour M, Holmvang G, Sosnovik D, Migrino R, Abbara S, Ruskin J, 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(4):387–93.
- [28] Scharf C, Sneider M, Case I, Chugh A, Lai SW, Pelosi Jr F, 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(2):150–5.
- [29] Kaseno K, Tada H, Koyama K, Jingu M, Hiramatsu S, Yokokawa M, et al. Prevalence and characterization of pulmonary vein variants in patients with atrial fibrillation determined using 3-dimensional computed tomography. *Am J Cardiol* 2008;101(11):1638–42.
- [30] Marom EM, Herndon JE, Kim YH, McAdams HP. Variations in pulmonary venous drainage to the left atrium: implications for radiofrequency ablation. *Radiology* 2004;230(3):824–9.
- [31] 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):1–9.
- [32] Kato R, Lickfett L, Meiningner G, Dickfeld T, Wu R, Juang 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(15):2004–10.
- [33] Ahmed J, Sohal S, Malchano ZJ, Holmvang G, Ruskin JN, Reddy VY. Three-dimensional analysis of pulmonary venous ostial and atrial anatomy: implications for balloon catheter-based pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2006;17(3):251–5.
- [34] 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(7):837–43.
- [35] Khoueir Z, Albenque JP, Providencia R, Combes S, Combes N, Jourda F, et al. Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy. *Europace* 2016;18(9):1343–51.
- [36] 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(8):1111–8.
- [37] Stroker E, Takarada K, de Asmundis C, Abugattas JP, Mugnai G, Velagic V, et al. Second-generation cryoballoon ablation in the setting of left common pulmonary veins: procedural findings and clinical outcome. *Heart Rhythm* 2017;14(9):1311–8.
- [38] 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(9):1021–7.
- [39] Sorgente A, Chierchia GB, de Asmundis C, Sarkozy A, Namdar M, Capulzini L, 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(2):205–12.
- [40] Knecht S, Kuhne 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(2):132–8.
- [41] Guler E, Guler GB, Demir GG, Kizilirmak F, Gunes HM, Barutcu I, et al. Effect of pulmonary vein anatomy and pulmonary vein diameters on outcome of cryoballoon catheter ablation for atrial fibrillation. *Pacing Clin Electrophysiol* 2015;38(8):989–96.
- [42] Ciconte G, Chierchia GB, de Asmundis C, Sieira J, Conte G, Julia J, et al. Spontaneous and adenosine-induced pulmonary vein reconnection after cryoballoon ablation with the second-generation device. *J Cardiovasc Electrophysiol* 2014;25(8):845–51.
- [43] Furnkranz A, Chun KR, Nuyens D, Metzner A, Koster I, Schmidt B, et al. Characterization of conduction recovery after pulmonary vein isolation using the "single big cryoballoon" technique. *Heart Rhythm* 2010;7(2):184–90.
- [44] Guhl EN, Siddoway D, Adelstein E, Bazaz R, Mendenhall GS, Nemej J, et al. Incidence and predictors of complications during cryoballoon pulmonary vein isolation for atrial fibrillation. *J Am Heart Assoc* 2016;5(7).
- [45] Andrade JG, Dubuc M, Guerra PG, Macle L, Mondesert B, Rivard L, et al. The biophysics and biomechanics of cryoballoon ablation. *Pacing Clin Electrophysiol* 2012;35(9):1162–8.

- [46] Sarabanda AV, Bunch TJ, Johnson SB, Mahapatra S, Milton MA, Leite LR, et al. Efficacy and safety of circumferential pulmonary vein isolation using a novel cryothermal balloon ablation system. *J Am Coll Cardiol* 2005;46(10):1902–12.
- [47] Nadjji G, Hermida JS, Kubala M, Quenum S, Mouquet V, Traulle S, et al. Dual balloon size strategy for cryoisolation of the pulmonary veins in patients with atrial fibrillation: comparison of 23 and 28 mm diameter cryoballoons. *Arch Cardiovasc Dis* 2011;104(2):70–6.
- [48] Tsyganov A, Petru J, Skoda J, Sediva L, Hala P, Weichet J, et al. Anatomical predictors for successful pulmonary vein isolation using balloon-based technologies in atrial fibrillation. *J Interv Card Electrophysiol* 2015;44(3):265–71.
- [49] Schmidt M, Dorwarth U, Straube F, Daccarett M, Rieber J, Wankel M, et al. Cryoballoon in AF ablation: impact of PV ovality on AF recurrence. *Int J Cardiol* 2013;167(1):114–20.
- [50] Tan AY, Li H, Wachsmann-Hogiu S, Chen LS, Chen PS, Fishbein MC. Autonomic innervation and segmental muscular disconnections at the human pulmonary vein-atrial junction: implications for catheter ablation of atrial-pulmonary vein junction. *J Am Coll Cardiol* 2006;48(1):132–43.
- [51] Yorgun H, Aytemir K, Canpolat U, Sahiner L, Kaya EB, Oto A. Additional benefit of cryoballoon-based atrial fibrillation ablation beyond pulmonary vein isolation: modification of ganglionated plexi. *Europace* 2014;16(5):645–51.
- [52] Oswald H, Klein G, Koenig T, Luesebrenk U, Duncker D, Gardiwal A. Cryoballoon pulmonary vein isolation temporarily modulates the intrinsic cardiac autonomic nervous system. *J Interv Card Electrophysiol* 2010;29(1):57–62.
- [53] Peyrol M, Barraud J, Koutbi L, Maille B, Trevisan L, Martinez E, et al. Vagal reactions during cryoballoon-based pulmonary vein isolation: a clue for autonomic nervous system modulation? *Biomed Res Int* 2016;6:7286074.
- [54] Furnkranz 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(5):492–7.
- [55] Sciarra L, Iacopino S, Palama Z, De Ruvo E, Filannino P, Borrelli A, et al. Impact of the third generation cryoballoon on atrial fibrillation ablation: an useful tool? *Indian Pacing Electrophysiol J* 2018;18(4):127–32.