## Review Article

# Third Generation Cryoballoon. Is It Better? A Meta-Analysis

**Mohammad Bilaal Toorabally[1], Beatrice Chung Fat King Brunet[2], Minglong Chen[1*]**

[1]Department of Cardiology, The First Affiliated Hospital, Nanjing Medical University, Nanjing 210029, PR China
[2]The State Key Laboratory of Reproductive Medicine, Clinical Center of Reproductive Medicine, First Affiliated Hospital, Nanjing Medical University, Nanjing 210029, PR China

[*]**Corresponding Author:** Minglong Chen, Section of Pacing and Electrophysiology, Division of Cardiology, Nanjing Medical University, No. 300 Guangzhou Road, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, PR China, Tel +8613809000791; E-mail: chenminglong@njmu.edu.cn

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## Abstract

Cryoablation for the isolation of the pulmonary veins is an established treatment for paroxysmal and persistent atrial fibrillation. The second generation cryoballoon improves the effectiveness of the procedure. Recently, a new third generation cryoballoon has been introduced with a 40% shorter tips which in theory, should impact the procedure efficacy and the real time visualization of pulmonary vein isolation due to a more proximal placement of the inner lumen mapping catheter. This meta-analysis analyses all the data available to compare the performance of the two latest generations of cryoballoons. Two investigators searched and analyzed all published literature comparing the second generation cryoballoon (Arctic fron Advance cryoballoon) to the third generation cryoballoon (Arctic front advance short tip cryoballoon) in Pubmed, Google Scholar and Cochrane library. 1625 patients from 6 published studies were included in this meta-analysis. 351 patients were in the third generation cryoballoon groups and 1243 patients were in the second generation cryoballoon groups. Analysis of the pooled data revealed that the third generation cryoballoon had a shorter procedure time and a higher freeze temperature. The fluoroscopy time was shorter in the second generation cryoballoons. As for real time recordings, it was more prevalent in the third generation group but this difference was not statistically significant. Cryoablation using the short tip third generation cryoballoon allows for a shorter procedure time and offers an enhanced ability to assess time to pulmonary vein isolation with equivalent procedural safety and efficacy.

**Keywords**: Cryoablation; Atrial fibrillation; Third generation cryoballoon; Second generation cryoballoon; Short tip cryoballoon; Pulmonary Vein isolation

## 1. Introduction

Since the introduction of the first generation cryoballoon in Europe in 2005 and its subsequent second and third generations, the cryoballoons have been an established tool for pulmonary vein isolation (PVI) as a treatment for symptomatic drug resistant atrial fibrillation [1-4]. The second generation cryoballoon (CB-2) improved pulmonary vein isolation by having an increased number and more distal coolant ports in the balloon thereby allowing a more even coolant distribution and lower temperatures [5,6]. The basic design of the third generation cryoballoon (CB-3) is quite similar to the second except for an 8 mm shorter tip compared to the 13mm tip in the second generation balloons, a 40% shorter tip, which in the second generation was positioned further from the balloon to offer stability. This created a distance between the ablation site and the inner lumen mapping catheter, inhibiting real time recording of pulmonary vein isolation. A shorter tip, in theory, improves visualization due to its proximity to the ablation site and facilitates real time recording of pulmonary vein isolation thereby reducing procedure time[7]. There are no specific guidelines, but several studies have shown that a shorter time to isolation is associated with lesion durability, number of cryoablation and fluoroscopy time whereas a long isolation time is associated with an increased risk of PV reconnection [8-10].

Our aim is to do a complete review of literature and pool the data of previously conducted studies for a systematic review and meta-analysis comparing CB-2 and CB-3.

## 2. Methods

We did an article search on Pubmed, Cochrane database and google scholar for all the papers that compared the second generation cryoballoon to the third generation cryoballoon in humans, until January 2018. Two investigators identified all the relevant literatures and any disputes were resolved by consensus among all the authors. With the keywords for the search as “third generation cryoballoon”, “second generation cryoballoon”, “short tip cryoballoon”, Pulmonary Vein isolation” and “atrial fibrillation”, 1270 articles were obtained. 1229 were excluded after title review and 8 were included after checking for duplicates and studies that did no mention the desired outcomes of our paper. Our investigators also manually searched the references of review articles.

### 2.1 Inclusion criteria

1. Articles comparing third and second generations cryoballoons
2. Cryoablation used to treat atrial fibrillation or pulmonary vein isolation
3. Patients were diagnosed with paroxysmal or persistent atrial fibrillation

The presence of a thrombus in the heart, anticoagulation was contraindicated, heart failure that is not controlled, moderate or severe valvular disease, and where general anesthesia was contraindicated were excluded from our study.

## 3. Results

After abstract reading, a total of 41 papers were obtained which were thoroughly read and reviewed by our investigators. Six papers which satisfied our inclusion and exclusion criteria were selected to be used in this meta-

analysis that compared the second generation cryoballoon with the third generation cryoballoon [11-16]. Most papers were discarded due to duplication, lack of required information or failure to compare the two generations of cryoballoon (Figure 1).

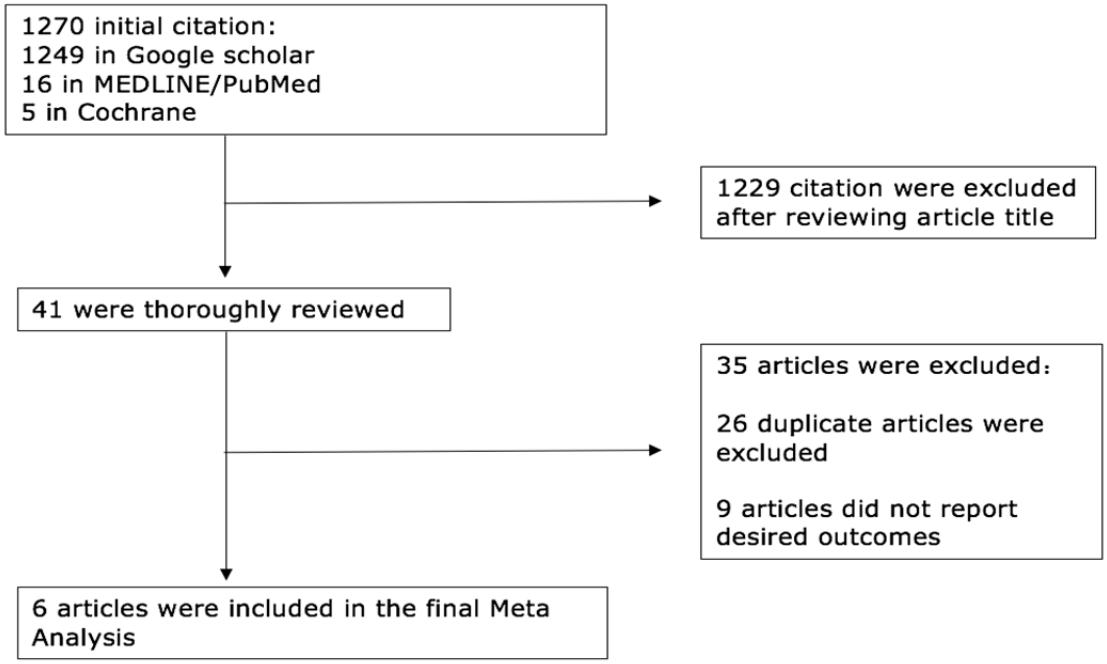


**Figure 1:** Search strategy

Table 1 shows the six studies that have met the inclusion and exclusion criteria. It shows more details about the studies including the name of the author, the year of publication, the inclusion and exclusion criteria of the studies, the total number of patients participating in the study, the number of patients in each groups and the mean left atrial diameters of each groups.

| First author | Year | Inclusion Criteria | Exclusion criteria | Total Pt (n) | Pt in CB-3 (n) | Pt in CB-2 (n) | LAD CB-3 (mm) | LAD CB-2 (mm) |
|---|---|---|---|---|---|---|---|---|
| Koektuerk | 2015 | Paroxysmal or persistent AF | Severe valvular disease, LAD >55mm, left atrial thrombus, thyroid dysfunction, decompensated HF, Pre-procedural CAD, Previous AFA, Pregnancy | 64 | 33 | 31 | 39.1 ± 3.4 | 38.3 ± 2.7 |
| Furnkranz | 2015 | Paroxysmal or | NS | 472 | 49 | 423 | 40 ± 5 | 40 ± 6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | persistent AF | | | | | | |
| Aryana | 2016 | Symptomatic Paroxysmal or persistent AF | NS | 355 | 102 | 253 | 45 ± 6 | 43 ± 6 |
| Heeger | 2015 | Symptomatic drug refractory Paroxysmal or short standing persistent AF(<3months) | Previous AFA, LAD>60mm, Severe valvular disease, Contraindication to anticoagulation | 60 | 30 | 30 | 45 ± 7 | 45 ± 5 |
| Mugnai | 2015 | Patients undergoing cryoballoon ablation | Intracavitary thrombus, uncontrolled HF, moderate/severe valvular disease, contraindicated general anesthesia | 600 | 100 | 500 | 43.8 ± 10.4 | 42.7 ± 8.8 |
| Pott | 2016 | Paroxysmal or persistent AF | Left common trunk forming 1 left sided PV ostium | 74 | 37 | 37 | 46 ± 7 | 44 ± 7 |

**Table 1:** Study characteristics

CB-2: Second generation cryoballoon, CB-3: Second generation cryoballoon, LAD: Left atrial diameter, AF: Atrial fibrillation, HF: Heart failure, CAD: Coronary artery disease, AFA: Atrial fibrillation ablation, NS: Not specified, PV: Pulmonary vein

Among the 6 studies in this paper, only two of them mentioned the arrhythmia recurrence after a mean follow-up of 12 ±2 months in Aryana et al. [13] and 6.2±2.9 months in Pott et al. [16]. Both of them showed that there was no difference between CB-2 and CB-3. In the other studies, freedom from arrhythmia recurrence was not recorded.

The combined difference in mean of all the six studies was favorable for the CB-3 group for the total procedural time (SDM=-0.45 [95% CI of -0.84; -0.07], p<0.01). It was observed to be shorter in the CB-3 group except in 2 studies [12, 13]. But the difference in total procedure time in those two studies was not statistically significant. For the total procedure time, there was a significant heterogeneity between the different trials ($I^2$=88%, $\tau^2$=0.1949, p<0.01) (Figure 2).

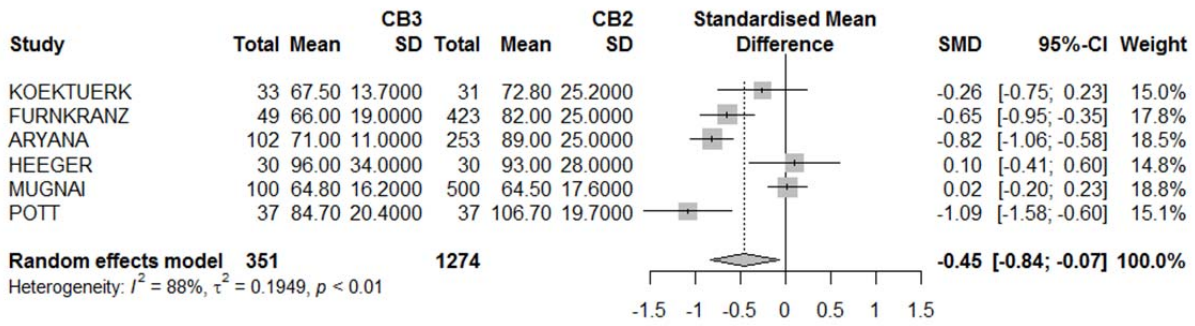


**Figure 2:** Procedure time

The analysis of fluoroscopy time favored the CB-2 group. The total fluoroscopy time was shorter in the CB-2 groups as compared to the CB-3 groups. The combined difference in mean of all the six studies was favorable for the CB-2 group for the total fluoroscopy time (SDM=0.19 [95% CI of -0.15; 0.53], p<0.01) with a significant heterogeneity ($I^2$=84%, $\tau^2$=0.1448, p<0.01) as shown in Figure 3.

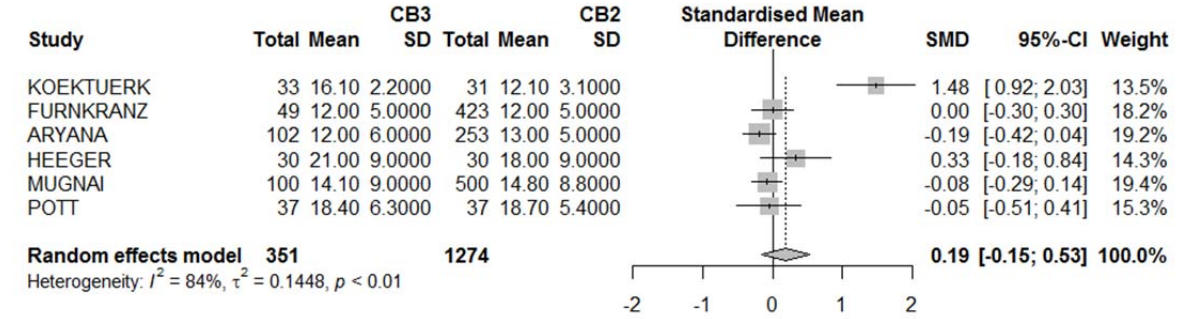


**Figure 3:** Fluoroscopy time

As for the nadir temperatures reached during the ablation, the results are as follows. In the LSPV, all the studies showed a higher temperature in the CB-3 groups, but the difference was statistically significant in only one trial [16]. The heterogeneity analysis was low ($I^2$=16%, $\tau^2$=0.0052, p=0.31). The combined mean difference showed a lower temperature reached in the CB-2 groups (SDM=0.19[95% CI of 0.06; 0.31], p=0.31) (Figure 4). In the LIPV, RSPV and RIPV the trials had high heterogeneities of 80% ($I^2$=80%, $\tau^2$=0.1108, p<0.01), 75% ($I^2$=75%, $\tau^2$=0.0826, p<0.01) and 57% ($I^2$=57%, $\tau^2$=0.0360, p=0.04) respectively. The combined standard mean difference also shows that the mean minimum temperature reached was higher for the CB-3 groups in LIPV (SDM=0.52[95% CI of 0.21; 0.83], p<0.01), RSPV (SDM=0.40[95% CI of 0.12; 0.67], p<0.01), and RIPV (SDM=0.26[95% CI of 0.05; 0.47], p=0.04) (Figures 5-7).

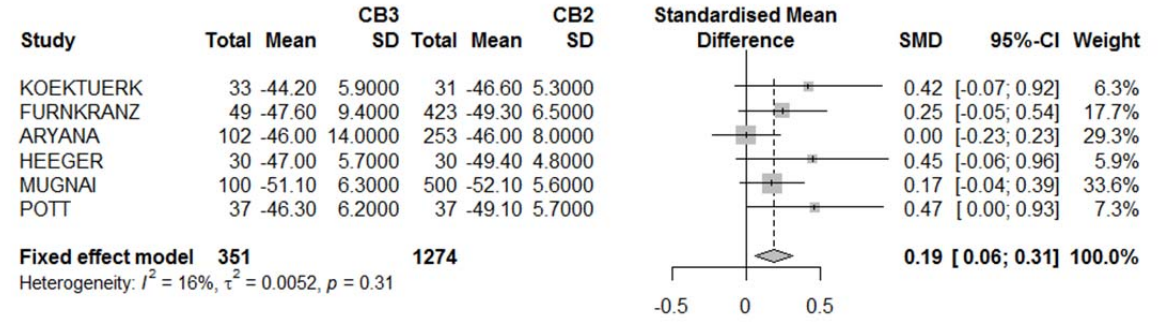


**Figure 4:** Minimum temperature in LSPV

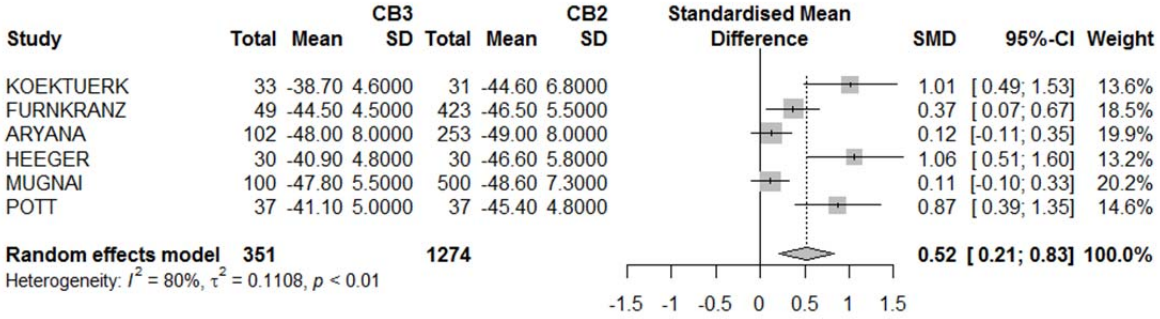


**Figure 5:** Minimum temperature in LIPV

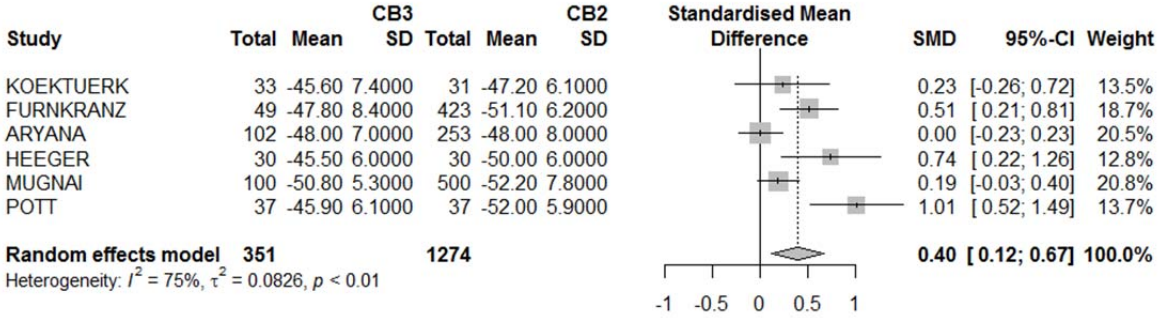


**Figure 6:** Minimum temperature in RSPV

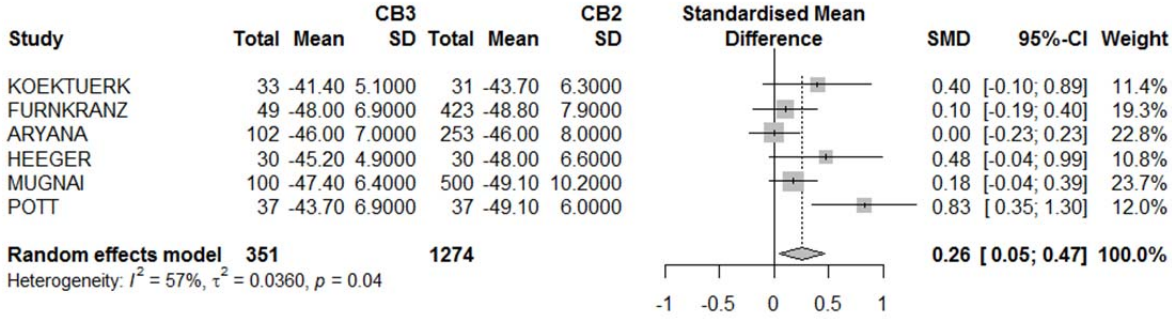


**Figure 7:** Minimum temperature in RIPV

Analysis of real time recording data showed that there was a higher isolation recording achieved with the CB-3 compared to that in CB-2 but the difference was not statistically significant [OR=3.53(95% CI 2.47,5.05), p=0.44]. The heterogeneity between the studies was not significant ($I^2$=0%, $\tau^2$=0, p=0.44) (Figure 8).

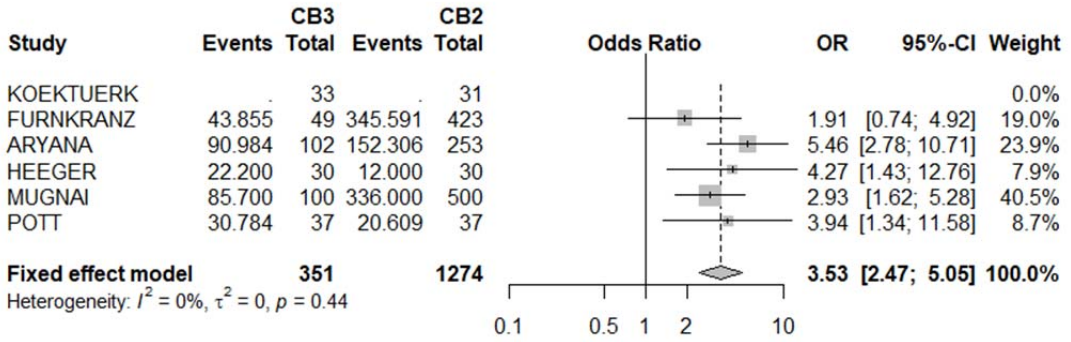


**Figure 8:** Real time recording

## 4. Complications

Transient ischemic attack, ischemic stroke, pulmonary vein stenosis, atrio-esophageal fistula, pericardial effusion and phrenic nerve palsy (PNP) have all been mentioned in several literatures as frequent complications that occur during cryoablation procedures. Except for one paper [16] which did not assess complications rates during the procedure, all the studies included in our paper also recorded those transient and persistent PNP, access site complications (hematoma, AV fistula, pseudoaneurysm), pericardial effusion and TIA. But, in all the papers, the difference was not statistically significant between the third generation and second generation cryoballoon ablation groups.

## 5. Discussion

The main difference between the third generation cryoballoon and the second generation cryoballoon is the 40% shorter tip of the third generation counterpart. In terms of other aspects, the two types of balloons have a rather similar design. This difference, in theory should provide a better visualization of pulmonary vein isolation allowing for quicker assessment of pulmonary isolation and thereby provide the operator with more information that can be used for an individualized treatment for each patient [15, 16].

The main findings of this meta-analysis are as follows. Firstly, the third generation cryoballoons are associated with a shorter total duration of the procedure. The fluoroscopy time with the third generation cryoballoon was significantly longer than that of the second generation. The minimum freeze temperature was significantly higher in the LIPV, the RSPV and the RIPV with the third generation cryoballoon. However, although the real time monitoring was more likely to be achieved in a greater proportion of patients with the CB-3, that difference showed to be not statistically significant.

The mean procedure time for the third generation cryoballoon group was 75min and that for the second generation was 84.7min. There are several reasons that may have lead to this shorter procedural time. As mentioned earlier, the

shorter tip of the CB-3 placed the electrode closer to the ablation site. This proximity to the ablation site provides a better measurement of the signals inside the pulmonary veins and helps the operator to assess the achievement of pulmonary vein isolation earlier than in the second generation cryoballoon[7]. This increases the efficiency of the procedure and shortens the procedure time. The pulmonary vein characteristics of each patient are different which means the amount of freezing required by each individual patient is also different. Provided with more information, operators can therefore design a tailored plan for every patient. This eliminate the standardized protocols and allows for a targeted and patient specific approach when using the CB-3. Fewer freeze cycles were administered in the CB-3 group and this did not affect the procedure outcome. An additional freeze means more time spent therefore making the procedure with the CB-2 longer. Pott et al. [16] also mentioned that the shorter tip helped when using this catheter in patients with short main trunk of the pulmonary veins. In this situation, compared to the longer tip counterpart, which may be problematic and require more maneuvers for positioning the catheter, the shorter tip eased the occlusion of the pulmonary vein making the whole procedure easier and faster. A shorter time to isolation means a more durable PVI while longer time to isolation has been associated with early recurrence [17-20].

Analysis of fluoroscopy time showed that more fluoroscopy was required for the CB-3 group than that of the CB-2 group. This may be attributed to the shorter tip of the CB-3 catheter. Furnkranz et al[12] describe a decrease in maneuverability and stability due to this shorter tip making it difficult to position the catheter and also, decreasing the stability of the catheter inside the pulmonary vein. The need for repeated positioning may account for the increased use of fluoroscopy with the third generation cryoballoons.

Pott. et al. [16] mentioned that the higher temperature recordings inside the pulmonary veins can be explained by the shorter duration of the freeze and quicker visualization of pulmonary vein isolation thereby allowing the freeze to be of shorter durations which did not allow the temperature in the pulmonary vein to drop as much as in patients treated with the second generation cryoballoons. This faster detection of isolation of the pulmonary veins helps to reduce the amount of freezing required to attain isolation. Another author, namely Heeger et al. [14] hypothesized that a modified freeze cycle duration may be the reason leading to these higher temperature recordings noted when using the third generation cryoballoons. Another plausible explanation for this finding can be explained by Furknanz et al. [12], Pott. et al. [16] and Aryana et al. [13] who mentioned that this higher nadir temperature maybe be due to the more proximal positioning of the catheter. Mugnai et al. [15] suggested that the difference in temperature maybe due to a longer distance between the thermocouple and the coil dispersing the refrigerant. Another explanation for this higher minimum temperature may be due to the decreased occlusion of the PV ostium when using the third generation cryoballoon [11].

All the papers included in our study showed a statistically significant real time recording of pulmonary vein isolation except one. Due to a lack of information, this paper was not included in our analysis of the real time recording. The insignificant difference between real time monitoring may be attributed to the artifact formation which is more prone to happen when using the short tip cryoballoon as compared to the second generation cryoballoon. In the CB-3, the short tip places the mapping catheter to the PV ostium. But this can also be achieved in most cases by prolapsing the circular mapping catheter of the CB-2. Only a few cases with anatomical varieties renders this

maneuver difficult. Koektuerk et al. also mentioned that the short tip caused more signal artifacts than the CB-2 [11].

## 6. Study limitations

Several limitations exist in this present meta-analysis. All the studies included in our paper were not randomized controlled trials. Any cofounding factors that may have lead to a difference between the two treatment arms cannot be excluded. Most of the studies had a short follow-up period or did not mention any follow-up. Longer follow-up studies to assess the long term outcomes are needed. Arrhythmia recurrence was not recorded in all the studies therefore only the procedural outcomes could be compared. The third generation cryoballoon arm in most studies had a small number of patients. Any conclusions should therefore be confirmed by larger randomized controlled trials. This paper also bears the limitations of a meta-analysis.

## 7. Conclusion

Pulmonary vein isolation using the third generation cryoballoon allows for a shorter procedure time, offers an enhanced ability to assess time to pulmonary vein isolation, facilitates the individual freeze strategy dosing scheme and enables a time dependent freeze protocol with equivalent procedural safety and efficacy.

## Funding details

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## Acknowledgements

None

## Conflict of interests

Authors declare that there is no conflict of interest

## 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 374 (2016): 2235-2245.
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 freezeAF study. Circulation 132 (2015): 1311–1319.
3. 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 61 (2013): 1713-1723.
4. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. Circ Arrhythm Electrophysiol 2 (2009): 626-633.

5. Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol 52 (2008): 273-278.
6. Tang M, Kriatselis C, Nedios S, Ye G, Roser M, Fleck E, Gerds-Li JH. A novel cryoballoon technique for mapping and isolating pulmonary veins: a feasibility and efficacy study. J Cardiovasc Electrophysiol 21 (2010): 626-631.
7. Chierchia GB, Mugnai G, Ströker E, Velagic V, Hünük B, et al. Incidence of real-time recordings of pulmonary vein potentials using the third-generation short-tip cryoballoon. Europace 18 (2016): 1158-1163.
8. Aryana A, Mugnai G, Singh SM, Pujara DK, de Asmundis C, Singh SK, et al. Procedural and biophysical indicators of durable pulmonary vein isolation during cryoballoon ablation of atrial fibrillation. Heart Rhythm 13 (2016): 424-432.
9. Ciconte G, Mugnai G, Sieira J, Velagic V, Saitoh Y, Irfan G, et al. On the quest for the best freeze: predictors of late pulmonary vein reconnections after second-generation cryoballoon ablation. Circ Arrhythm Electrophysiol 8 (2015): 1359-1365.
10. Ciconte G, Velagic V, Mugnai G, Saitoh Y, Irfan G, Hunuk B, et al. Electrophysiological findings following pulmonary vein isolation using radiofrequency catheter guided by contact-force and second generation cryoballoon: lessons from repeat ablation procedures. Europace 18 (2016): 71-77.
11. Koektuerk B, Yorgun H, Koektuerk O, Turan CH, Aksoy MN, et al. Cryoballoon ablation for pulmonary vein isolation in patients with atrial fibrillation: preliminary results using novel short-tip cryoballoon. J Interv Card Electrophysiol 47 (2016): 91-98.
12. Fürnkranz A, Bologna F, Bordignon S, Perrotta L, Dugo D, Schmidt B, Chun JK. Procedural characteristics of pulmonary vein isolation using the novel third-generation cryoballoon. Europace 18 (2016): 1795-1800.
13. Aryana A, Kowalski M, O'Neill PG, Koo CH, Lim HW, et al. Catheter ablation using the third-generation cryoballoon provides an enhanced ability to assess time to pulmonary vein isolation facilitating the ablation strategy: Short- and long-term results of a multicenter study. Heart Rhythm 13 (2016): 2306-2313.
14. Heeger CH, Wissner E, Mathew S, Hayashi K, Sohns C, et al. Short tip-big difference? First-in-man experience and procedural efficacy of pulmonary vein isolation using the third-generation cryoballoon. Clin Res Cardiol 105 (2016): 482-488.
15. Mugnai G, de Asmundis C, Hünük B, Ströker E, Moran D, et al. Improved visualisation of real-time recordings during third generation cryoballoon ablation: a comparison between the novel short-tip and the second generation device. J Interv Card Electrophysiol 46 (2016): 307-314.
16. Pott A, Petscher K, Messemer M, Rottbauer W, Dahme T. Increased rate of observed real-time pulmonary vein isolation with third-generation short-tip cryoballoon. J Interv Card Electrophysiol 47 (2016): 333-339.
17. Dorwarth U, Schmidt M, Wankerl M, Krieg J, Straube F, Hoffmann E. Pulmonary vein electrophysiology during cryoballoon ablation as a predictor for procedural success. J Interv Card Electrophysiol 32 (2011): 205-211.

18. Chun KR, Fu¨rnkranz A, Metzner A, Schmidt B, Tilz R, Zerm T, et al. Cryoballoon pulmonary vein isolation with real-time recordings from the pulmonary veins. J Cardiovasc Electrophysiol 20 (2009): 1203-1210.
19. Chierchia GB, de Asmundis C, Namdar M, Westra S, Kuniss M, Sarkozy A et al. Pulmonary vein isolation during cryoballoon ablation using the novel Achieve inner lumen mapping catheter: a feasibility study. Europace 14 (2012): 962-967.
20. AryanaA, MugnaiG, SinghSM, PujaraDK, deAsmundisC, et al. Procedural and biophysical indicators of durable pulmonary vein isolation during cryoballoon ablation of atrial fibrillation. Heart Rhythm 13 (2016): 424–432.

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