# Three-year follow-up results of cryoablation of atrial fibrillation patients:A comparison of 1st-generation and 2nd-generation cryoballoons

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**Abstract**

objective: Both first and second generation cryoballoons (CB1 and CB2) are efficient and safe treatments for patients with atrial fibrillation (AF). However, the superiority of CB2 over CB1 remains controversial. Our purpose was to compare ablation outcomes and complications between two generation CB especially in the long-term follow-up and in Chinese population. Methods: 278 consecutive patients underwent CB ablation were included, with 139 cases of 1st and 2nd generation CB respectively. Patients profiles, periprocedural details and clinical events were recorded and compared between two cohorts. Results: Baseline characteristics were similar. 1st generation CB group showed more overall times of freeze per vein (1.8±1.0 vs 1.6±0.8, p¡0.01) and longer time-to-isolation in left superior pulmonary vein (91.0 +-49.1s vs 54.1+-32.4 p=0.01). After three-years follow-up, the procedure complications had no difference between two groups. Through a mean follow-up period of 19.00+-10.66 months, overall recurrence was comparable(62.4% vs 74.2%, p=0.13)and the survival analysis shows no difference either (Logrank P = 0.1807). The complications during follow-up showed no differences, including stroke events [3/133 vs 1/128, p=0.62], major hemorrhagic events [3/133 vs 1/128, p=0.62] and death of any cause [5/133 vs 2/128, p=0.25]. Conclusions: 1st and 2nd generation CBs are equally efficient and safe for PV ablation procedure and they are both suitable for Chinese population

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Methods: 278 consecutive patients underwent CB ablation were included, with 139 cases of $1^{st}$ and $2^{nd}$ generation CB respectively. Patients profiles, periprocedural details and clinical events were recorded and compared between two cohorts.

Results: Baseline characteristics were similar. $1^{st}$generation CB group showed more overall times of freeze per vein (1.8±1.0 vs 1.6±0.8, p¡0.01) and longer time-to-isolation in left superior pulmonary vein (91.0 +-49.1s vs 54.1+-32.4 p=0.01). After three-years follow-up, the procedure complications had no difference between two groups. Through a mean follow-up period of 19.00+-10.66 months, overall recurrence was comparable(62.4% vs 74.2%, p=0.13)and the survival analysis shows no difference either (Logrank P = 0.1807). The complications during follow-up showed no differences, including stroke events [3/133 vs 1/128, p=0.62], major hemorrhagic events [3/133 vs 1/128, p=0.62] and death of any cause [5/133 vs 2/128, p=0.25].

Conclusions: $1^{st}$ and $2^{nd}$ generation CBs are equally efficient and safe for PV ablation procedure and they are both suitable for Chinese population.

Background

Since ectopic electrical activity of the pulmonary veins has been found to be a major trigger for paroxysmal atrial fibrillation(PAF)[1] , pulmonary vein isolation (PVI) has become the cornerstone for AF ablation. On the one hand, since CB2 came into clinical practice in China, it has quickly taken place of CB1, while the affection of innovation from CB1 to CB2 remains unknown. On the other hand, CB2 can create larger and deeper lesion, it gives us an opportunity to reevaluate the potential of cryoballoon ablation. Therefore, our study was designed to compare the clinical effects of CB1 and CB2 in atrial fibrillation cryoablation for Chinese patients in a single-center.

Methods

Inclusion and exclusion criteria

Patients with paroxysmal or persistent drug-resistant non-valvular AF underwent cryoablation with CB1 or CB2 at the Shanghai Tenth People's Hospital from January 2016 to October 2018 were enrolled. Exclusion criteria included previous AF ablation transthoracic echocardiography with a left atrial diameter $> 55$ mm, and transesophageal echocardiography(TEE) revealed thrombosis in the left atrial appendage, uncorrected heart failure(NYHA III or IV), and confirmed malignancy (expected life was less than 1 year). Written informed consent was obtained from each patient prior to the ablation procedure. Our research was approved by the Shanghai Institutional Review Committee of the Tenth People's Hospital and complied with the Helsinki Declaration.

Preprocedural preparation

For all patients, medical histories were acquired after admission. Physical examinations were performed by experienced physicians, and laboratory examinations were carried out routinely. All patients also received chest X-ray and TTE to evaluate cardiopulmonary status. A TEE was performed 1 day prior to surgery to rule out thrombosis in LA or LAA, re-evaluate LA size and identify possible structural variation.

Preprocedural drug therapy strategy was that antiarrhythmic drugs were discontinued at the point at which five half-lives would elapse before surgery and all patients received anticoagulation therapy for at least 8 weeks. New oral anticoagulants (NOACs, dabigatran 110mg twice daily or rivaroxaban 10 mg once daily) were commonly prescribed and discontinued 24 hours before the procedure. For patients taking warfarin, ablation was considered only if the INR was stable and within 2.0 to 3.0, and no withdrawal of warfarin occurred before the procedure.

Cryoballoon ablation

Local anesthesia with sedation was employed for every patient. Under X-ray guidance, a single transseptal puncture was completed. The first- generation cryoballoon (CB1) was used for patients who underwent CBA before Aug 2016. Afterward, the second-generation cryoballoon (CB2) was used. The procedure strategy was described in previous study[2].

During the freezing of the RSPV and RIPV, continuous phrenic pacing (8-10 V, pace interval 2000 ms) with an electrode placed in the superior vena cava was applied. Phrenic nerve palsy was detected and monitored through the observation of the decrease in diaphragm movement under fluoroscopy. If this occurred, the freezing procedure was subsequently halted to prevent further injury. To protect the esophagus and avoid complications such as atrial esophageal fistula12 and to prevent interference in the operation, loss of phrenic nerve capture or balloon temperature lower than -60degC. During the procedure, heparin was intravenously administered with and the activated clotting time (ACT) was monitored to ensure it remained >300 seconds.

Postprocedural management

During the hospital stay, patients without bradycardia, conductive disease, or severe heart failure (NYHA grade [?]III) were prescribed sotalol (40 or 80 mg, twice daily) for rate control after the procedure and NOACs (dabigatran or rivaroxaban, same dosage as above) for anticoagulation after CBA. Patients were required to fast for 6 hours after the procedure. During fasting, proton pump inhibitors (PPIs) were administered intravenously to protect the esophagus and stomach.

After discharge, antiarrhythmic therapy was then adjusted according to the occurrence of arrhythmia with evidence from ECG or a Holter monitor. Anticoagulants were generally prescribed for at least 3 months after the procedure. With regard to the CHA2DS2- VASc score, it was subsequently either no longer monitored in patients with a low risk of stroke ([?]2 in females, [?]1 in males) or continually monitored in patients at high risk of stroke. Oral PPIs were prescribed for 2 months after the procedure.

Follow-up

In the 1st, 2nd, 6th, and 12th months, and then every year after the procedure, outpatient clinic follow-up visits were required for every patient, and Holter monitor testing was required. During follow-up, 12-lead ECG was used to confirm recurrence. Telephone follow-up was also conducted before the scheduled follow-up month. Recurrence of AF was defined as episodes of AF lasting longer than 30 seconds after the blank period (3 months from the procedure), which was confirmed by Holter monitor, 12-lead ECG or data from a previously implanted device. The continuation of AADs was not considered recurrence in our study. Additional laboratory, radiological or echocardiographic examinations were not required except when certain indications were presented.

Result

Baseline characteristics

The study includes 139 consecutive patients who underwent cryoballoon ablation using CB1 and another 139 consecutive patients who underwent cryoballoon ablation using CB2. There were 6 and 11 patients losing to follow-up with CB1 and CB2 respectively. Baseline characteristics are presented in Table 1.There were no differences in age、AF type、Left atrial diameter and anti-arrhythmic drugs, only the rate of using warfarin had significant difference between CB1 and CB2.

Procedure outcomes

The procedure outcomes are reported in table2. Mean nadir temperature of LIVP was lower with CB1 than CB2. There were significant reductions in overall times of freeze per vein (1.8±1.0 vs 1.6±0.8, p¡0.01) using second generation cryoballoon. More time-to- isolation was recorded in LSPV (26 vs 40 p=0.04)with the second generation balloon .In LSPV ,TTI was also significantly shorter(91.0 +-49.1s vs 54.1+-32.4 p=0.01).with CB2.

During procedure more vagal reflex happened with CB1 then CB1 (16 vs 3, p=0.28) but didn't have statistic difference. PNI (Phrenic nerve injury) didn't show significant difference between two groups. No cardiac tamponade happened during the study.

Endpoints

Patients received over 3-yuers follow-up, and the mean follow-up period was 19.00+-10.66 months. Neither recurrent nor complications presents any statistical differences(table3). 22 rehospitalizations due to cardiovascular event happened in patients with CB2 and the number was only 12 with CB1, but there was no statistic difference(p=0.07). The freedom from AF were 62.4% vs 74.2% with CB1 and CB2 respectively(p=0.13). The survivor functions demonstrated no significant difference between the two cohorts (p =0.18) (Figure 1).

Discussion

This is a retrospective cohort study comparing the efficient of cryoballoon ablation with CB1 and CB2. Our result reveals that patients without significant differences in baseline received CB1 and CB2 ablation have consistency outcomes. Our study has several advantages. First, all procedures were accomplished by experienced operators who were proficient in transseptal puncture and RF ablation. Second, both cohorts were followed up by the same team including the operators themselves with consistent follow-up protocol and endpoints adjudication. Third, The baseline had no differences between two groups including ages, AF-type, LA diameter and $CH_2DS_2$-VASc score. All of our study population were single race. The Han nationality in China consists of over 90% Chinese population. At last our follow-up was over three-years, although patients underwent procedure withCB1 had significantly longer follow-up time, the freedom from AF and the complications didn't show a significant difference.

The rationale of cryoballoon ablation is that a previous study found that 94% ectopic foci of AF patients were located at PVs[1]. We use cryoballoon to create continuous transmural lesion which usually resulting in durable PV isolation. For that CB1 could only deliver cryo-energy around the equator, the freezing area is narrow. The operator has to choose the optimal cryoballoon size and transseptal puncture position. Improper coaxality and too deep or too superficial balloon position will cause the ablation area mismatch to the target area and fail to achieve PV potential isolation. CB2 has doubled injection ports and its ports have been positioned not only on the equator area, but also on the distal area of catheter's shaft, resulting in a wider and more uniform freezing zone on the balloon surface.

In our study, we didn't find a significant difference in recurrent rate between two groups. Some previous studies didn't agree with our opinions, support that CB2 has better outcomes than CB1[3-5]. The rates of freedom from AF with CB1 and CB2 in these studies were from 63.9% to 66% and from 78.6% to 84% after 1-year follow-up, only Davies, A. *et al.* had 2 year follow up data which were 51% and 72.6% respectively. In our study, the rates of freedom from AF with CB1 were 74% after one year and 62.4% after three-years follow-up, which was obviously higher than those study.

Although CB2 has some advantages, its theory foundation and ablation target haven't changed. If the coaxality and the matching of balloon and PV were solved, the efficiency of PVI is reasonable to remain similar between CB1 and CB2. LGE-MRI is a useful tool to evaluate the lesion created by ablation and have a strong connection with procedure outcomes[6-8]. Using LGE-MRI, previous study found that the amount of ablation lesions didn't show a significant difference between CB1 and CB2, but showed more lesion in left PVs than right PVs[9]. The reason of our undifferentiated is probably that our study started from January 2016, by that time the operate skill was proven, we learned the previous experiences from other centers and our operators were skillful in transseptal puncture, which made our ablation more efficient. In another study [10] ,they showed the evidence that the freedom from AF was similar between CB1 and CB2 after 2 years follow-up (72% vs 72%, p=0.95), which agrees with our study. They also underwent repeat procedures on all patients with arrhythmia recurrence, and the PV reconnection rate didn't show any difference between two groups. These evidences proved that with proper use, CB1 has equal ablation ability as B2. The study of repeat procedure showed that PV reconnection happened in 69%- 81.8% of AF patients underwent ablation with CB2[11,12], it's the main reason of AF recurrent.

There some other factors can affect the success rate of procedure. Non-enlarged left atrium and short AF history predicts better outcomes[13]. In Davies, A. *et al's*study[5], the patients underwent procedure with CB1 have significantly symptom duration (60months vs 36months, p¡0.001) and wider LA diameter (43.0.mm vs 40.7mm, p=0.003). This could affect the compare between CB1 and CB2.In our study, although we don't have data of AF history, there isn't any significant difference in patient's characteristics including LA diameter(42.5+-6.0 vs 41.8+-6.0, p=0.35)and AF type, the only difference was the rate of using warfarin. More patients with CB1 used warfarin may because that they accepted treatment earlier than those with CB2, by that time NOACs was more expensive and it was self-paying.

During the procedure, TTI is an important parameter, it predicts both early PV reconnection and late PV reconnection [14,15]. The TTI of LSPV showed a difference between two groups (91s vs 54.1s, p=0.01). But this could mean CB1 have a poorer efficient, CB1 usually needs longer freeze application than CB2[16]. In some study, the application of freeze was up to 5 minutes per time, 2 times per PV with CB1[17], while with CB2, a single shot won't surpass 3 minutes with or without recording TTI[18-20]. In our study, patients with CB1 require more overall times of freeze per vein (1.8+-1.0 vs 1.6+-0.8, p¡0.01). What's more, the PVI reconnection happens more in the right side. The longer procedure time may make up for the longer TTI then guarantee the ablation effect. Whereas the right side plays a more important role.

In our study, the procedure complications had no statistic differences between two groups, their safety remains conformity. In the follow-up, we didn't find any differences in stroke,rehospitalization due to cardiovascular event and death of any cause between two groups. This also proves that CB1 has the similar effect as CB2.

Our research is the first study comparing the clinical outcomes of CB1 and CB2 in Chinese population. Previous study included 164 patients underwent CB2 ablation, 77.66AF[21]. In another study using CB1, the rate of freedom from AF was 76% after one- year[22]. In our study, the rates of freedom from AF with CB1 and CB2 were 74% and 81% after one-year, 64% and 76% after a 19-months follow-up. Our study agrees with the previous studies and supplements the long-term study and the comparison of CB1 and CB2.

Cryoballoon ablation have some advantages such as easy to learn[23,24], improving the prognosis of AF patients combined with congestive heart failure[25] and maintaining the same efficiency among patients over and under 75years old[2]. CB2 has its advantages over CB1 such as shorter procedure duration and fluoroscopy time[3-5] and it's much easier to operate. But it doesn't solve coaxality problem once for all. Both CB1 and CB2 have more PV reconnection in right PVs[10,11,26]. Judged by our operate experience, the ablation of RIPVs still needs experience and skill even with CB2. Our study not only proves that CB1 is as efficient and safe as CB2, and both CB1 and CB2 are efficient and safe in Chinese population. We also prove that although CB2 has many improvements, as a PVI based therapy, it doesn't necessarily have better outcomes. The limitations which comes with PVI theory itself prevent cryoballoon ablation from higher rate of freedom from AF. The trail STAR AF II has confirmed that neither extra linear ablation nor additional ablation of complex fractionated electrograms could reduce the recurrent rate of AF[27], the improvement of PVI faces

great challenge too. Now we urgently need a new theory to help us modify current ablation strategy.

Limitations

This study is a retrospective comparison of outcomes comparing theCB1 and CB2. For the patient selection was non-randomized, we cannot avoid unmeasured confounders that may have interfered the study outcome. Our study was a single center study and the study population was limited. All periods including the experience accumulation stage of both CB1 and CB2 were incorporate into our study, the different learning curve may affect the study result. The follow-up was performed using continuous monitoring, but there is still the chances that we failed to catch the recurrent.

Conclusions

Our findings suggest that CB1 and CB2 are equally effective and safe for AF catheter ablation. Also, CB1 requires more cryo-energy applications, both freedom from AF and other complications during follow-up show no significant difference. The cryoballoon ablation is a useful treatment for patients of Chinese population with AF.

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FIGURE 1 Freedom of AF by survival analysis. Survival analysis of 133 patients underwent procedure with 1st generation cryoballoon (CB1, blue) and 128 patients underwent procedure with 2nd generation cryoballoon (CB2, red) patients. First 3-month was regarded as a blank period. The dashed line presented follow-up time on the 3rd month. AF, atrial fibrillation

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