

Comparison of Cryoballoon and Radiofrequency Ablation of Pulmonary Veins in 40 Patients with Paroxysmal Atrial Fibrillation: A Case-Control Study

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Comparison of Cryoballoon and RF Ablation of PV. *Introduction:* Ablation of pulmonary veins (PV) is an established therapeutic option for patients with symptomatic drug-refractory paroxysmal atrial fibrillation (AF). Radiofrequency (RF) is currently the most widespread energy source for PV ablation. Cryothermal energy applied with a cryoballoon technique as an alternative has recently evolved.

Methods and Results: In a case-control setting, we compared 20 patients with paroxysmal AF who underwent their first PV ablation with the cryoballoon technique to 20 matched patients with conventional RF ablation. In the case of persistent electrical potentials after cryoballoon ablation, it was combined with ablation with a conventional cryocatheter. All patients performed daily event recording for 3 months after ablation procedure. Ablation parameters and success rate after 3 and 6 months were compared. In the cryoballoon group, the overall success rate was 55% (50% in the cryoballoon only group [14 patients] and 66% in the combination group [6 patients]), as opposed to the RF group with 45%. AF episode burden was lower after cryoballoon ablation. There was no significant difference between cryoballoon and RF ablation regarding procedure parameters. In the cryoballoon group, 3 phrenic nerve palsies occurred using the 23 mm balloon that resolved spontaneously.

Conclusion: PV ablation with the cryoballoon technique is feasible and seems to have a similar success rate in comparison to RF ablation. Procedure- and fluoroscopy duration are not longer than in conventional RF ablation. (*J Cardiovasc Electrophysiol*, Vol. pp. 1-6)

pulmonary vein ablation, cryoballoon ablation, radiofrequency ablation, paroxysmal atrial fibrillation

Introduction

Transcatheter ablation of pulmonary veins (PV) has been established as a therapeutic option for patients with symptomatic drug-refractory paroxysmal atrial fibrillation (AF). PV ablation usually results in elimination or significant reduction of the AF burden in this patient population.¹⁻⁴ Various techniques and different ablation strategies have been developed, with radiofrequency (RF) currently being the most widespread energy source. RF ablation is limited by several potential procedure complications such as PV stenosis, pericardial effusion, atrioesophageal fistula, thrombembolism, and left atrial flutter.⁵⁻⁹ Cryothermal energy is an alternative energy source that has been developed to overcome some of the disadvantages of RF ablation such as tissue disruption by excess heating and generation of inhomogeneous lesions.¹⁰

The first two authors contributed equally to this work.

No conflicts of interest were declared.

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It has been shown that catheter point by point cryoablation is an effective method to create electrical PV isolation with clinically satisfactory results and no risk of PV stenosis.¹¹ However, procedure time is long, which is mostly due to the longer individual ablation applications required to produce equivalent lesions. The recent introduction of a novel balloon-based cryothermic technology appears to be a safe and feasible approach for PV isolation in animal models.¹²⁻¹⁴ The first results in humans were promising as well.^{15,16} The aim of this study was to compare the efficacy and safety of cryoballoon ablation with the RF approach in the treatment of paroxysmal AF.

Methods

Patients and Design

Patients of the prospective AF register of the University Hospital of Bonn were included. All patients had ECG-documented symptomatic nonvalvular paroxysmal AF and failure of at least 2 antiarrhythmic drugs. No one had undergone prior PV ablation. Informed consent was obtained from all patients. Twenty consecutive patients were treated with the double-lumen cryoballoon (Arctic Front[®], 23 mm or 28 mm, Cryocath, Montreal, Canada). All patients underwent transthoracic and transesophageal echocardiography the day before ablation. Additionally, a CT scan was performed in 15 patients for the reconstruction of PV anatomy.

TABLE 1
Baseline Patient Characteristics

	Cryoablation	RF Ablation	P-Value
Patients	20	20	ns
Sex (male/female)	15/5	15/5	ns
Age (years, median, [range])	59.9 [38–77]	58.5 [40–73]	ns
BMI (kg/m ²)	28.38	28.07	ns
Symptoms of AF			
Palpitation	14	14	ns
Dyspnea	10	10	ns
Vertigo	11	9	ns
Adynamia	8	10	ns
AF history (years, median, [range])	7 [1–26]	7 [1–17]	ns
Mean frequency of AF episodes			
Daily	9	7	ns
Several per week	6	5	ns
Several per month	4	7	ns
Less than 1 per month	1	1	ns
Mean duration of AF episodes			
<12 hours	5	7	ns
12–24 hours	11	10	ns
24–48 hours	2	2	ns
>48 hours	2	1	ns
LVEF (% , median, [range])	59.5 [46–73]	62.5 [50–71]	ns
LA volume (ml)	60.8 ± 12.9	57.5 ± 8.5	ns
CHD	2	0	ns
Arterial hypertension	12	5	ns
Valvular heart disease	0	0	ns
Diabetes mellitus	0	1	ns
Thyroid disorders	0	0	ns
Betablocker pre/post ablation	9/10	11/12	ns
Class Ic antiarrhythmics pre/post ablation	5/6	12/13	ns
Class III antiarrhythmics pre/post ablation	6/4	5/3	ns

LVEF = left ventricular ejection fraction; LA volume = left atrial volume; CHD = coronary heart disease; ns = not significant.

No patient (0/15) in the cryoballoon group and 1 patient (1/15) in the RF group had common ostia of the left PV. All 20 patients were matched for sex, age, left ventricular ejection fraction, and AF history to 20 patients from the PV ablation register of the University Hospital of Bonn who were treated with RF energy during the same time interval. The baseline characteristics of both groups are shown in Table 1.

Cryoballoon Procedure

Venous access was obtained through the right femoral vein. A decapolar catheter was advanced over a 7 French sheath and positioned in the coronary sinus. A fluoroscopy-guided double transseptal puncture was performed applying the Brockenbrough technique. Hereafter, angiography of the PV was performed through a 14 F sheath (Flexcath[®], Cryocath). Then the 20 polar circumferential mapping catheter (Lasso 2515[®], Biosense Webster, Diamond Bar, CA, USA) was introduced and placed in the very proximal PV. A 23-mm or 28-mm balloon was advanced, its size depending on the PV diameter estimated during angiography. The balloon was introduced into the PV ostium with the best possible occlusion of the PV. Every step was controlled by fluoroscopy. Cryoenergy was applied for maximal 6 minutes per application for 2 times, resulting in a circumferential ablation lesion.¹⁷ Before the right superior vein (RSPV) was treated, a quadripolar catheter was placed in the superior vena

cava to continuously stimulate the right phrenic nerve during cryoapplication. The application was stopped immediately in the case of diminished diaphragm movements. While one PV was treated with the cryoballoon, the ablation success of the previous PV was evaluated with the Lasso 2515[®] mapping catheter. Remaining electrical potentials were treated with the balloon again. If they still persisted, the balloon was repositioned or replaced with a conventional shaped tip cryocatheter (Freezor Max[®], Cryocath Inc.) to place point by point lesions, so called “touch ups.” In the following, this subset of patients will be referred to as the “combination group.” The target of ablation was the elimination of any ostial PV potential. In every patient, acute isolation success was confirmed by the circumferential Lasso[®] catheter. Twenty minutes after the last PV was ablated, ablation success was verified again in all PVs. The day after the ablation procedure, patients received a 12-lead surface ECG and a transthoracic echocardiogram to rule out pericardial effusion and were discharged to home. Peri- and postprocedural anticoagulation was performed in accordance to current guidelines.^{17,18}

RF Ablation Procedure

The RF ablation was performed using the technique described by Haissaguerre and coworkers.¹ After placing diagnostic catheters into the coronary sinus and at the His-bundle region via the right femoral vein, the interatrial septum was punctured and a guide wire was placed into the left superior PV. An irrigated tip ablation catheter (ThermoCool, Biosense Webster Inc. or Sprinklr, Medtronic Inc., Meerbusch, Germany) was advanced along the guide wire into the left atrium. Following this, the transseptal sheath was again advanced over the guide wire into the left atrium. Venography of all 4 PVs was performed by giving contrast material through the transseptal sheath or through a 6 French multipurpose catheter into the proximal PVs. Next, a circumferential mapping catheter (Lasso, Biosense Webster or Encirclr, Medtronic Inc.) was introduced into the proximal PVs. The transseptal sheath was then drawn back into the right atrium, where it stayed throughout the procedure without being continuously flushed. RF energy was applied in a power-controlled mode with a power limit of 25–30 Watts and a maximum temperature of 47°C. Ablation was performed at the atriovenous junction proximal to the circumferential mapping catheter at sites showing the earliest PV potentials performing a segmental ablation of the PV ostia. As in the cryoballoon group, acute isolation success was confirmed by the circumferential Lasso[®] catheter in every patient. Also, 20 minutes after the last PV was ablated, ablation success was verified again in all PVs. Peri- and postprocedural anticoagulations were performed in accordance to current guidelines.^{17,18}

Follow-Up

The follow-up period started at the day of ablation and was continued for 6 months. The day before ablation, patients received an ECG event recorder. They were instructed to transmit 1 ECG per day via telephone and to do additional recordings if they felt any symptoms of AF. Standard duration for all recordings was 1 minute. Recording was started at day 1 after the ablation procedure and was continued for 3 months. All recordings were analyzed for heart rate and rhythm. The first 4 weeks after ablation were considered as

TABLE 2
Results of Cryoablation of Each Pulmonary Vein (PV)

Vein		Number of PV	Number of Applications (Median, [Range])	Average Temperature (°C)	Isolated With Balloon Only	Total Isolated
LSPV	Combination	20	2 [2–4]	–47.2	17 (85%)	19 (95%)
LIPV		2 (10%)	3 [2–8]			
LIPV	Combination	20	3 [1–4]	–42.4	17 (85%)	18 (90%)
RSPV		1 (5%)	3 [2–4]			
RSPV	Combination	20	2 [1–3]	–45.1	16 (80%)	20 (100%)
RIPV		4 (20%)	4 [2–4]			
RIPV	Combination	18	3 [0–3]	–42.8	13 (72%)	17 (94%)
Total		4 (22%)	3 [2–5]			
		78	10 [6–13]	–44.6	63 (81%)	74 (95%)

LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; Combination = ablation with cryoballoon and subsequently cryotip catheter.

blanking period and all episodes in this period were excluded from analysis. Success rate was defined as the percentage of patients who did not have any documented AF episode or any symptoms suggesting AF recurrence after the blanking period within the follow-up period. The number of documented AF episodes in relation to all ECG transmissions was defined as AF episode burden. After 1, 3, and 6 months, an additional 12-channel surface ECG was recorded. At the 6-month follow-up, patients were interrogated about their AF symptoms with standardized questionnaires.

Statistical Analysis

Continuous measures are expressed as the mean value \pm standard deviation and were analyzed with the two-sided *t*-test after testing for normal distribution with the method of Kolmogorov and Smirnov. χ^2 test was used for between-groups comparison. A P-value <0.05 was considered statistically significant. Since there is no parameter that predicts the need for additional use of a conventional cryocatheter before the actual procedure, comparative calculations to RF ablation cannot be made with the “balloon only group,” but were made with the overall group, i.e., the “balloon only group” plus “combination group.”

Results

Ablation Procedure

In the cryo group, electrical potentials were recorded in 78 of the 80 mapped PV, all of which were targeted with ablation (Table 2). A median of 10 (2 in the upper PVs, 3 in the lower PVs) cryoballoon applications per cryoprocedure at an average temperature of -44.6°C were applied. Sixty-three of the 78 (81%) veins could be isolated employing the balloon only. In 11 veins (14%, 6 patients), the conventional cryocatheter was used in addition to the balloon point by point to close electrical gaps. In that case, the median of applications per procedure was 16. Using both approaches, 74 of the 78 veins were isolated by means of cryoenergy. The average procedure time was 174 ± 50 minutes and the fluoroscopy time 49 ± 17 minutes. Both procedure and fluoroscopy duration depended strongly on the additional need of a conventional tip cryocatheter. If only the balloon was used, the duration of procedure and of fluoroscopy were 166 ± 39 minutes and

41 ± 13 minutes, respectively. When “touch-ups” with the conventional cryocatheter were necessary, it raised to 278 ± 50 minutes and 67 ± 14 minutes ($P < 0.0001$ and $P < 0.01$, respectively). During the cryoprocedures, the 28-mm balloon was used in 15, the 23-mm balloon in 2, and either balloon in 3 cases (Table 3).

In the RF group, 77 of the 80 mapped veins showed electric potentials. All 77 veins were approached and successfully isolated. The mean procedure duration and the fluoroscopy duration in the RF group were longer than in the cryo group without reaching statistical significance (200 ± 67 minutes and 55 ± 23 minutes; $P = 0.18$ and $P = 0.15$, respectively). The data of both approaches are presented in Table 4.

Outcome Data

All patients completed the follow-up. In the cryoballoon group, a total of 1,150 event recorder strips were analyzed. AF was documented in 75 recordings (7%, nine patients) after the 4-week blanking period. Eleven patients (55%) were free from recurrence of AF within the 3 months follow-up. Patients whose PV were isolated with the cryoballoon only had a success rate of 50%. Patients in the combination group whose PVs were isolated with the cryoballoon and the cryotip catheter had a success rate of 66% (Fig. 1A).

In the RF group, 997 event recorder strips were analyzed. AF was documented in 182 recordings (18%, 11 patients) after the 4-week blanking period. Nine patients (45%) were free from recurrence of AF. The success rate after 6 months

TABLE 3
Cryoablation Procedure Data

Balloon Size	Approach	Patients	Procedure Duration (minutes)	Fluoroscopy Duration (minutes)
28 mm	Balloon only	11	166 ± 39	41 ± 12
	Combination	4	290 ± 58	70 ± 17
23 mm	Balloon only	1	155	27
	Combination	1	240	68
23 + 28 mm	Balloon only	2	197 ± 32	56 ± 11
	Combination	1	265	54
Total	Balloon only	14	166 ± 39	41 ± 13
	Combination	6	278 ± 50	67 ± 14

TABLE 4
Comparison of Cryoballoon and Radiofrequency (RF) Ablation

	Cryoballoon			RF	P-Value*
	Balloon Only	Combination	Cryo Overall		
Treated veins (n)	67	11	78	77	ns
Isolated veins (n)	63	11	74	77	ns
LSPV (treated/isolated) (n)	18/17	2/2	20/19	20/20	ns
LIPV (treated/isolated) (n)	19/17	1/1	20/18	20/20	ns
RSPV (treated/isolated) (n)	17/17	3/3	20/20	20/20	ns
RIPV (treated/isolated) (n)	13/12	5/5	18/17	17/17	ns
Procedure time (minutes)	166 ± 39	278 ± 50	174 ± 50	200 ± 67	ns
Fluoroscopy time (minutes)	41 ± 13	67 ± 14	49 ± 17	55 ± 23	ns
AF recurrence (%)	50	33	45	55	ns

LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein.
*P-value refers to comparison of cryo overall group versus RF group; ns = not significant.

was the same as after the 3-month intense follow-up period (11 [55%] vs 9 [45%]) in patients without recurrence in the cryoballoon and RF groups, respectively). These differences did not reach statistical significance. Between the 3- and 6-month follow-up, 4 patients in the cryoballoon group and 7 in the RF group underwent reablation procedures.

In patients with recurrence of AF, the AF episode burden was determined as described above. AF episode burden was less in patients with AF recurrence after cryoablation than patients with AF recurrence after RF ablation ($P = 0.16$, Fig. 1B).

Complications

In the cryo group, 3 patients suffered reversible right-sided phrenic nerve palsy (PNP) during ablation of the RSPV with temporary reduction of diaphragm function. In all cases, the 23-mm balloon had been used. The procedures were stopped immediately, whereupon phrenic nerve function recovered spontaneously in all cases. Normal function of diaphragm could be confirmed by fluoroscopy directly afterward. During ablation of the LSPV and LIPV, 2 patients developed bradycardia with heart rates <50/min that required temporary ventricular pacing. During ablation of left PV, 3 patients

reported severe headaches and nausea as well as dry cough. None of the complications resulted in a prolongation of the hospital stay, which was 3 days.

In the RF group, no complications were noticed. There was no clinical relevant PV stenosis, cerebrovascular accident, atriopharyngeal fistula, or groin hematoma in either group, although 14 French sheaths had to be used in the cryoballoon group.

Discussion

RF ablation has been developed over the last 10 years as the current standard approach for PV ablation. Previous studies showed that cryothermia as opposed to RF energy produces homogeneous lesions, maintaining the endothelium intact with a low thrombogenic potential, and thus potentially minimizing the complication rate.^{10,19-22} The recently developed cryoballoon has the potential to significantly reduce procedure and fluoroscopy times compared to ablation with a cryotip catheter.¹⁵ To our knowledge, these are the first published data to compare the feasibility and efficacy of cryoballoon ablation in circumferential PV isolation with conventional RF ablation.

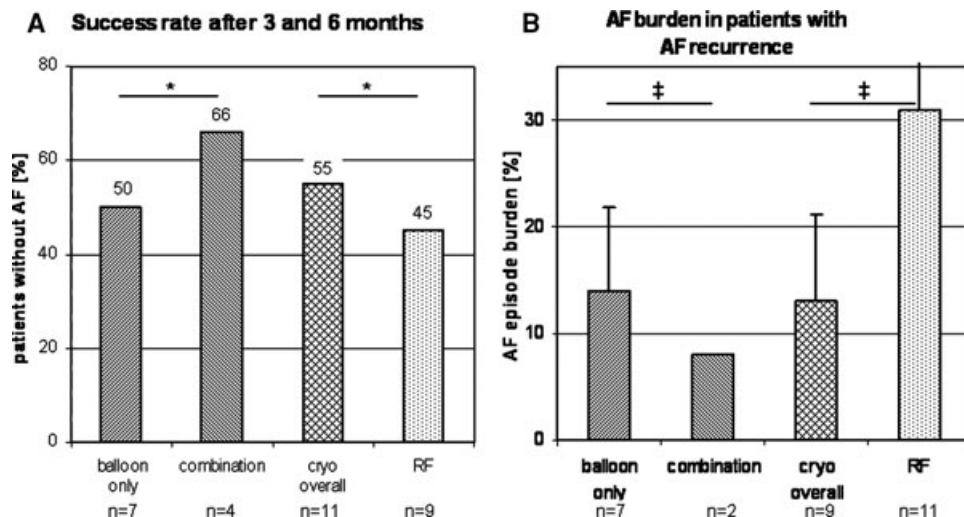


Figure 1. A: Ablation success rate defined as patients without any documented AF after PV ablation procedure (* $P = ns$); B: AF episode burden in patients with AF recurrence ($\ddagger P = ns$).

Acute Success

In our study, complete circumferential PV isolation could be achieved in 70% (14 patients) with the cryoballoon technique only. Fluoroscopy duration and total procedure duration were numerally lower than in the conventional RF group without reaching statistical significance. In cases with adverse anatomic conditions such as angulated vein insertions and common PV ostia, additional catheter point by point ablation was required to achieve complete isolation. In these cases, we noted a markedly prolonged procedure duration, which exceeded the RF procedure duration (Table 4).¹⁵ It appears important for the isolation success to achieve complete occlusion of the vein. This is indicated by lower ablation temperatures. Probably, the blood flow alongside the balloon accounts for the higher temperatures in cases of incomplete occlusion, which has been made responsible for reversible lesions.^{15,23-25} This problem does not occur with RF. Because of the better flexibility of the RF catheter, adverse anatomic features could be managed easier. Yet, as mentioned above, procedure duration and fluoroscopy duration were longer when using RF compared to cryoballoon only in our study.

Outcome

Freedom from AF was reached in 55% of patients treated with cryothermia and 45% of patients treated with RF in both 3-month and the 6-month follow-up. The success rate was higher in the combination group as opposed to the larger balloon only group (Fig. 1A). The differences in success rates did not reach statistical significance. We deliberately chose a short blanking period of 4 weeks to document early recurrence of atrial fibrillation that might have remained undetected with a blanking period of 3 months. Interestingly, the AF episode burden after the blanking period in patients with AF recurrence was numerally much lower in patients with cryoablation compared to RF ablation (Fig. 1B, $P = ns$).

In the first published series of 57 patients treated with cryoballoon PV isolation, freedom from AF after 3 months was reached in 60%.¹⁵ Recently, Neumann *et al.* achieved maintenance of sinus rhythm in 74% of patients with paroxysmal AF and 42% with persistent AF without antiarrhythmic drug therapy after cryoballoon ablation of 346 patients with a mean follow-up of 12 months. The difference to our lower success rate can be explained by our intensive follow-up with daily event recording as opposed to 7-day Holter ECG recordings at their quarterly follow-up visits. If intensive follow-up is performed, the overall success rate of the first PV ablation appears to be quite low.

Complications

Three patients treated with cryoenergy suffered from PNP that recovered immediately after interruption of cryoapplication in all cases. PNP seems to be one limitation of the approach with cryoballoon catheters, independent of the type of energy that is used.^{26,27} It is striking that all 3 paralyzes occurred using the 23-mm balloon during ablation of the RSPV as opposed to the 28-mm balloon. This is consistent with the observations from van Belle and Naumann, where most PNP were observed with 23-mm balloon.^{15,16} It appears that the small balloon can reach relatively deep into the PV and thereby gets in a closer proximity to the phrenic nerve.

Thus, it seems advisable to avoid the 23-mm balloon in the RSPV. In a very recent study that investigated the PV ablation with a "single big cryoballoon," PNP occurred in 3 out of 27 patients (11%), although a 28-mm balloon was used.²⁸ PNP obviously occurred when the balloon was unintentionally placed deeper inside the septal PV instead of the atrium region. These findings indicate that the closer proximity to the phrenic nerve is responsible for the damage, and that the actual balloon size might only be a subordinated factor. With superior caval vein pacing during ablation of the RSPV, the ablation can be stopped immediately at a loss of capture. In ablation with RF, severe complications are rare and fortunately did not occur in our small number of cases.²⁹

Study Limitations

The design of the current study as a case-control comparison of 2 patient groups implies general limitations. The major difficulty was the matching of the patients for the case-control setting. Nevertheless, key data in the patients were very similar, which allowed us a direct comparison between these 2 different strategies of PV isolation. Furthermore, several different RF ablation strategies of PV are being currently evaluated. All our patients received segmental PV isolation. It cannot be ruled out that outcome might have been different with another ablation strategy. Another shortcoming is the small number of patients and a relatively short follow-up duration. Our data should be confirmed in a larger randomized trial.

Conclusion

We compared the efficacy and safety of cryoballoon with RF as an initial ablation technique for patients with paroxysmal AF. Both strategies appear to be equivalent in terms of practicability. AF recurrence and AF episode burden were lower after cryoablation. The most frequent complication was the reversible PNP when ablating the RSPV with the 23-mm cryoballoon. On this account, usage of the 28-mm balloon should be preferred for ablation of the RSPV.

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