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Repeat cryoablation as a redo procedure for atrial fibrillation ablation: Is it a good choice?

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Abstract

Background: *Ablation of atrial fibrillation (AF), both cryoballoon ablation (CBA) and radiofrequency catheter ablation (RFCA), have demonstrated to be safe and effective. About 1 in 3 patients may face a redo due to recurrence and the best technique is unknown. The aim of this study is to assess the efficacy of CBA as a repeat procedure in patients with prior CBA or RFCA.*

Methods: *A nation-wide CBA registry (RECABA) was analyzed and patients were compared who had previously undergone CBA (Prior-CB) or RFCA (Prior-RF). The primary endpoint was AF recurrence at 12 months after a 3-month blanking period. A survival analysis was performed, univariate and multivariate Cox models were also built.*

Results: *Seventy-four patients were included. Thirty-three (44.6%) were in the Prior-CB group and 41 (55.4%) in the Prior-RF. There were more reconnected pulmonary veins in the Prior-RF than in Prior-CB group (40.4% vs.16.5%, p = 0.0001). The 12-month Kaplan–Meier estimate of freedom from AF recurrence after the blanking period was 61.0% (95% confidence interval [CI] 41.4–75.8%) in the Prior-CB, and 89.2% (95% CI 73.6–95.9%) in the Prior-RF group (p = 0.002). Multivariate Cox regression pointed Prior-CB as the sole independent predictor of AF recurrence, with an adjusted hazard ratio of 2.67 (95% CI 1.05–6.79).*

Conclusions: *Repeat CBA shows higher rates of AF recurrences compared to CBA after a previous RFCA despite presenting less reconnected veins at the procedure. These data suggest that patients with AF recurrence after CBA may benefit from other ablation techniques after a recurrence.*

RECABA is registered at clinicaltrials.gov with the Unique Identifier NCT02785991. (Cardiol J)

Key words: cryoablation, atrial fibrillation, catheter ablation, radiofrequency catheter ablation

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Introduction

Pulmonary vein (PV) isolation is a well-established, safe, and effective treatment for symptomatic atrial fibrillation (AF) [1, 2]. Radiofrequency catheter ablation (RFCA) and cryoballoon (CB) ablation (CBA) have shown similar results in randomized trials [3, 4]. Nevertheless, between 15% and 43% of patients may require a repeat AF ablation procedure due to symptomatic recurrence [5–7]. It is, however, not established which is the most suitable ablation technique for patients undergoing a repeat AF ablation and the possible influence of the technique used in the index procedure. The use of CBA for repeat ablation has been studied in small works with conflicting results [8–12]. The aim of this study is to evaluate the efficacy of CBA as a redo procedure for patients with prior AF ablation, by either CBA or RFCA.

Methods

Study design

The Spanish Registry of Cryoballoon Ablation (RECABA) [13] (NCT02785991) was an observational, prospective, nation-wide, multicenter study of cryoballoon AF ablation in Spanish centers. Patients were enrolled between September 2016 and January 2019. Inclusion criteria were: 1) person older than 18 years, 2) eligible for CBA according to local practice, 3) life expectancy longer than 1 year, and 4) signed informed consent.

Presented herein, is a post-hoc retrospective analysis of patients who were included for a repeat AF ablation and the previous procedure could be either CBA or RFCA. AF classification as paroxysmal (PAF) or persistent (PerAF) followed the current European Society of Cardiology guidelines at the inclusion period [14]. Data were gathered during a baseline visit at the procedure and at an established 12-month follow-up visit. For this analysis, the selected patients were those who completed a 12-month follow-up. Ethics Committee approval was obtained following local regulations, and the study was conducted in compliance with the Declaration of Helsinki and Spanish laws and regulations (Royal Decree 1090/2015, Royal Decree 1616/2009, Order SAS/3470/2009 of 16 December). The study was approved by the IRB, Comité Ético de Investigación Clínica de Euskadi (CEIC-E) on May 9, 2016. All patients signed informed consent upon inclusion.

Objective and endpoints

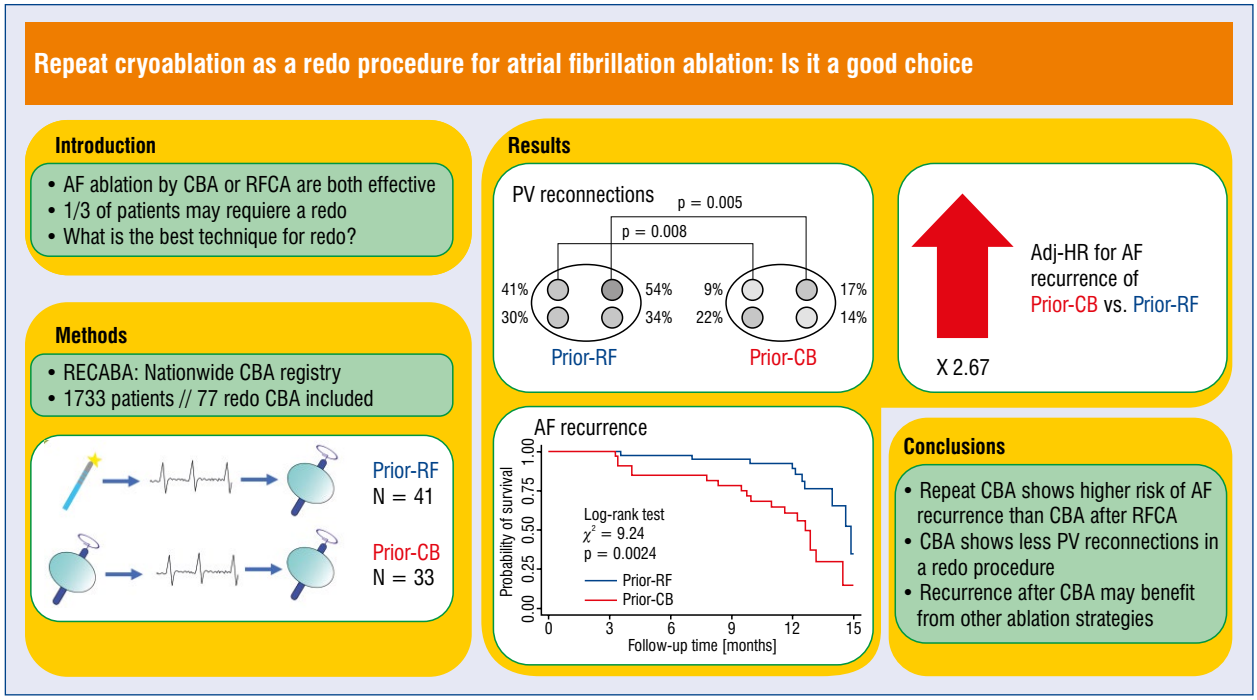
The main purpose of RECABA was to assess the standard clinical practice of CBA in Spanish centers. Considering the aim of this analysis, two groups were defined within the population, including: 1) Prior-CB: Patients referred for CBA who had undergone a previous CBA, and 3) Prior-RF: Patients referred for CBA who had undergone previous RFCA. The primary endpoint of the study was freedom from AF at 12 months after a 3-month blanking period. Secondary endpoints were clinical characteristics of the patients, dose and biophysical variables of CBA applications, vein reconnection pattern, and efficacy and safety of the procedure in the defined groups.

Cryoballoon ablation

The description of CBA has been widely reported elsewhere [15–17]. In the RECABA study, each center followed their local standards practices. In general, the procedure took place under sedation or general anesthesia. Left atrial access was performed using a dedicated needle followed by a heparin bolus. Anticoagulation status was monitored using activated clotting time with a target of 300–350 s. A 23- or 28-mm second-generation cryoballoon catheter (ArticFront ADV; Medtronic, Inc.) was deployed in the left atrium through a dedicated delivery sheath (Flexcath of Flexcath ADV; Medtronic, Inc.). Operators used a dedicated inner-lumen diagnostic catheter (Achieve of Achieve ADV; Medtronic, Inc.) to monitor local vein electrograms status during freeze applications. The initial presence of electrograms in PVs were considered reconnections. Number and length of CB applications were at the discretion of local operator, including applications on PVs isolated in previous procedures or the use of bonus freeze-applications. The use of adenosine challenge and the length of the post isolation waiting period were at the discretion of the operator. The procedure endpoint was the persistent isolation of all PVs.

Post-ablation management and follow-up

Patient's anticoagulation and antiarrhythmic drug regime followed local protocols and were at the treating cardiologist discretion. Follow-up visits were in accordance with local practice, with a pre-stablished 12-month follow-up visit. Arrhythmia detection could be based on Holter monitoring, event recording systems, implantable devices, and/



Central illustration. Graphical abstract showing group definition, pulmonary veins reconnection pattern, Kaplan-Meier survival curves and main findings; Adj-HR — adjusted hazard ratio; AF — atrial fibrillation; CBA — cryoballoon ablation; PV — pulmonary veins; RECABA — *Registro Español de Crioablación de con Balón* — Spanish registry of cryoballoon ablation; RFCA — radiofrequency catheter ablation; Prior-RF — patients subjected to cryoballoon ablation after a failed previous radiofrequency atrial fibrillation ablation; Prior-CB — patients subjected to cryoballoon ablation after a failed previous cryoballoon atrial fibrillation ablation.

/or in-clinic electrocardiogram (ECG) recording. AF recurrence was defined as an AF event lasting longer than 30 s registered by the abovementioned methods.

Statistical analysis

Quantitative variables are summarized with means and standard deviations or median and interquartile range when appropriate. Differences between groups were assessed using the t-test, or the Kruskal-Wallis test when a parametric test could not be performed. Categorical variables are summarized with percentages and differences assessed by the Pearson χ^2 test. The Kaplan-Meier method was used to build event-curves of survival from the primary endpoint and to calculate the 12-month freedom from AF estimates for each group. Log-rank test assessed the difference between groups. Univariate and multivariate Cox proportional-hazards regression models were built to evaluate possible predictors of AF-recurrence. Predictors were included in the multivariate model when a significance level of p-value below 0.10 was achieved. Statistical significance was assumed for two-sided p-values below 0.05. Data were analyzed using STATA v.15 software (StataCorp LLC).

Results

Population baseline characteristic

In total, 1733 patients from 27 Spanish centers were included in RECABA between September 2016 and January 2019. Seventy-seven (4.3%) patients underwent CBA as a redo procedure due to recurrence after an index procedure and 74 completed a 12-month follow-up visit and were included in this analysis. Thirty-three (44.6%) subjects had undergone a previous CBA (Prior-CB group) and 41 (55.4%) a previous RFCA (Prior-RF group) (Central illustration). Twenty-seven (36.5%) patients were female and mean age was 58.8 ± 10.2 years. Additionally, 60 (81.1%) subjects had PAF and 14 (18.9%) had PerAF.

Table 1 summarizes patients baseline characteristics. Thirty-one patients from the Prior-CB group (93.9%) underwent a sole index procedure, while 30 from the Prior-RF (73.2%) underwent more than one preceding AF ablation procedures ($\chi^2 = 5.4$, $p = 0.02$).

Table 1. Patients baseline characteristics and between groups differences. Categorical data are summarized in number and percentage.

	All patients (n = 74)		Prior-CB (n = 33; 44.59%)		Prior-RF (n = 41; 55.41%)		P-value
Age [years]	58.8	10.2	57.2	12.1	60.0	8.3	0.251
Female sex	27	36.5%	15	45.45%	12	29.30%	0.151
Weight [kg]	81.22	15.3	84.5	15.9	78.6	14.4	0.1
Height [cm]	171.9	11.3	171.0	11.6	172.6	11.1	0.6
BMI [kg/m^2]	27.5	4.4	28.9	4.6	26.4	3.8	**0.01**
Obesity: BMI > 30 kg/m^2	20	27.3%	13	39.4%	7	17.1%	**0.03**
Persistent AF	14	18.92%	6	18.18%	8	19.51%	0.885
Time since AF onset							0.51
< 1 year	10.2	10.2	1	3.03%	0	0.00%	
1–5 years	36.5%	36.5%	12	36.36%	14	34.15%	
> 5 years	15.3	15.3	20	60.61%	27	65.85%	
Number of previous procedures	1	1–1	1	1–1	1	1–2	**0.024**
Heart disease	5	6.76%	0	0.00%	5	12.20%	**0.038**
Ischemic heart disease	2	2.70%	0	0.00%	2	4.88%	0.198
Tachymyocardiopathy	2	2.70%	0	0.00%	2	4.88%	0.198
Hypertrophic cardiomyopathy	1	1.35%	0	0.00%	1	2.44%	0.366
Heart failure	4	5.41%	1	3.03%	3	7.32%	0.418
Risk factors							
Hypertension	32	43.24%	14	42.42%	18	43.90%	0.898
Diabetes mellitus	5	6.76%	1	3.03%	4	9.76%	0.252
Dyslipidemia	25	33.78%	12	36.36%	13	31.71%	0.674
Current smoking	8	10.81%	2	6.45%	6	15.38%	0.243
Peripheral vascular disease	3	4.05%	0	0.00%	3	7.32%	0.113
Stroke/TIA	1	1.35%	1	3.03%	0	0.00%	0.262
OSA	7	9.46%	7	21.21%	0	0.00%	**0.002**
$CHADS_2$ Score	1	(0–1)	0	0–1	1	0–1	0.634
CHA_2DS_2-VASC Score	1	(0–2)	1	0–2	1	1–2	0.666
Pacemaker carrier	2	2.70%	1	3.03%	1	2.27%	0.876
Physical activity							0.987
None	45	63.38%	21	63.64%	24	63.16%	
Mild (less 150 min/week)	14	19.72%	6	18.18%	8	21.05%	
Moderate (150–300 min/week)	10	14.08%	5	15.15%	5	13.16%	
Intense (> 300 min/week)	2	2.82%	1	3.03%	1	2.63%	
Antiarrhythmic drugs							
Current use of AAD	62	84.93%	30	90.91%	32	80.00%	0.195
Flecainide	41	66.13%	21	70.00%	20	62.50%	0.533
Propafenone	5	8.06%	2	6.67%	3	9.38%	0.696
Amiodarone	11	17.74%	4	13.33%	7	21.88%	0.379
Dronedarone	3	4.84%	1	3.33%	2	6.25%	0.593
Sotalol	3	4.84%	2	6.67%	1	3.12%	0.516
Beta-blockers	50	67.57%	22	66.67%	28	68.29%	0.882
CCB	5	7.14%	3	9.68%	2	5.13%	0.463

→

Table 1 (cont.). Patients baseline characteristics and between groups differences. Categorical data are summarized in number and percentage.

	All patients (n = 74)		Prior-CB (n = 33; 44.59%)		Prior-RF (n = 41; 55.41%)		P-value
Cardiac imaging							
LVEF:							0.688
> 50	60	95.24%	24	96%	36	94.74%	
35–50	2	3.17%	1	4%	1	2.63%	
< 35%	1	1.59%	0	0.00%	1	2.63%	
LVH	9	14.29%	2	8.00%	7	18.42%	0.247
LA enlargement	33	53.23%	17	70.83%	16	42.11%	**0.027**
Left PV							0.885
2 veins	60	81.08%	27	81.82%	33	80.49%	
Common trunk	14	18.92%	6	18.18%	8	19.51%	
Right PV							0.99
2 veins	62	84.93%	28	84.85%	34	85.00%	
Common trunk	2	2.74%	1	3.03%	1	2.50%	
> 2 veins	9	12.33%	4	12.12%	5	12.50%	

Quantitative data are summarized either with mean and standard deviation or median and interquartile range when appropriate. P-values in bold when reaching statistical significance ($p < 0.05$); AAD — antiarrhythmic drug; AF — atrial fibrillation; BMI — body mass index; CB — cryoballoon; CCB — calcium channel blocker; LA — left atrium; LVEF — left ventricular ejection fraction; LVH — left ventricular hypertrophy; OSA — obstructive sleep apnea; PV — pulmonary vein; RF — radiofrequency; TIA — transient ischemic attack

The median CHA_2DS_2-VASc score was 1 (interquartile range [IQR] 0–2) with no differences between groups (Kruskal-Wallis test $p = 0.67$). Overall, 84.9% of patients were on anti-arrhythmic drugs (AADs) at the time of the procedure, 1.6% had left ventricular ejection fraction below 35%, and 53.2% of subjects had a dilated left atrium (LA) defined as either LA diameter larger than 40 mm or LA area larger than 20 cm^2.

Cryoballoon ablation

Table 2 summarizes procedural data. From 74 procedures, 60 (82.2%) were performed using a single 28-mm CB, without differences between groups ($\chi^2 = 2.04$, $p = 0.361$).

Routine bonus freeze-application was more common in the Prior-CB group, with 51.6% of patients vs. 13.9% of the Prior-RF group ($p = 0.003$). Adenosine challenge was not used in any patient. The average procedure duration was 115.1 ± 44.5 min, with no differences between groups. In total, 49 (66.2%) patients were on AAD at discharge, being flecainide the most common AAD prescribed with 59.6% of patients, followed by amiodarone in 19.1% of them, without existing differences between groups. Patients were discharged on anticoagulation, with 66.2% of them on a direct oral anticoagulant drug, also without differences between groups.

Pulmonary vein reconnections after a previous procedure

Sixty-three out of 156 (40.4%) veins were reconnected in the Prior-RF group as compared with 17 out of 103 (16.5%) in the Prior-CB group (χ^2 test $p = 0.0001$). The mean number of reconnected PVs per patient was 0.5 ± 0.7 in the Prior-CB group vs. 1.5 ± 1.4 in the Prior-RF group. t-test = 3.8, $p = 0.0003$. The most frequently reconnected PV in the Prior-RF group was the left superior pulmonary vein (LSPV) with 54.1%, whereas in the Prior-CB group it was the right inferior PV with 22.2%, without statistically significant differences within groups. The 66.7% of the Prior-RF group and 40% of Prior-CB left common trunks were reconnected, without statistically significant differences between groups (χ^2 test $p = 1$). Both superior PVs were more commonly reconnected in the Prior-RF group than in the Prior-CB group, with 41% vs. 9% in right superior pulmonary vein (RSPV) (χ^2 test $p = 0.008$) and 54.1% vs 17% in LSPV (χ^2 test $p = 0.005$). Table 3 and Figure 1 show the pattern of vein reconnection within Prior-RF and Prior-CB groups.

Table 2. Procedure-related data and between group differences.

	All patients (n = 74)		Prior-CB (n = 33; 44.59%)		Prior-RF (n = 41; 55.41%)		P-value
Balloon size:							0.361
28 mm	60	82.2%	27	81.8%	33	82.5%	
23 mm	11	15.1%	6	18.2%	5	12.5%	
28 mm + 23 mm	2	2.7%	0	0.0%	2	5.0%	
Sedation method:							**0.001**
General anesthesia	5.0	6.8%	2	6.1%	3	7.3%	
Light sedation	47.0	63.5%	14	42.4%	33	80.5%	
Deep sedation	22.0	29.7%	17	51.5%	5	12.2%	
Assisted transeptal puncture	5.0	6.8%	3.0	9.1%	7.0	17.1%	0.318
Base rhythm:							0.984
Sinus rhythm	59.0	80.8%	26	78.8%	33	82.5%	
Atrial fibrillation	10.0	13.7%	5	15.2%	5	12.5%	
Typical flutter	2.0	2.7%	1	3.0%	1	2.5%	
Atypical flutter	2.0	2.7%	1	3.0%	1	2.5%	
Number of CB applications (median IQR)	6	5–7	6	5–7	6	4–8	0.63
Total cryoablation dose [min]	17.11	5.97	16.96	5.66	17.85	6.57	0.31
Number of reconnected veins (mean SD)	1.08	1.25	0.52	0.71	1.54	1.40	**0.0003**
Number of reconnected veins (median IQR)	1	0–2	0	0–1	1	1–3	**0.0002**
All veins already isolated	30	40.5%	20	60.6%	10	24.4%	**0.002**
Average TTI [s]	42.90	33.84	39.17	33.42	44.19	34.55	0.7074
Average temperature at isolation [°C]	–28.58	9.79	–28.27	8.62	–28.70	10.35	0.913
Average nadir temperature [°C]	–43.84	5.56	–44.00	6.04	–43.72	5.20	0.837
Average CBD per application [s]	177.95	29.53	175.09	30.10	180.26	29.23	0.4577
Average thawing time [s]	33.89	10.66	30.63	8.49	36.28	11.55	0.0581
Average time to –30°C [s]	38.26	8.14	38.14	6.92	38.35	9.08	0.9285
Total left atrial time [min]	71.94	29.02	64.08	23.37	78.45	31.93	0.073
Post-isolation waiting period (n)	12	16.9%	4	12.1%	8	21.1%	0.317
Post-isolation waiting period [min]	18.4	8.15	16.3	5.54	19.5	6.91	0.541
Total procedure duration [min]	115.09	44.46	112.15	47.75	117.46	42.08	0.613
Total fluoroscopy time [min]	31.29	15.38	29.42	13.70	32.83	16.66	0.351
Electrical cardioversion during procedure	19	26.0%	9	28.1%	10	24.4%	0.718
CTI ablation	3	4.1%	1	3.1%	2	4.9%	0.708
AAD on discharge	47	64.4%	22	66.7%	25	62.5%	0.711
Flecainide	28	59.6%	13	59.1%	15	60.0%	
Amiodarone	9	19.1%	4	18.2%	5	20.0%	
Dronedarone	3	6.4%	1	4.6%	2	8.0%	
Propafenone	4	8.5%	2	9.1%	2	8.0%	
Sotalol	3	6.4%	2	9.1%	1	4.0%	
Other	3	0.3%	0	0.0%	0	0.0%	
Discharge anticoagulation with DOAC (vs. AVK)	49	66.2%	24	71.7%	25	61.0%	0.288
Bonus application strategy:							**0.003**
Routine bonus application	21	31.3%	16	51.6%	5	13.9%	
Depending on vein	14	20.9%	6	19.4%	8	22.2%	

Categorical data are summarized in number and percentage. Quantitative data are summarized either with mean and standard deviation or median and interquartile range when appropriate (number of reconnected pulmonary veins, while presenting a not normal distribution, is summarized in both ways to facilitate comparison with other published works). P-values in bold when reaching statistical significance ($p < 0.05$); AAD — anti-arrhythmic drug; AVK — anti-vitamin-K anticoagulant drug; CB — cryoballoon; CBD — cryoablation dose; CTI — cavo-tricuspid isthmus; DOAC — direct oral anticoagulant; IQR — interquartile range; RF — radiofrequency; SD — standard deviation; TTI — time to isolation. Time from the beginning of a freeze application until vein isolation is achieved.

Table 3. Pulmonary vein reconnection pattern in patients undergoing a repeat procedure.

	Prior RF (n = 41)		Prior CB (n = 33)		P-value
Total number of reconnected veins	63/156 (40.4%)		17/103 (16.5%)		0.0001
Number of reconnected veins per patient:					0.008
0	10	24.4%	20	60.6%	
1	16	39.0%	9	7.3%	
2	4	9.8%	4	2.1%	
3	6	14.6%	0	0.0%	
4	4	9.8%	0	0.0%	
5	1	2.4%	0	0.0%	
Left, n (%):					
LSPV	20	54.1%	4	17.4%	0.005
LIPV	12	34.3%	3	13.6%	0.0848
Left common trunk	2	66.7%	2	40.0%	1
Right, n (%):					
RSVP	16	41.0%	2	9.1%	0.0086
RIVP	11	29.7%	6	22.2%	0.5019

The table shows the proportion of reconnected veins and differences between groups performing a χ^2 test; CB — cryoballoon; LIPV — left inferior pulmonary vein; LSPV — left superior pulmonary vein; RF — radiofrequency; RIPV — right inferior pulmonary vein; RSVP — right superior pulmonary vein

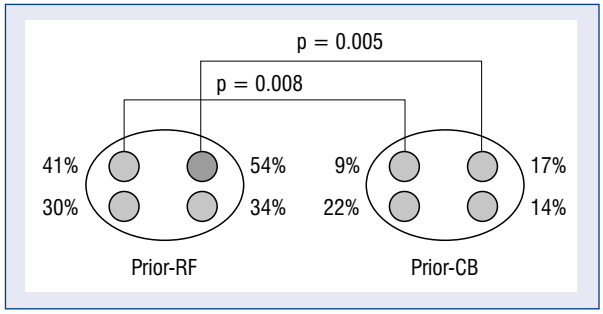


Figure 1. Distribution of pulmonary vein reconnection in patients who had undergone a previous radiofrequency ablation (Prior-RF) or cryoballoon ablation (Prior-CB). Pearson's χ^2 test performed to show differences in the proportion of reconnection for each vein between groups.

Procedural and peri-procedural adverse events

Only 1 patient in the Prior-RF group had a procedural adverse event which presented as temporary phrenic nerve palsy and none of the Prior-CB patients had any procedural adverse events. More detailed information on adverse events in the RECABA study is described elsewhere [13].

Follow-up and AF recurrences

Patients included in this analysis were followed for a mean of 12.6 ± 1.8 months. AF detection was performed with an ECG at clinic visit in 35.1% of patients, 62.1% received a Holter monitor and 2.7% a loop recorder. There were no differences between groups (χ^2 test p = 0.28). Kaplan-Meier survival estimates of 12-month freedom from AF recurrence were 61.0% (95% confidence interval [CI]: 41.4–75.8%) for the Prior-CB group and 89.2% (95% CI: 73.6–95.9%) for the Prior-RF group. Log-rank test for equality of survival function χ^2 = 9.24, p = 0.002. Figure 2 depicts the Kaplan-Meier curves.

Table 4 shows univariate Cox regression models of possible predictors of AF recurrence. Figure 3 depicts the multivariate model that points to prior CBA as the sole independent predictor of AF recurrence, adjusted by obesity, obstructive sleep apnea, CHA_2DS_2-VASc score equal or greater than 2 points and finding all PVs already isolated. Prior-CB patients had more than double the likelihood of AF recurrence, with and adjusted hazard ratio of 2.67 (95% CI: 1.05–6.79). There were 6 hospitalizations in 5 patients due to AF-related events not linked to the procedure.

Discussion

The study results demonstrated that repeat CBA shows higher rates of AF recurrences compared to after a previous RFCA. Multivariate Cox regression pointed Prior-CB as the only

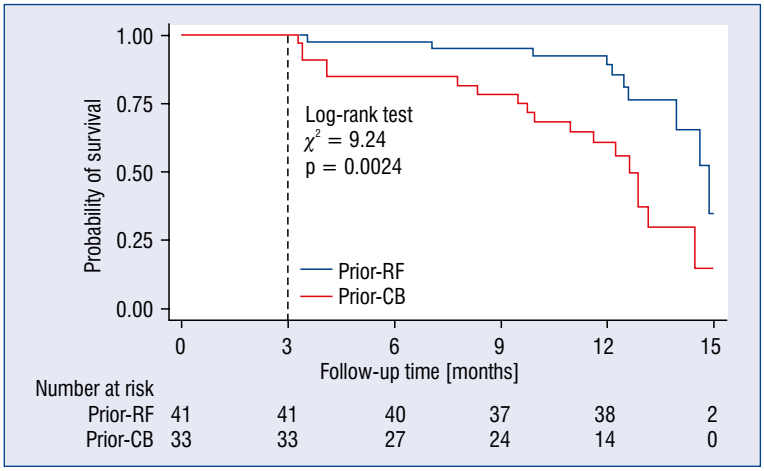


Figure 2. Kaplan-Meier survival curves for atrial fibrillation recurrence after a 3-month blanking period. Log-rank test is performed to compare the predefined groups, showing significant differences between them; Prior-RF — patients subjected to cryoballoon ablation after a failed previous radiofrequency atrial fibrillation ablation; Prior-CB — patients subjected to cryoballoon ablation after a failed previous cryoballoon atrial fibrillation ablation.

Table 4. Univariate Cox regression models of possible predictors of atrial fibrillation (AF) recurrence.

Predictors of AF recurrence	Hazard ratio	95% CI	P-value
Prior-CB vs. Prior-RF	3.15	1.44–6.88	**0.004**
Number of previous procedures	0.91	0.40–2.03	0.812
All PVs already isolated	2.05	0.97–4.31	**0.060**
Age (≥ 65 years)	0.90	0.38–2.13	0.818
Obesity (BMI ≥ 30 kg/m^2)	2.73	1.22–6.14	**0.015**
Female sex	1.71	0.77–3.81	0.191
Obstructive sleep apnea	4.88	1.73–13.74	**0.003**
Hypertension	1.84	0.83–3.93	0.118
Persistent AF	0.93	0.38–2.3	0.875
CHA_2DS_2-VASc ≥ 2	2.03	0.92–4.46	0.078
No physical exercise	1.71	0.75–3.91	0.204
Structural heart disease	0.72	0.10–5.41	0.753
LA enlargement	1.10	0.49–2.48	0.813
Heart failure	1.04	0.14–7.86	0.968
LVEF < 50%	1.07	0.14–7.86	0.968
Bonus strategy	1.68	0.73–3.85	0.220

P-values in bold when reaching the prespecified threshold to be included in the multivariate model (p < 0.10); AF — atrial fibrillation; BMI — body mass index; CB — cryoballoon; CHA_2DS_2-VASc — Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischemic attack, Vascular disease, Age 65–74 years, Sex category; CI — confidence interval; LA — left atrium; LVEF — left ventricular ejection fraction; PVs — pulmonary veins; RF — radiofrequency

independent predictor of AF recurrence in the present series. These data suggest that patients with AF recurrence after CBA may benefit from another ablation technique after a recurrence. In summary, RFCA may be more suitable for repeat procedures for the ability of performing non-PV related ablations.

Pulmonary vein reconnection after a previous procedure

In the present study, a larger number of reconnected PVs are described in patients after a previous RFCA procedure (40.4%, 1.5 ± 1.4 per patient) than after a previous CBA (16.5%, 0.5

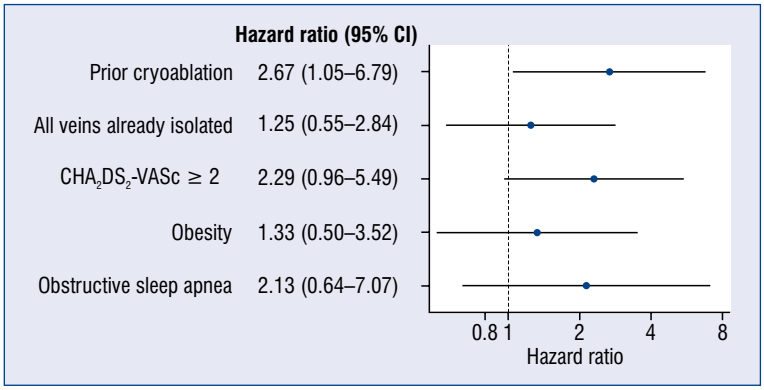


Figure 3. Multivariate Cox regression model of atrial fibrillation recurrence. Being subjected to cryoballoon ablation after a failed previous cryoballoon atrial fibrillation ablation vs. a previous radiofrequency catheter ablation was the only independent predictor of atrial fibrillation recurrence; CI — confidence interval; CHA_2DS_2-VASc — Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischemic attack, Vascular disease, Age 65–74 years, Sex category.

± 0.7 per patient) and an overall low number of reconnected PVs in the latter group.

Ciconte et al. [18] described a 20.4% of reconnected PVs after an index CBA (1.2 PV per patient) vs. 36.1% after contact-force RFCA (1.8 PV per patient), with a similar pattern as in the current study. In their series, LSPV were less frequently reconnected after CBA than after RFCA (8% vs. 38%). Pointing in this direction is also noted in Kuck et al. [19] analyzing the repeat procedures after the FIRE and ICE trial. They report an average of 2.1 reconnected PV per patient after RFCA vs. 1.4 after CBA. Moreover, there were less reconnected LSPV in the CBA group (28% vs. 60%) and a trend in RSPV (29% vs. 52%).

However, other published works did not find differences. Zeljkovic et al. [20] presented a series of patients with an index CBA or RFCA that underwent a repeat procedure using RFCA. The average reconnected PVs per patient were 2.1 for CBA and 2.2 for RFCA. In addition, Cheung et al. [21] analyze the repeat procedures from the CIRCA-DOSE trial, where patients were randomized to contact-force RFCA, 2-min CBA, or 4-min CBA. There were no differences in the reconnection pattern in those patients submitted to a repeat procedure, with a median and IQR of 2 (1–2), 2 (1–3), and 1 (1–4) of reconnected PVs per patient, respectively. Glowniak et al. [8] presented a similar series of patients with an index CBA or RFCA that underwent CBA as a repeat procedure. In their series, there was a larger proportion of reconnected PVs with 66.9% after an index RFCA and 51.5% after CBA.

In general, the present results are driven by a high burden of isolated veins after an index CBA, while reconnection pattern after RFCA is more like the abovementioned studies. These can be explained by the difficulties in keeping the catheter stable while ablating the LSPV ridge and LA roof at RSPV antrum. On the other hand, the CBA technique has improved in recent years, with standardized dosing protocols and lessons learnt from repeat procedures that may have led to more durable PV isolations in current procedures [16, 17, 22–28].

Cryoballoon ablation after an index procedure

Despite the abovementioned differences in PV reconnections between the Prior-CB and Prior-RF groups, no differences could be found in the number of CB freeze-applications, nadir temperature, thawing time, or fluoroscopy time. This means that it was common to perform CB applications on previously isolated veins, maybe aiming to perform wider, more antral lesions.

In the present series, up to 60.6% of Prior-CB patients had no reconnected PVs in the redo procedure, compared to 24.4% in the Prior-RF group. Being CBA, a technique designed to perform only PV isolation, it is intuitive to think that another round of freeze applications on already-isolated PVs will not be of much effect.

There were also slightly more patients in the Prior-CB group that used a 23-mm CB. This could be in the setting of changing the balloon size from the previous procedure as has been proposed, aiming to change the effect of CBA on an already ablated atrium [12].

Atrial fibrillation recurrence

According to available research, this is the largest series of patients that used CBA as a redo technique, with 33 patients. Data regarding a second CBA as a repeat ablation procedure are scarce. Schade et al. [11] published a series in 2013 of 47 patients that underwent a second CBA after AF recurrence. They used the first-generation CB (Artic Front, Medtronic) for both procedures and the rates of subjects with 1, 2, 3, or 4 reconnected PVs were 19.1%, 47.6%, 30.9%, and 2.4%, respectively. The pattern of reconduction was evenly distributed, which was between 63% of LSPV and 43% of right inferior pulmonary vein (RIPV). Sixty percent of patients remained AF-free after 12 months. Westra et al. [12] tried a different approach. They performed repeat ablations in 40 patients with recurrent AF after an index CBA, a repeat CBA using a different sized CB (i.e., changing from 23-mm to 28-mm in the second procedure and vice versa). The first procedures were performed with either the first- or second-generation CB and the repeat CBA only with the second-generation CB. Vein reconnection rates were 36% after first--generation CB (1.4 PVs per patient) and 18% for second-generation one (0.7 PVs per patient). The 1-year AF recurrence-free survival rate was 70%, with no differences regarding the index procedure balloon generation. The use of a 23-mm CB failed to be a predictor of recurrence in the current series, which could be driven by a small number of patients. However, the use of different sized CB remains an interesting concept.

The clinical outcomes of Glowniak's study differ from the present results. In his series, both groups (CBA after and index CBA or RFCA) reach a 70.3% AF-free survival rate at 15 months. This divergence may be driven by the differences in PV reconnections. Their patients present more reconnected veins in the repeat CBA group (51.5% vs. 16.5% in the current series) which may be the reason for the AF recurrence and therefore solved with a new CBA. However, the current Prior-CB group has lower reconnection rates and relapse could be driven by non-PV triggers, which would not benefit from another PV isolation-only procedure [29]. Nevertheless, regression analysis showed that a Prior-CB was the strongest predictor of recurrence, overcoming the rate of already isolated veins (Fig. 3). This could mean that this effect is not only driven by the rate of reconnected PVs, but by the previous CBA procedure itself and thus selecting a population with worse arrhythmic prognosis.

On the other hand, the Prior-RF group had better outcome with a survival estimate of almost 90% at 12 months, which is consistent to other published works. De Regibus et al. [30] used a second-generation CB in 47 patients with recurrent AF after RFCA. Fifty-three percent of patients presented with one reconnected PV, 23.4% with 2, 17% with 3, and 6.4% with all-four PVs reconnected. After a follow-up of 15 months, 83% remained AF-free after a 3-month blanking period. Verlato et al. [9] share a work, where they alternate the ablation technique for the repeat procedure (i.e., index CBA followed by RFCA and vice versa). They included 349 patients in the RF-then-CB group and 125 in the CB-then-RF group. Ablation of non-PV triggers, left atrial flutter or cavo-tricuspid isthmus in the redo RFCA procedure was at the operators' discretion. They showed a reconnection rate of 3.7 PVs per patient in the RF-then-CB group and 1.4 PVs the CB-then-RF, and an outcome of freedom from AF at 12 months after a 3-month blanking period of 76.6% vs. 89.1%, respectively. Forty-seven percent of patients in the CB-then-RF group underwent additional non-PV ablation. The RF-then-CB population is represented in the current study and presents a similar outcome, while the CB-then-RF shows the best results. These findings are consistent with those herein, and points in the direction that RFCA may be more suitable for repeat procedures for the ability of performing non-PV ablations.

Limitations of the study

This is a non-predefined analysis of a prospective cohort study, with a limited number of patients compared to the whole population included. However, it is the largest cohort of patients with CBA as a redo procedure with 74 patients. The main limitation of the present study is the lack of procedural data from previous ablations, like the size or generation of the CB used, the CB application protocol or if RFCA consisted of more than PVI. Another limitation would be the method for AF detection, as only 2.7% of patients would receive an insertable loop recorder.

Nevertheless, this does not invalidate the present work since results are consistent with previously published data and the groups were mostly homogeneous. Moreover, RECABA was a multicentric study focused on describing everyday practice, and having present results despite heterogenous protocols weighed more on validating them.

Conclusions

Pulmonary vein reconnections are more frequently found in patients submitted to repeat AF ablation after an index RFCA than after an index CBA. Patients submitted to a repeat CBA have more AF recurrences than those that undergo CBA as a redo after an index RFCA. These data suggest that patients with AF recurrence after CBA may benefit from other ablation techniques after a recurrence.

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References

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
2. Bertaglia E, Senatore G, De Michieli L, et al. Twelve-year follow-up of catheter ablation for atrial fibrillation: A prospective, multicenter, randomized study. Heart Rhythm. 2017; 14(4): 486–492, doi: 10.1016/j.hrthm.2016.12.023, indexed in Pubmed: 27989681.
3. Andrade J, Champagne J, Dubuc M, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: A Randomized Clinical Trial. Circulation. 2019; 140(22): 1779–1788, doi: 10.1161/circulationaha.119.042622.
4. Kuck KH, Brugada J, Fürnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med. 2016; 374(23): 2235–2245, doi: 10.1056/NEJMoa1602014, indexed in Pubmed: 27042964.
5. Wokhlu A, Hodge DO, Monahan KH, et al. Long-term outcome of atrial fibrillation ablation: impact and predictors of very late recurrence. J Cardiovasc Electrophysiol. 2010; 21(10): 1071–1078, doi: 10.1111/j.1540-8167.2010.01786.x, indexed in Pubmed: 20500237.
6. Shah AN, Mittal S, Sichrovsky TC, et al. Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence. J Cardiovasc Electrophysiol. 2008; 19(7): 661–667, doi: 10.1111/j.1540-8167.2008.01101.x, indexed in Pubmed: 18284502.
7. Gaita F, Scaglione M, Battaglia A, et al. Very long-term outcome following transcatheter ablation of atrial fibrillation. Are results maintained after 10 years of follow up? Europace. 2018; 20(3): 443–450, doi: 10.1093/europace/eux008, indexed in Pubmed: 28340043.
8. Glowniak A, Tarkowski A, Fic P, et al. Second-generation cryoballoon ablation for recurrent atrial fibrillation after an index procedure with radiofrequency versus cryo: Different pulmonary vein reconnection patterns but similar long-term outcome-Results of a multicenter analysis. J Cardiovasc Electrophysiol. 2019; 30(7): 1005–1012, doi: 10.1111/jce.13938, indexed in Pubmed: 30938917.
9. Verlato R, Pieragnoli P, Iacopino S, et al. Cryoballoon or radiofrequency ablation? Alternating technique for repeat procedures in patients with atrial fibrillation. PACE. 2020; 43(7): 687–697, doi: 10.1111/pace.13975.
10. Pokushalov E, Romanov A, Artyomenko S, et al. Cryoballoon versus radiofrequency for pulmonary vein re-isolation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2013; 24(3): 274–279, doi: 10.1111/jce.12038, indexed in Pubmed: 23210695.
11. Schade A, Langbein A, Spehl S, et al. Recurrence of paroxysmal atrial fibrillation after cryoisolation of the pulmonary veins. Is a "redo" procedure using the cryoballoon useful? J Interv Card Electrophysiol. 2013; 36(3): 287–295, doi: 10.1007/s10840-012-9725-y, indexed in Pubmed: 23132349.
12. Westra SW, van Vugt SPG, Sezer S, et al. Second-generation cryoballoon ablation for recurrent atrial fibrillation after an index cryoballoon procedure: a staged strategy with variable balloon size. J Interv Card Electrophysiol. 2019; 54(1): 17–24, doi: 10.1007/s10840-018-0418-z, indexed in Pubmed: 30090996.
13. Ferrero-De-Loma-Osorio Á, Cózar R, García-Alberola A, et al. RECABA Investigators. Primary results of the Spanish Cryoballoon Ablation Registry: acute and long-term outcomes of the RECABA study. Sci Rep. 2021; 11(1): 17268, doi: 10.1038/s41598-021-96655-3, indexed in Pubmed: 34446764.
14. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. Revista Española de Cardiología (English Edition). 2017; 70(1): 50, doi: 10.1016/j.rec.2016.11.033.
15. Chen S, Schmidt B, Bordignon S, et al. Atrial fibrillation ablation using cryoballoon technology: Recent advances and practical techniques. J Cardiovasc Electrophysiol. 2018; 29(6): 932–943, doi: 10.1111/jce.13607, indexed in Pubmed: 29663562.
16. Su W, Kowal R, Kowalski M, et al. Best practice guide for cryoballoon ablation in atrial fibrillation: The compilation experience of more than 3000 procedures. Heart Rhythm. 2015; 12(7): 1658–1666, doi: 10.1016/j.hrthm.2015.03.021, indexed in Pubmed: 25778428.
17. Su W, Aryana A, Passman R, et al. Cryoballoon Best Practices II: Practical guide to procedural monitoring and dosing during atrial fibrillation ablation from the perspective of experienced users. Heart Rhythm. 2018; 15(9): 1348–1355, doi: 10.1016/j.hrthm.2018.04.021, indexed in Pubmed: 29684571.
18. Ciconte G, Velagić V, Mugnai G, 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. 2016; 18(1): 71–77, doi: 10.1093/europace/euv224, indexed in Pubmed: 26445821.

19. Kuck KH, Albenque JP, Chun KRJ, et al. FIRE AND ICE Investigators. Repeat ablation for atrial fibrillation recurrence post cryoballoon or radiofrequency ablation in the FIRE AND ICE trial. Circ Arrhythm Electrophysiol. 2019; 12(6): e007247, doi: 10.1161/CIRCEP.119.007247, indexed in Pubmed: 31693319.
20. Zeljkovic I, Knecht S, Spies F, et al. Paroxysmal atrial fibrillation recurrence after redo procedure-ablation modality impact. J Interv Card Electrophysiol. 2020; 57(1): 77–85, doi: 10.1007/s10840-019-00694-w, indexed in Pubmed: 31912448.
21. Cheung CC, Deyell MW, Macle L, et al. Repeat Atrial Fibrillation Ablation Procedures in the CIRCA-DOSE Study. Circ Arrhythm Electrophysiol. 2020; 13(9): e008480, doi: 10.1161/CIRCEP.120.008480, indexed in Pubmed: 32701361.
22. Aryana A, Kenigsberg DN, Kowalski M, et al. Verification of a novel atrial fibrillation cryoablation dosing algorithm guided by time-to-pulmonary vein isolation: Results from the Cryo-DOSING Study (Cryoballoon-ablation DOSING Based on the Assessment of Time-to-Effect and Pulmonary Vein Isolation Guidance). Heart Rhythm. 2017; 14(9): 1319–1325, doi: 10.1016/j.hrthm.2017.06.020, indexed in Pubmed: 28625929.
23. Aryana A, Mugnai G, Singh SM, et al. Procedural and biophysical indicators of durable pulmonary vein isolation during cryoballoon ablation of atrial fibrillation. Heart Rhythm. 2016; 13(2): 424–432, doi: 10.1016/j.hrthm.2015.10.033, indexed in Pubmed: 26520204.
24. Ciconte G, Mugnai G, Sieira J, et al. On the quest for the best freeze: predictors of late pulmonary vein reconnections after second-generation cryoballoon ablation. Circ Arrhythm Electrophysiol. 2015; 8(6): 1359–1365, doi: 10.1161/CIRCEP.115.002966, indexed in Pubmed: 26527624.
25. Álvarez-Ortega CA, Ruiz MA, Solórzano-Guillén C, et al. Time to -30°C as a predictor of acute success during cryoablation in patients with atrial fibrillation. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0135, indexed in Pubmed: 34708863.
26. Wissner E, Heeger CH, Grahn H, et al. One-year clinical success of a ‚no-bonus' freeze protocol using the second-generation 28 mm cryoballoon for pulmonary vein isolation. Europace. 2015; 17(8): 1236–1240, doi: 10.1093/europace/euv024, indexed in Pubmed: 25868468.
27. Chun KR, Stich M, Fürnkranz A, et al. Individualized cryoballoon energy pulmonary vein isolation guided by real-time pulmonary vein recordings, the randomized ICE-T trial. Heart Rhythm. 2017; 14(4): 495–500, doi: 10.1016/j.hrthm.2016.12.014, indexed in Pubmed: 27956248.
28. Chen S, Schmidt B, Bordignon S, et al. Impact of cryoballoon freeze duration on long-term durability of pulmonary vein isolation: ICE re-map study. JACC Clin Electrophysiol. 2019; 5(5): 551–559, doi: 10.1016/j.jacep.2019.03.012, indexed in Pubmed: 31122376.
29. Aryana A, Chierchia GB, de Asmundis C. Recurrent Atrial Fibrillation After Cryoballoon Ablation: What to Expect! Card Electrophysiol Clin. 2020; 12(2): 199–208, doi: 10.1016/j.ccep.2020.02.002, indexed in Pubmed: 32451104.
30. De Regibus V, Iacopino S, Abugattas JP, et al. Repeat procedures using the second-generation cryoballoon for recurrence of atrial fibrillation after initial ablation with conventional radiofrequency. J Interv Card Electrophysiol. 2017; 49(2): 119–125, doi: 10.1007/s10840-017-0236-8, indexed in Pubmed: 28315135.