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ORIGINAL ARTICLE

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Repeat procedures for recurrent persistent atrial fibrillation: A propensity-matched score comparison between left atrial linear ablation with radiofrequency and posterior wall isolation with the cryoballoon

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Abstract

Aims: To evaluate the clinical outcome in patients undergoing repeat procedures for recurrent persistent atrial fibrillation following an index cryoballoon (CB-A) pulmonary vein isolation ablation on a mid-term follow-up of 12 months.

Methods: In this propensity score-matched comparison, 50 patients undergoing left atrial posterior wall isolation (LAPWI) with the CB-A were matched to 50 patients treated with additional linear ablation using radiofrequency catheter ablation (RFCA).

Results: Meantime to repeat the procedure was 9.74 ± 4.36 months. At 12 months follow-up freedom from atrial tachyarrhythmias (ATas) was achieved in 82% of patients in the LAPWI group and in 62% of patients in the linear ablation group ($P = .03$). Regression analysis demonstrated that relapses during the blanking period and LA dimensions were independent predictors of ATas recurrences following the repeat procedure.

Conclusion: LAPWI using CB-A is associated with a significantly higher freedom from atrial arrhythmias when compared with the RFCA mediated left atrial linear lesions on a mid-term follow-up of 12 months in patients with persAF undergoing a redo procedure.

KEYWORDS

cryoballoon, left atrial posterior wall ablation, persistent atrial fibrillation, pulmonary vein isolation, radiofrequency ablation

Carlo de Asmundis and Gian-Battista Chierchia contributed equally as senior authors.

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1 | INTRODUCTION

Pulmonary vein isolation (PVI) has demonstrated to provide limited clinical benefit in patients with persistent atrial fibrillation (persAF).[1-3] Left atrial (LA) substrate modification is frequently performed in addition to redo pulmonary vein isolation with different energy modalities.[4-7] A consensus on the best ablation strategy or on the best ablation source to adopt during repeat procedures is yet to be reached. Cryoballoon ablation (CB-A) has demonstrated comparable results with radiofrequency in patients with paroxysmal AF,[8] whereas there is paucity of data on its effectiveness in patients with persAF. Aim of the current study was to compare the mid-term clinical outcome of left atrial posterior wall isolation (LAPWI) obtained with CB-A with a left atrial roof and mitral isthmus lines obtained with radiofrequency catheter ablation (RFCA) in patients with persistent AF undergoing a redo AF ablation procedure.

2 | METHODS

This study cohort consisted of consecutive patients undergoing a repeat ablation procedure for recurrence of PersAF, following an index procedure with the CB-A for the treatment of the same arrhythmia.

Fifty patients undergoing redo PVI + LAPWI with the CB-A at Universitair Ziekenhuis Brussel (UZB), Brussels, Belgium, between September 2016 and March 2018 were included in a propensity matching analysis. During the same period, 106 patients underwent redo PVI + additional linear ablation (roof and mitral line) using point by point RFCA; of these, 83 patients both lines were blocked.

Propensity score matching was performed with a 1:1 ratio taking into account the following variables: (a) age, (b) gender, (c) CHA2DS2–VASc score, (d) mean duration of persistent AF, (e) LA size, (f) left ventricular ejection fraction (LVEF), and (g) current antiarrhythmic drugs (AAD).

The study protocol was carried out in accordance with the ethical principles for medical research involving human subjects established by the Declaration of Helsinki and was approved by the local ethics committee of our Institution. All patients provided written informed consent to the ablation procedure.

2.1 | Procedures

2.1.1 | Index procedure: PVI with CB-A

Our standard preprocedural management and ablation have been previously described in detail.[9,10] After a single transseptal puncture LA access was gained, through a steerable 15 Fr sheath (FlexCath Advance®, Medtronic©) and an inner lumen mapping catheter (MC; Achieve®, Medtronic©) was advanced and positioned in each PV ostium. A 28 mm CB-A (Arctic Front Advance™, Medtronic©) was advanced inflated and positioned at PV ostium. Contrast injection was performed to check for optimal vessel occlusion. The ablation sequence was: left superior PV (LSPV) first, followed by the left inferior PV (LIPV), right inferior PV (RIPV), and right superior PV (RSPV). Cryoapplication was started only once vessel occlusion was deemed satisfactory. As per our standard protocol, cryoapplications lasted 180 seconds if meeting the following criteria: target temperature −40°C within the first 60 seconds and real-time isolation less than 60 seconds. If the application did not meet these criteria, a 180 seconds extra freeze was delivered. Successful PVI was defined as an absence of all PV potentials or their dissociation from an atrial activity. In order to avoid phrenic nerve palsy (PNP), diaphragmatic stimulation was achieved by pacing the phrenic nerve during right PVs ablation. Target activated clotting time was over 250 seconds.

2.2 | Repeat ablation

2.2.1 | Redo PVI + LAPW CB-A group

After single transseptal LA access, all PVs were mapped by the Achieve®catheter. Whenever PV reconnection was identified, repeat PVI was performed using CB-A as previously described. Our approach to LAPWI with CB-A was described in detail elsewhere.[9,10] Briefly, after PVI, in order to achieve LAPWI, the Achieve®catheter was placed deeply in the LSPV to stabilize the CB-A that was positioned with the distal freezing surface oriented towards the LAPW. As per our standard protocol, cryothermal lesions ranged from 120 to 180 seconds. The first cryoapplication was performed partially overlapping left superior pulmonary vein (LSPV) ostium. By a slight clockwise rotation and progressive "pull-back" of the sheath while keeping the CB in contact with the posterior wall, consecutive overlapping freezes were applied along the LAPW. The same maneuver was performed from the right superior pulmonary vein (RSPV) and from inferior PVs for the inferior portion of LAPW. At the end of the procedure, in order to evaluate LAPWI pacing maneuvers to test entrance and exit block were performed with Achieve®catheter. After LAPWI, high-density 3D electroanatomical map (CARTO 3, Biosense Webster) was performed with a multielectrode mapping catheter (Pentaray, Biosense Webster) and areas of low voltage were defined as <0.15 mV (Figure 1). LAPWI was performed under esophageal temperature monitoring with CIRCA's S-CATH™ Esophageal Temperature Monitoring System (Circa Scientific) dedicated probe and cryoenergy applications were interrupted if measured inner esophageal temperatures was less than 15°C.

2.2.2 | Redo PVI + additional linear ablation with point by point RFCA group

After double transseptal puncture, 3D electroanatomical map (EAM) of LA was acquired with a circular mapping catheter (Carto, Biosense Webster© or NavX, St. Jude Medical©). PVI was checked

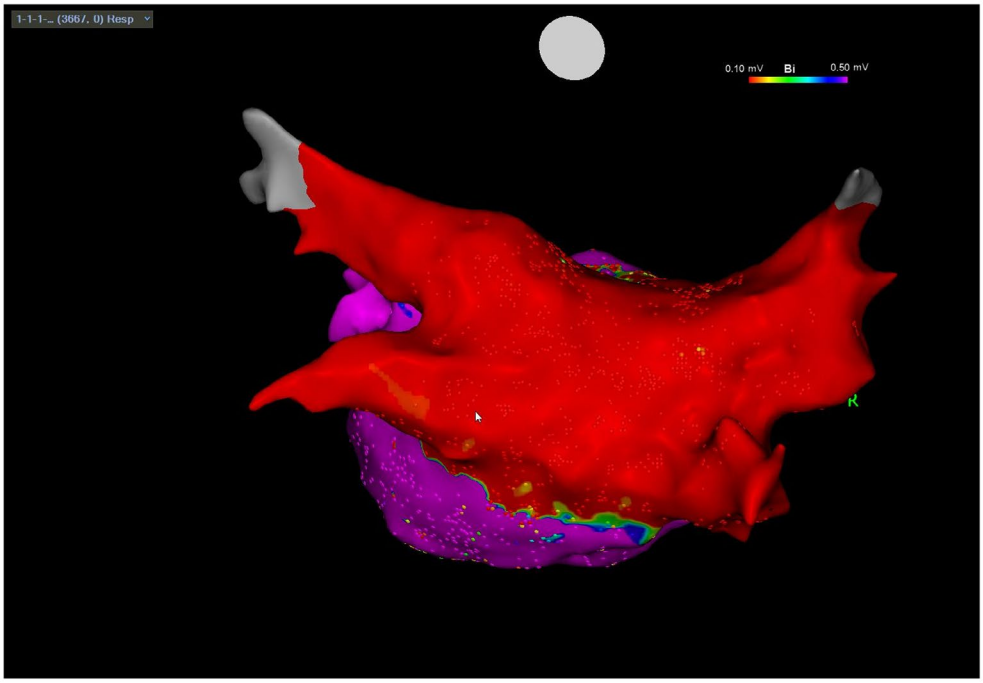

FIGURE 1 Voltage map of Left Atrium after posterior wall isolation using cryoballoon. The red region represents voltage <0.1 mV

and, if a PV was not isolated, radiofrequency applications were performed with an open irrigated tip catheter with contact-force (CF) monitoring (Thermocool®, SmartTouch™, Biosense Webster©; Tacticath®, Endosense, St. Jude Medical©) in power-controlled mode with a power limit of 35 W and maximum temperature of 48°C. A 25 W power limit was used for posterior sites. Moreover, during ablation with SmarTouch catheter, each lesion was guided by ablation index targets of 550 at the anterior walls and roof and 400 at the posterior and inferior walls. The endpoint of PVI was defined as bidirectional block within a waiting time of 20 minutes after last application. Patients experiencing reconnection underwent re-PVI.

After PVI, as per standard protocol two additional empirical linear ablation were performed: roof line and mitral isthmus line. Roof line was performed between the superior PVs while the mitral isthmus line was placed between the posterolateral mitral annulus and the left inferior PV ostium. Point by point RFCA was performed with the same ablation catheter used during PVI and a long-sheath (SL-0, St. Jude Medical©), in a power-controlled mode with a power limit of 35 W for the mitral line and 30 W for the roof line. At each site, RFCA endpoint was electrogram amplitude decrease by >80% or local potential split. Bidirectional block across roof and mitral line was confirmed in all patients with differential pacing from LA appendage versus LA posterior wall and pacing from the LA appendage versus LA septum confirmed. If mitral isthmus linear block was not achieved by an endocardial ablation, additional ablation inside the coronary sinus (CS) was performed. Ablation within the CS was performed in a power-controlled mode with a power limit of max 25 W and RFCA applications of 40–120 seconds.

2.3 | Postprocedural management and follow-up

All patients underwent continuous telemetry monitoring for at least 18 hours after the procedure. Before discharge, transthoracic echocardiography was performed in all patients to exclude postprocedural complications. Oral anticoagulation was started the same evening of ablation and continued for at least 3 months. Previously ineffective AADs were continued for at least 3 months and subsequently discontinued. After discharge, patients were scheduled for follow-up visits with baseline ECG and 24 hours Holter recordings at 3, 6, and 12 months. Primary endpoint at follow-up was recurrence of any atrial tachyarrhythmias (ATas) defined as episodes >30 seconds after a 90-day post-ablation blanking period (BP). Recurrence was assessed with standard ECG or 24 hours ECG Holter monitoring or with implantable loop recorders or implanted devices interrogation if applicable. Moreover, any symptoms following ablation were deemed as deserving a Holter monitoring.

3 | Statistical analysis

Continuous variables are reported as mean ± standard deviation while categorical variables are presented as absolute numbers and percentages. Comparison of continuous data between 2 groups was performed with the Student t test for independent samples or Mann-Whitney U test while Pearson χ 2 were used for comparison of categorical variables. Kaplan-Meier plots were used to report arrhythmia-free survival curves for each group and time-to-event analysis was performed using the logrank test.

All tests were 2-sided, and a P value of 0.05 was considered statistically significant. Analyses were performed with SPSS 23.0 statistical software (IBM Company, Chicago, IL, USA).

4 | RESULTS

A total of 100 patients were included in our analysis. All patients underwent PVI using CB-A as an index procedure. Fifty in the LAPWI group and 50 in the linear ablation group. The two groups were well balanced with no significant differences in baseline characteristics (Table 1). Meantime to repeat the procedure was 9.04 ± 3.93 months in the first group and 10.44 ± 4.68 months in the second group ($P = .11$). Conversion to SR occurred during ablation in 20 patients (20%) [8 patients (16%) in the LAPWI group and 12 patients (24%) in the linear ablation group ($P = .32$)]. Among 100 patients, 47 (47%) showed a PV reconnection, 26 patients (52%) in the LAPWI group, and 21 patients (42%) in the linear ablation group ($P = .31$). The RIPV was the most frequently reconnected vein (Table 2). Repeat PVI procedural outcomes are reported in Table 3. The total procedure time (LAPW group 85.75 ± 15.24 minutes; linear ablation group 152.65 ± 36.77 minutes) and the mean fluoroscopy time (LAPW group 19.6 ± 7.32 minutes; linear ablation group 40.5 ± 10.82 minutes) were significantly shorter in the LAPWI group ($P < .001$ for both comparison).

TABLE 1 Baseline characteristics

	LAPWI (CB-A) (n = 50)	Lines (RFCA) (n = 50)	P
Age (y)	62.5 ± 11.8	63.4 ± 9.4	.69
Gender (male)	30 (60%)	36 (72%)	.2
BMI (kg/m^2)	27.8 ± 6.0	26.9 ± 4.4	.42
Hypertension	24 (48%)	23 (46%)	.84
Diabetes	6 (12%)	8 (16%)	.56
Dyslipidemia	21 (42%)	25 (50%)	.42
IHD	2 (4%)	3 (6%)	.65
OSAS	10 (20%)	7 (14%)	.42
CHA2DS2–VASc score	1.7 ± 1.3	1.9 ± 1.4	.66
LVEF (%)	55.1 ± 8.2	57. 4 ± 5.7	.11
LA dimension (mm)	44.4 ± 8.3	44.9 ± 9.2	.75
Duration of persistent AF (mo)	9.5 ± 4.5	8.4 ± 4.1	.24
Cycle length of AF	163.8 ± 32.9	173.1 ± 28.3	.15
Antiarrhythmic medications			
Class IC	12 (24%)	10 (20%)	.63
Class II	26 (52%)	29 (58%)	.55
Class III	16 (32%)	23 (46%)	.15
Class IV	1 (2%)	1 (2%)	1

Abbreviations: AF, atrial fibrillation; IHD, ischemic heart disease; LA, left atrium; LVEF, Left Ventricular Ejection Fraction; OSAS, Obstructive Sleep Apnea Syndrome.

4.1 | LAPW group

The LAPW was successfully isolated solely by CB-A ablation in 46 (92%) patients, in the four remaining patients, isolation of the LAPW was completed by touch-up RFCA.

The mean number of CB-A applications required for the LAPWI was 8.26 ± 0.87. Of these, 4.75 ± 0.62 applications for the superior portion isolation and 3.52 ± 0.61 for the inferior portion of the LAPW. Mean duration of single cryoenergy application on the LAPW was 177.17 ± 9.5 seconds. During the application in the superior portion of the LAPW, cryoenergy delivery was interrupted in three patients (6%), because of a luminal esophageal temperature (LET) below 15°C. Complete LAPW isolation could be observed in all patients. The mean minimum temperature reached was −41.07 ± 4.23.

4.2 | Linear ablation group

A LA roof line block was successfully performed in all patients, whereas mitral line bidirectional block was obtained endocardially in 41 patients (82%). In the remaining nine patients (18%) mitral line block was completed by RFCA within the CS. Mean RF energy

TABLE 2 Pulmonary vein at the repeat procedure

PV	LAPWI + PVI	Linear ablation	P
Left superior	5 (10%)	8 (16%)	.37
Left inferior	10 (20%)	7 (14%)	.42
Right superior	11 (22%)	8 (16%)	.44
Right inferior	17 (34%)	14 (28%)	.52

Abbreviations: LAPWI, left atrium posterior wall isolation; PV, pulmonary vein.

TABLE 3 PVI characteristics at the repeat procedure

	LAPWI group (CB-A)	Linear ablation group (RFCA)
Duration single application (s)	181.1 ± 9.69	—
Time to isolation PV (s)	37.66 ± 13.61	—
Isolation temperature (°C)	−31.27 ± 7.65	—
Min Temperature (°C)	−51.31 ± 4.43	—
Energy application time PVI (min)	—	41.02 ± 7.33
Contact-force PVI (g)	—	17.02 ± 7.21

Abbreviations: CB-A, cryoballoon; LAWI, left atrium posterior wall isolation; PVI, pulmonary vein isolation; RFCA, radiofrequency catheter ablation.

application time was 8.7 ± 2.97 minutes per patient for the roof line and 12.6 ± 4.83 minutes for the mitral line.

4.3 | Procedural adverse events

Major complications occurred in six patients (6%). Transient phrenic palsy was observed in 4/50 patients (8%) in the LAPWI group, with complete resolution before the end of the procedure. Pseudoaneurysm requiring surgical treatment occurred in 2/100 patients (2%), one in both groups.

There were no deaths or cerebrovascular events in the periprocedural period and during the entire follow-up.

4.4 | Follow-up

4.4.1 | Freedom from arrhythmia recurrences

All patients completed the 1-year follow-up. Overall 72 patients (72%) did not experience recurrence of atrial tachyarrhythmia (ATas) during follow-up.

At 12 months follow-up freedom from ATas was achieved in 82% of patients in the LAPWI group and in 62% of patients in the linear ablation group ($P = .03$). Kaplan-Meier survival curves showing each group's cumulative arrhythmia-free survival are presented in Figure 2.

If relapses during the BP were also considered, freedom from ATas was 70% and 48%, respectively ($P = .02$).

4.4.2 | Atrial arrhythmias recurrences

At 12 months follow-up, 28 patients (28%) had arrhythmia recurrences, 9 (18%) patients in the LAPWI group and 19 patients (38%) in the linear ablation group ($P = .03$).

During the BP 29 patients (29%) experienced arrhythmic recurrences, 12/50 patients (24%) in the first group and 17/50 patients (34%) in the second group ($P = .27$). Of these, 13/29 (44.8%) were not recorded after the BP, 6 (20.7%) in LAPWI group and 7 (24.1%) in the linear group. Among the 28 ATas recurrences, 10 (35.7%) were atrial tachycardia (AT), 13 (46.5%) were AF and 5 (17.8%) typical atrial flutter. AT and AF recurrences were significantly lower in the LAPWI group: AT recurred in two patients (4%) in the LAPWI group and in eight patients (16%) in the linear ablation group ($P = .04$), whereas AF was recorded in three patients (6%) in the LAPWI group and in 10 patients (20%) in the RFCA group ($P = .04$).

On the other hand, there was no difference in typical atrial flutter recurrence between the two groups, four (8%) in the LAPWI group and one (2%) in the linear ablation group ($P = .17$).

Furthermore, in a Cox regression analysis, among the variables tested, LA dimension (HR 1.097; 95% CI: 1.025, 1.173, $P = .007$) and recurrence during BP (HR: 4.121; 95% CI: 1.489,11.409,

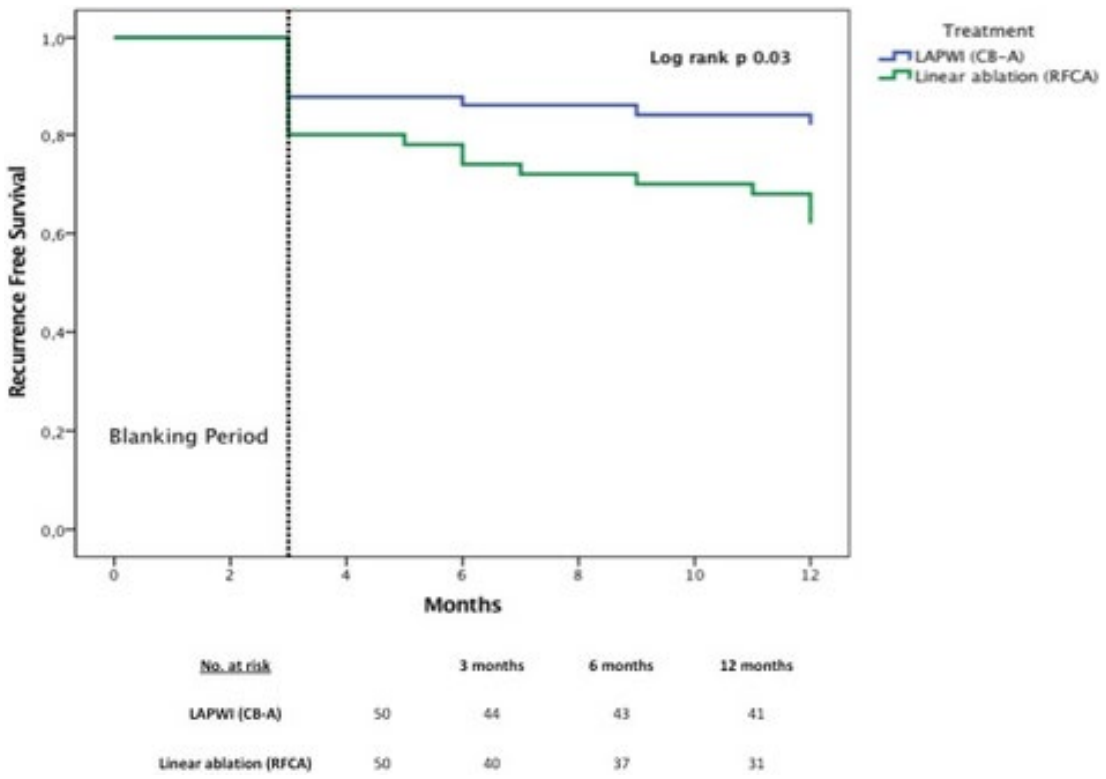

FIGURE 2 Kaplan–Meier curves illustrating the cumulative freedom from recurrent atrial tachyarrhythmia after the 3-month blanking period in LAPWI group (blue line) and in linear ablation group (green line)

$P = .006$) were independently associated with recurrence of ATas (Table 4).

5 | DISCUSSION

To the best of our knowledge, this is the first study comparing LAPWI isolation using CB-A and linear ablation (roof and mitral line) using RFCA for the treatment of recurrence of PersAF on a midterm follow-up of 1 year.

The main findings of the current study are: (a) freedom from atrial arrhythmias at 12 months follow-up was significantly higher in patients undergoing second-generation CB-A LAPWI compared with linear RFCA ablation, without compromising safety and (b) LA dimensions and relapses during the BP were independent predictors of arrhythmia recurrence.

CB-A and RF ablation have demonstrated similar results for PVI while the outcome of the two technologies beyond PVI is still unclear.[2,11,12] For this reason this retrospective study was designed to compare difference approaches using the two technologies.

A large amount of evidence demonstrates the role of LAPW, among other extra-PVs sites, in the pathogenesis and maintenance of persAF. Indeed, intrinsic properties of LAPW such as larger late sodium and intracellular, higher sarcoplasmic reticulum Ca^{2+} content and smaller inward rectifier potassium currents[13-16] make this area prone to harbor AF substrate. Moreover, the common embryologic origin with PVs might explain its arrhythmogenic potential.[17]

Consistent with preclinical data, a recent meta-analysis[18] reported that adjunctive LAPWI in PersAF resulted in a significant reduction in the recurrence rate of ATas, without an increased risk of atrial flutter, compared to patients who had PVI only. Noticeably, only in one of the included studies PVI and LAPWI were performed with a second-generation CB-A and few studies focusing on LAPWI with CB-A have been published so far.

In a multicentre study, Aryana et al[6] reported additional benefits of LAPWI over PVI alone using CB-A in the treatment of persAF, with lower recurrence rate in LAPWI group comparing to PVI group at 12 months of follow-up. Consistent with these data, our study showed a rate of freedom of ATas of around 80%. Interestingly, Aryana et al included ablation-naive patients undergoing PVI+ LAPWI as an index procedure for persistent AF, while the current study focused on patients undergoing LAPWI as a repeat procedure for persAF recurrence after an initial PVI with the CB. In index procedure, also our group has already reported the

TABLE 4 Logistic regression analysis of variables for prediction of arrhythmia recurrences

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (y)	1.010 (0.969, 1.053)	.63		
Gender (male)	0.900 (0.360, 2.248)	.82		
BMI (kg/m^2)	1.057 (0.969, 1.153)	.21		
Hypertension	0.969 (0.404, 2.234)	.94		
Diabetes	1.033 (0.296, 3.613)	.96		
Dyslipidemia	1.250 (0.521, 2.997)	.62		
IHD	1.769 (0.280, 11.198)	.54		
OSAS	1.087 (0.345, 3.428)			
$CHA_2DS_2VASc_{score}$	1.072 (0.778, 1.477)	.67		
LVEF	1.006 (0.945, 1.071)	.85		
SR during ablation	2.00 (0.716, 5.590)	.13		
LA dimension (mm)	**1.118 (1.050, 1.191)**	**.001**	**1.096 (1.025, 1.172)**	**.007**
Duration of persistent AF (mo)	0.98 (0.88, 1.083)	.64		
Cycle length	0.99 (0.98, 1.008)	.40		
PV reconnection	1.44 (0.60, 3.46)	.41		
Class IC	0.703 (0.232, 2.123)	.53		
Class II	0.756 (0.315, 1.815)	.53		
Class III	0.824 (0.333, 2.037)	.675		
Class IV	2.630 (0.159, 43.547)	.5		
Recurrence in BP	**6.051 (2.318, 15.798)**	**<.001**	**4.132 (1.493, 11.435)**	**.006**

Abbreviations: AF, atrial fibrillation; BP, blanking period; IHD, ischemic heart disease; LA, left atrium; LVEF, Left Ventricular Ejection Fraction; SR, sinus rhythm.

Bold values indicates the significance is due to $p < 0.01$ as reported in statistical analysis paragraph.

feasibility and safety of CB-A for the LAPWI during persistent AF ablation, with similar results and, again, superior to linear RFCA lesion.[10]

In the present study, when compared to LAPWI with CB-A, additional linear ablation showed lower freedom from recurrence and higher procedural times. Most studies on additional linear RFCA lesions reported conflicting results for persAF. The randomized clinical trial STAR-AF[2] demonstrated that, compared to PVI only approach, additional linear lesions plus PVI did not offer higher freedom rates from ATas. On the other hand, some studies report satisfactory outcomes.[4,5] Recently, the MARSHALL-PLAN study, employing a standard linear RFCA lesion sets (coronary sinus, Vein of Marshall alcoholization, mitral, roof, and cavotricuspid isthmus) reported a single procedure success rate of 79% after 1 year.[19] This outcome is similar to the success rate reported in the current study for LAPWI with CB-A but at the expense of large atrial lesions and longer procedural time (277 ± 41 minutes).

The higher recurrence rate of ATas after linear RFCA can be explained by the intrinsic technical challenge of the procedure and incomplete bidirectional conduction block. Previous data show late line gaps formation in the roof and mitral lines in around 40%-60% and 60%-90% of cases, respectively.[20-23]

Finally, regression analysis showed that recurrences in the BP and LA dimension predicted freedom from ATas at 1 year follow-up and our results are in agreement with these observations.[24-27] This finding is clinically relevant and stresses out the need for early referral to AF ablation before atrial remodeling occurs. In this setting, one session ablation with PVI and LAPWI CB-A is an appealing approach with potentially low procedure timings and high success rate.

The ablation strategy for recurrence of persAF after PVI is still a matter of debate and an unmet clinical issue. In the *expert consensus statement on catheter ablation of AF*, 25% of the writing group members perform linear ablation at the time of an initial ablation procedure, increasing to 45% when redo procedures are performed in patients with persistent and long- standing persistent AF.[1] Our study provides a scientific support to the recent published expert best practice document,[28] which encourages the use of LAPWI with CB-A in this group of patients with drug and ablation refractory persAF.

6 | LIMITATIONS

The study was retrospective in nature and conducted on a relatively limited number of patients. Furthermore, it reports a single-center experience. Although the groups were well matched, the potential for residual unmeasured confounding factors or uncontrolled selection bias cannot be excluded. In the LAPWI group using CB-A, RFCA was used to achieve posterior wall isolation. In addition, no pharmacological testing was used to elicit non-PVI foci. No long-term monitoring has been performed (loop-recorder or 7 days Holter), accordingly the arrhythmia recurrence rate and asymptomatic episodes might have been underestimated. Finally, esophageal damage might have been underestimated as no esophagogastroduodenoscopy (EGDS) was performed after ablation.

7 | CONCLUSIONS

LAPWI obtained using CB-A was associated with a better outcome compared to the linear lesions with RFCA on a mid-term follow-up of 12 months in a selected group of patients undergoing repeat ablation for persAF, following an index CB PVI procedure. Larger randomized studies are warranted in order to confirm these findings.

CONFLICTS OF INTEREST

GBC reports speaker fees for Medtronic, Biotronik, Biosense Webster, and Abbott; teaching honoraria from Medtronic and Biotronik; proctoring honoraria from Medtronic; AB is consultant for Biotronik; PB reports consulting fees and speaker honoraria from Medtronic; C.d.A. reports speaker fees for Medtronic, Biotronik, Biosense Webster, Abbott, and Boston Scientific; teaching honoraria from Medtronic, Biotronik, Abbott, and Boston Scientific; proctoring honoraria from Medtronic, Abbott, and Biotronik.

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