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DOI:
10.1111/jce.16343

Received: 13 April 2024 | Revised: 16 May 2024 | Accepted: 6 June 2024
DOI: 10.1111/jce.16343

ORIGINAL ARTICLE

WILEY

Pulmonary vein reconnection and repeat ablation characteristics following cryoballoon-compared to radiofrequency-based pulmonary vein isolation

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Disclosures: None.

Abstract

Background: Despite advances in efficacy and safety of pulmonary vein isolation (PVI), atrial fibrillation (AF) recurrence after PVI remains common. PV-reconnection is the main finding during repeat PVI procedures performed to treat recurrent AF.

Objective: To analyze pulmonary vein (PV) reconnection patterns during repeat ablation procedures in a large cohort of consecutive patients undergoing radio frequency or cryoballoon-based PVI.

Methods: Retrospective analysis of PV-reconnection patterns and analysis of re-ablation strategies in consecutive index RF- and CB-based PVI and their respective re-ablation procedures during concomitant usage of both energy sources at a single high-volume center in Germany.

Results: A total of 610 first (06/2015–10/2022) and 133 s (01/2016–11/2022) repeat ablation procedures after 363 (60%) RF- and 247 (40%) CB-based index PVIs between 01/2015 and 12/2021 were analyzed. PV-reconnection was found in 509/610 (83%) patients at first and 74/133 (56%) patients at second repeat procedure. 465 of 968 (48%) initially via CB isolated PVs were reconnected at first re-ablation but 796 of 1422 initially RF-isolated PV (56%) were reconnected (OR: 0.73 [95% CI: 0.62–0.86]; $p < .001$). This was driven by fewer reconnections of the left PVs (LSPV: OR: 0.60 [95% CI: 0.42–0.86]; $p = .005$ and LSPV: 0.67 [0.47–0.95]; $p = .026$). PV-reconnection was more likely after longer, RF-based index PVI and in older females. Repeat procedures were shorter after CB-compared to after RF-PVI.

Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; CAD, coronary artery disease; CB, cryoballoon; CI, confidence interval; CKD, chronic kidney disease; CTI, cavotricuspid isthmus; IQR, interquartile range; LA, left atrium; LCPV, common ostium of the left-sided PVs; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; OR, odds ratio; PV, pulmonary vein(s); PVI, pulmonary vein isolation; RF, radiofrequency (energy); RIPV, right inferior pulmonary vein; RRR, relative risk reduction; RSPV, right superior pulmonary vein; SD, standard deviation.

J. Obergassel and M. Nies contributed equally.

Conclusions: Reconnection remains the most common reason for repeat AF ablation procedures after PVI. Our data suggest to preferentially use of the cryoballoon during index PVI, especially in older women.

KEYWORDS

cryoballoon ablation, energy, pulmonary vein reconnection, radiofrequency ablation, reisolation, repeat ablation

1 | INTRODUCTION

Durable pulmonary vein isolation (PVI) is the recommended procedural endpoint and most effective treatment in catheter ablation of atrial fibrillation (AF).[1,2] Electrical reconnection of previously isolated PVs is the most common finding in patients with arrhythmia recurrence in repeat ablation procedures.[3–6] Currently, PV-reconnection can only be evaluated invasively,[7] limiting routine evaluation of lesion durability after PVI.

Cryoballoon (CB) and radiofrequency (RF)-based PVI remain widely used throughout the world. Different ablation modalities have individual advantages and limitations, such as lesion formation and maneuverability. This may predispose to less durable lesions in certain PVs or patient populations. While the efficacy of CB versus RF ablation has been extensively studied,[3,5,8–10] comparative data on reconnection patterns and repeat procedure characteristics such as radiofrequency-energy consumption and procedure duration are limited. Efficacy data, particularly of re-ablation procedures, is becoming increasingly important due to increasing referral rates for PVI.[11,12] Besides, investigations on patient-specific predictors for PV-reconnection are not available from large cohorts.

The aim of this study is to provide an in-depth analysis of PV-reconnection patterns and characteristics of first and second re-ablation procedures after thermal index ablation in a recent, unselected cohort of AF patients at a German high-volume center.

2 | METHODS

2.1 | Study population, ethics, and data acquisition

Consecutively performed index PVI and re-ablation procedures between January 2015 and November 2022 were identified at a high-volume ablation center in Germany using semi-automatic data mining in written procedural reports, extracting basic demographic and procedure related structured tabulated data. Natural language processing was applied for basic classification tasks, as well as extraction of catheter names, operator names and further utilized semi-structured data. All data (including operator data) were deidentified before analysis. The ethics committee of the Ärztekammer (General Medical Council) Hamburg has declared its nonjurisdiction for this study (processing number 2022-300220-WF) since usage of fully deidentified retrospective data is covered by local law (§ 12 HmbKHG).

All procedures were independently classified by two electrophysiology-experienced physicians blinded to the index procedure's energy source. Classification included determination of procedure type (PVI, additional lesion set, type of repeat ablation, appearance and type of PV-reconduction, etc.).

Patients with a CB- or RF-based index PVI at our center who underwent at least one re-ablation for AF at our center were included in the final analysis, irrespective of the occurrence of PV-reconnection and irrespective of potential additional lesion sets (beyond PVI) at index procedure. Patients with an anatomic variant other than a common ostium of the left PVs (LCPV) were excluded.

A sensitivity analysis was performed in a time-wise unselected data set of all available first re-ablation procedures following an index PVI since January 2009.

2.2 | Index and repeat ablation procedures

All patients gave written informed consent for AF ablation. Intracardiac thrombi were routinely ruled out via transesophageal echocardiography. All procedures were performed under deep sedation or under general anesthesia (only when necessary, according to patient characteristics). Standard vascular access was via the right femoral vein. A decapolar diagnostic catheter (SJM Inquiry, Abbott) was placed into the coronary venous sinus (CS). For all procedures, independent of the used energy, minimal procedural endpoint was PVI confirmed by entrance-block after a waiting period of 20 min. Additional lesion sets were added upon the operator's discretion.

Following standard operating procedures, all index PVIs were performed with only one energy form (no RF touch-up ablation after CB-PVI). A standard to choose CB-based over RF-based PVI did not exist during the analyzed timeperiod. One only preference for CB- over RF-PVI may have occurred in highly comorbid patients to achieve shorter procedure times, and RF-PVI was rarely preferred in patients with renal disease to minimize exposure to contrast-dye.

Selective PV-angiography was regularly performed for both RF- and CB-procedures.

2.2.1 | RF-based index PVI

In RF-based index PVIs, CARTO 3 (80%; Biosense Webster), EnSite Velocity or Precision (15%; Abbott) or Rhythmia HDx (5%; Boston

Scientific) were used as 3D-mapping systems. Wide-antral circular ablation lesions over 60 s were created around the ipsilateral PVs with 40 watts at the anterior wall, 30 watts at the posterior wall and 25 watts at the LA roof.

2.2.2 | CB-based index PVI

CB-based index PVIs were performed using the second or third generation of the Medtronic Arctic Advance^{TM} (Arctic Front Advance^{TM}, Arctic Front Advance Pro^{TM}) cryoablation system. The corresponding Achieve™ and Achieve Advance™ mapping catheters were used for all CB-PVI procedures. PV-occlusion was routinely assessed via occlusion angiography in most cases and via KODEX-EPD's occlusion tool in few cases.[13] One freeze per PV up to 240 s was applied. Additional freeze cycles were applied upon operators' discretions with different strategies over the long period of index procedures performed between January 2015 and December 2021.

2.2.3 | Repeat ablations

All re-ablations were performed solely with RF energy and 3D-mapping. Reconnection of PVs, defined as lack of entrance block, was assessed via a multipolar, circular mapping catheter placed inside the PV ostium. All PVs showing reconnection were targeted for re-isolation via RF-ablation by closing identified gaps or by repeating wide-antral isolation of ipsilateral PVs in cases with large or multiple gaps. Re-isolation was confirmed as described before by entrance block.

In both index and repeat RF-procedures, additional lesions (beyond PVI), e.g., linear lesions, or left- or bi-atrial defragmentation were performed based on patients' individual substrates and disease patterns upon the operators' discretion.

2.3 | Data handling and statistical analyses

Variables are displayed as absolute numbers and percentages, medians with interquartile ranges (IQR), or means with standard deviation (SD) depending on distribution. Normality was assessed for all continuous variables using Shapiro-Wilk and Q-Q plots. Descriptive statistics were obtained for patient-specific details, medical history, and procedural parameters for PVI and re-ablation procedures. Reconnected PVs were described using absolute counts, relative risk reductions (RRR), and Odds ratios (OR) with 95% confidence intervals (CI). Chi-squared test was used to test reconnection rates between different groups. General linear modeling was used to analyze energy source effects on re-ablation characteristics (duration, fluoroscopy, energy). Multivariate logistic regression adjusted for patient- and index-procedure-related factors was performed to test PV-reconnection at first repeat ablation. For sensitivity analysis, Chi-square tests were repeated in subsets of procedures to investigate operator effects and multivariate ordinal regression was used to assess the effect of CB-based PVI adjusted for operator and procedure year. A second sensitivity analysis was conducted in a time-wise unselected data set (also containing all RF-PVI before the introduction of the cryoballoon) in which Chi-squared tests were repeated for reconnection patterns. A significance level of $p \leq .05$ was used. Python 3.10 with common data science packages was used for statistical analyses and graph plotting. Adobe InDesign and Illustrator CC were used to draw the graphical abstract and to compose figure panels.

3 | RESULTS

3.1 | Study cohort and index PVI

610 eligible patients (232 (38%) female, median age 67 [IQR: 57–74] years, 386 (63%) with non-paroxysmal AF at index PVI) underwent RF- ($n = 363$ (60%)) or CB-based ($n = 247$ (40%)) index PVI plus at least one re-ablation procedure. RF- and CB-patients were equally old (median age 66 [58,73] vs. 68 [57,74], $p = .377$), had a similar distribution of sex (36% vs. 42% females, $p = .186$) and rate of non-paroxysmal AF (65% vs. 61%, $p = .412$). Comorbidities were equally distributed between both groups with an exception for additional diagnosis of typical atrial flutter which was much more common in the RF-PVI group (21% vs. 5%, $p < .001$). Presence of a LCPV was found in 50 (8%) patients, thereof 20/247 (8%) in CB-PVI and 30/363 (8%) in the RF-PVI group without statistical differences between groups ($p = 1.000$).

CB-based index PVIs were performed with the second (104/247 (42%)) and third (143/247 (58%)) generation CB. Noncontact-force and contact-force catheters were used in 216/363 (60%) and 147/363 (40%) index RF-PVIs. Additional lesions sets (beyond PVI) at index procedure were more frequently observed in the RF-group: 61% received PVI alone, 24% had additional ablation of the cavotricuspid isthmus (CTI), and 15% received additional left- or biatrial defragmentation or substrate modification based on linear ablation and ablation of complex fractionated atrial electrograms (CFAE). In the CB-group, 8% received additional CTI-ablation (X^2 $p < .001$). Acute electrical PVI was achieved in all patients of both the CB- and RF-PVI group.

Further patient and procedural characteristics at baseline are summarized in Table 1.

3.2 | Characteristics of repeat procedures

Median time to first repeat ablation was 359 [204,738] days and was shorter in the CB-group (313 [189–653] days) compared to the RF-group (400 [220,827] days; $p = .001$). PV-reconnection at first re-ablation was found in 509/610 (83%) PVs, with 2.1 ± 1.3 reconnected PVs per patient. After CB-PVI, PV-reconnection was observed in

TABLE 1 Patient- and procedural characteristics of index pulmonary vein isolation (PVI) and repeat procedures, grouped by cryoballoon-based PVI (CB-PVI) or radiofrequency-based PVI (RF-PVI) at index procedure.

			Overall **610**	**CB-PVI** **247**	**RF-PVI** **363**	***p* value**
Baseline	Age at index PVI[†]		66.6 [57.4,73.5]	67.7 [56.6,74.0]	66.1 [57.7,73.3]	.377
	Sex (%)	Female	232 (38%)	102 (42%)	130 (36%)	.186
	Nonparoxysmal AF (%)		386 (63%)	151 (61%)	235 (65%)	.412
	Atrial flutter, typical (%)		87 (14%)	13 (5%)	74 (21%)	**<.001**
	LCPV (%)		50 (8%)	20 (8%)	30 (8%)	1.000
	Time to first re-ablation[†]	days	359 [204,738]	313 [189,653]	400 [220,827]	**.001**
	CHA_2DS_2-VASc-score[†]		3 [1,4]	2.5 [1,4]	3 [1,4]	.895
	Arterial hypertension		383 (63%)	147 (60%)	236 (65%)	.187
	Diabetes mellitus		55 (9%)	17 (7%)	38 (11%)	.168
	Heart failure (ICM/DCM)		96 (16%)	37 (15%)	59 (16%)	.750
	Coronary artery disease		127 (21%)	51 (21%)	76 (21%)	1.000
	Chronic kidney disease		74 (12%)	31 (13%)	43 (12%)	.897
	Hyperthyroidism		29 (5%)	13 (5%)	16 (4%)	.772
Index PVI	Procedure duration[†]	minutes	118 [85,150]	85 [72,112]	135 [110,165]	**<.001**
	Fluoroscopy duration[†]	minutes	14.2 [9.7,21.0]	16.8 [12.7,22.9]	12.6 [8.5,18.9]	**<.001**
	Contrast dye[†]	mL	45 [40,65]	60 [45,75]	45 [33,45]	**<.001**
	DAP[†]	$cGy*cm^2$	496 [314,877]	608 [391,1017]	441 [261,768]	**<.001**
	Lesion set – PVI – PVI + CTI – PVI + AL		451 (74%) 106 (17%) 53 (9%)	228 (92%) 19 (8%) 0 (0%)	223 (61%) 87 (24%) 53 (14%)	**<.001**
	Contact-force catheter			///	147 (41%)	
	Third generation cryoballoon			143 (58%)	///	
First repeat procedure	Procedure duration[†]	minutes	113 [85,148]	100 [81,130]	120 [90,158]	**<.001**
	Fluoroscopy duration[†]	minutes	13.2 [9.7,18.2]	12.8 [9.3,16.6]	13.8 [9.9,19.2]	.079
	Contrast dye[†]	mL	45 [30,50]	45 [30,50]	45 [35,50]	.784
	DAP[†]	$cGy*cm^2$	463 [285,755]	440 [266,683]	490 [307,799]	.052
	Total RF energy	kJ	37.9 (28.8)	35.5 (26.0)	39.5 (30.5)	.085
	PV-reconnection, *n* (%)		509 (83%)	202 (82%)	307 (85%)	.424
	Reconnected PVs[#]		2.1 (1.3)	1.9 (1.3)	2.2 (1.3)	**.005**
	AT occurrence		152 (25%)	50 (20%)	102 (28%)	**.035**
Second repeat procedure	Patients with second RABL		133 (22%)	49 (20%)	84 (23%)	
	Procedure duration[†]	minutes	120 [90,150]	108 [84,143]	128 [95,165]	**.041**
	Fluoroscopy duration[†]	minutes	13.9 [9.8,19.2]	12.5 [9.5,16.6]	14.9 [9.9,20.8]	.075
	Contrast dye[†]	mL	45 [30,55]	45 [30,60]	40 [30,50]	.399
	DAP[†]	$cGy*cm^2$	542 [343,797]	467 [311,717]	610 [350,860]	.155
	Total RF energy	kJ	39.7 (29.5)	34.6 (26.2)	42.7 (31.0)	.234
	PV-reconnection, *n* (%)		74 (56%)	24 (49%)	50 (60%)	.317
	Reconnected PVs[#]		1.2 (1.4)	1.0 (1.3)	1.4 (1.4)	.155

TABLE 1 (Continued)

	Overall 610	CB-PVI 247	RF-PVI 363	p value
AT occurrence	46 (35%)	14 (29%)	32 (38%)	.355

Abbreviations: AF, atrial fibrillation; AL, additional left-atrial lesions (including defragmentation, linear lesions, substrate modification); AT, atrial tachycardia; CB, cryoballoon ablation; DAP, dose-area-product; DCM, dilative cardiomyopathy; ICM, ischemic cardiomyopathy; LCPV, common ostium of the left pulmonary vein; PV, pulmonary vein; PVI, pulmonary vein isolation; RF, radiofrequency ablation.

[†]Data displayed as median and interquartile range [IQR] in brackets.

[#]Number of data displayed as means and (standard deviations) in brackets for scalar variables and absolute counts and (percentages) in brackets for countable variables, if not stated otherwise.

202/247 (82%) patients and after RF-PVI in 307/363 (85%; $p = .424$). The number of reconnected PVs was significantly lower after CB-PVI (1.9 ± 1.3 vs. 2.2 ± 1.3; $p = .005$). Details are specified in the subsequent chapter.

Out of the complete data set, 133/610 (22%) patients received a second repeat ablation procedure at our center (49/247 (20%) after CB-PVI vs. 84/363 (23%) after RF-PVI, $p = .384$). Patients that underwent a second repeat ablation procedure, compared to those who only underwent one first repeat ablation procedure, were much more likely to suffer from persistent AF (100/133 (75%) vs. 286/477 (60%), $p = .002$) and have a common ostium of the left PVs (18/133 (14%) vs. 32/477 (7%), $p = .018$). There were no differences in index ablation energy source (49/133 (37%) vs. 198/477 (42%) Cryo-based index PVI, $p = .384$).

PV-reconnection at second repeat ablation was observed in 74/133 (56%) procedures (first *vs.* second repeat ablation: $p < .001$), thereof 25 after CB- and 34 after RF-based index PVI (CB-RF vs. RF-RF $p = .317$), with a mean of 1.2 ± 1.4 reconncted PVs (CB-RF vs. RF-RF $p = .155$). PV-reconnection occurred less often at second (56%) compared to first (83%) repeat -ablation ($p < .001$). The number of reconnected PVs was 40% lower at second compared to first re-ablation ($p < .001$).

Both first and second repeat procedures were shorter following CB-PVI compared to RF-PVI. First repeat procedures were 20 min (median) shorter after CB- compared to RF-PVI (100 [81,130] minutes *vs.* 120 [90,158] minutes; $p < .001$). Second repeat procedures were also 20 min (median) shorter after CB-compared to RF-PVI (108 [84,143] minutes *vs.* 128 [95,165] minutes; $p = .041$). Fluoroscopy durations were similar between the CB-PVI and RF-PVI group at both first (CB-PVI: 12.8 [9.3,16.6] minutes; RF-PVI: 13.8 [9.9,19.2] minutes; $p = .079$) and second (CB-PVI: 12.5 [9.5,16.6] minutes; RF-PVI: 14.9 [9.9,20.8] minutes; $p = .075$) repeat procedures (Table 1; Supporting Information S1: Supplementary Figure 1). Both procedure duration and fluoroscopy duration were similar between first and second repeat ablations (Supporting Information S1: Supplementary Table 1).

Occurrence of atrial tachycardia (AT) during first repeat ablation was lower in patients after CB-PVI (20%) compared to patients after RF-PVI (28%; $p = .035$). At second repeat ablation, occurrence of AT was numerically but not significantly lower in patients after CB-ablation at index PVI (29%) versus patients after RF-based index PVI (38%; $p = .355$). AT occurred more frequently during second compared to first re-ablation (35% total at 2nd *vs.* 25% total at 1st re-ablation; $p < .001$). An adjusted, multivariate sub-analysis showed that the additional lesion set beyond PVI was predictive of AT occurrence at first repeat ablation procedure. The results of this sub-analysis are displayed in Supporting Information S1: Supplementary Table 2.

Other procedural characteristics like procedure duration (113 [85,148] minutes versus 120 [90,150] minutes, $p = .351$) and fluoroscopy duration (13.2 [9.7,18.2] minutes versus 13.9 [9.8,19.2] minutes, $p = .549$) were similar between first and second repeat ablations, respectively.

3.3 | Pulmonary vein reconnection patterns

Of 2390 sucessfully treated PVs at index PVI, 1291 (53%) were reconnected at first repeat ablation. Thereof, 465/968 (48%) were reconnected after CB-PVI which was less compared to 796/1422 (56%) reconnected PVs after RF-PVI (OR 0.73 [95%-CI 0.62-0.86], X^2 $p < .001$). This finding relates to a relative risk reduction (RRR) of 14%.

Reconnection was less frequently observed for the left-sided PVs (except for the LCPV) after CB-PVI: 91/227 (40%) LSPVs were reconnected after CB-PVI, and 175/333 (53%) LSPVs were reconnected after RF-PVI (OR: 0.60 [95% CI: 0.42–0.86], X^2 $p = .005$). Comparably, 98/227 (43%) LIPVs were reconnected after CB-PVI, and 177/333 (53%) LIPVs were reconnected after RF-PVI (OR 0.67 [95% CI: 0.47–0.95], X^2 $p = .026$). The highest reconnection rate was observed for the LCPV in 13/20 (65%) patients after CB-PVI and 23/30 (77%) patients after RF-PVI (CB vs. RF X^2 $p = .563$), followed by the RIPV in normal anatomy with 140/247 (57%) patients after CB-PVI and 214/363 (59%) patients after RF-PVI (CB vs. RF: X^2 $p = .635$). Individual PV data for all first and second repeat ablations are provided in Table 2 and visualized in Figure 1. Patient flows from index to first and from first to second repeat ablation are visualized in Figure 2.

The number of reconnected PVs was analyzed in patients with normal PV anatomy (excluding LCPV patients) at first repeat ablation: After CB-PVI, 43/227 (19%) patients did not show any PV-reconnection, 47 (21%) patients showed reconnection of

TABLE 2 Individual reconnection rates per pulmonary vein (PV) at first and second repeat ablation.

	PV	Group	Isolated n	Isolated %	Reconnected n	Reconnected %	p value CB versus RF	Odds ratio 95% confidence interval
Repeat ablation 1	**LSPV**	CB-PVI	136	60%	91	40%	**.005**	**0.60 [0.42–0.86]**
		RF-PVI	158	47%	175	53%		
	LIPV	CB-PVI	129	57%	98	43%	**.026**	**0.67 [0.47–0.95]**
		RF-PVI	156	47%	177	53%		
	RIPV	CB-PVI	107	43%	140	57%	.635	0.91 [0.65–1.28]
		RF-PVI	149	41%	214	59%		
	RSPV	CB-PVI	124	50%	123	50%	.094	0.75 [0.53–1.05]
		RF-PVI	156	43%	207	57%		
	LCPV	CB-PVI	7	35%	13	65%	.563	0.57 [0.14–2.38]
		RF-PVI	7	23%	23	77%		
Repeat ablation 2	**LSPV**	CB-PVI	35	81%	8	19%	.136	0.46 [0.16–1.22]
		RF-PVI	48	67%	24	33%		
	LIPV	CB-PVI	35	81%	8	19%	.136	0.46 [0.16–1.22]
		RF-PVI	48	67%	24	33%		
	RIPV	CB-PVI	32	65%	17	35%	.837	0.86 [0.38–1.91]
		RF-PVI	52	62%	32	38%		
	RSPV	CB-PVI	35	71%	14	29%	.430	0.68 [0.29–1.55]
		RF-PVI	53	63%	31	37%		
	LCPV	CB-PVI	3	50%	3	50%	.864	2.00 [0.17–22.39]
		RF-PVI	8	67%	4	33%		

Note: All numerical counts and percentages are displayed, together with results of Chi-squared tests and Odds ratios. Cryoballoon pulmonary vein isolation (CB-PVI) was associated with fewer reconnections of the left pulmonary veins at first repeat ablation compared to radiofrequency pulmonary vein isolation (RF-PVI). Bold vaules indicate significant *p*-values below a pre-specified alpha = .05.

1 PV, 69 (30%) of 2 PVs, 27 (12%) of 3 PVs and 41 (18%). After RF-PVI, this distribution shifted towards multiple reconnected PVs with 54/333 (16%) without reconnection, 41 (12%) with 1 reconnected PV, 97 (29%) with 2, 60 (18%) with 3 and 81 (24%) with 4 reconnected PVs (RF vs. CB at first repeat ablation: X^2 $p = .015$).

3.4 | Additional lesions at repeat ablation

Ablation of AT was more frequently performed in patients after RF-PVI compared to the CB-PVI group (28% *vs.* 20%; X^2 $p = .035$). However, additional linear lesions (28% *vs.* 23%; X^2 $p = .243$) and substrate modification (including defragmentation; 27% *vs.* 26%; X^2 $p = .834$) were both numerically performed more frequently after CB-PVI, although not statistically different.

De-novo ablation of the CTI was performed in 23% after CB- and 20% after RF-PVI (X^2 $p = .288$), and re-ablation of the CTI was performed more frequently after RF-PVI in 13% of patients compared to 4% after CB-PVI (X^2 $p < .001$). This is most likely due to the low number of CTI-ablations in the CB-group at index PVI (Figure 3A). Repeating this analysis in the subgroup of patients without any reconnected PVs at first repeat procedure, no significant differences were observed (Figure 3B).

3.5 | Contact-force and cryoballoon-generation

The outcome PV-reconnection at first repeat procedure was assessed within the CB-PVI group splitted by second and third cryoballoon generation. PV-reconnection was observed in 92/104 (88%) after second generation CB-PVI and in 110/143 (77%) after third generation CB-PVI (OR 0.44 [95% CI: 0.19–0.93], X^2 $p = .031$). In the RF-PVI subgroup, contact force ablation was not associated with fewer PV-reconnections (OR 0.72 [95% CI: 0.37–1.35], X^2 $p = .347$): 128/147 (87%) patients had PV-reconnection following contact-force RF-PVI while 179/216 (83%) had PV-reconnection following conventional RF-PVI.

There was no difference in patients undergoing a second repeat ablation procedure (n = 133) compared to those who only underwent

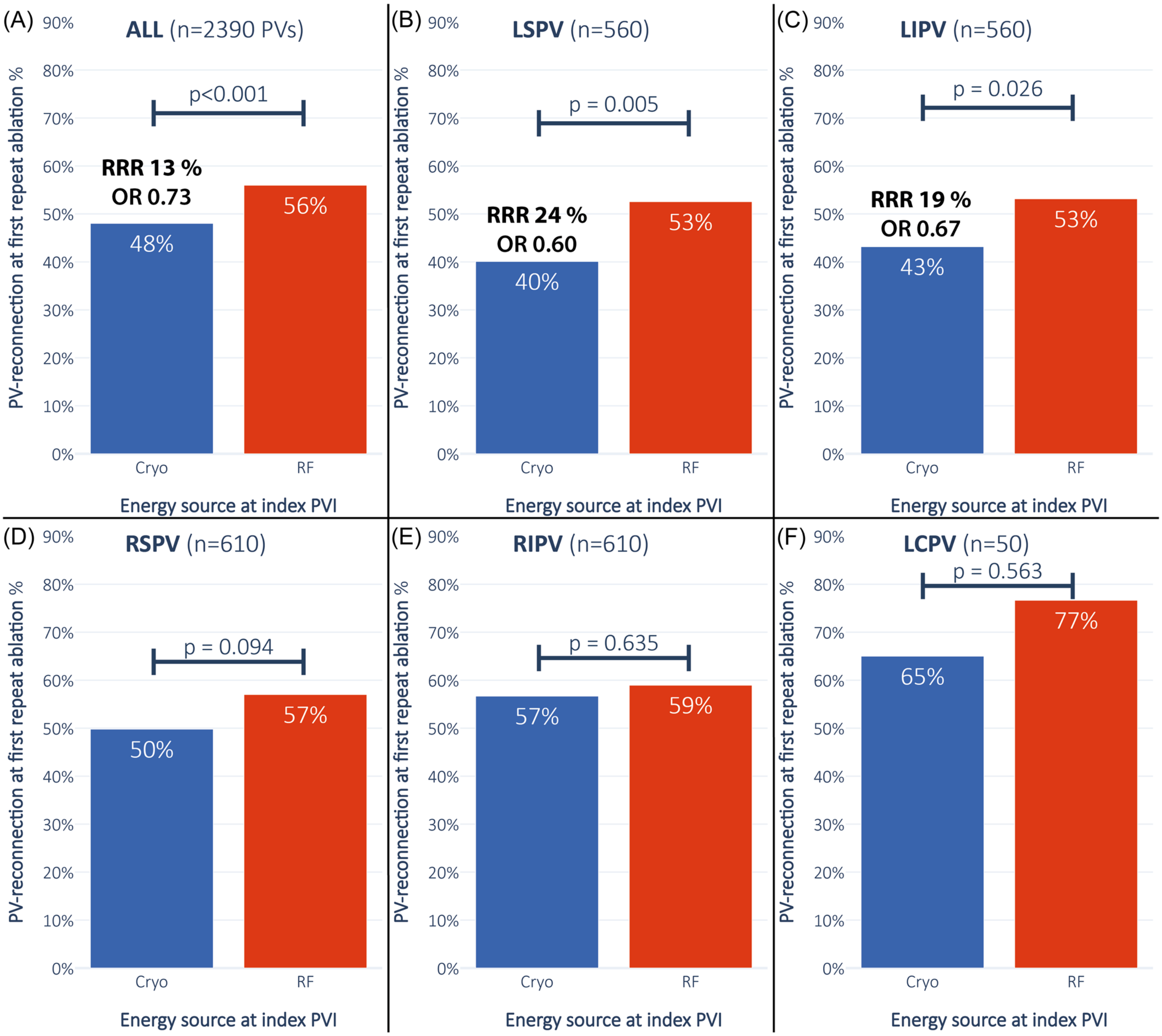

FIGURE 1 Percentage of reconnected pulmonary veins (PV) at first repeat ablation grouped by energy source at index pulmonary vein isolation (PVI). Chi-square tests showed fewer PV-reconnections after cryoballoon-based (Cryo) PVI compared to radiofrequency- (RF)-PVI in the overall analysis (relative risk reduction (RRR) 5%, Odds ratio (OR) 0.81 [95% confidence interval (CI): 0.70–0.93), and for the left superior PV (LSPV: RRR 16%, OR: 0.68 [95% CI: 0.50–0.92], $p = .013$).

a first ablation procedure (n = 477) for usage of third-generation CB at index CB-PVI (25/49 (51%) vs. 118/198 (60%), $p = .354$) nor usage of contact-force sensing catheters in index RF-PVI (33/84 (39%) vs. 114/279 (41%), $p = .896$).

3.6 | Clinical and procedural predictors of PV-reconnection

Multivariate adjusted regression analysis was performed to test effects of clinical (age, sex, presence of LCPV, nonparoxysmal AF, arterial hypertension, diabetes mellitus, heart failure, coronary artery disease, valvular heart disease, chronic kidney disease and hyperthyroidism) and procedural (total duration, fluoroscopy duration, interaction term of contact force, interaction term of third cryoballoon-generation) predictors along with the grouping variable CB- versus RF-PVI on the outcome number of reconnected PVs at first repeat procedure. Results are shown in Table 3 and Figure 4. The following factors predicted PV-reconnection: RF-PVI (OR: 1.39 [95% CI: 1.03–1.89]; $p = .034$), female sex (OR 1.48 [95% CI: 1.15–1.89]; $p = .002$), 10 year increase of age (OR 1.17 [95% CI: 1.10–1.24]; $p < .001$) and longer durations of index procedures (per 10 min: OR: 1.10 [95% CI: 1.06–1.13]; $p < .001$).

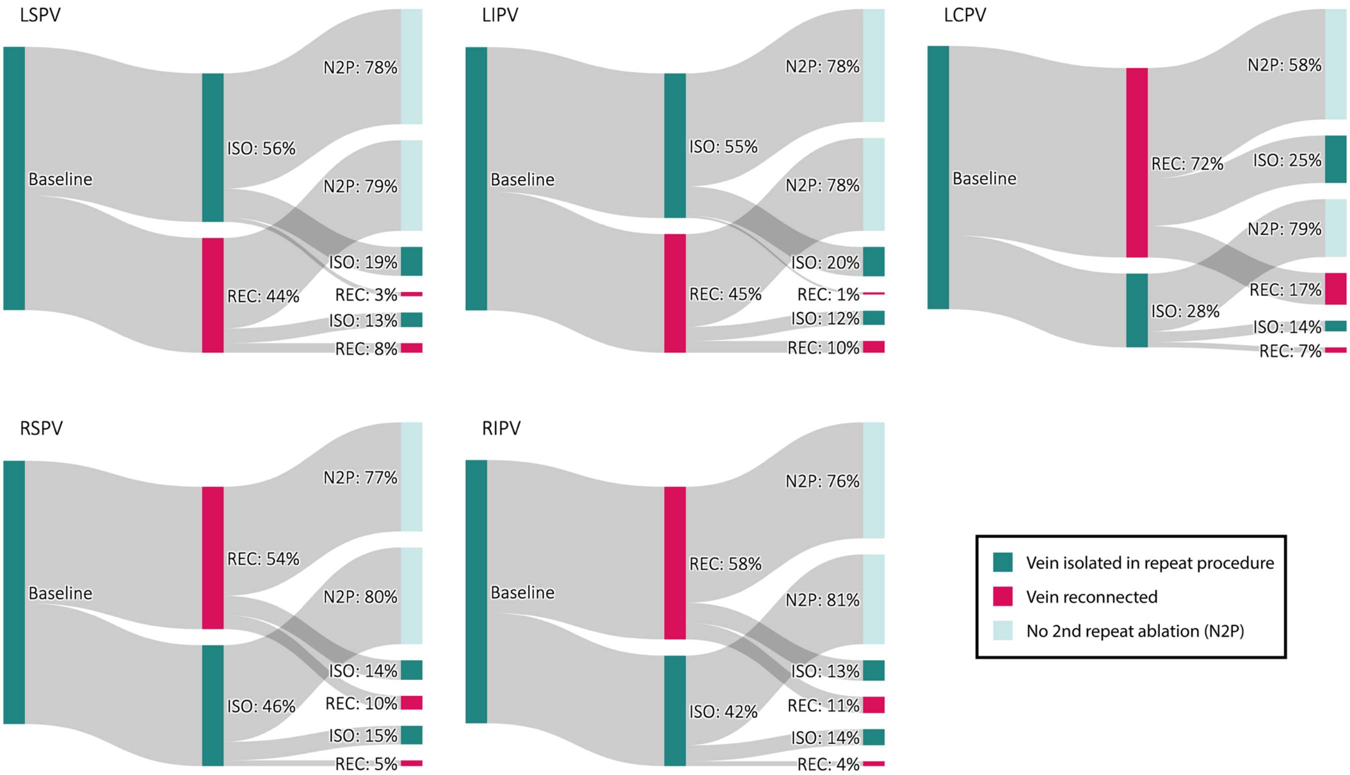

FIGURE 2 Patient flow-diagram, plotted for each individual pulmonary vein (PV). A relevant proportion of pulmonary veins (PV) is reconnected (REC) at second re-ablation although isolated (ISO) at first re-ablation (LSPV and LIPV 3%, RSPV 9%, RIPV 11%). Approximately 3/4 patients did not undergo a second repeat procedure at our center.

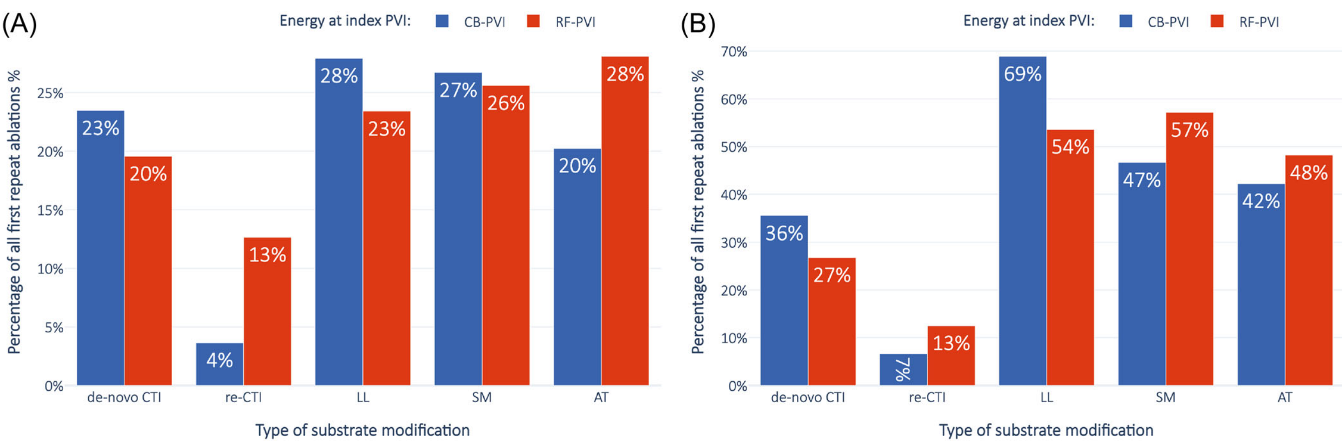

FIGURE 3 Additional lesion set at first repeat ablation in the overall data set (A) and the subset of patients with all pulmonary veins found isolated at first repeat ablation (B). AT, occurrence and/or ablation of atrial tachycardia; CB-PVI, cryoballoon-based pulmonary vein isolation; CTI, cavotricuspid isthmus; LL, linear lesions; RF-PVI, radiofrequency-based pulmonary vein isolation; SM, substrate modification.

3.7 | Sensitivity analyses

For sensitivity analysis, the effect of the operator performing the index PVI on the number of reconnected PVs at first repeat ablation was analyzed in 401 index procedures in patients with normal PV-anatomy performed by experienced operators *(defined as having performed more than 50 index and/or repeat procedures within this data set)*. Three of four experienced operators performed between 22% and 28% of the index PVIs using the CB while 1/4 operator used the CB in 66% of index PVIs (Supporting Information S1: Supplementary Figure 2A). The number of reconnected PVs after CB-PVI was lower for all four operators (Supporting Information S1: Supplementary Figure 2B) which was statistically significant for two operators (operator #2: OR 0.69 [95% CI: 0.47–1.00], p = .047 and operator #1: OR 0.61 [95% CI: 0.41–0.89], p = .010). Multivariate ordinal regression was used to assess the effect of CB-based PVI adjusted for

TABLE 3 Multivariate generalized linear model to assess the influence of clinical and index procedure related factors on the outcome number of reconnected pulmonary veins (PV) at first repeat procedure, aside from the effect of cryoballoon-(CB)-based index pulmonary vein isolation (PVI).

		95% Confidence Interval		
	Odds ratio	Lower boundary	Upper boundary	corrected *p* value
Female sex	**1.48**	**1.15**	**1.89**	**.002**
Valvular heart disease	1.46	0.98	2.18	.065
RF-based index PVI	**1.39**	**1.03**	**1.89**	**.034**
Diabetes mellitus	1.38	0.92	2.07	.123
Heart failure	1.18	0.81	1.72	.379
Age (per 10 year increase)	**1.17**	**1.10**	**1.24**	**<.001**
Longer index procedure (per 10 min increase)	**1.10**	**1.06**	**1.13**	**<.001**
Hyperthyroidism	1.06	0.62	1.78	.839
Common ostium of the left PV	1.04	0.69	1.56	.852
Fluoroscopy duration at index PVI	1.01	0.99	1.03	.172
Arterial hypertension	0.99	0.77	1.27	.949
Chronic kidney disease	0.99	0.69	1.42	.942
Coronary artery disease	0.97	0.69	1.36	.845
Nonparoxysmal AF	0.86	0.68	1.10	.227

Bold values indicate significant *p*-values below a pre-specified alpha = .05.

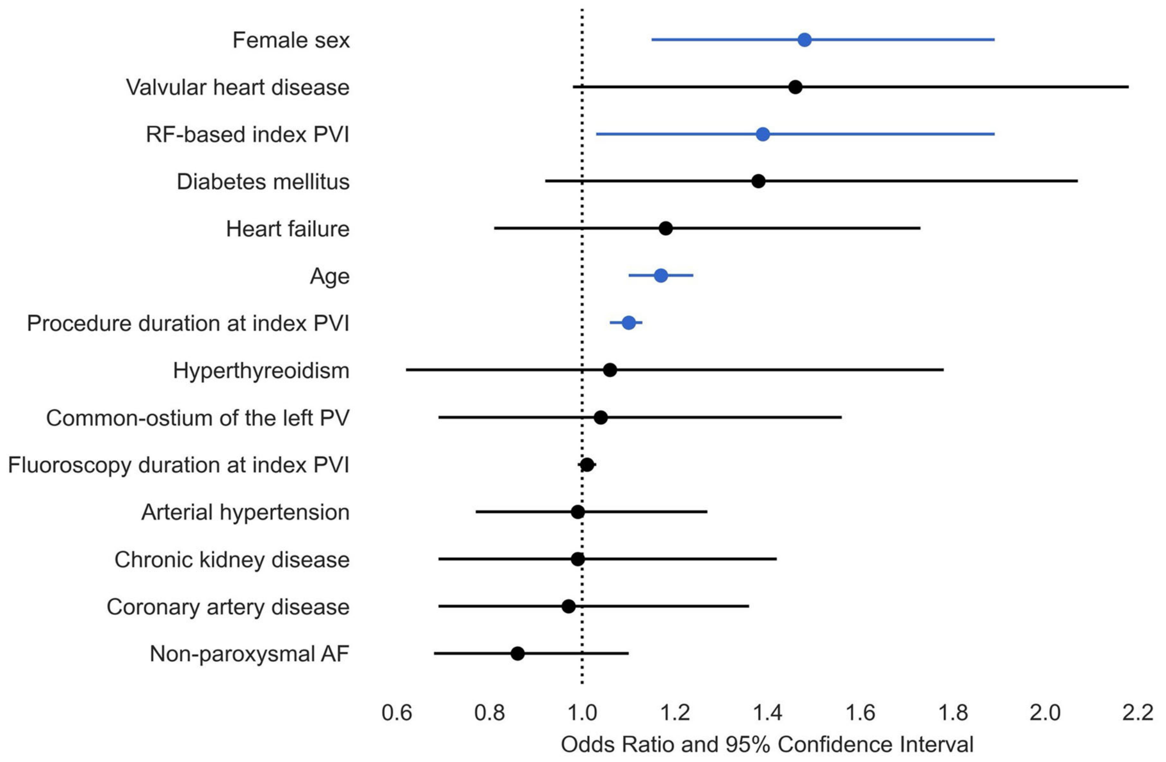

FIGURE 4 Forest plot, showing the results of a multivariate generalized linear regression assessing the influence of clinical and index procedure related factors on the outcome number of reconnected pulmonary veins (PV) at first repeat procedure, aside from the beneficial effect of cryoballoon-(CB)-based index pulmonary vein isolation (PVI). Relevant identified predictors were female sex (OR 1.48 [95% CI: 1.15–1.89], $p = .002$), RF-based index procedures (OR 1.39 [95% CI: 1.03–1.89], $p = .034$), older age (per 10 year increase: OR: 1.17 [95% CI: 1.10–1.24], $p < .001$) and longer index procedures (per 10 min increase: OR: 1.10 [95% CI: 1.06–1.13], $p < .001$).

experienced operator and year of procedure. The effect of CB-PVI was significant across this adjusted sensitivity analysis (OR: 0.72 [95% CI: 0.58–0.90], $p = .004$, Supporting Information S1: Supplementary Table 3).

A second sensitivity analysis was performed regarding PV-reconnection patterns in an unselected data set of all available patients (also including RF-based index PVI before the introduction of the CB) undergoing both index PVI and first repeat procedure at our center. In this larger data set of 1072 patients (825/1072 (77%) RF-PVI; baseline and procedural characteristics shown in Supporting Information S1: Supplementary Table 4), CB-PVI was also favorable with 465/968 (48%) reconnected PVs following CB-PVI but 1727/3246 (53%) reconnected PVs following RF-PVI (OR: 0.81 [95% CI: 0.70–0.94]; $p = .005$). In the individual PV analysis, reconnection of the LSPV was reduced following CB-PVI (OR: 0.68 [95% CI: 0.50–0.93]; $p = .016$). Complete analysis results are shown in Supporting Information S1: Supplementary Table 5.

4 | DISCUSSION

This study analyzed findings of repeat AF ablation procedures using semi-automated, manually validated, querying of a large, single-center medical records and ablation database containing 14,314 procedures within the analyzed timeframe. With a homogenous data set of 610 included patients, this study is–to our knowledge–the largest one comparing PV-reconnection patterns after index CB- versus RF-PVI.

The main findings are:

- First, PV-reconnection of at least one PV is found in the vast majority of patients (83%) at first repeat procedures following index PVI for AF. This number decreases in second repeat ablations to 56%.
- Second, CB-based index PVI was superior to RF-based index PVI for durable PVI, especially of the left PVs, namely the left superior and the left inferior PV. This finding was validated in two sensitivity analyses.
- Third, CB-based index PVI is associated with fewer atrial tachycardia occurrences at first repeat ablation and shorter procedure times at first repeat ablation.
- Fourth, RF-based index PVI, female sex, older age and longer index procedures were predictive of the number of reconnected PVs at first repeat ablation among multiple tested clinical and procedure related predictors.

The study has several strengths: It is performed in a large data set with minimized selection and investigator bias by semi-automatic procedure selection and data extraction. As the patient cohort started with the introduction of the CB at our center, it also included the learning curve associated with the device which supports the finding of CB-superiority over RF-based PVI (short learning curve and/or strong(er) effect of the CB). The patient cohort represents a typical collective of AF patients undergoing index PVI with a typical and equally distributed prevalence of comorbidities. It contains all thermal ablation systems that are currently established worldwide, with 40.5% contact-force procedures in the RF-PVI group and most procedures in the CB-PVI group performed with the latest generation CB. Since this study only included patients with both index and at least first repeat ablation performed at our center, adherence to our center standards can be assumed.

With a moderate median CHA_2DS_2-VASc-Score of 3, the distribution of comorbidities was similar between both analyzed groups. However, median time to first repeat ablation was significantly shorter for patients in the CB-PVI group. This may reflect a general shift towards shorter times to re-ablation during the analyzed timeframe which was accompanied by a transition from initially many RF- and few CB-based PVIs to an increasing share of CB- and decreasing share of RF-PVI towards the end of the observed timeframe.

PV-reconnection was found in the vast majority of first repeat procedures (83%). This finding is undisputed[14,15] and drives technology advancements in this clinical field, including pulsed field ablation.[16] The current study shows significantly fewer PVs with electrical reconnection following CB-PVI, which was mainly driven by less reconnection of the left-sided PVs. This finding is in line with prior observations made in a subanalysis of 89 patients from the FIRE AND ICE-trial[9] who underwent re-ablation due to arrhythmia recurrence. Another retrospective study focusing on PV-reconnection comparing CB- and RF-PVI found less frequent reconnection of PVs overall and of the LSPV in individual PV analysis following CB-PVI.[10] However, the study did not report fewer reconnections of the LIPV.[10] It also noted first repeat procedures to be shorter following index CB-PVI and that less extensive ablation was required compared to RF-based index PVI. This is in line with our results, including the sensitivity data set (Supporting Information S1: Supplementary Table 4), suggesting superior lesion formation capacities of the CB for the left PVs. The RIPV appears to be the most challenging PV when targeted by the CB, which is also in line with further studies.[17,18] However, there are two smaller studies (n = 53 and n = 69), designed to compare different ablation strategies for index PVI but not ablation modalities, which reported opposing results to those found in the current study.[8,19] Follow-up in one study was comparatively short[19] but may influence the observed pattern as PV-reconnection may occur or lead to arrhythmia recurrence only after longer follow-up periods.[20]

The here and elsewhere observed differences in PV-reconnection patterns are likely the result of inherent strengths and limitations of the ablation modalities. For durable PVI with RF-ablation, a continuous line of effective ablation lesions is essential. There are several anatomical localizations,[3] in which the creation of a transmural lesion is challenging, for example, the ridge between the left-sided PVs and the left atrial appendage. In contrast, the compliant CB can easily be placed in a stable position at the PV-ostia allowing for effective energy transfer less dependent on anatomical properties. Additionally, ice formation during ablation attaches the balloon to the tissue, providing optimal energy transfer during freeze-cycles. These advantages in energy transfer and device stability likely explain the significantly better results of the CB for isolation of the LSPV. The difficulty to induce durable isolation of the RIPV with CB-ablation is plausibly caused by limitations of steerability and access to this specific PV with the large balloon device. Balloon contact to the inferior aspect of the RIPV can be difficult to achieve, especially in patients with a low insertion level of the RIPV or after a high and/or anterior transseptal puncture.

The current study found a significantly higher incidence of AT at first repeat ablation following RF-PVI compared to CB-PVI (28% vs. 20%). However, a multivariate sub-analysis found the additional lesion set performed during RF-based PVIs to be a more relevant predictor compared to the ablation modality (Supporting Information S1: Supplementary Table 2). Occurrence of AT following first-time AF ablation is a common finding. A considerable proportion of ATs is gap-related and of macro-reentrant type.[21] The incidence of AT during first repeat ablation procedure following PVI was high compared to a study following up on 238 CB-PVI (incidence 11%)[22] and another study which compared AT occurrence following 415 RF- versus 215 CB-PVI procedures (incidence 8%, thereof 4% left atrial AT).[23] The latter study did not find a difference between CB- and RF-PVI procedures which is in line with our results, considering our sub-analysis which excluded RF-PVI as an independent predictor of incident AT. The higher number of ATs observed in our study can be explained by counting not only clinical apparent but also intraprocedural, spontaneous or procedure-related AT occurrences.

Multivariate analysis performed in our data set identified mainly female sex and RF-based index PVI, as well as age and longer index procedures as clinical and/or procedure-related factors predisposing to PV-reconnection (Table 3). This is in line with other studies following up on CB-PVI procedures which identified female sex as a predictor for AF and/or AT recurrence.[24,25] Aryana et al. identified only CB-ablation and procedure duration as significant predictors for PV-reconnection.[10] All studies including ours share the result that durable PVI is mostly dependent on technical aspects rather than patient characteristics. As sex is a fixed factor, the observation made in our study has only limited impact on management.

4.1 | Limitations

Due to its retrospective design, this trial can neither link PV-reconnection to clinical AF recurrence nor report the latter which is why survival analyses were omitted. We also abstained from performing time-to-event analyses since PV-reconnection may occur before symptomatic recurrence of AF while only the latter would have triggered re-ablation. The present study has a purely technical focus, evaluating the effect of the ablation modality at index PVI on PV-reconnection rates and patterns. Therefore, and in line with our observation that patient characteristics were not predictive of PV-reconnection, a selection bias of the patients themselves would only be of subordinate importance. Patients were regularly scheduled for re-ablation at our center upon symptomatic AF recurrence and patients not consenting to repeat procedures can be assumed to be equally distributed between both groups. Operator-associated bias, typically associated with monocentric studies, has only minimal effects in the current study as a conducted sensitivity analysis excluded the performing operator as a confounder of the results. Our second sensitivity analysis in an unselected data set containing all available procedures additionally excluded a selection bias by limiting the main data set to the introduction of the CB. The data set is limited to the reported level of detail, therefore not able to report on precise gap locations. Also, we cannot link procedural characteristics (RF energy, fluoroscopy usage, etc.) at repeat ablations directly with the PV re-isolation part of the repeat procedures which could be of interest as well, although not the primary focus of this analysis. The present data set with a long observation period inherently reflects temporal trends and developments in PVI technology, including the introduction of contact force technology and third-generation CB. Therefore, transferability of the results to contemporary cohorts applying only these new techniques is limited.

5 | CONCLUSION

Electrical reconnection of at least one PV following CB- and RF-index PVIs was found in 83% of patients undergoing first repeat procedures. PV-reconnection was most frequently observed for the right PVs and in patients with a left-common PV. Fewer PVs were reconnected following index PVIs using the CB which was driven by fewer reconnections of the left-sided PVs. Repeat procedures were also shorter following CB-based index PVI. AT occurrence at repeat procedures was frequently associated with RF-procedures and the additional lesion set beyond PVI performed in RF-PVI. Patient specific characteristics, except for female sex and older age, were not predictive for the number of reconnected PVs. These hypothesis-finding observations call for external validation; they may also help operators to focus on difficult anatomical aspects, e. g. the inferior PVs.

AUTHOR CONTRIBUTIONS
Obergassel J. has received travel grants from Abbott and research grants from German Heart Foundation, the University of Hamburg and the German Federal Ministry of Education and Research (BMBF). Rottner L. has received travel grants from EPD Solutions/Philips (KODEX-EPD). Lemoine M.D. received a travel grant biosense webster, a research grant from Farapulse and was supported by the Research Promotion Fund of the Faculty of Medicine Hamburg. Reißmann B. received speaker's honoraria and travel grants from Medtronic. Meyer C. has received speaker honoraria and provided consulting for Abbott, Biosense Webster, Biotronik, and Boston Scientific. Willems S. received research grants from Boston Scientific, as well as speaker and consulting fees from Boston Scientific, Böhringer Ingelheim, Abbott, Bristol Myers Squibb, Bayer, Daiichi, Medtronic. Kirchhof P. received research support for basic,

translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in AF, and has received honoraria from several such companies in the past, but not in the last 3 years. P. Kirchhof is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). Rillig A. received travel grants from Biosense, Medtronic, St. Jude Medical, Cardiofocus, EP Solutions, Ablamap and EPD Solutions/Philips (KODEX-EPD) and lecture and consultant fees from St. Jude Medical, Medtronic, Biosense, Cardiofocus, Novartis and Boehringer Ingelheim, Galaxy medical. Metzner A. received speaker's honoraria and travel grants from Medtronic, Biosense Webster, Bayer, Boehringer Ingelheim, EPD Solutions/Philips (KODEX-EPD) and Cardiofocus. The other authors do not have conflicts of interests to disclose.

ACKNOWLEDGMENTS

The authors thank Dr. Amelie Ohlrogge for drawing vector images of the left atrium with normal and pulmonary vein anatomy and anatomic variants which were used in the graphical abstract. Besides, the authors thank all physicians and assistant personnel at the University Heart and Vascular Center Hamburg who were involved in the electrophysiological procedures analyzed in this study. This study did not receive specific funding determined for this analysis from funding agencies in the public, commercial or not-for-profit sectors. JO has received travel grants from Abbott and research grants from German Heart Foundation, the University of Hamburg and the German Federal Ministry of Education and Research (BMBF). LR has received travel grants from EPD Solutions/Philips (KODEX-EPD). MDL received a travel grant biosense webster, a research grant from Farapulse and was supported by the Research Promotion Fund of the Faculty of Medicine Hamburg. BR received speaker's honoraria and travel grants from Medtronic. CM has received speaker honoraria and provided consulting for Abbott, Biosense Webster, Biotronik, and Boston Scientific. SW received research grants from Boston Scientific, as well as speaker and consulting fees from Boston Scientific, Böhringer Ingelheim, Abbott, Bristol Myers Squibb, Bayer, Daiichi, Medtronic. PK received research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in AF, and has received honoraria from several such companies in the past, but not in the last 3 years. P. Kirchhof is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). AR received travel grants from Biosense, Medtronic, St. Jude Medical, Cardiofocus, EP Solutions, Ablamap and EPD Solutions/Philips (KODEX-EPD) and lecture and consultant fees from St. Jude Medical, Medtronic, Biosense, Cardiofocus, Novartis and Boehringer Ingelheim, Galaxy medical. AM received speaker's honoraria and travel grants from Medtronic, Biosense Webster, Bayer, Boehringer Ingelheim, EPD Solutions/Philips (KODEX-EPD) and Cardiofocus. Open Access funding enabled and organized by Projekt DEAL.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Obergassel J, Nies M, Taraba S, et al. Pulmonary vein reconnection and repeat ablation characteristics following cryoballoon-compared to radiofrequency-based pulmonary vein isolation. *J Cardiovasc Electrophysiol*. 2024;1-13. doi:10.1111/jce.16343