

# Effect of cryoballoon and radiofrequency ablation for pulmonary vein isolation on left atrial function in patients with nonvalvular paroxysmal atrial fibrillation: A prospective randomized study (Cryo-LAEF study)

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## Abstract

**Background:** Isolation of the pulmonary veins (PVI) has become a mainstay in atrial fibrillation (AFib) therapy. Lesions in left atrial tissue lead to scar formation and this may affect left atrial function.

**Methods:** Patients with paroxysmal AFib were randomly assigned in a 1:2 allocation scheme to radiofrequency (RF) ablation or cryoballoon. Real-time three-dimensional echocardiography was performed (under sinus rhythm in all cases) before ablation and at 1 and 3 months to evaluate the left atrial functional indices. The primary outcome measure was change in left atrial ejection fraction (LAEF) at 1 month.

**Results:** 120 patients were randomized (80 to cryoballoon, 40 to RF). The absolute change in LAEF at 1 month was 4.0 (Q1-Q3, -0.1 to 7.6)% in the cryoballoon group and -0.8 (Q1-Q3, -1.9 to 0.9)% in the RF group ( $P < 0.001$  for the comparison between groups). At 3 months, the corresponding changes were 6.7 (Q1-Q3, 3.4-11.2)% and 0.7 (Q1-Q3, -0.7 to 3.5)%, respectively ( $P < 0.001$ ). Overall, the rate of patients with lower LAEF at 3 months compared to baseline was 2.5% in the cryoballoon group and 32.5% in the RF group ( $P < 0.001$ ). AFib recurrence rate at 6 months was higher in patients with decreased LAEF (odds ratio, 6.2; 95% confidence interval, 2.0-19.5;  $P = 0.002$ ).

**Conclusion:** The Cryo-LAEF study prospectively compared the effects of RF and cryoballoon ablation on left atrial function. Both at 1 and 3 months postablation, LAEF was either improved or stable in both ablation groups.

## KEYWORDS

ablation, atrial fibrillation, cryoablation, emptying fraction, left atrial ejection fraction

## 1 | INTRODUCTION

Atrial fibrillation (AFib) is the most common sustained arrhythmia and a significant source of morbidity and mortality.<sup>1</sup> Radiofrequency (RF) ablation of AFib, which initially tried to mimic the surgical interventions of atrial compartmentalization (eg, the Maze-Cox procedure),<sup>2</sup> evolved, following the seminal publication of Haïssaguerre et al<sup>3</sup> on the triggering role of pulmonary veins (PVs),<sup>3</sup> into essentially a technique of electrical isolation of the PVs, which is the mainstay in current AFib ablation therapy.<sup>4</sup> However, creation of continuous transmural RF lesions in the PV antrum is often technically challenging. This led to alternative modalities of ablation, including cryoablation,<sup>5</sup> utilizing alternative energy sources and different ways of applying energy to the atrial myocardium.

Delivering a large number of RF lesions to left atrial (LA) tissue leads to scar formation (that is, after all, the mechanism of creating an electrical barrier)<sup>6,7</sup> and this may conceivably affect LA function. A number of studies have indeed shown deterioration in LA ejection fraction (LAEF) following ablation for PV isolation.<sup>8,9</sup> However, not all studies have provided similar results,<sup>10,11</sup> and the question of whether PV isolation results in deterioration of LA function remains a controversial issue. Especially in light of recent data from the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial<sup>12</sup> which were largely neutral as to the efficacy of ablation in terms of clinical endpoints, a better understanding of its pathophysiological effects appears to be in order.

To our knowledge, this is the first randomized, and largest, study to prospectively evaluate the effect of both cryoballoon and RF ablation on LA functional indices. The primary objective of the present study was to describe the effects of RF and cryoballoon PV isolation (PVI) on LA function and in a head-to-head comparison of the postablation LAEF between RF PV antral isolation, with a contact-force-sensing catheter system, and second-generation cryoballoon ablation.

## 2 | METHODS

### 2.1 | Population

Consecutive patients with paroxysmal AFib, slated for PVI, were randomly assigned to RF or cryoballoon ablation. Inclusion criteria included at least two symptomatic AFib episodes within the last 12 months (either self-terminating within 7 days or cardioverted, medically or electrically, in less than 48 hours), failure of at least one class I or III antiarrhythmic to prevent AFib episodes, and age 40 to 80 years. Patients with a history of previous LA ablation procedure, LA diameter more than 50 mm on the transthoracic echocardiogram (parasternal long axis view), known primary electrical heart disease (eg, Brugada syndrome), presence of atrial thrombus, prosthetic valve at any position, moderate/severe mitral stenosis, severe mitral regurgitation, active infectious disease or malignancy, moderate or severe hepatic impairment (Child-Pugh class B or C), severe renal failure (estimated glomerular filtration rate <20 mL/min per 1.73 m<sup>2</sup>), participation in a different research

protocol (current or within 1 year), inability or unwillingness to adhere to standard treatment or to provide consent.

### 2.2 | Ethics

The study protocol was approved by the respective Ethics Committees (Scientific Boards) of the participating centers. All recruited patients had an indication for catheter ablation treatment of AFib, according to current guidelines at the time of protocol approval (Class I and IIa indications for ablation treatment of AFib in the European Society of Cardiology guidelines—2012 update)<sup>13</sup> and local insurance-provider rules. All patients provided written informed consent. The study protocol was registered in a clinical trials database (ClinicalTrials.gov/NCT02611869).

### 2.3 | Interventions, investigations, and follow-up

The study involved two interventions, cryoballoon and RF ablation, to which patients will be randomly assigned (in a 2:1 allocation scheme). Each patient's randomization was known only to the operator of the ablation procedure. All personnel involved in patient follow-up and echo data analysis were blinded to patient randomization. Repeat ablation was not allowed over the 6-month follow-up of the study. Antiarrhythmic drugs were allowed, on the discretion of the attending physicians, over the 2-month blanking period postablation, and were then discontinued. Patients were followed for 6 months with hospital visits, telephone contacts, and 24-hour ambulatory electrocardiographic recordings.

Antral PV isolation was performed in all patients randomized to RF ablation, without additional ablation of extrapulmonary sites, with the exception of individuals with documented typical atrial flutter. An irrigated radiofrequency ablation catheter with real-time contact-force sensing (Thermocool SmartTouch; Biosense Webster, Diegem, Belgium) was used to perform ablation, with the aid of electro-anatomical mapping (Carto 3; Biosense Webster), following a transseptal puncture. Pulmonary vein potentials were recorded with a circular mapping catheter (Lasso NAV eco; Biosense Webster) before, during, and following antral ablation (the default strategy was to create two ablation lines, around the two ipsilateral PVs, unless LA anatomy dictated another approach). The endpoint of the ablation procedure was entrance and exit block in all PVs. A waiting time of 20 to 30 minutes was observed after initial pulmonary vein isolation and further ablation was performed in case of reconnection between the veins and the atrium.

For the cryoablation procedure, a 28-mm cryoballoon (Arctic Front Advance Cardiac CryoAblation Catheter; Medtronic, Minneapolis, MN) was used. The cryoballoon catheter was introduced into the LA following a single transseptal puncture, through a 12-F FlexCath steerable sheath, constantly flushed with heparinized saline. A circular mapping catheter (Achieve, Medtronic) was advanced through the cryoballoon to the PV orifice and positioned as proximally as possible inside the vessel to record the PV potentials at baseline and monitor the isolation

procedure in real time. The cryoballoon was inflated and advanced to the ostium of each PV. The quality of vascular occlusion was ascertained by injection of diluted contrast material into the PV. Once the best occlusion was obtained, cryothermal energy was applied for 240 seconds, as recommended by the manufacturer. If no PV signals were recorded in a vein the time of energy delivery was reduced to 180 seconds. Before ablation of the right-sided PVs, a quadripolar electrode catheter was positioned in the superior vena cava to constantly pace the right phrenic nerve at a 2-second cycle length during freezing. In case of cessation or weakening of diaphragmatic contraction, freezing was immediately discontinued.

Real-time three-dimensional (3D) echocardiography (RT3DE) was performed before the ablation procedure and at 1 and 3 months postablation, on iE33 machines (Philips Medical Systems, Bothell, Washington) equipped with X3, a fully sampled matrix transducer. Apical full-volume data sets were obtained during end-expiratory apnea within one breath hold. The RT3DE data sets were stored digitally and quantitative analyses were performed off-line at a core echo laboratory by personnel blinded as to each patient's treatment allocation and as to the timing of data acquisition (all RT3DE analyses were performed by two experienced echocardiologists, simultaneously by consensus; approximately 20% of data sets were analyzed twice, unbeknown to the reviewers, to check for within-reviewer repeatability of measurements). Quantification of LA volumes was performed using a semiautomated contour-tracing algorithm, marking five atrial reference points: four at the anterior, inferior, lateral, and septal parts of the atrial dome and one at the level of the mitral annulus. Volumes were measured at three time points during the cardiac cycle: (a) L<sub>max</sub> at end-systole, just before mitral valve opening, (b) L<sub>min</sub> at end-diastole, just before mitral valve closure; and (c) L<sub>apreA</sub> obtained at the time of the P wave on the surface electrocardiogram. All echo studies were performed with patients in sinus rhythm. If a patient was in AFib, the study was rescheduled 48 hours later. If the patient was still in AFib, cardioversion was performed and the RT3DE study was rescheduled for 5 days later.

LA functional quantification was assessed by calculating the following indices:

- Left atrial ejection fraction:  $LAEF = ((L_{max} - L_{min})/L_{max}) \times 100\%$
- Active atrial-emptying fraction:  $LActive = ((L_{apreA} - L_{min})/L_{apreA}) \times 100\%$
- Passive atrial-emptying fraction:  $Lpassive = ((L_{max} - L_{apreA})/L_{max}) \times 100\%$
- Atrial expansion index:  $LReservoir = ((L_{max} - L_{min})/L_{min}) \times 100\%$ .

Patients returned for two visits after the ablation procedure (at 1 and 3 months) for RT3DE, symptom review, assessment for potential complications, clinical and electrocardiographic evaluation, and a 24-hour Holter recording.

## 2.4 | Outcome measures

The primary study endpoint was the change in LAEF (LAEF after ablation minus LAEF before ablation) at 1 month. Secondary outcome measures were the change in LAEF at 3 months, postablation LAEF, change in active atrial-emptying fraction, change in passive atrial-emptying fraction, and change in atrial expansion index.

## 2.5 | Statistical analysis

A sample size of 120 subjects (with a 2:1 allocation scheme to cryoballoon and RF ablation, respectively) provided 83% probability (power, 0.83) of detecting an absolute difference of 5 percentage units in LAEF change between groups (assuming a standard deviation of the difference of 8 percentage units, taken from the study of Wylie et al<sup>9</sup>), with an expected type I error rate of 5% (alpha level, 0.05). Continuous variables are summarized as median (Q1-Q3) and compared using nonparametric tests. Categorical variables were summarized as counts and percentages and compared using the  $\chi^2$  or Fisher exact tests (if the generated contingency matrices contain cells with expected values <5). A multivariable binary logistic regression model was constructed to adjust the association of reduced LAEF with recurrence for potential confounders.  $P < 0.05$  were considered as indicating statistical significance. In the particular case of testing for significant differences in the indices of atrial function between baseline and 1 and 3 months (pairwise in-group comparisons and between-group comparisons; 28 tests in total), the Dunn-Šidák correction was applied to account for multiple comparisons and the limit of statistical significance was set at <0.002).

## 3 | RESULTS

One hundred and twenty patients with drug-refractory paroxysmal AFib were randomized to cryoballoon (80 patients) or RF ablation (40 patients). The two groups were balanced in terms of epidemiologic profile and AFib characteristics (Table 1). The overall rate of acute confirmed PV isolation was 98.7% (315 of 319 veins) in the cryoballoon group (in one patient the right inferior PV converged to a single orifice with the right superior PV) and 98.1% (157 of 160 veins) in the RF group. Total procedure duration was 80 (70 to 99) and 100 min (92 to 108), respectively ( $P < 0.001$ ). The six-month arrhythmia recurrence rate (2 months blanking period) was 23.8% in the cryoballoon group compared with 26.3% in the RF group ( $P = 0.762$ ; Mantel-Haenszel odds ratio, 1.15; 95% confidence interval, 0.47-2.78). In 71 RT3DE studies which were analyzed twice (to check for repeatability), the Pearson correlation index was 0.894 (the median of differences between the two measurements was not statistically different from zero,  $P$  for the Wilcoxon signed rank test, 0.329).

LA diameter, as measured in the parasternal long axis view on two-dimensional echocardiography, was 40 mm (36-43) in the cryoballoon group and 41.5 (38-44) mm in the RF group ( $P = 0.690$ ). At 1 month, the corresponding measurements were 41 (39-43) and 42.5 (40-44) mm, respectively ( $P = 0.285$ ), and at 3 months 41 (38-43)

**TABLE 1** Study population characteristics

	Cryoballoon group (N = 80)	RF group (N = 40)	P
Age (range), y	61 (55-67)	58 (53-66)	0.191
BSA (interquartile range), m <sup>2</sup>	1.99 (1.81-2.16)	1.95 (1.84-2.02)	0.145
BMI (interquartile range), kg/m <sup>2</sup>	28.4 (25.2-31.0)	30.6 (24.2-34.8)	0.072
Coronary artery disease, n (%)	6 (7.5)	2 (5.0)	0.717
Diabetes mellitus, n (%)	9 (11.3)	6 (15.0)	0.558
Hypertension, n (%)	41 (51.3)	18 (45.0)	0.519
Smoking (ever), n (%)	44 (55.0)	17 (42.5)	0.197
Dyslipidemia, n (%)	32 (40.0)	17 (42.5)	0.793
Heart failure, n (%)	2 (2.5)	2 (5.0)	0.600
Duration of AFib Hx (interquartile range), y	5 (2-10)	2 (0.5-10)	0.069
AFib episodes in past year (interquartile range), N	10 (3-30)	11 (9-45)	0.083
Worst EHRA class in past year (interquartile range), N	2 (1.25-3)	2 (2-3)	0.683
CHA <sub>2</sub> DS <sub>2</sub> VASc score	1 (1, 2)	1 (1, 2)	0.847
Distribution, n (%)			
0	14 (17.5)	6 (15.0)	0.877
1	28 (35.0)	15 (37.5)	
2	20 (25.0)	10 (25.0)	
3	13 (16.3)	4 (10.0)	
4	1 (1.3)	5 (12.5)	
5	4 (5.0)	0 (0.0)	
Left ventricular ejection fraction (interquartile range), n (%)	60 (54-65)	60 (55-65)	0.884
LA diameter at baseline (interquartile range), mm	40.0 (36.0-43.0)	41.5 (38.0-43.8)	0.690
Total fluoro time (interquartile range), min	28.2 (24.4-37.3)	30.5 (29.0-32.8)	0.110
Dose area product (interquartile range), Gy-cm <sup>2</sup>	71.0 (46.6-138.4)	103.9 (80.3-126.0)	0.091
Troponin I 4-6 h post (interquartile range), pg/mL	7933 (4179-11 020)	9302 (6520-11 060)	0.155
Troponin I 16-24 h post (interquartile range), pg/mL	6326 (3545-7509)	8550 (6296-9973)	0.003
C-reactive protein 4-6 h post (interquartile range), mg/mL	3.16 (1.8-5.13)	3.35 (1.45-9.44)	0.623
C-reactive protein 16-24 h post (interquartile range), mg/mL	10.9 (6.8-19.3)	13.0 (10.0-23.0)	0.009

Abbreviations: AFib, atrial fibrillation; BMI, body-mass index; BSA, body-surface area; EHRA, European Heart Rhythm association; RF, radiofrequency.

and 41 (39-43) mm, respectively ( $P = 0.634$ ). The pairwise difference between 3 months and baseline was nonsignificant in both groups ( $P = 0.192$  and  $0.904$ , respectively).

Baseline values of LA function indices, derived from RT3DE measurements, and their evolution at 1 and 3 months postablation are summarized in Table 2. Atrial expansion index (LA reservoir) was significantly increased at 1 and 3 months ( $P < 0.001$  for both) compared to baseline in the cryoballoon group. LA active and passive emptying increased numerically (the  $P$  values did not exceed the more stringent margin of  $< 0.002$ , set to account for multiple comparisons;  $P = 0.002$  and  $0.014$ , respectively) in the cryoballoon group at 3 months. In the RF group, marginal variations were observed in these secondary measures of atrial function (see Table 2).

LAEF (RT3DE-derived) was higher at 1 month and at 3 months compared with baseline ( $P < 0.001$  for both) in the cryoballoon group, while in the RF group there was a small increase at 3 months ( $P = 0.016$ ) (Figure 1A). The primary outcome measure, namely the absolute change in LAEF at 1 month was  $4.0$  ( $-0.1$  to  $7.6$ )% in

the cryoballoon group and  $-0.8$  ( $-1.9$  to  $0.9$ )% in the RF group ( $P < 0.001$ ). At 3 months, the corresponding changes were  $6.7$  ( $3.4$ - $11.2$ )% and  $0.7$  ( $-0.7$  to  $3.5$ )%, respectively ( $P < 0.001$ ). Overall, the rate of patients with lower LAEF at 3 months compared with baseline was  $2.5$ % in the cryoballoon group and  $32.5$ % in the RF group ( $P < 0.001$ ) (Figure 1B). As stated in Section 2, all echocardiographic studies were performed with patients in sinus rhythm (if a patient was in AFib, the study was rescheduled). Rescheduling for LAEF measurement after sinus rhythm restoration on follow-up occurred in  $8.8$ % of patients in the cryoballoon group and in  $10$ % of patients in the RF group ( $P = 0.823$ ). The median absolute change in LAEF at 3 months was  $5.3$  ( $-1.3$  to  $16.3$ )% in patients who had to reschedule vs  $3.6$  ( $0.8$ - $7.9$ )% in those who did not ( $P = 0.800$ ), indicating that this procedure was not a source of systematic bias in LAEF evaluation.

Of interest, AFib recurrence rate at 6 months was higher in patients with decreased LAEF at 3 months compared with baseline as opposed to those with unchanged or increased LAEF (Mantel-Haenszel

**TABLE 2** Left atrial functional indices measured by 3D transthoracic echocardiography

	Baseline	1 mo	3 mo	P values	
				1-mo BL	3-mo BL
Atrial expansion index, %					
Cryoballoon	66 (45-84)	77 (57-107)	91 (69-116)	<b>&lt;0.001</b>	<b>&lt;0.001</b>
RF	74 (56-90)	74 (64-88)	77 (64-85)	0.702	0.242
P	0.267	0.344	0.003		
Active atrial-emptying fraction, %					
Cryoballoon	22 (15-28)	22 (16-30)	27 (23-33)	0.219	0.002
RF	23 (18-28)	21 (19-22)	25 (22-27)	0.017	0.011
P	0.496	0.556	0.121		
Passive atrial-emptying fraction, %					
Cryoballoon	26 (17-34)	29 (25-38)	32 (24-36)	0.009	0.014
RF	27 (22-33)	29 (26-32)	26 (24-27)	0.060	0.081
P	0.465	0.408	<b>&lt;0.001</b>		
Left atrial ejection fraction, %					
Cryoballoon	43 (31-46)	44 (37-53)	49 (42-54)	<b>&lt;0.001</b>	<b>&lt;0.001</b>
RF	42 (36-46)	41 (37-46)	43 (40-45)	0.086	0.016
P	0.775	0.045	<b>&lt;0.001</b>		

Abbreviations: 3D, three-dimensional; BL, baseline; RF, radiofrequency.

To account for multiple comparisons, the Šidák correction was applied and the threshold for statistical significance was set at less than 0.002 for the above-summarized tests. Significant results are printed in bold.

odds ratio, 6.2; 95% confidence interval, 2.0-19.5;  $P = 0.002$ ) (Figure 2). After adjustment for age, gender and procedure, reduced LAEF was associated with a hazard ratio of 13.9 (95% confidence interval, 2.9-66.5;  $P = 0.001$ ) for recurrence. On the contrary, baseline LAEF was not associated with recurrence (43 [34-48]% in patients with recurrence vs 42 [35-46]% in those without;  $P = 0.663$ ).

## 4 | DISCUSSION

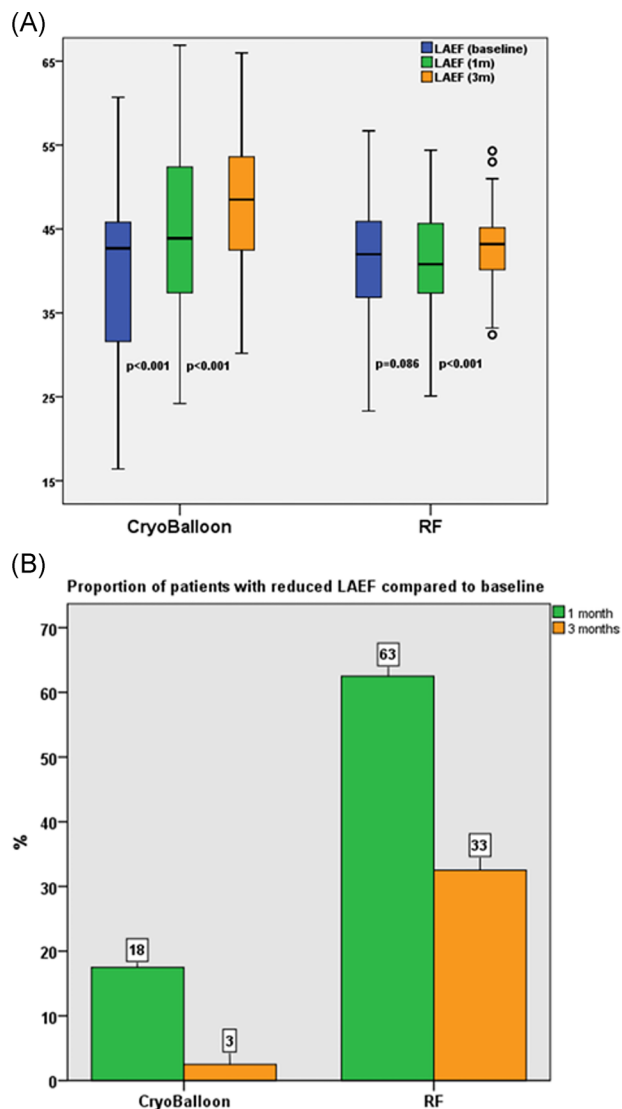
The Cryo-LAEF study prospectively evaluated—by means of RT3DE—and compared, in a randomized fashion, the effects of RF and cryoballoon ablation for paroxysmal AFib on LA function. Both at one (primary study endpoint) and 3 months postablation, LAEF was either improved or stable in both ablation groups. The improvement was greater in the cryoballoon group.

Ablation-related left atrial scar tissue formation could be best described as a “frenemy.” It is an unavoidable “friend” under the scope of pulmonary vein isolation and an “enemy” in terms of potential effects on LA contractile function, given that the role of the LA surpasses that of a mere conduit.<sup>14</sup> The discussion of whether the overall benefits (reverse left atrial remodeling) from sinus rhythm maintenance (or AFib control and, thus, reduced arrhythmia burden) compensate for the adverse effects of LA scarring is, therefore, a valid one, along with the question of whether a different technical approach could enhance the former and limit the latter. In the present study, the association between sinus rhythm maintenance and higher LAEF suggests that improved atrial function results from lowered AFib burden. Reverse causation (ie, higher LAEF resulting in less AFib) cannot be excluded, and it is actually possible that a “virtuous cycle” comes into play: the idea that ablation interrupts the sequelae of AFib on the atrial myocardium by reducing AFib burden, which in turn

allows for reversal of remodeling and functional recovery of the atrium, resulting in less propensity for AFib recurrences appears to be a plausible explanation for the observations of this study.

Available evidence regarding myocardial necrosis induced by catheter ablation for AFib is controversial. The majority of available evidence shows that myocardial necrosis is more extensive after cryoballoon,<sup>15-18</sup> although there are studies reporting the opposite<sup>19</sup> or present comparable findings<sup>20</sup> with the two techniques. In our cohort, troponin levels tended to be lower in the cryoballoon group. Another hypothesis that may be taken into account is that pulmonary vein isolation may lead to loss of their contractile capability, and this could cause blood regurgitation from the LA to the veins during atrial systole, which might result in a decrease in atrial systolic volume and improvement in LAEF.<sup>11</sup> One should also not discount the possibility that there may be interindividual differences between operators in terms of the extent of the atrial myocardial area which is electrically isolated and may, thus, be functionally impaired. A wider—that is, more distal to the pulmonary vein ostia—zone of ablation may be more prone to cause functional impairment of the LA. However, since we did not map the cryoballoon set of lesions in the context of the present study, our data do not allow for direct comparisons between the two modalities as far as the extent of the ablated myocardium is concerned and, as a result, do not provide further insight in this matter.

An interesting finding of the present study (which highlights the importance of studying the different modalities of ablation which may work in different ways) was that while more patients had reduced LAEF in the RF group and lower LAEF was associated with more recurrence, the overall recurrence rate was similar in the two groups. This was due to the fact that while in the cryoballoon group recurrence rate in patients without LAEF reduction at 3 months was 23.1% (close to the overall recurrence rate and to what can be considered as “expected”), the corresponding recurrence rate in the

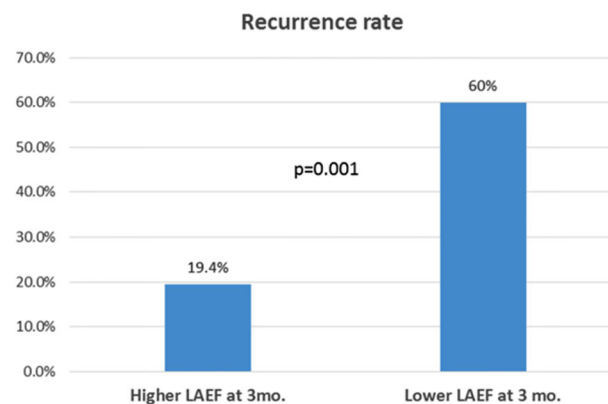


**FIGURE 1** A, Left atrial ejection fraction at baseline, 1 and 3 months in the two ablation groups. The indicated *P* values correspond to pairwise in-group comparisons. The thick horizontal lines correspond to the median, the boxes to the interquartile range and the whiskers to the range, bar outliers, which are depicted as circles. B, Proportion of patients with reduced left atrial ejection fraction compared with baseline at 1 and 3 months in the two groups

RF group in patients without reduced LAEF (which were proportionally less than in the cryoballoon group) was as low as 8.0%. In short, when the RF procedure achieved PV isolation without reducing the LAEF, it was more “effective” (in terms of recurrence) compared to the cryoballoon procedure, which however resulted less frequently in reduced LAEF. These opposing effects resulted in balanced outcomes between procedures.

#### 4.1 | LAEF significance as an endpoint

While LA function or volume are not taken into account in traditional clinical risk scores for thromboembolism, there is pathophysiological evidence that an impaired LAEF in the setting of high LA volumes may



**FIGURE 2** Six-month recurrence rates in patients with reduced and increased left atrial ejection fraction at 3 months compared with baseline. LAEF, left atrial ejection fraction

promote blood stasis and hence thrombus formation.<sup>21</sup> LAEF has been shown to predict acute embolism in AFib patients independently of age and sex.<sup>22</sup> Further insight in the significance of echo-derived parameters of LA and ventricular function is expected from the ongoing “EACVI AFib Echo Europe Registry,” which aims to correlate such indices with thromboembolic risk in patients with AFib.<sup>23</sup> Moreover, LAEF has been associated with AFib ablation outcomes and baseline LAEF has been reported to independently predict LAEF improvement<sup>21,24</sup> or AFib recurrences<sup>25–28</sup> after RF ablation.

As far the choice of the imaging approach is concerned, in conventional two-dimensional echocardiography<sup>29</sup> for LA volume evaluation, either the disc-summation (Simpson’s rule) or the area-length biplane algorithms are used. However, both rely on geometrical assumptions on LA morphology and are reliant on imaging plane positioning and angulation and subject to manual tracing (boundary recognition) errors.<sup>30</sup> Conversely, RT3DE overcomes geometric limitations and is reported to be more reliable in comparison with two-dimensional echocardiography in terms of accuracy,<sup>31,32</sup> and prognostic significance<sup>33–35</sup> for LA volume quantification. Additionally, LA functional aspects, which have incremental prognostic value over the routinely measured maximal LA volume,<sup>36,37</sup> require time-consuming two-dimensional measurements, while they may be quite effortlessly evaluated with RT3DE.<sup>30</sup> This has been acknowledged in the most recent (2015) recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging<sup>29</sup> for cardiac chamber quantification. Moreover, it is noted that RT3DE volumes are typically greater than those measured with two-dimensional echocardiography.<sup>29</sup>

#### 4.2 | Prior studies evaluating LAEF after pulmonary vein isolation

Current data regarding left atrial function, as expressed by LAEF, after catheter ablation are conflicting. It is noteworthy that two-dimensional echocardiography,<sup>21,38–40</sup> RT3DE,<sup>10,41</sup> computed tomography<sup>8,24,39,42</sup> and cardiac magnetic resonance<sup>9,11</sup> have all been utilized in studies for this purpose. LAEF preservation,<sup>10,11,41</sup>

deterioration<sup>8,9,40,42</sup> or improvement<sup>21,24,38,39</sup> in distinct subgroups (based on baseline atrial function or on AFib recurrence) after pulmonary vein isolation have been reported. The intrinsic dissimilarities of different imaging approaches along with potential methodological issues (for instance, heart rhythm at the time of measurement acquisition) may be responsible for the contradictory findings.<sup>21</sup> Remarkably, most of these studies used relatively small sample sizes. Finally, only one study, to the best of our knowledge, has evaluated the effects of cryoablation.<sup>43</sup>

### 4.3 | Limitations

The population selected for this study was a fairly healthy population with good LA function; it is not clear whether the same results would apply to different AFib patient subsets. Other LA function parameters, such as strain and strain rates were not assessed. Furthermore, we were not able to demonstrate a direct link between the level of delivered energy and LAEF changes. The assessment of the functional status of the left atrium is based on indices which are not unequivocal measures of functional integrity. To put it simply, LAEF, irrespective of the method used to evaluate it, is not what ejection fraction is for the left ventricle, especially as a prognostic marker. Still, existing evidence suggests that LA function is a parameter with significant prognostic value for a number of endpoints (as outlined above).

## 5 | CONCLUSION

The present study is, to our knowledge, the first one to provide prospective randomized data on the effect of both cryoballoon and RF ablation on LA functional indices. The results are quite reassuring, showing that both techniques either improve or preserve LAEF in the midterm.

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