The International Journal of Cardiovascular Imaging (2024) 40:2271–2281
https://doi.org/10.1007/s10554-024-03218-4

ORIGINAL PAPER

Comprehensive analysis of recurrence factors in cryoballoon AF ablation: integrating clinical, biomarkers, and echocardiographic parameters

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Received: 16 April 2024 / Accepted: 5 August 2024 / Published online: 16 August 2024

Abstract

Atrial fibrillation (AF) poses substantial challenges in cardiovascular diseases, impacting patient health and economic burdens. Understanding the mechanical effects of AF on the left atrium (LA) and assessing the influence of treatment modalities on LA functions are critical. This study aims to assess the efficacy of echocardiographic and biochemical parameters in predicting AF recurrence following second generation cryoballoon ablation (CB-2). Ninety-two patients with symptomatic AF, treated with CB-2 at Istanbul University-Cerrahpaşa, Faculty of Medicine, Department of Cardiology, were prospectively examined from January 2021 to July 2023. The study endeavors to develop a predictive model for AF recurrence, investigating the relationship between echocardiographic measurements and serum biomarkers with recurrence. The follow-up duration for echocardiographic assessments and biochemical analyses was systematically documented. The study revealed a significant enhancement in LA mechanical functions during echocardiographic follow-ups three months post-procedure. Specifically, LA strain parameters emerged as significant predictors of recurrence (LAsr: 95%CI 1.004–1.246, $p=0.047$; LAsct: 95%CI 1.040–1.750, $p=0.024$). Biochemical analyses demonstrated a correlation between elevated PRO-BNP levels and an increased risk of recurrence (95%CI 1.000–1.003, $p=0.012$). Moreover, specific biomarkers such as MYBPHL, which demonstrated increased levels post-procedure, were deemed indicative of atrial damage, suggesting potential additional atrial substrate modification beyond PVI. Consequently, improvements in LA function post-cryoballoon ablation and biochemical markers have surfaced as potential indicators for predicting AF recurrence. This study elucidates the effectiveness of CB-2 in treating AF and its impact on LA functions. Notably, LA strain measurements and PRO-BNP levels have emerged as reliable indicators for predicting recurrence. Beyond clinical implications, our research establishes a foundation for a deeper understanding of the role of CB-2 in AF management and factors associated with recurrence.

Keywords Atrial fibrillation · Cryoballoon · Echocardiography · Biomarker · Recurrence

Abbreviations

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
AT	Atrial tachycardia
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentry tachycardia
BMI	Body mass index
BNP	Brain natriuretic peptide
CT	Computed Tomography
CB-2	2nd generation cryoballoon
CFAEs	complex fractionated atrial electrograms
CRP	C-reactive protein

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DOACs	Direct oral anticoagulants
DM	Diabetes Mellitus
EHRA	European Heart Rhythm Association
ECG	Electrocardiogram
EMD	Electromechanical Delay
HBA	Hot Balloon Ablation
HLD	Hyperlipidemia
HTN	Hypertension
ICD	Implantable cardioverter-defibrillator
CAD	Coronary Artery Disease
LA	Left atrium
LAA	Left atrial appendage
LAscd	Left atrial conduit strain
LAsct	Left atrial contractile strain
LAsr	Left atrial reservoir strain
LAVI	Left atrial volume index
LV	Left ventricle
MRI	Magnetic resonance imaging
MYBPHL	Myosin binding H like protein
PAF	Paroxysmal atrial fibrillation
PIIINP	N terminal procollagen type 3 propeptide
PVI	Pulmonary vein isolation
RF	Radiofrequency
SVC	Superior Vena Cava
CVA	Cerebrovascular Accident
TSP	Transseptal puncture
TRV	Tricuspid regurgitation velocity

Introduction

Atrial fibrillation (AF) is associated not only with increased mortality and morbidity but also places a significant burdens on healthcare systems worldwide, currently affecting 2–4% of adults. While age remains the most crucial risk factor, hypertension, diabetes mellitus (DM), heart failure, coronary artery disease, chronic kidney disease, obesity, and obstructive sleep apnea are also noteworthy contributors. AF, through various pathophysiological mechanisms, leads to left atrial enlargement, dysfunction, and fibrosis [1].

Besides being one of the primary causes of an enlarged left atrium (LA) and mechanical dysfunction, AF disrupts the overall mechanics of the heart. Mechanical remodeling, in addition to reducing atrial contractility, imposes increased stress on the atrial myocardium [2]. Restoring normal sinus rhythm is a crucial step in treating AF, with studies demonstrating the positive effects of rhythm control on the mechanical functions of the LA [3]. Pulmonary vein isolation (PVI) is an accepted invasive treatment for AF, and the "FIRE AND ICE" study indicates that cryoballoon ablation (CB-2) is not inferior to radiofrequency (RF)-PVI ablation in terms of efficacy and safety [4]. CB-2 has demonstrated compellingly positive clinical outcomes, boasting a high procedure success ratio and a short procedure time [5–8]. Moreover, it is emphasized that the chosen ablation method may impact mechanical dysfunction in the LA [9].

There are numerous studies assessing the effects of RF-PVI modality on LA function in AF patients [10, 11]. Particularly in the early stages following RF ablation, it has been demonstrated that the mechanical function of the LA is compromised in PAF patients, using echocardiographic methods, including cardiac MRI and Doppler parameters [12–14]. Despite previous studies evaluating the impact of RF ablation on LA function, there is currently no study in the literature assessing the early changes in LA function after CB-2 procedure and the impact of these changes on the recurrence of AF.

While various models have been developed to predict AF recurrence, establishing the superiority of one model over another remains uncertain. Some studies indicate that, beyond echocardiographic parameters, several serum biomarkers are associated with AF recurrence. Biomarkers such as hs-CRP, ANP, and N-terminal pro-collagen type III propeptide, implicated in pathogenesis of AF and reflective of inflammation, fibrosis, and mechanical remodeling, have demonstrated predictive value for recurrence following RF-PVI procedures. However, a gap exists in the current literatüre regarding their predictive efficacy in the context of CB-2 [15–17]. While there is a suggestion that the biomarker Human Myosin Binding Protein H-like (MYBPHL) could serve as a precise and reliable indicator for predicting atrial myocardial damage after cryoablation or RF ablation, a comprehensive study demonstrating its early post-ablation association with recurrence is lacking. Presently, no established model exists for predicting AF recurrence after cryoablation [18].

The primary endpoint of our study is to develop a novel prediction model for anticipating AF recurrence after CB-2. This entails integrating clinical data, biomarkers, and echocardiographic parameters, including Doppler and strain methods, along with procedure-related information. The implementation of this innovative prediction model will facilitate vigilant monitoring of patient groups with a high risk of recurrence in the early post-cryoablation period, enabling intisified medical treatments and ultimately improving the long-term outcomes of ablation. The secondary endpoint of our study includes evaluating the impact of the CB-2 procedure on LA functions and detecting atrial damage as a surrogate marker of additional atrial substrate modification following the ablation process using biochemical methods.

Methods

Study design and participants

The study included 92 patients (73 with paroxysmal AF, 19 with persistent AF) who underwent CB-2 due to symptomatic AF at the Department of Cardiology, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, between January 2021 and July 2023. The study was designed as a single-center, prospective clinical study. Paroxysmal atrial fibrillation (PAF) was defined as AF that spontaneously terminates or with intervention within 7 days of onset. Persistent atrial fibrillation was defined as the group AF that persists for more than 7 days and is terminated after 7th day with either medical or electrical cardioversion. Exclusion criteria comprised patients with left atrial thrombus, those in a non-sinus rhythm during the procedure, uncontrolled thyroid dysfunction, contraindications to anticoagulation, pregnancy, a history of previous AF ablation, severe valvular disease, and a left atrial size greater than 60 mm. The severity of symptoms was documented using the European Heart Rhythm Association (EHRA) score. Informed consent was obtained from each patient before the procedure. The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the local Ethics Committee.

Study protocol

Preprocedural assessment and management

All patients underwent transesophageal echocardiography and baseline echocardiographic measurements on the morning of the procedural day. Additional imaging was not applied to the patients. In those using vitamin K, anticoagulation was continued during the procedure, aiming for an INR value between 2 and 3. Of the 88 patients treated with new oral anticoagulants (NOACs), 40 were on apixaban, 30 on rivaroxaban, 13 on dabigatran, and 5 on edoxaban. In patients taking NOACs twice a day with a 12-hour interval, the last dose of anticoagulation was skipped before the procedure. In contrast, treatment was not interrupted for patients taking NOACs once a day. Oral anticoagulation was not administered on the day of the procedure. NOAC treatment was continued with the same dose the day after the procedure in all patients.

Procedural management

All procedures were conducted under deep sedation using midazolam, fentanyl, and propofol. Before the transseptal puncture (TSP), a coronary sinus catheter was positioned within the coronary sinus through the left femoral vein. A single TSP was performed via the right femoral vein under fluoroscopic guidance using the modified Brockenbrough technique and an 8 F transseptal sheath (Preface Guiding Sheath, Biosense Webster, Johnson & Johnson Medical, NJ, USA). The transseptal sheath was exchanged with a 12 F steerable sheath (Flexcath Advance, Medtronic, Inc., Minneapolis, MN, USA) over a guidewire. To achieve an activated clotting time of >300 s, intravenous (IV) bolus heparin was administered. Subsequently, a 28 mm cryoballoon (Arctic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) was advanced within the FlexCath sheath and guided by a circular mapping catheter (Achieve, Medtronic, Inc., Minneapolis, MN) to the antrum of each pulmonary vein. The primary ablation target was broad antral isolation, and no additional LA intra-ablation was performed. During pulmonary vein isolation (PVI), a freeze-thaw-freeze technique was employed, applying a 240-second cryoballoon freeze for all four pulmonary veins. To minimize the risk of phrenic nerve injury, pacing of the right phrenic nerve was achieved with an electrode catheter in the superior vena cava (SVC), confirmed by capture, palpation, and intermittent fluoroscopy. Cryo-energy application was promptly terminated in case of phrenic nerve capture or weakening. The procedural endpoint was defined as persistent PVI, confirmed by spiral mapping catheter recordings 30 min after the last cryo-energy application. All pulmonary veins were isolated during the procedure. In cases where AF persisted during the procedure and was not terminated by ablation, sinus rhythm was restored using electrical cardioversion. No additional ablation line was performed to the patients other than PVI.

Postprocedural management

Following ablation, all patients underwent transthoracic echocardiography (TTE) to rule out pericardial effusion. All patients were treated with a proton pump inhibitor (PPI) twice daily for two months. Anticoagulation was continued for a minimum of 3 months, and thereafter, the decision to continue anticoagulation therapy was based on individual CHA2DS2-VASc scores and other stroke risk factors. To prevent early post-procedural recurrences, antiarrhythmic drugs were administered for 3 months. Discontinuation of antiarrhythmic therapy was recommended after the third month. Persistent AF patients were converted to sinus rhythm with medical or electrical cardioversion at least one week before the procedure. Patients were followed with 48-hour rhythm holter at the 3rd, 6th, 12th months and annually thereafter for recurrence. Recurrence was defined as atrial tachycardias occuring 3 months after the procedure.

Echocardiographic assessment

All patients underwent baseline echocardiographic measurements on the morning of the procedural day. During the echocardiographic examination, all patients were in sinus rhythm. In three patients, electrical cardioversion was performed before the procedure to achieve sinus rhythm. Echocardiographic assessments were conducted by an experienced echocardiography specialist blinded to clinical data, using the Philips EPIQ7 ultrasound system equipped with a 1-5 MHz X5-1 sector array transducer (Philips Medical Systems, Andover, Massachusetts, USA). Left atrial (LA) diameter was obtained from apical long-axis images. Two-dimensional LA volume was evaluated from apical 4- and 2-chamber views and indexed to body surface area to obtain indexed LA volume (LAVI). Diastolic dysfunction was assessed from transmitral E and A velocities, septal and lateral annular e' velocities, the average E/e' ratio, LAVI measurements, and tricuspid regurgitation (TR) velocities. Electromechanical conduction time was defined from the onset of the p-wave to the beginning of the late diastolic A-wave followed by tissue Doppler imaging (TDI) of the lateral and medial mitral annulus.

Left ventricle (LV) and left atrium (LA) strain analyses were performed by experienced operators using customized strain software (Qlab, Philips, NL). An 18-segment model was applied for the assessment of wall motions []. Global longitudinal strain was automatically calculated as the average of the 18 segments. For LA strain analysis, the LA contour was evaluated at the end of systole, excluding the pulmonary veins and LA appendage. LA strain was automatically calculated in apical 4-chamber and 2-chamber views. LA myocardial deformation analysis was evaluated during all three phases of the atrial cycle (reservoir, conduit, contraction). Specifically, LA reservoir strain (LAsr) was measured as the highest positive value at the end of LA filling before mitral valve opening. LA contractile strain (LAsct) was measured as the highest strain value during atrial contraction. LA conduit strain (LAscd), occurring after mitral valve opening and before LA contraction, represents the atrial mechanics during the passive LA filling phase, measured as the difference between peak reservoir and peak contractile strain.

Biochemical assessment

Samples obtained from patients were collected in serum-separating tubes on the morning of the procedure. After clotting at room temperature for 2 h, they were centrifuged at 1000 xg for 20 min. Serum samples were stored at -80 °C until analysis.

Human PIIINP (N-Terminal Procollagen III Propeptide) - Elabscience - Catalog Number: E-EL-H0183: The kit is based on the sandwich-ELISA method. Both intra-assay and inter-assay measurement variations are less than 10%.

Human MYBPHL (Myosin-binding protein H-like) - Mybiosource - Catalog Number: MBS8820001: The test is based on the sandwich enzyme immunoassay method. Intra-assay and inter-assay measurement variations are less than 8% and less than 10%, respectively. In addition to before the procedure, MYBPHL levels were assessed at the 2nd and 24th hours after the procedure.

C-Reactive Protein HS - DRG International - Catalog Number: EIA-3954: The hs-CRP ELISA is based on the solid-phase enzyme-linked immunosorbent assay principle. While intra-assay variation ranges from 2.3 to 7.5%, inter-assay variation ranges from 2.5 to 4.1%.

Statistical analysis

All statistical tests were conducted using Statistical Package for the Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA). The sample size was determined using the G-power program based on effect size, type 1 error, and study power. Type I error was set at 5%, study power at 80%, and effect size was determined from previous studies in the literature. The normality of data was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk test. Numerical data showing normal distribution were expressed as mean ± SD, while parameters that did not exhibit normal distribution were expressed as median (25–75 percentiles). Categorical data were presented as percentages. The comparison of echocardiographic parameters between baseline and 3-month measurements in patients was performed using the paired t-test and/or Wilcoxon test based on the distribution of data. The comparison of categorical data between groups was conducted using the chi-square test. The comparison of independent numerical data was performed using the Student t-test and/or Mann-Whitney U test based on the distribution of data. Univariate and multivariate logistic regression analyses were conducted to evaluate parameters independently predicting AF recurrence in patients. After univariate analysis, a multiple regression model was created based on the obtained results. A two- tailed p value < 0.05 was considered statistically significant.

Results

The demographic data of the patients were examined in Table 1. No significant difference was found in demographic characteristics between the PAF and persistent AF groups. When the demographic characteristics of the patients and

Table 1 Demographic data and effects on recurrence

Parameters	Study Population ($n=92$)	Recurrence ($n=19$)	No AF recurrence ($n=73$)	p-value
Age	59 ± 11.7	60,2 ± 8,4	56,4 ± 12,4	0,199
Male sex n(%)	50 (54,3)	8 (16)	42 (84)	0,145
HTN n(%)	50 (54,3)	13 (26)	37 (74)	0,280
DM n(%)	23 (25)	7 (30,4)	16 (69,6)	0,243
HLD n(%)	12 (13,3)	1 (8,3)	11 (91,7)	0,452
CAD history n(%)	10 (10,9)	1 (10)	9 (90)	0,685
CVA history n(%)	1 (1,1)	0 (0)	1 (100)	1
Pacemaker/ICD implantation n(%)	3 (3,3)	0 (0)	3 (100)	1
AAD use n(%)	75 (81,5)	17 (22,7)	58 (77,3)	0,651
Previous SVT Ablation n(%)	3 (3,3)	0 (0)	3 (100)	1
Paroxysmal AF n (%)	73 (79,3)	11 (15,1)	62 (84,9)	**0,005**
BMI (kg/m2)	28,8 ± 4,6	30,2 ± 6,2	28,3 ± 4	0,109
CHA2DS2-VASc score	1,7 ± 1,3	2,35 ± 1,3	1,56 ± 1,3	**0,023**

AF indicates atrial fibrillation; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; CAD, coronary artery disease; ICD, implantable cardioverter-defibrillator; CVA, cerebrovascular accident; BMI, Body Mass Index; AAD, Antiarrhythmic drug; SVT, supraventricular tachycardia

Table 2 Baseline biomarker values in Paroxysmal and Persistent AF patients

Parameters	Study Population ($n=92$)	Paroxysmal AF ($n=73$)	Persistent AF ($n=19$)	p-value
PRO-BNP (pg/mL)	241 (66–580)	171 (51–387)	909 (304–1660)	**< 0,001**
Human ANP (pg/mL)	274 ± 215,4	276,3 ± 233	265,2 ± 132,1	0,847
hs-CRP (mg/L)	6,0 (4,0–18,0)	6,0 (4,0–19,0)	6,5 (4,7–18,5)	0,838
PIIINP (pg/mL)	1320,9 ± 604,4	1293,5 ± 532,7	1425,9 ± 835,7	0,411
MYBPHL 0 h (ng/mL)	15,9 ± 10,6	16,4 ± 11,3	13,8 ± 7,2	0,349
MYBPHL 2nd hour (ng/mL)	44,3 ± 38,6	41,5 ± 38,7	54,8 ± 37,5	0,199
MYBPHL 24th hour (ng/mL)	15 ± 11	14,3 ± 11,1	17,6 ± 10,7	0,274

Abbreviations: PIIINP: N-terminal pro-collagen type III propeptide, hs-CRP: high-sensitive C-reactive protein, BNP: brain natriuretic peptide, MYBPHL: myosin-binding protein H-like, AF: Atrial Fibrillation

their association with post-procedural recurrence were examined (Table 1), significantly more AF/AT recurrences were observed in patients with persistent AF compared to those with PAF ($p=0.005$). Additionally, the statistical significance of the association between higher CHA2DS2-VASc scores and AF/AT recurrence was demonstrated. The average duration from femoral sheath insertion to the end of the procedure was 60 ± 11.8 min. Additionally, the effect of the time from AF diagnosis to cryoballoon procedure on recurrence was investigated in patients with persistent AF. No significant difference was found in the mean time from diagnosis to the CB-2 procedure between persistent AF patients with recurrence and those without recurrence (12.6 ± 3.8 months vs. 11.6 ± 2 months, $p=0.457$).

Biochemical findings

The baseline levels of PRO-BNP, human ANP, PIIINP, MYBPHL, and hs-CRP were examined for each patient before the procedure (Table 2). Additionally, the MYBPHL value was assessed at 2 h and 24 h after the procedure.

When the biochemical values were examined in PAF and persistent AF subgroups (Table 2), the PRO-BNP value was statistically significantly higher in persistent AF patients compared to PAF patients [909(304–1660) vs. 171(51–387); $p<0.001$]. Although PIIINP, 2nd and 24th hour MYBPHL values were higher in the persistent AF group compared to the PAF group, they did not reach statistical significance. Consistent with the literature, MYBPHL values peaked at 2 h post-procedure and returned to baseline values at 24 h post-procedure.

The relationship between PRO-BNP, human ANP, PIIINP, hs-CRP, and 0-2-24-hour MYBPHL values and AF/AT recurrence was examined (Table 3). Although 0-2-24-hour MYBPHL values and hs-CRP values did not reach statistical significance, they were higher in patients with recurrence compared to those without recurrence. ROC analysis revealed that the predictive effect of MYBPHL values on recurrence was weak.

Further analysis revealed that the rise in MYBPHL biomarker from 0 h to the peak at 2 h post-procedure did not impact recurrence determination (34.7 ± 4.2 vs. 42.4 ± 9.7; $p=0.356$). However, the PRO-BNP value was significantly higher in patients with recurrence compared to those without recurrence [544(243–1477) vs. 196(58–426); $p=0.005$] (Fig. 1).

Table 3 Effects of biomarker values on recurrence

Parameters	Recurrence ($n=19$)	No AF recurrence ($n=73$)	p-value
PRO-BNP (pg/mL)	544 (243–1477)	196 (58–426)	**0,005**
Human ANP (pg/mL)	265,5 ± 132,3	276,3 ± 234,1	0,848
hs-CRP (mg/L)	13,0 (6,0–27,0)	6,0 (3,2–14,5)	0,082
PIIINP (pg/mL)	1282,4 ± 495,2	1331,6 ± 634,5	0,755
MYBPHL 0 h (ng/mL)	16,7 ± 8,1	15,6 ± 11,3	0,699
MYBPHL 2nd hour (ng/mL)	52,1 ± 42,8	42,1 ± 37,4	0,327
MYBPHL 24th hour (ng/mL)	15,3 ± 7,2	14,9 ± 11,9	0,904

Abbreviations: PIIINP: N-terminal pro-collagen type III propeptide, hs-CRP: high-sensitive C-reactive protein, BNP: brain natriuretic peptide, MYBPHL: myosin-binding protein H-like, AF: Atrial Fibrillation

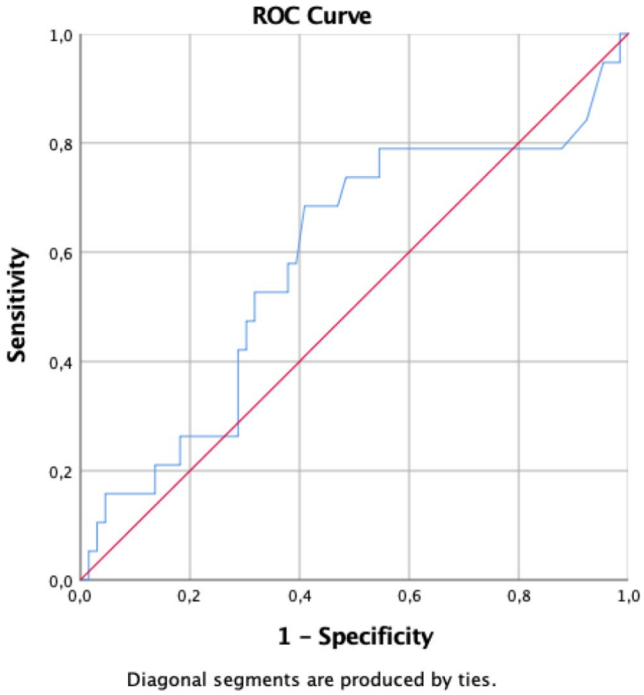

Fig. 1 Evaluation of the predictive effect of MYBPHL values on recurrence through ROC analysis

Echocardiographic findings

A comparative echocardiographic evaluation, including strain parameters, was conducted for each patient before the procedure and at the 3-month follow-up (Table 4). The measured LA diameter from the apical long-axis view was 41.1 ± 5.8 mm before the procedure and 41.2 ± 5.7 mm at the 3-month follow-up (p = 0.191). There was no significant change observed in the left atrium volume index (LAVI) measured using the biplane method and indexed to body surface area. No significant changes were noted in the E and A wave velocities measured by the Doppler method in the 3-month follow-up echocardiogram compared to before the procedure. Similarly, there were no statistically significant changes in lateral and septal E/e' values, which are indicators of left ventricular diastolic dysfunction. Although the electromechanical delay measured from lateral and medial

Table 4 Comparison of pre-procedural and 3-month follow-up echocardiographic values for the entire patient population

Parameters	Pre-procedure ($n=92$)	3-month follow up ($n=92$)	p value
LA diameter (mm)	41,1 ± 5,8	41,2 ± 5,7	0,191
LAVI (mL/m2)	30,6 ± 11,4	29,8 ± 11	0,199
LA-EMD medial (msn)	74,3 ± 19,6	77,2 ± 19,4	0,182
LA-EMD lateral (msn)	94,4 ± 19,7	98,1 ± 19	0,056
E/e'	9,4 ± 2,7	9,5 ± 3	0,700
Medial E/e'	10,1 ± 3,1	10,2 ± 3,6	0,715
Lateral E/e'	9,2 ± 3,1	9,3 ± 3,1	0,666
E wave velocity (m/sn)	83,6 ± 20,2	83 ± 20,3	0,767
A wave velocity (m/sn)	66 ± 20,6	67,3 ± 19	0,630
TRV (m/sn)	2,4 ± 0,2	2,4 ± 0,27	0,808
LAsr	28,6 ± 13	34,3 ± 13,5	**< 0,005**
LAsct	-11,9 ± 5,6	-14,2 ± 6,9	**0,005**
LAscd	-18 ± 9	-20,5 ± 8,9	**0,015**
LV endo average strain	-20,4 ± 3,7	-22 ± 5,8	**0,014**

Abbreviations: LA: left atrium, LAVI: left atrial volume index, EMD: electromechanical delay, TRV: tricuspid regurgitation velocity, LAsr: left atrium reservoir strain, LAsct: left atrium contractile strain, LAscd: left atrium conduit strain, LV: left ventricle

mitral annular tissue showed an increase at the 3-month follow-up compared to before the procedure, it did not reach statistical significance. In the analyses conducted using the strain method, the calculated LAsr (28.6 ± 13.1 vs. 34.3 ± 13.5; $p < 0.005$), LAsct (-11.9 ± 5.6 vs. -14.2 ± 6.9; $p = 0.005$), LAscd (-18 ± 9 vs. -20.5 ± 8.9; $p = 0.015$), and LV endo average strain (-20.4 ± 3.7 vs. -22 ± 5.8; $p = 0.014$) values showed a significant increase at the 3-month follow-up compared to before the procedure.

In the paroxysmal AF group, echocardiographic changes were generally consistent with the overall patient population, although an increase was observed in LAscd (-19.6 ± 8.9 vs. -21.3 ± 8.9; $p = 0.129$) and LV endo average strain (-21.5 ± 2.9 vs. -22.5 ± 6.3; $p = 0.193$) values at 3 months, it did not reach statistical significance (Table 5).

In patients with persistent AF, unlike the general patient population, the increase in LAsct values at 3 months did

Table 5 Comparison of echocardiographic values before the procedure and at the 3-month follow-up in paroxysmal and persistent AF patients

Parameters	Paroxysmal AF population			Persistent AF population		
	Pre-procedure ($n=73$)	3-month follow-up ($n=73$)	p-value	Pre-procedure ($n=19$)	3-month follow-up ($n=19$)	p-value
LA dimension (mm)	39,6 ± 5,4	39,8 ± 5,4	0,129	46,3 ± 3,8	46,3 ± 3,7	0,841
LAVI (mL/m2)	27,4 ± 9,4	27,1 ± 9,8	0,664	42,2 ± 10,7	39,7 ± 9,5	0,168
LA-EMD medial (msn)	72,5 ± 19,6	75,4 ± 18,9	0,182	88,1 ± 14,1	90,7 ± 18,5	0,734
LA-EMD lateral (msn)	91,5 ± 18,3	95,3 ± 17,6	0,052	116,3 ± 16,9	119,2 ± 16,1	0,643
E/e'	8,9 ± 2,5	9,3 ± 2,7	0,268	11,1 ± 3,1	10,3 ± 4	0,134
Medial E/e'	9,9 ± 2,6	9,9 ± 2,8	0,986	10,8 ± 4,2	11,3 ± 5,7	0,440
Lateral E/e'	9 ± 3,1	9,1 ± 3	0,597	9,9 ± 3,3	9,9 ± 3,7	0,939
E wave velocity (m/sn)	80,2 ± 20	81,2 ± 19,9	0,666	95,7 ± 16,6	89,5 ± 20,9	0,187
A wave velocity (m/sn)	67,5 ± 20,3	66 ± 18,3	0,540	54 ± 20,2	77,9 ± 22,6	0,061
TRV (m/sn)	2,38 ± 0,24	2,39 ± 0,27	0,605	2,6 ± 0,25	2,5 ± 0,24	0,229
LAsr	31,8 ± 12,2	36,2 ± 12,8	**< 0,005**	16,5 ± 8,5	26,7 ± 13,6	**0,015**
LAsct	-12,9 ± 5,5	-15,2 ± 6,7	**0,008**	-7,9 ± 4,4	-10,2 ± 6,5	0,271
LAscd	-19,6 ± 8,9	-21,3 ± 8,9	0,129	-12,1 ± 6,9	-17,6 ± 8,3	**0,035**
LV endo average strain	-21,5 ± 2,9	-22,5 ± 6,3	0,193	-16,6 ± 3,8	-20,3 ± 3,6	**< 0,005**

Abbreviations: LA: left atrium, LAVI: left atrial volume index, EMD: electromechanical delay, TRV: tricuspid regurgitation velocity, LAsr: left atrium reservoir strain, LAsct: left atrium contractile strain, LAscd: left atrium conduit strain, LV: left ventricle

Table 6 Comparison of pre-procedural and 3-month follow-up echocardiographic parameters in patients with and without recurrence after the procedure

Parameters	No AF recurrence			AF recurrence		
	Pre-procedure ($n=73$)	3-month follow-up ($n=73$)	p-value	Pre-procedure ($n=19$)	3-month follow-up ($n=19$)	p-value
LA dimension (mm)	40,4 ± 5,9	40,4 ± 5,8	1	43,5 ± 4,6	44 ± 4,8	**0,002**
LAVI (mL/m2)	28,9 ± 10,5	27,3 ± 8,1	**0,013**	36,3 ± 12,9	38,6 ± 14,6	**0,006**
LA-EMT medial (msn)	73,1 ± 18,5	75,4 ± 17,1	0,309	80,3 ± 24,3	85,8 ± 27,3	0,378
LA-EMT lateral (msn)	92,2 ± 19,2	96,8 ± 19,4	0,060	105,3 ± 19,1	104,6 ± 15,7	0,843
E/e'	9,1 ± 2,5	9,3 ± 2,7	0,605	10,4 ± 3,3	10,3 ± 3,9	0,787
Medial E/e'	10 ± 2,7	9,9 ± 2,9	0,795	10,6 ± 4	11,3 ± 5,4	0,155
Lateral E/e'	9 ± 2,9	9,2 ± 2,9	0,351	9,9 ± 3,8	9,5 ± 3,9	0,512
E wave velocity (m/sn)	81,1 ± 18,7	80,5 ± 19,6	0,807	92,1 ± 23,4	91,5 ± 20,6	0,859
A wave velocity (m/sn)	66,9 ± 20,4	68 ± 17,5	0,642	61,5 ± 21,7	63,3 ± 26	0,863
TRV (m/sn)	2,4 ± 0,25	2,39 ± 0,24	0,525	2,54 ± 0,28	2,57 ± 0,33	0,599
LAsr	30,5 ± 12,4	37,3 ± 12	**< 0,005**	22,3 ± 13,3	24,2 ± 13,4	0,383
LAsct	-12,9 ± 5,6	-15,5 ± 6,3	**0,006**	-8,5 ± 4,5	-9,7 ± 7,3	0,423
LAscd	-18,7 ± 8,7	-22 ± 9,1	**0,005**	-16 ± 10	-15,6 ± 6,1	0,828
LV endo average strain	-20,8 ± 3,5	-22,4 ± 6,3	**0,048**	-19,2 ± 4,1	-20,7 ± 3,5	**0,017**

Abbreviations: LA: left atrium, LAVI: left atrial volume index, EMD: electromechanical delay, TRV: tricuspid regurgitation velocity, LAsr: left atrium reservoir strain, LAsct: left atrium contractile strain, LAscd: left atrium conduit strain, LV: left ventricle

not reach a statistically significant level (-7.9 ± 4.4 vs. -10.2 ± 6.5; $p=0.271$) (Table 5).

The changes in echocardiographic parameters of patients without recurrence were consistent with the general patient population (Table 6). Additionally, the 3-month follow-up LAVI value in this patient group was significantly lower compared to the pre-procedural value (28.9 ± 10.5 vs. 27.3 ± 8.1; $p=0.013$).

In the group of patients with recurrence, a significant increase was observed in the 3-month LA diameter and LAVI values compared to pre-procedural values (43.5 ± 4.6 mm vs. 44 ± 4.8 mm; $p=0.002$) (36.3 ± 12.9 vs. 38.6 ± 14.6; $p=0.006$) (Table 6). Unlike the group of patients without recurrence, no significant change was observed in LA strain values in the recurrent group. However, a significant increase was observed in LV endo average strain value at 3 months (-19.2 ± 4.1 vs. -20.7 ± 3.5; $p=0.017$).

The impact of demographic data, biochemical, and echocardiographic parameters on predicting recurrence in 92 atrial fibrillation (AF) patients was examined through logistic regression with univariate and multivariate analysis (Table 7). AF type ($p=0.004$), CHA2DS2-VASc score

Table 7 Univariate and multivariate analysis with logistic regression

Univariate and multivariate analyses for recurrence						
	Univariate			Multivariate		
	CI	OR(ExpB)	*P*-value	CI	OR(ExpB)	*P*-value
Demographic Data						
AF type (Paroxysmal:1, persistant:2)	1,679 – 15,32	5,073	**0,004**	0,072 – 52	1,940	0,693
CHA2DS2-VASc	1,048 – 2,208	1,521	**0,027**	0,928-3,231	1,731	0,085
Biochemical Finding						
PRO-BNP	1,000–1,002	1,001	**0,022**	1,000–1,003	1,002	**0,012**
Echocardiographic Results						
LA dimension	1,007 – 1,211	1,104	**0,035**	0,825-1,221	1,004	0,970
LAsr	0,901-0,990	0,945	**0,018**	1,004 – 1,246	1,113	**0,047**
LAsct	1,056 – 1,369	1,202	**0,005**	1,040 – 1,750	1,349	**0,024**
LV endo average strain	0,987-1,281	1,124	0,078	0,794-1,479	1,084	0,611
LA-EMD lateral	1,006 – 1,069	1,037	**0,018**	0,963-1,066	1,013	0,622
E wave velocity	1,002 – 1,058	1,030	**0,033**	0,960-1,056	1,007	0,782

Abbreviations: LA: left atrium, LAVI: left atrial volume index, EMD: electromechanical delay, TRV: tricuspid regurgitation velocity, LAsr: left atrium reservoir strain, LAsct: left atrium contractile strain, LAscd: left atrium conduit strain, LV: left ventricle, AF: atrial fibrillation

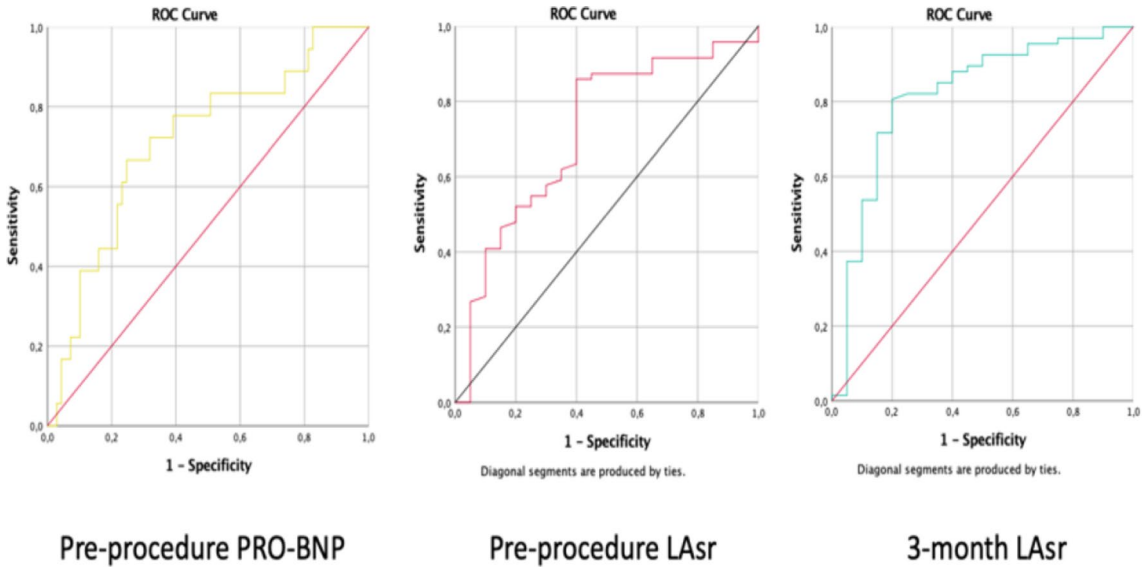

Fig. 2 Evaluation of the predictive effect of PRO-BNP and LAsr cutoff values on recurrence through ROC analysis

($p=0.027$), PRO-BNP value ($p=0.022$), LA diameter ($p=0.035$), LAsr ($p=0.018$), LAsct ($p=0.005$), LA-EMT lateral duration ($p=0.018$), and E-wave velocity ($p=0.033$) were found to be significantly associated with recurrence. Parameters with p-values <0.1 in univariate analysis were further evaluated using multivariate analysis, consistent with the literature. In the multivariate analysis of patients, PRO-BNP value ($p=0.012$), LAsr ($p=0.047$), and LAsct ($p=0.024$) were independently associated with recurrence.

The aim was to determine the cutoff values of PRO-BNP and LAsr through ROC analysis, following their significant effects on recurrence identified in multivariate analysis. Among patients with PRO-BNP levels above 330 pg/ml, a significantly higher likelihood of recurrence was found, with 72% sensitivity and 68% specificity ($p=0.006$). Pre-procedural strain measurements showed that among patients with LAsr values below 19.75, there was a significantly higher likelihood of recurrence, with 84% sensitivity and 60% specificity ($p=0.003$). Post-procedural measurements at 3 months indicated that among patients with LAsr values below 27.6, there was a significantly higher likelihood of recurrence, with 80% sensitivity and 80% specificity ($p<0.001$) (Fig. 2).

Discussion

The results of our study, which included a follow-up of an average of 2 years for a total of 92 AF patients, are as follows:

i) For predicting recurrence as a primary endpoint, demographic data indicated that AF type and CHA2DS2-VASc score were associated with recurrence. Biomarker analysis revealed an association between PRO-BNP values and recurrence. Additionally, multivariate analysis highlighted the relationships between LAsr and LAsct values and recurrence.
ii) Regarding the secondary endpoint, the MYBPHL value, as an indicator of atrial damage, peaked at 2 h post-procedure and returned to baseline at 24 h, consistent with the literature. Echocardiographic evaluation, including strain parameters, was conducted in patients before the procedure and 3 months after the procedure, demonstrating improvement in strain parameters post-procedure.

AF, a prevalent arrhythmia, significantly contributes to cardiovascular morbidity. Electrical and structural remodeling play pivotal roles in initiating and perpetuating this condition. Inflammatory processes result in myocyte degeneration and fibrosis, forming the basis for structural remodeling. Despite recent studies exploring biomarkers for inflammation, fibrosis, and atrial damage, a definitive link with recurrence after CB-2 ablation remains elusive. While Kızılırmak and colleagues associated Troponin I (TnI) increase with AF recurrence post-cryoablation, specific biomarkers for atrial myocytes and their correlation with recurrence are unexplored. Lahm et al. introduced MYBPHL, an atrial myocyte-specific biomarker, indicating atrial damage post-cardiac interventions. Our study assessed atrial damage using MYBPHL levels, peaking at 2 h and returning to baseline at 24 h. Although not statistically significant, MYBPHL was higher in recurrence at 0-2-24 h. The lack of correlation with strain parameters suggests MYBPHL elevation during cryoballoon procedures due to posterior wall damage, with independent recovery of atrial mechanical functions after the procedure.

BNP and NT-proBNP, released due to cardiomyocyte wall stress, are associated with adverse events in atrial fibrillation (AF) [19]. While high baseline natriuretic peptide levels predict recurrence after radiofrequency catheter ablation, this effect is unproven for CB-2 [20]. LA dilation in AF leads to muscle bundle disruption, causing hypokinesia, remodeling, and fibrosis. Elevated pressure and natriuretic peptide levels result from AF burden [21], increasing the risk of recurrence. Our study, aligning with literature and pathophysiology, demonstrates an association between baseline pro-BNP levels and recurrence after cryoballoon ablation through multivariate analysis.

LA strain analysis, an echocardiographic technique assessing three phases of left atrial (LA) function—reservoir, contractile, and conduit—by analyzing LA myocardium deformation, serves as an indicator for LA dysfunction and structural fibrotic remodeling. Previous studies underline the significance of utilizing LA strain to predict AF recurrence following both radiofrequency (RF) ablation and CB-2 [22]. In our study, we evaluated LA compliance using strain parameters after CB-2, revealing a notable improvement in post-procedural LAsr and LAscd values [23]. However, existing literature lacks a well-established relationship between echocardiographic follow-up after CB-2 and recurrence. Our findings align with prior research, showing substantial enhancement in all LA strain parameters (LAsr, LAscd, LAsct) at 3 months post-procedure compared to baseline values. This improvement is attributed to the reversal of remodeling through ablation, leading to the recovery of LA mechanical functions.

Upon separate analysis of paroxysmal and persistent AF patients, the paroxysmal AF group exhibited improvement across all LA strain parameters, consistent with the general patient population. Conversely, in the persistent AF group, significant improvement was not observed in LAsct values. Anticipated further studies with a larger volume of persistent AF cases may shed light on improvement in this parameter as well. Comparison of baseline and 3-month echocardiographic variables of patients experiencing recurrence post-procedure unveiled an increase in LAVI and LA diameter. Additionally, there was no significant improvement in LA strain values. The substantial increase in LAVI and LA diameter at 3 months suggests that existing structural and functional remodeling cannot be reversed. Consequently, LA mechanical functions cannot recover. Therefore, extending use of antiarrhythmic drugs beyond the blanking period (< 3 months) after ablation may be considered to prevent recurrence, especially in the patients whose left atrial functions do not improve at the 3rd month follow-up echocardiography. In this respect, our study has the feature of generating hypotheses. These results propose that LA strain values, indicative of left atrial remodeling and mechanical functions, may effectively predict recurrence. In our multiple variable analysis, we demonstrated the relationship between LAsr and LAsct parameters and recurrence.

Among the limitations of our study, the relatively small number of patients is notable. LA mapping was not conducted to evaluate any possible atrial debulking effect of CB-2 beyond PVI. Additionally, redo mapping and ablation were not performed routinely in patients experiencing recurrence, leaving the recurrence mechanism in these patients undisclosed. No implantable monitor was utilized to assess AF burden in the patients before or after the procedure. Additionally, the time elapsed from AF diagnosis to cryoballoon ablation was not included as a parameter. Patients in the persistent AF group were not subdivided into subgroups based on the duration of AF, such as long-standing persistent AF and non-long-standing persistent AF, and the

impact of these subgroups on recurrence was not elucidated. Cardioversion was performed in three patients within the 24 h preceding the procedure, and the negative effects of the "stunning" effect on the pre-procedural left atrial and left ventricular functions in these patients were not definitively determined. Imaging methods such as cardiac CT and cardiac MR were not utilized in patients before the procedure. Therefore, cardiac anatomy, including the pulmonary veins, was not assessed before the procedure. Furthermore, an esophageal temperature probe, which could indirectly demonstrate the impact of cryoballoon ablation on the esophagus, was not employed in the procedures.

Conclusion

This study elucidates the effectiveness of CB-2 in treating AF and its impact on LA functions. Notably, LA strain measurements and PRO-BNP levels have emerged as reliable indicators for predicting recurrence. Beyond clinical implications, our research establishes a foundation for a deeper understanding of the role of CB-2 in AF management and factors associated with recurrence.

Author contributions The individual contribution of each co-author is listed below using the the following keys: 1. Conception of design or analysis and interpretation of data, or both. 2. Drafting the article or revising it. 3. Providing interlectual content of importance to the work described. 4. Final approval of the version to be published. Ali Ugur Soysal: 1, 2, 3, 4 Asli Gulfidan: 1, 4. Damla Raimoglou: 2,3. Adem Atici: 2,3. Hakan Yalman: 1, 2, 4. Mine Kucur: 2, 4. Sukriye Ebru Onder: 1, 4. Eser Durmaz: 1, 3, 4. Baris Ikitimur: 4. Kivanc Yalin: 1, 2, 3, 4.

Funding information The authors have no funding sources to disclose.

Data availability The data is available and permission might be sought per reasonable request.

Declarations

Ethical approval The study was approved by the institutional ethics committee. Informed consent was provided by all patients.

Conflict of interest The authors have no conflicts of interest to disclose.

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