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Clinical outcome of the 2nd generation cryoballoon for pulmonary vein isolation in patients with persistent atrial fibrillation — A sub-study of the randomized trial evaluating single versus dual cryoballoon applications

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ABSTRACT

Aims: To assess the efficacy of the 2nd generation Cryoballoon for pulmonary vein isolation (PVI) in patients with persistent atrial fibrillation (PersAF), and to compare it to patients with paroxysmal atrial fibrillation (PAF).
Methods: The outcome (arrhythmia recurrence at 12 months) was prospectively assessed in patients with PersAF ($n = 77$) and compared to that in patients with PAF($n = 62$), who underwent PVI within a randomized trial evaluating single versus dual applications with the 2nd generation cryoballoon. Other endpoints included symptoms of AF, quality of life, procedure related characteristics, redo ablation rates and adverse events. Variables predicting recurrences were studied including all patients.
Results: Freedom from arrhythmia recurrence was 64.9% after a single ablation and 68.8% after one or more procedures, which was significantly lower compared to PAF patients; 82.2% ($p = 0.029$) and 83.9% ($p = 0.048$) respectively, at 12 months. The improvements in EHRA score (-1.3 ± 0.8, $p < 0.0001$), symptom severity score (SSQ) (-5.0 ± 4.2, $p < 0.0001$) and EQ5D-5 L global score ($+10.4 \pm 20.3$, $p = 0.0002$) after ablation was significant compared to baseline. The re-ablation rate was 7/77 (9.1%) which did not differ from that in PAF patients, 9/62 (14.5%), $p = 0.42$. Procedure duration, 104.8 ± 37.4 versus 113 ± 31.2 min ($p = 0.129$), application time, 1605 ± 659 versus 1521 ± 557 s ($p = 0.103$) and total adverse events after 12 months, 8/77 (10.4%) versus 5/62 (8.1%) ($p = 0.77$) did not differ in PersAF versus PAF patients.
Conclusion: Both symptoms and QoL improved significantly in patients with PersAF after ablation. Freedom from AF was clinically significant but lower than in PAF patients. The cryoballoon seems an effective technique also in patients with persistent AF.

1. Introduction

The 2nd generation cryoballoon has been shown to be an efficient technique for pulmonary vein isolation (PVI) for the maintenance of sinus rhythm and improved quality of life in patients with paroxysmal atrial fibrillation (PAF) [1–3]. Freedom from atrial arrhythmia recurrence was high (81.8–85.8%) in patients with PAF after one year follow-up and repeated ablation procedures were required in only 10.9–16.7% [4,5]. Studies on persistent AF (PersAF), however, are limited to a few small retrospective registry studies [6,7] and non-randomized prospective trials [8–10]. While they all reported a 60–69% freedom from arrhythmia recurrence at 12 months, none of the trials assessed symptoms or quality of life, improvement of which is the primary goal of the ablation procedure.

Studies assessing predictive factors for AF recurrences after PVI have up to date mainly included procedures using radiofrequency energy [11–15] while those using the 2nd generation cryoballoon [16,17] are limited.

Our primary aim was therefore to assess the efficacy in terms of AF recurrence, symptoms and quality of life (QoL) of the 2nd generation cryoballoon for PVI in patients with PersAF and to compare it with that in PAF. We also aimed to assess safety and predictors for recurrences of atrial fibrillation.

2. Material and methods

2.1. Study population

Patients with symptomatic PersAF and PAF, who were included in a randomized study showing no difference in outcomes between single versus dual applications using the 2nd generation cryoballoon [3], constituted the study group and control group, respectively. Inclusion criteria were symptoms corresponding to an EHRA (European Heart Rhythm Association) score of at least 2, age <76 years, and a primary AF ablation procedure, as described elsewhere [3]. The major exclusion criteria included heart failure with New York Heart Association class III or more, left ventricular ejection fraction of 35% or lower, left atrial (LA) diameter of 55 mm or larger, and longstanding persistent AF defined as ongoing persistent AF >12 months [3]. A transthoracic and a transoesophageal echocardiogram

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were performed the day before the ablation to rule out any thrombi and calculate LA volume. Left atrial volume indexed to body surface area (LAVI, ml/m^2) over 42 ml/m^2 was defined as definite pathological left atrial volume [18]. The study was approved by the local ethical committee. All patients gave their written informed consent.

2.2. Study design and endpoints

The efficacy outcome in the present pre-specified sub-study was freedom from arrhythmia recurrence (defined as the absence of any AF or atypical flutter episode longer than 30 s on Holter or telemetry ECG or AF on any other surface ECG recording) after 12 months of follow-up in patients with PersAF and compared to those with PAF. The other efficacy outcomes were symptoms of AF assessed by EHRA scale and total symptom severity questionnaire score (SSQ), quality of life (QoL) assessed by the EQ5D-5 L questionnaire, continued treatment with class I or III antiarrhythmic drugs (AAD), number of cardioversions, and the re-ablation rate after 12 months of follow-up. The EHRA score assessed the severity of symptoms (I-IV) attributable to atrial fibrillation; class I indicated no symptoms and class II, III and IV indicated mild, severe and disabling symptoms, while the SSQ had five different symptoms each graded 1–5 points (1 = no symptoms to 5 = severe symptoms) with maximum score 25. The EQ5D-5 L had five modalities indexed to score from minimum 0 to maximum 1, and EQ5D-5L global score ranging from minimum 0 to maximum 100 points.

The procedure-, fluoroscopy- and cryo-ablation times were analysed and compared with that of PAF patients. The multivariate prediction analysis for AF recurrence included the following predefined patient specific characteristics; age, body mass index (BMI), hypertension, ischemic heart disease, congestive heart failure, diabetes, EHRA score, CHA_2DS_2VASc score, duration of AF history, failed one or more class I or III AAD prior procedure, LA volume, LA volume index and NT-pro BNP. Procedural related prediction variables included LA conduction times and LA pressure. The rate of complications after 12 months was also analysed.

2.3. Ablation procedure

The ablation procedure has been described in detail elsewhere [3]. The LA pressure was measured directly after the transseptal puncture [19] using a standard pressure transducer connected to the transseptal sheath at steady state while the patient was breathing spontaneously. A 20–polar circular mapping catheter was then positioned in the right superior PV orifice and a decapolar catheter in the coronary sinus. Atrial pacing was then performed for measurement of conduction times at a cycle length of 400 milliseconds from the upper poles of the circular mapping catheter in the right superior pulmonary vein (RSPV) and then from the proximal and distal coronary sinus electrodes, respectively, for 10 s each. Conduction times were measured after steady state at the end of the pacing sequence. The measured time intervals were i) from the proximal coronary sinus to RSPV (CS prox-RSPV), ii) from the distal coronary sinus to RSPV (CS dist-RSPV), and iii) from the proximal to the distal coronary sinus (CS prox-CS dist). Inverting pacing vector, i.e. pacing in the other direction was also done for measurement of bidirectional conduction times.

Following the pacing maneuverers, a 28 mm cryoballoon (Arctic Front Advance^R, Medtronic) was placed in the left atrium for either two 4-minute applications or a single 4-minute application, as described elsewhere [3]. Once all PVs had been ablated, the cryoballoon was exchanged for a separate 20–polar circular mapping catheter to verify complete entrance block.

2.4. Follow up

Patients were followed by the investigators at 3, 6 and 12 months at our clinic. The three-month visit could be conducted at the referring hospitals. A 12-lead ECG was performed at each clinical visit and a 7-day Holter recording was performed at 6 months and 12 months.

A one-month blanking period was used when calculating arrhythmia recurrence. Antiarrhythmic drugs were withdrawn after 3 months in asymptomatic patients free from AF recurrences. *Re*-ablation could be performed at earliest after 6 months.

2.5. Statistics

Student's *t*-test was used for continuous variables (mean ± standard deviation), nominal variables expressed as frequencies or proportions were analysed with Fisher's exact test or Pearson's chi squared test where applicable. Kaplan-Meier curves were constructed to describe freedom from AF recurrence in PersAF patients as compared to those with PAF. Univariate and multivariate analysis (nominal logistic regression) was performed for baseline and pre-ablation predictors for freedom from arrhythmia recurrence, but no >3 variables were used in the multivariate analysis due to the limited number of events. A separate Kaplan-Meier curve combining the type of AF and the strongest predictor for the same outcome was created to illustrate the effect of the predictor between the AF types. A p value <0.05 was considered to be significant.

3. Results

3.1. Study participants

In total, 77 patients with PersAF underwent ablation, of whom 75 completed 12 months of follow-up. Sixty-two PAF patients underwent ablation and 61 completed follow-up. Three patients refrained from the 12-month clinical visit due to long travel distance but had no symptoms of AF and presented with sinus rhythm on resting ECG at the local hospital. Patients with PersAF had a significantly higher body mass index and a higher LA volume index than those with PAF, while the other pre-specified baseline clinical variables did not differ between groups (Table 1).

3.2. Arrhythmia recurrence

The rate of freedom from atrial arrhythmias was 64.9% after a single cryoballoon ablation procedure and 68.8% after one or more procedures in the PersAF group, which was significantly lower compared to PAF patients; 82.2% ($p = 0.029$) and 83.9% ($p = 0.048$) respectively, at 12 months (Fig. 1A). There was no significant difference regarding freedom of atrial arrhythmia between the PersAF groups undergoing single (21/35 patients, 60.0%) versus dual (29/42 patients, 69.0%) cryoballoon applications, $p = 0.298$.

In the PersAF group, 55/77 (71.4%) were completely asymptomatic at 12 months. Of the 22 PersAF patients with symptoms and recurrence of AF, 9 had very short burst of AF (PAF) which did not cause significant symptoms in the patients, while of the remaining 13 patients, only 7 patients (with EHRA-score > 2) elected to undergo a second AF ablation procedure. The rate of re-ablations was thus 7/77 (9.1%) among PersAF patients, all of whom had reconduction in at least 1 PV except for one patient with left atrial macro-reentry tachycardia. The re-do ablation rate was 9/62 (14.5%) among PAF patients, who all had reconduction in at least 1 PV, $p = 0.42$ between groups. All reconnected PVs were reisolated with cryoballoon ablation at the reablation procedure. The rate of cardioversion was 13/75 (17.3%) in PersAF patients, which exceeded that in the PAF group, 0/61, $p = 0.0003$.

3.3. Symptoms, quality of life and continued treatment

The EHRA score, SSQ score and the EQ5D-5L global score improved significantly in the PersAF group (Table 2). The PAF group improved as well. Even though the magnitude of EHRA score improvement during follow-up was significantly lower in the PersAF than in the PAF group (Table 2), the 12 months scores were not significantly different between PersAF and PAF groups; 1.3 ± 0.6 versus 1.2 ± 0.5, $p = 0.313$.

Table 1
Baseline demographics including procedural left atrial pressure and conduction times.

Parameter	PersAF $N = 77$	PAF $N = 62$	*P*-value
Age (years)	62.0 ± 9.1	61.0 ± 10.0	0.522
Sex, males, N (%)	59 (76.6)	43 (69.4)	0.343
BMI (kg/m^2)	28.5 ± 4.3	27.0 ± 4.3	0.041
Hypertension, N (%)	38 (49.4)	26 (41.9)	0.398
Ischemic heart disease, N (%)	5 (6.5)	4 (6.5)	>0.99
Congestive heart failure, N (%)	8 (10.4)	4 (6.5)	0.548
Diabetes, N (%)	6 (7.8)	7 (11.3)	0.564
EHRA score (1–4)	2.6 ± 0.6	2.8 ± 0.7	0.076
CHA_2DS_2VASc (1–9)	1.4 ± 1.2	1.4 ± 1.1	0.706
AF history (months)	88.2 ± 74.8	81.2 ± 95.0	0.641
AAD treatment, N (%)	51 (66.2)	34 (54.8)	0.221
LA volume index (ml/m^2)	42.9 ± 16.0	38.1 ± 9.9	0.043
LA pressure, max (mm Hg)	23.8 ± 7.9	22.2 ± 7.1	0.222
LACT CS prox — RSPV (ms)	102.4 ± 21.6	93.3 ± 19.8	0.024
LACT CS dist - RSPV (ms)	105 ± 19.1	98.7 ± 28.2	0.117
LACT CS prox - CS dist (ms)	40.5 ± 10.1	40.1 ± 9.6	0.812

Figures are mean ± 1 standard deviation unless otherwise stated. Figures in parentheses are %.
Abbreviations: PersAF = Persistent atrial fibrillation; PAF = Paroxysmal atrial fibrillation; N = number of patients; BMI = body mass index; EHRA = European Heart Rhythm Association; AF = atrial fibrillation; AAD = Antiarrhythmic drug; LA = left atrium; LACT = left atrial conduction time; ms = milliseconds; CS prox = coronary sinus proximal electrodes; RSPV = right superior pulmonary vein; CS dist = coronary sinus distal electrodes.

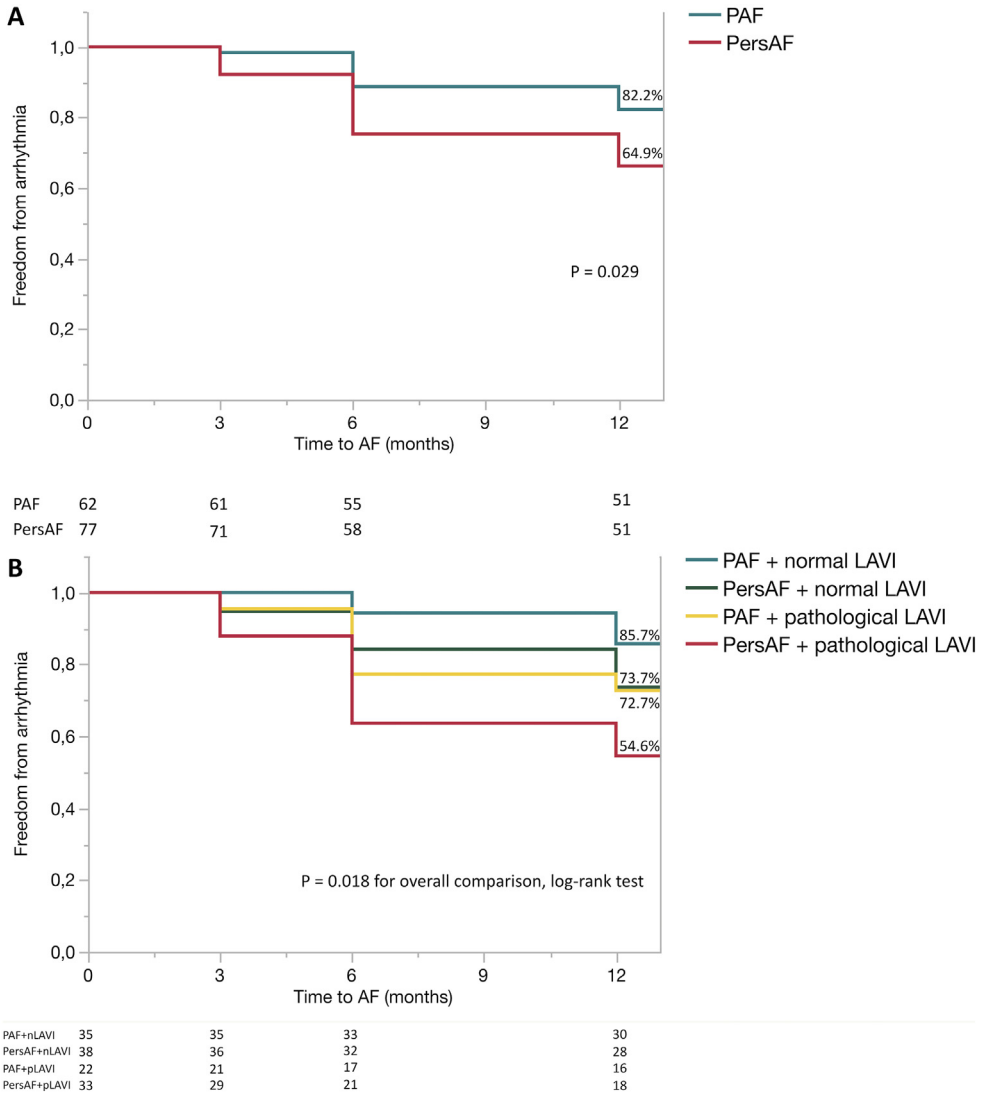

Fig. 1. Kaplan-Meier curves of freedom from arrhythmia after a first AF ablation procedure after 12 months follow up in patients with persistent AF (PersAF) and paroxysmal AF (PAF) in A, and in subgroups delineated by normal or pathological LAVI size in B. Footnote: The numbers below the figures denote the number of patients 'at risk' in each group. Abbreviations: PAF = paroxysmal AF; PersAF = persistent AF; PAFnLAVI = paroxysmal AF and normal left atrial volume index; PersAFnLAVI = persistent AF and normal left atrial volume index; PAFpLAVI = paroxysmal AF and pathological left atrial volume index; PersAFpLAVI = persistent AF and pathological left atrial volume index.

The frequency of continued AAD treatment after 12 months was 5/75 (6.7%), which did not differ from that in patients with PAF, 1/61 (1.6%), $p = 0.22$.

3.4. Procedure and acute outcome

The procedure time, fluoroscopy time, need for a touch-up with a focal catheter, single/dual application strategy and acute complete PVI are shown in Table 3, and none of the variables differed from those observed in the PAF group.

3.5. Left atrial pressure and conduction times

The left atrial pressures at baseline are shown in Table 1 and did not differ from those in PAF patients. Patients with PersAF had a longer LA conduction time on the vector between proximal electrodes on the coronary sinus catheter and the right superior PV (CS prox-RSPV) than in patients with PAF, while the other 2 vectors did not differ between the groups. Pacing in the other direction for each vector showed no differences between AF types (not displayed in Table 1).

3.6. Predictors of AF recurrences

Univariate analysis identified LA volume index ($p = 0.0046$) and type of AF ($p = 0.0345$) as predictors of freedom from arrhythmia recurrence. LA conduction time also entered analysis but added nothing significant to the model and only LA volume index remained significant in the multivariate regression analysis ($p = 0.0239$). The baseline LAVI in PersAF patients was 42.9 ± 16.0 ml/m^2, which was significantly higher than that in the PAF group (Table 1). The AF recurrence rate differed significantly between the patient groups related to AF type and LAVI (Fig. 1B) with the poorest outcome in PersAF patients with pathological LAVI while those with normal LAVI did not differ from PAF patients with pathological LAVI. Intergroup differences were not significant except for the group with PersAF and pathological LAVI, which had significantly worse outcome (freedom from AF) compared to all other groups, i.e. to PAF and high LAVI, 54.6% vs 72.7%,

Table 2
Treatment differences regarding symptoms and quality of life in patients with persistent AF as compared to those with paroxysmal AF.

Parameter	PAF		P value	PersAF		P value	Treatment Differences		P-value
	Baseline N = 62	12 mo *N* = 61		Baseline N = 77	12 mo *N* = 75		PAF	PersAF	
SSQ total	15.3 ± 4.1	9.3 ± 4.3	<0.0001	14.0 ± 3.9	9.0 ± 3.5	<0.0001	−6.0 ± 5.2	−5.0 ± 4.2	0.27
EHRA score	2.8 ± 0.7	1.2 ± 0.5	<0.0001	2.6 ± 0.6	1.3 ± 0.6	<0.0001	−1.6 ± 0.9	−1.3 ± 0.8	0.03
EQ5D-5L global	70.4 ± 15.8	78.4 ± 16.7	0.0036	67.2 ± 19.4	76.6 ± 18.6	0.0002	+7.7 ± 17.3	+10.4 ± 20.3	0.47
EQ5D-5L index	0.83 ± 0.14	0.88 ± 0.17	0.0896	0.84 ± 0.14	0.87 ± 0.18	0.1078	+0.05 ± 0.21	+0.03 ± 0.14	0.55

Figures are mean ± 1 standard deviation unless otherwise stated.
Abbreviations: PAF = Paroxysmal atrial fibrillation; PersAF = Persistent atrial fibrillation; mo = months; SSQ = Symptom severity questionnaire; EHRA = European Heart Rhythm Association; EQ5D-5 L = EuroQol Group 5 level EQ5D.

$p = 0.036$, and compared to PAF and normal LAVI, 54.6% vs 85.7%, $p < 0.0001$ (Fig. 1B).

3.7. Safety

Adverse events including hospitalization for any cardiac cause occurred in 8/77 (10.4%) PersAF patients which did not differ from the rate seen in PAF patients, 5/62 (8.1%), $p = 0.77$. The number of phrenic nerve paresis at discharge was 2/77 (2.6%), which was comparable to that in PAF patients, 2/62 (3.2%). There were no strokes, oesophageal fistulas or deaths and no patient had an unresolved adverse event at the 12 months follow-up.

4. Discussion

4.1. Freedom from arrhythmia recurrence

In this prospective study evaluating the outcomes of the 2nd generation cryoballoon for PVI in persistent AF patients, the observed rate of 64.9% freedom from arrhythmia was higher than reported for the first generation balloon [20] but comparable, 60–67%, to others using the 2nd generation cryoballoon [9,10]. The improved outcomes observed with the 2nd generation cryoballoon may be related to more durable PVI although one cannot rule out that the extensive antral lesions [21] also eliminates potential perpetuators/triggers. When compared to trials using RF energy in patients with PersAF, the freedom from atrial arrhythmia after a single procedure has varied between 35 and 67% in both controlled [22,23] and observational studies [24,25]. Despite the use of additional ablation strategies including a "step-wise approach" [26], ablation of complex fractionated atrial electrograms and extra linear lesions on top of PVI in PersAF patients [27–29], the freedom from recurrences have not exceeded those achieved with PVI using the 2nd generation cryoballoon, as seen in the present and other trials [9,10]. These findings are in line with the present perception that extra ablation lesions on top of PVI may be of limited value [30]. Randomized studies comparing the 2nd generation cryoballoon and the open-irrigated contact force RF ablation catheter for PVI are lacking, although in a small non-randomized study, the freedom from arrhythmia after a single procedure off AAD at 12 months was 28/50 (60%) for the cryotechnique and 27/50 (56%) for RF, $p = 0.71$ [31], which was comparable or somewhat lower than found in the present study.

The higher recurrence rates in patients with persistent as compared with paroxysmal AF has been well known for both RF energy [32] and the first generation cryoballoon technique [33]. In a retrospective study with the 2nd generation cryoballoon, the freedom from arrhythmia recurrence after a single procedure was 61.3% for PersAF and 85.8% for PAF patients, $p < 0.001$ [34]. Despite improved properties developed in the 2nd generation balloon with a wider cooling area encompassing the entire frontal hemisphere rather than an equatorial band [35], the AF recurrence rate has still remained higher in PersAF patients than in PAF patients, as was shown in the present prospective trial.

The procedure, fluoroscopy, and cryoapplication time, as well as the achieved acute complete PVI were similar in both patient groups, indicating that the anatomy or tissue characteristics did not infer a more demanding procedure or that acute PVI was more difficult to achieve in PersAF versus PAF patients. Although the mechanism behind AF recurrences after PVI is most commonly PV re-conduction [24,25], as confirmed in the present study, it remains unclear why the AF recurrence rate is higher for PersAF than for PAF. A possible explanation may be that it is more difficult to achieve durable PVI in PersAF patients, as indicated by the higher AF recurrence and PV reconduction rates. Moreover, one cannot exclude that, in terms of durable PVI, a double freeze by the cryoballoon may be more effective, even though the comparison of outcome between single and double freezes in this study gave no indication of such difference. A contributing explanation for the poorer outcome in patients with persistent AF may be that other mechanisms beyond the PVs such as atrial substrates may be of importance. This was explored in a recent small randomized study [36], comparing ablation of repetitive-regular activities added to PVI versus PVI alone, although the results needs to be confirmed in larger prospective randomized trials.

Table 3
Procedure characteristics.

Parameter	PersAF N = 77	PAF N = 62	P-value
Procedure time (minutes)	104.8 ± 37.4	113.7 ± 31.2	0.129
Fluoroscopy time (minutes)	15.7 ± 10.7	18.7 ± 10.7	0.103
Cryoapplication time (seconds)	1605 ± 659	1521 ± 557	0.415
Single/dual application, N	35/42	34/28	0.308
Touch-up catheter[a], N (%)	2 (2.6)	4 (6.5)	0.407
Complete PVI	75 (97.4)	61 (98.4)	>0.999

Figures are mean ± 1 standard deviation unless otherwise stated.
Abbreviations: PersAF = Persistent atrial fibrillation; PAF = Paroxysmal atrial fibrillation; N = number of patients; Cryoapplication = Cryoballoon application; PVI = pulmonary vein isolation.
[a] Use of any focal catheter to add additional lesions to achieve pulmonary vein isolation.

4.2. Symptoms of AF and QoL

The observation that the improvement in EHRA score was significantly larger in the PAF group, may in part be related to their lower quality of life (numerically higher EHRA score) at baseline than observed in the PersAF group, which was an expected finding as PAF patients are more symptomatic than PersAF patients [37]. Even though the AF recurrence rate was higher in the PersAF group, it did not translate into a higher re-ablation rate, which was not surprising as the main driver for redo ablation is AF symptoms and QoL, which did not differ between the patient groups at 12 months. It is further consistent with the equal rate of continued AAD treatment and similar level of quality of life at 12 months, and casts further doubt on the usefulness of "short episodes

of atrial arrhythmia" as the primary outcome when comparing clinical efficacy in AF ablation trials.

4.3. Predictors of arrhythmia recurrence

Among the clinical variables analysed for predicting AF recurrence, LA volume was equally important as the type of AF in the present study (Fig. 1B). The LA volume has been identified as a predictor for AF recurrence after both RF [38] and 2nd generation cryoballoon procedures [17]. In the latter observational study [17], an LA area > 21 cm^2 and a history of AF > 2 years were the two most important risk factors for AF relapses in patients with PersAF. The observation that LAVI >42 ml/m^2 in our study predicted relapse of arrhythmia and that PersAF patients with normal LAVI had comparable outcomes as PAF patients with increased LAVI is consistent with a previous trial using RF energy [39], which also showed that depending on the LA volume the relapse rate in PAF patients could even be higher than that observed in patients with non-paroxysmal AF (20.0% vs. 10.9% per person-year, respectively, $p = 0.041$). The higher AF recurrence rate in PersAF patients versus in those with PAF in the present study, may in part be explained by their higher BMI, and higher LAVI, shown to be predictors of AF recurrence [13,14,39].

The longer LA conduction times in one of the explored pacing vectors at baseline in the PersAF versus the PAF group may reflect their larger LA volume or the presence of fibrosis. Large areas of low voltage (> 30% of the LA area) has been reported as a powerful predictor of AF recurrence after AF ablation [15]. The acquisition of high-density voltage maps is time-consuming whereas a conduction time is easily acquired, the value of which needs to be further explored for prediction of outcome in PersAF patients.

5. Limitations

Patients and physicians were not blinded to AF type or findings at follow up. While repeated 7-day Holter's constitutes a reasonable level of arrhythmia monitoring, implantable loop recorders would have been more accurate for the assessment of arrhythmia recurrence and AF burden, which may be more closely linked to symptoms of AF. The study is based on a small number of patients and findings need to be confirmed in a larger trial.

6. Conclusion

Both symptoms and QoL improved significantly in patients with PersAF after ablation compared to baseline. Freedom from AF was clinically significant but lower than in PAF patients. The cryoballoon seems to be a feasible and effective technique also in patients with persistent AF.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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