Results and Predictive Factors After One Cryoablation for Persistent Atrial Fibrillation

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Cryoballoon pulmonary vein isolation (PVI) for persistent atrial fibrillation (AF) ablation is an increasingly used strategy. We aimed to determine the results and predictors of arrhythmia recurrence after a single procedure of cryoballoon PVI for patients with persistent and long-standing persistent AF. We included all consecutive patients who underwent cryoballoon PVI for the treatment of persistent symptomatic drug-refractory AF since 2012. All patients were prospectively followed to detect the recurrence of atrial tachyarrhythmia (ATa). Predictors of recurrence were assessed. Cryoballoon PVI was performed on 399 patients with persistent AF, among whom 52 (13%) had long-standing persistent AF. Patients with long-standing persistent AF had a significantly larger left atrium than those with persistent AF. A 28-mm cryoballoon was used for 322 patients (93%). In total, 359 patients (90%) completed the 12-month follow-up visit and the median follow-up was 24 months (interquartile range 43 to 13). The 2-year probability of freedom from ATa recurrence was 51% for persistent AF and 27% for long-standing persistent AF. Long-standing persistent AF and left atrial area/volume were independent predictors of ATa recurrence. Ten patients (2.5%) experienced phrenic nerve palsy, 1 tamponade (0.25%), 2 stroke (0.5%), 2 pericardial effusions (0.5%), and 5 vascular complications (1.25%). In conclusion, 2-year ATa-free survival rates were 51 and 27% for persistent and long-standing persistent AF patients, respectively. Complications were rare. Long-standing persistent AF and left-atrial area/volume were predictors of recurrence. **(Am J Cardiol 2021;159:65−71)**

Standalone pulmonary vein isolation (PVI) as the first step of a strategy for the ablation of persistent atrial fibrillation (AF) may be an option, as the addition of linear ablation or the ablation of complex fractionated electrograms is not superior to PVI alone.[1] The proportion of patients in sinus rhythm after one procedure of cryoballoon PVI for persistent AF ranges from 50 to 72%.[2−16] The interpretation of the results of these studies is limited by the short follow-up of under 2 years, except for one, which reached 37 months.[11] Moreover, only 2 studies have followed large cohorts of 609[14] and 486 patients[10] and provided results for patients with long-standing persistent AF. Given the recurrence rate, it would be useful to identify long-term predictors of recurrence before performing the procedure. Data concerning such predictors have been published[2,3,6,7,9,11,12,14,15] but only 3 studies included left atrium dimension.[11,14,15] Here, we evaluated the results and predictors of recurrence after a long follow-up of 2 years for a large cohort of patients who were treated for persistent and long-standing persistent AF by cryoablation.

Method

We prospectively included all consecutive patients who underwent cryo-PVI for the treatment of persistent drug-refractory AF from the introduction of second generation cryoballoon ablation to the Amiens University Hospital in September 2012 to November 2019. Patients provided their signed informed consent to participate in the registry and the study was approved by the local ethics committee. Data files of the registry were declared to and authorized by the French data protection committee (Commission Nationale Informatique et Liberté, CNIL) (PI2020_843_0120).

The primary objectives of the study were to assess the success rates and complication rates after one cryo-PVI procedure. The secondary objective was to establish the long-term predictive factors of ATa.

Patients were included if they presented symptomatic persistent AF, documented by 12-lead ECG, refractory to at least one class I or III antiarrhythmic drug. AF was classified according to the 2020 ESC Guidelines for the management of AF.[17] The diagnosis-to-ablation time was defined by the time between the first episode of AF and ablation. Exclusion criteria were (1) prior left atrial (LA) ablation, (2) LA tachycardia at the time of cryoablation, (3) having a

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prosthetic heart valve, (4) being a minor (<18 years old), and (5) no follow-up after the cryo-PVI procedure.

LA area was measured during echocardiography in a 4-chamber view. LA volume was obtained from multidetector computed tomography and segmentation by AW VolumeShare 5 software (General Electric Company, Fairfield, CT). The first centimeter of each pulmonary vein and the LA appendage were included in the determination of LA volume. Hypertension was defined as repeated office or out-of-office systolic blood pressure values ≥140 mm Hg and/or diastolic blood pressure values ≥90 mm Hg[18] before treatment for hypertension.

Cryoballoon ablations were preceded by at least 3 weeks of treatment with an oral anticoagulant and then contrast-enhanced multislice CT of the left atrium. The cryo-PVI procedure has been described in detail elsewhere.[19] Briefly, access to the left atrium was gained after fluoroscopy-guided trans-septal puncture (SL1, St Jude Medical). Only one 4-minute application was performed with a second- or third-generation cryoballoon (the 23- or 28-mm Advance balloon, Cryocath, Medtronic, Dublin, Republic of Ireland). An intraluminal catheter (Achieve, Medtronic) was used for all procedures. A second cryoapplication was performed (to achieve a complete block) only if there was persistent atrio-venous conduction. A quadripolar catheter was used to continuously pace the phrenic nerve adjacent to the superior vena cava during cryoablation over the right pulmonary veins. Cryoablation was discontinued immediately if there was loss of diaphragmatic contraction to avoid right phrenic nerve palsy. A temporary subcutaneous venous figure-of-eight suture was used for all patients to achieve hemostasis.

Oral anticoagulation was maintained for patients treated with a vitamin K antagonist. Oral anticoagulation was withdrawn 48 hours before the procedure for patients treated with a direct oral anticoagulant (until October 2017) or maintained (from November 2017 onwards). For all patients, heparin was administered as an initial bolus after the trans-septal puncture and then administered continuously to maintain the target activated clotting time (>300 seconds).

Data collected during the procedure included the duration of the time to effect (TTE), minimal temperature reached during application in each PV, cumulative duration of cryo-application in each PV, number of cryo-applications for each PV, and the duration of the time under fluoroscopy and fluoroscopy exposure.

All adverse events occurring during the procedure or within the following month were recorded and described. Vascular complications included vascular pseudo aneurysms, arteriovenous fistulae, hematomas, and puncture-side hemorrhages. After ablation, antiarrhythmic drugs were maintained for at least the blanking period of 3 months. Anticoagulants were continued for at least the first 3 months.

Patients were followed up in our institution at 3, 6, and 12 months with a physical examination, questions about arrhythmia-related symptoms, a 12-lead ECG, and 24-hour Holter monitoring. After the first year, patients were followed up by their cardiologists at least once a year with a 12-lead ECG and 24-hour Holter monitoring. Any symptoms following ablation were evaluated by 12-lead ECG and 24-hour Holter monitoring. Previously implanted pacemakers or dual-chamber implantable cardioverted defibrillators were assessed at each visit.

The primary end point was the recurrence of atrial tachyarrhythmia (ATa), defined as a documented episode of AF, LA flutter, or atrial tachycardia (whether symptomatic or not) lasting for 30 seconds or more on any cardiac rhythm recording made during a planned or symptom-driven consultation after the 3-month blanking period. Recurrences of right atrial flutter (confirmed by an electrophysiological study) were not included.

The secondary end point was the frequency of complications of any type during the procedure or within the following month. Continuous variables are expressed as the mean ± standard deviation (SD) or median interquartile range for normally and non-normally distributed data, respectively, and were compared using Student's *t* test or the Mann-Whitney-Wilcoxon test, as appropriate. Categorical variables are expressed as the frequency (percentage) and were compared using a chi-squared test or Fisher's exact test.

The cumulative probability of ATa-free survival was estimated using the Kaplan-Meier method. Survival curves were compared using the Log-rank test. Cox proportional hazard models were used to identify factors associated with ATa recurrence, with an estimation of the hazard ratios (HRs) and 95% confidence intervals. Variables with a p value <0.10 in univariate analysis were included in a multivariate Cox model. All tests were 2-tailed and the limit for statistical significance was set at p <0.05. Statistical analysis was performed using SPSS for Windows software, version 22.0 (SPSS Inc., Chicago, IL). The only missing data concerned the LA area (27%), procedure time (6%), balloon in/out (5%), fluoroscopy time (9%), fluoroscopy exposure (11%), and cryotherapy time (8%).

Results

In total, 417 patients met the inclusion criteria. Two patients were in LA flutter during the procedure, 7 were lost to follow-up immediately after the procedure, and 9 had a prosthetic heart valve; all 18 were excluded. Cryo-PVI was performed on 399 patients with persistent AF (mean age: 61 ± 9 years; males = 316, 79%). Among them, 52 (13%) had long-standing persistent AF (Table 1). The mean time between the first AF episode and ablation (diagnosis to ablation time) was 17 ± 19 months.

Patients with long-standing persistent AF had a significantly larger left atrium than patients with persistent AF: area: 30 ± 4 vs 26 ± 5 cm^2 (p <0.001), volume: 197 ± 37 vs 161 ± 41 ml (p <0.001), and indexed volume: 89 ± 16 vs 77 ± 20 ml/m^2 (p <0.001).

Eighty-six persistent AF patients (25%) were in sinus rhythm at the beginning of the procedure (Supplementary Table 1). A 28-mm cryoballoon was used for 322 patients (93%). A left PV block was achieved for all patients. A right superior PV block was achieved for 394 patients (99%) and a right inferior PV block for 396 (99%).

We observed 10 cases (2.5%) of unresolved phrenic nerve palsy at discharge, one of tamponade (0.25%), 2 of stroke (0.5%), 2 of pericardial effusion (0.5%), and 5 of vascular complications (1.25%). There was no procedure-related death. There was no diminution/attenuation of

Table 1
Patient characteristics at baseline

Variable	All patients	Persistent AF (n = 347)	Long-standing persistent AF (n = 52)	p
Age (years ± SD)	61 ± 9	60 ± 9	61 ± 9	0.82
Men	316 (79%)	272 (78%)	44 (85%)	0.36
Height (m)	1.75 ± 0.1	1.75 ± 0.1	1.76 ± 0.1	0.46
Weight (kg)	91 ±18	90 ± 17	98 ± 18	**0.002**
Body mass index (kg/m^2)	30 ± 5	29 ± 5	32 ± 5	**0.002**
Body surface area (m^2)	2.1 ± 0.2	2.1 ± 0.2	2.2 ± 0.2	**0.003**
Diagnosis-to-ablation time (months)	17 ± 19	16 ± 20	28 ± 16	**<0.001**
Number of cardioversions	0.8 ± 0.9	0.7 ± 0.9	1.2 ± 0.9	**0.001**
Clearance (ml/min)	81 ± 21	81 ± 21	83 ± 26	0.51
Clearance < 60ml/min	61 (15%)	51 (15%)	10 (19%)	0.41
Hypertension	193 (48%)	164 (47%)	29 (56%)	0.30
Diabetes mellitus	52 (13%)	44 (13%)	8 (15%)	0.66
Stroke	28 (7%)	25 (7%)	3 (6%)	1
Heart failure	78 (19%)	67 (19%)	11 (21%)	0.71
Coronary artery disease	46 (11%)	38 (11%)	8 (15%)	0.35
Absence of SHD	259 (65%)	228 (66%)	31 (60%)	0.44
Antiarrhythmic drug therapy	232 (58%)	208 (60%)	24 (46%)	0.07
CHA_2DS_2-VASc score	1.7 ± 1.4	1.7 ± 1.4	1.7 ± 1.5	0.07
0	96 (24%)	86 (25%)	10 (19%)	
1	115 (29%)	97 (28%)	18 (35%)	
2	77 (19%)	68 (20%)	9 (17%)	
3	64 (16%)	53 (15%)	11 (21%)	
4	33 (8%)	31 (9%)	2 (4%)	
≥ 5	14 (4%)	12 (3%)	2 (4%)	
Previous cavotricuspid isthmus ablation	29 (7%)	26 (7%)	3 (6%)	1
LA and LV parameters				
LA area (cm^2)	26 ± 5	26 ± 5	30 ± 4	**<0.001**
LA volume (ml)	165 ± 42	161 ± 41	197 ± 37	**<0.001**
LA volume Index (ml/m^2)	78 ± 20	77 ± 20	89 ± 16	**<0.001**
LVEF (%)	54 ± 12	54 ± 12	53 ± 12	1
LVEF ≤ 40%	74 (18%)	62 (18%)	12 (23%)	0.68
PV anatomy				
LSPV diameter (mm)	19 ± 2	19 ± 2	20 ± 2	0.08
LIPV diameter (mm)	17 ± 2	17 ± 2	18 ± 2	**0.02**
RSPV diameter (mm)	20 ± 2	20 ± 2	20 ± 2	0.06
RIPV diameter (mm)	19 ± 2	19 ± 2	20 ± 3	0.004
LCT	63 (16%)	54 (16%)	9 (17%)	0.69
Accessory vein	51 (13%)	48 (14%)	3 (6%)	0.12

AF = atrial fibrillation; LA = left atrium; LCT = left common trunk of pulmonary veins; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; LVEF = left ventricular ejection fraction; LV = left ventricle; PV = pulmonary veins; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SHD= structural heart disease.

diaphragm contractions in any of the 10 phrenic nerve palsy cases. The minimum temperature for these patients was 52 ± 6°C (vs 48 ± 8°C, p = 0.12) for RIPV and 51 ± 7°C (vs 50 ± 10°C, p = 0.83) for RSPV. Eight patients had persistent phrenic nerve palsy at the first follow-up visit and only one at the 1-year follow-up. There was no significant difference in the duration of the procedure between the 2 patients who experienced stroke and those who did not. There were no long-term complications directly relatable to the cryoablation procedure identified during follow up, in particular, atrio-oesophageal fistulae. Eleven patients died during follow-up (3 cancer, 4 terminal heart failure, 1 car accident, 1 stroke, 2 no information). Three patients experienced a late thromboembolic event.

All patients completed the 6-month follow-up visit and 359 (90%) the 12-month follow-up visit. The median follow-up was 24 months (interquartile range 43 to 13). Among all patients, ATa recurred for 211 (53%) within a mean of 12 ± 14 months. Seventy-one patients (34%) relapsed after 12 months. The 1-, 2-, and 3-year probabilities of freedom from ATa recurrence were 63% [60; 65], 48% [45; 51], and 38% [35; 42], respectively. Fifty-six patients (30%) without recurrence were still on an antiarrhythmic drug at last follow-up (31 on Amiodarone, 18 on Flecaïnide, 7 on Sotalol). Among the 347 patients with persistent AF, the 1-, 2- and 3-year probabilities of freedom from ATa recurrence were 66% [64; 69], 51% [48; 54], and 42% [38; 45], respectively (Figure 1). Among the 52 patients with long-standing persistent AF, the 1-, 2- and 3-year probabilities of freedom from ATa recurrence were 40% [33; 47], 27% [20; 33], and 18% [10; 25], respectively.

The results of the univariate analysis concerning the risk of ATa recurrence are shown in Table 2. After multivariate

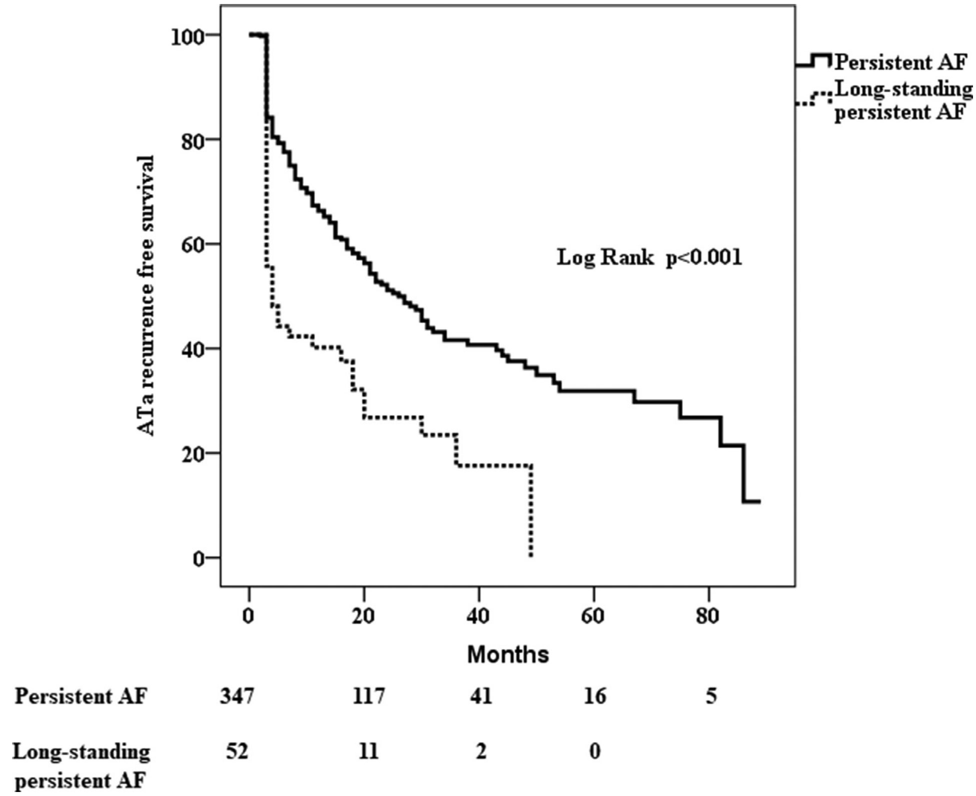

Figure 1. ATa-free survival for persistent versus long-standing persistent AF.

Table 2
Predictive factors of ATa recurrence after univariate analysis

Variable	No ATa recurrence (n = 188)	ATa recurrence (n = 211)	HR univariate analysis CI [95% CI]	p
Age (years ± SD)	60 ± 9	61 ± 9	1.01 [0.99; 1.02]	0.18
Men	146 (78%)	170 (81%)	0.96 [0.68; 1.35]	0.81
Height (m)	1.76 ± 0.1	1.75 ± 0.1	0.91 [0.19; 4.18]	0.90
Weight (kg)	89 ± 18	93 ± 17	1.006 [0.99; 1.01]	0.14
Body mass index (kg/m^2)	29 ± 5	30 ± 5	**1.03 [1.00; 1.05]**	**0.051**
Body surface area (m^2)	2.1 ± 0.2	2.1 ± 0.2	1.47 [0.86; 2.53]	0.16
Diagnosis-to-ablation-time (months)	15 ± 18	19 ± 21	1.005 [0.99; 1.01]	0.15
Long standing persistent AF	13 (7%)	39 (18%)	**2.06 [1.45; 2.93]**	**<0.001**
Clearance (ml/min)	81 ± 21	82 ± 22	0.99 [0.99; 1.004]	0.52
Clearance ≤ 60 ml/min	30 (16%)	31 (15%)	1.02 [0.70; 1.49]	0.92
Hypertension	82 (44%)	111 (53%)	**1.37 [1.05; 1.80]**	**0.022**
Diabetes mellitus	23 (12%)	29 (14%)	1.26 [0.85; 1.87]	0.25
Heart failure	46 (24%)	32 (15%)	0.69 [0.47; 1.007]	0.054
Coronary artery disease	14 (7%)	32 (15%)	1.42 [0.98; 2.08]	**0.07**
Absence of SHD	125 (66%)	134 (63%)	0.92 [0.70; 1.22]	0.57
CHA_2DS_2-VASc score	1.6 ± 1.4	1.7 ± 1.4	1.09 [0.99; 1.20]	**0.08**
Previous cavotricuspid isthmus ablation	14 (7%)	15 (7%)	0.94 [0.55; 1.59]	0.81
LA area (cm^2)	25 ± 5	27 ± 5	**1.07 [1.03; 1.10]**	**<0.001**
LA volume (ml)	158 ± 43	172 ± 40	**1.007 [1.004; 1.01]**	**<0.001**
LA volume index (ml/m^2)	76 ± 20	81 ± 20	**1.01 [1.006;1.02]**	**<0.001**
LVEF (%)	53 ± 12	54 ± 12	1.001 [0.99; 1.01]	0.82
LVEF < 50%	53 (28%)	46 (22%)	0.86 [0.62; 1.20]	0.37
LVEF ≤ 40%	39 (21%)	35 (17%)	0.92 [0.64; 1.32]	0.66
LCT	28 (15%)	35 (17%)	1.02 [0.71; 1.46]	0.92
Accessory vein	20 (11%)	31 (15%)	1.39 [0.95; 2.03]	0.09
Third-generation balloon	24 (13%)	26 (12%)	0.92 [0.61; 1.39]	0.69
Fourth-generation balloon	51 (27%)	27 (13%)	0.98 [0.65; 1.48]	0.93
Cavotricuspid isthmus ablation at PVI	31 (16%)	37 (17%)	0.91 [0.64; 1.30]	0.61

AF = atrial fibrillation; ATa = atrial tachyarrhythmia; LA = left atrium; LCT = left common trunk; LV = left ventricle; LVEF = left ventricle ejection fraction; PVI = pulmonary vein isolation; SHD = structural heart disease.

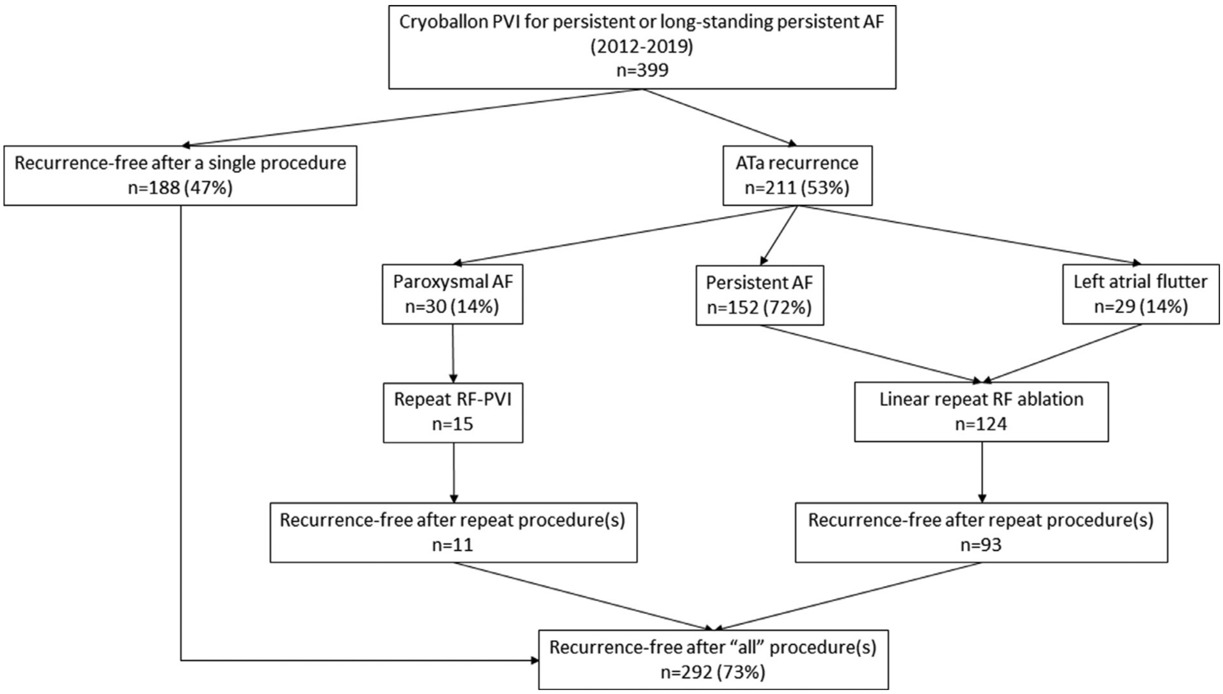

Figure 2. Results after 1 cryo-PVI and repeat procedures.

analysis that included BMI, long-standing persistent AF, hypertension, coronary artery disease, CHA_2DS_2-VASc score, and LA area, the predictors of recurrence of ATa were long-standing persistent AF (HR = 1.83, CI [1.22; 2.75], p = 0.003) and LA area (HR = 1.05, CI [1.02; 1.09], p = 0.002). After multivariate analysis that included the same variables but in which LA area was replaced with LA volume, the predictors of recurrence of ATa were long-standing persistent AF (HR = 1.68, CI [1.16; 2.44], p = 0.006) and LA volume (HR =1.006, CI [1.002; 1.009], p = 0.001).

Among the 211 patients who had a recurrence, 139 (66%) underwent at least one repeat procedure (Figure 2). Patients who had a recurrence of paroxysmal AF underwent radiofrequency (RF) repeat PVI. Patients who had a recurrence of persistent AF or left atrial flutter underwent linear RF ablation. During the first repeat procedure, 80 patients (58%) had at least one reconnected PV. The mean number of reconnected PVs was 0.94. Along these 139 patients, 104 (75%) had not experienced a recurrence at the last follow-up. Finally, 292 patients (188 after a single procedure and 104 after repeat procedures, 73%) were free of recurrence at the last follow-up.

Discussion

In this large cohort, we establish that cryo-PVI alone for persistent AF is a safe and effective strategy. Long-term predictors of recurrence were long-standing persistent AF and LA dimension.

Among the 347 patients with persistent AF, the 2- and 3-year probabilities of freedom from ATa recurrence were 51% and 42%. Sawhney et al[14] recently published a long-term follow-up study of 487 patients with persistent AF, with a success rate of 64% at 24 months after a single cryoballoon PVI procedure. The difference from our reported success rate of 51% at 2 years, while all patients were off-AADs (vs 30% on AADs in our study), may be explained by more evolved AF in our study, with a mean atrial area of 26 cm^2. Four other studies with a long follow-up of 22,[6] 20,[5] and 18 months[10,15] reported recurrence rates similar to ours of 56%, 50%, 51.5%, and 53%, respectively. Other studies published on this subject[2–4,7–9,12,13,16] reported results after short-term follow-up of approximately 1 year, with logically better success rates than ours (from 54.8% to 72%, Supplementary Table 2). An alternative strategy for persistent AF ablation is to add substrate modification to PVI. In the meta-analysis of Clarnette et al,[20] the single-procedure success rate was 46% for both PVI plus complex fractionated atrial electrograms ablation and PVI ablation plus linear lesions, within the same range as our success rate.

Studies of Tondo et al[10] and Sawhney et al[14] provide data about one procedure of cryoballoon PVI for long-standing persistent AF. Tondo et al[10] reported a probability of 1-year freedom from AF recurrence of 63.1% for 52 patients with long-standing persistent AF. Sawhney[14] reported an arrhythmia-free survival rate of 57% at 24 months follow-up. We report worse results, with only 27% of patients free of ATa after 2 years. This difference could be explained by the longer follow-up in our study (vs Tondo). Moreover, the mean LA volume was 74.8 ml in the study of Tondo et al, whereas it was 165 ml in ours, which confirms that we included more evolved patients. In any case, the difference cannot be explained by the rate of AAD maintenance, which was similar between the study of Tondo and ours. Our results lead to 2 conclusions. First, cryoballoon PVI as an index procedure for long-standing persistent AF should, in most cases, be the first step of a stepwise approach, which should include (an)other procedure(s). Second, our results provide a supplementary argument for the strategy of early intervention to improve the outcome after AF ablation. Kirchhof et al[21] recently showed that early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes.

In the meta-analysis of Andrade,[22] as well as in the Fire and Ice trial,[23] complication rates of cryoballoon ablation were found to be very low. The phrenic-nerve palsy rate was 4.73% and 2.7%, respectively. Our results are in the same range, with a rate of 2.5%. In our study, 0.5% of patients had strokes, 0.25% tamponade, and 1.25% vascular complications. Our results are very close to those of the aforementioned studies, which showed 0.57% and 0.5% thromboembolic events, 0.47 and 0.3% tamponade, and 1.79% and 1.9% vascular complications, respectively.

After multivariate analysis, we found long-standing persistent AF and LA area/LA volume to be predictors of recurrence. It is logical that we found the LA area/volume to be predictors of recurrence, as published studies already identified LA diameter[14,15] and LA area[11] as predictors. Only 2 studies[2,11] included LA area (measured in echocardiography) in their Cox Model and none included LA volume, which is less subject to interobserver variability.[24,25] Long-standing persistent AF has already been described as a strong predictive factor of recurrence. Thus, this item is included in the MB LATER[26] and CAAP AF[27] scores. Similarly, diagnosis-to-ablation time[3,7,11,14] has been shown to be predictor of recurrence after cryoballoon PVI for persistent AF, in numerous studies. Relapse during the blanking period[2,3,9,12] is widely cited as an independent predictor, but we chose not to test it in our study because these data are available only after the decision to perform the procedure. It has no clinical relevance in the decision of whether to perform the procedure nor how to perform the first procedure.

This was a single-center study, and its conclusion can therefore not be extrapolated to other centers. However, we present the third largest cohort of cryoballoon ablation for persistent AF. Our protocol of atrial arrhythmia monitoring after cryo-PVI does not include continuous monitoring but corresponds to that of other studies and to real-life practice. Given the fact that 30% of the patients without recurrence were still on antiarrhythmic drugs at the last follow-up, we cannot exclude that the success rates described here are due to the combined effects of the cryo-PVI and continued medication. The measurement of the LA area in echocardiography is subject to interobserver variability and conclusions based on these data need to be made with caution. However, volume measurements by tomography are readily available but rarely mentioned in published studies. They represent an original parameter that is less subject to imprecision.

In conclusion, 2-year ATa-free survival rates were 51 and 27% for persistent and long-standing persistent AF patients, respectively. Complications were rare. The independent long-term predictors of recurrence were long-standing persistent AF and LA area/volume. Treatment by cryo-PVI for persistent AF appears to be reasonable, but insufficient for long-standing persistent AF.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.07.052.

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