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Linear lesions for treating the recurrence of persistent atrial tachyarrhythmia after cryoballoon ablation of atrial fibrillation

Abbreviated title: Lines for persistent recurrences after cryoablation of AF

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Summary

Background. – There is no consensus on the most effective radiofrequency ablation strategy for the initial or repeated treatment of persistent atrial tachyarrhythmia (ATa).

Objective. – To describe success and complication rates after the creation of left atrial (LA) linear lesions for recurrent persistent ATa following an index cryoballoon pulmonary vein isolation (PVI), and to identify predictors of ATa recurrence.

Methods. – During March 2013 to March 2020, we prospectively included all consecutive patients undergoing repeat procedures for the treatment of persistent ATa. Radiofrequency ablation consisting of the creation of linear lesions: a roof line, a mitral isthmus and/or septal line, and a cavotricuspid isthmus line. All patients were prospectively followed up for ATa recurrence.

Results. – Overall, 133 patients underwent 170 procedures after initial cryoballoon PVI ($n = 715$). At least one pulmonary vein reconnection was observed in 60 patients (45.1%), all of whom underwent successful re-disconnection. After all the procedures, > 90% of patients had a lesion pattern consisting of a roof line, a mitral isthmus and/or septal line, and a cavotricuspid isthmus line. ATa was terminated in 41 patients (35%). There were three cases of tamponade (3/170 procedures, 1.8%). Ninety-two patients (69.2%) were in sinus rhythm after a median (interquartile range) of 36 (21–53) months since the index cryoballoon PVI. Diagnosis-to-ablation time and LA area were predictors of recurrence in multivariable analysis.

Conclusion. – The creation of linear lesions is a safe and effective treatment strategy for the recurrence of persistent ATa after cryoballoon PVI. Longer diagnosis-to-ablation time and larger LA area were predictive of ATa recurrence.

Résumé

Contexte. – Il n'y a pas de consensus sur la stratégie d'ablation la plus efficace pour le traitement des tachyarrhythmies atriales (TAa) persistantes, que cela soit au moment d'une première procédure, ou au moment d'une reprise.

Objectif. – Etablir les taux de succès et de complication après la création de lignes dans l'oreillette gauche (OG), pour traiter les récurrences de TAa persistantes après une première procédure d'isolation des veines pulmonaires (IVP) par cryoballoon, et identifier les facteurs de risque de récurrence.

Méthodes. – Nous avons inclus de façon prospective tous les patients consécutifs de Mars 2013 à Mars 2020 ayant bénéficié d'une ou plusieurs reprise(s) pour le traitement de TAa persistantes.

L'ablation par radiofréquence consistait à la création de lignes : une ligne du toit, une ligne de l'isthme mitral et/ou une ligne septale, et une ligne de l'isthme cavo-tricuspide. Les patients ont été suivis prospectivement pour détecter les récurrences de TAa.

Résultats. – Au total, 133 patients ont bénéficié d'un total de 170 reprises en radiofréquence après une première IVP par cryoballoon ($n = 715$). Au moins une veine pulmonaire était reconnectée pour 60 patients (45.1%). Après la dernière reprise, plus de 90 % des patients ont bénéficié de la création de trois lignes. La TAa s'est arrêtée pendant les tirs pour 51 patients (35%). Nous déplorons trois tamponnade (3/170, 1.8%). Quarante-deux patients (69.2%) étaient en rythme sinusal après un suivi médian de 36 (21–53) mois. L'ancienneté de la fibrillation auriculaire et la surface de l'OG sont les facteurs pronostics indépendants de récurrence.

Conclusion. – La création de ligne est une stratégie ablatrice sûre et efficace pour traiter les récurrences de TAa persistante après une IVP par cryoballoon. L'ancienneté de la fibrillation auriculaire et la surface de l'OG prédisent les récurrences.

KEYWORDS

Persistent atrial fibrillation;

Atrial tachyarrhythmia;

Cryoballoon pulmonary vein isolation;

Radiofrequency ablation;

Linear lesions

MOTS CLÉS

Fibrillation atriale persistante ;

Tachyarrhythmie atriale ;

Isolation des veines pulmonaires par cryoballoon ;

Ablation par radiofréquence ;

Lignes

Abbreviations: AF, atrial fibrillation; ATa, atrial tachyarrhythmia; CFAE, complex fractionated atrial electrograms; CI, confidence interval; CIRCA-DOSE, Cryoballoon vs Irrigated Radiofrequency Catheter Ablation: Double Short vs Standard Exposure Duration; CT, computed tomography; CTI, cavotricuspid isthmus; ECG, electrocardiogram; HR, hazard ratio; IQR, interquartile range; LA, left atrial; LAT, left atrial tachycardia; LVEF, left ventricular ejection fraction; PV, pulmonary vein; PVI, pulmonary vein isolation; PWI, posterior wall isolation; RF, radiofrequency; SD, standard deviation; STAR AR II, Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II.

Background

There is no consensus on the most effective lesion strategy for the ablative treatment of persistent atrial fibrillation (AF). Isolation of the pulmonary veins (PVs) is necessary, but not always sufficient [1]. However, the addition of linear lesions or the ablation of complex fractionated atrial electrograms (CFAEs) did not improve outcomes in the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II (STAR AF II) [2]. This finding has been confirmed by two recent meta-analyses. The first [1] concluded that PV isolation (PVI) is at least as effective as other contemporary persistent AF ablation strategies. The second [3] showed that linear ablation, posterior wall isolation (PWI), and CFAE ablation improve intraprocedural AF termination, but that this termination is not predictive of improved long-term outcomes.

The question of the best lesion strategy also arises for patients in whom persistent, symptomatic, atrial tachyarrhythmia (ATa) recurs after initial cryoballoon PVI. Coutiño et al. [4] and Heeger et al. [5] studied small series of patients ($n = 24$ and 32 , respectively) treated with linear lesions and/or CFAE ablation. The success rates after the various procedures were 75.0% and 65.6%, respectively.

In our institution (Amiens University Hospital, Amiens, France), we have used the same strategy (three linear lesions) since 2013 to treat recurrences of persistent ATa after an index cryoballoon PVI. In the present study, we assessed the outcomes of this strategy and evaluated predictors of recurrence after long-term (2-year) follow-up in a cohort of consecutive patients having been treated for recurrent, persistent ATa by the creation of three linear lesions after an index cryoballoon PVI.

Methods

Study design

We prospectively included all consecutive patients who underwent ≥ 1 radiofrequency (RF) ablation procedures between March 2013 and March 2020 for the treatment of persistent ATa recurring after an index cryoballoon PVI at Amiens University Hospital. Patients provided their written informed consent to participate in the registry. In line with the French legislation on studies of routine clinical practice, the study protocol was approved by a hospital committee with competency for studies not requiring approval by an institutional review board. The registry database was registered with the

French National Data Protection Commission (Commission nationale de l'informatique et des libertés; Paris, France; reference: PI2020_843_0130).

The primary objective of the current study was to evaluate the success and complication rates after repeat procedures. The secondary objective was to identify factors that were predictive of the recurrence of ATa.

Study population

Patients were included when they underwent a repeat RF ablation after an index cryoballoon PVI for the treatment of recurrent, persistent ATa (including AF and left atrial tachycardia [LAT]). We excluded patients: (1) aged < 18 years; (2) who did not consent to participate; (3) with a prosthetic heart valve and (4) lost to follow-up after the last procedure.

AF was classified according to the 2020 European Society of Cardiology guidelines for the management of AF [6]. Persistent AF was defined as AF lasting > 7 days, including episodes terminated by cardioversion. Patients with long-standing persistent AF (i.e. continuous AF for ≥ 1 year) were also included. The diagnosis-to-ablation time was defined as the time interval between the first episode of AF and ablation.

The left atrial (LA) area was measured during echocardiography with a four-chamber view. The left ventricular ejection fraction (LVEF) was also estimated before cryoballoon ablation. The LA volume was obtained from multidetector computed tomography (CT) and segmentation using AW VolumeShare 5 software (General Electric, Fairfield, CT, USA). The first centimetre of each PV and the LA appendage were included in the LA volume. The presence of an accessory vein or a left common trunk was assessed on CT.

The cryoballoon ablation procedure

Cryoballoon ablations were preceded by ≥ 3 weeks of treatment with an oral anticoagulant and then contrast-enhanced multislice CT of the left atrium.

The cryoballoon ablation procedure has been described in detail elsewhere [7]. Briefly, access to the left atrium was gained after fluoroscopy-guided transseptal puncture (SL1, St Jude Medical). The sheath was flushed continuously with heparinized saline. 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; it enabled real-time visualization of the atriovenous block during the cryoapplication. A second cryoapplication was performed (to achieve a complete block) only if there was persistent atriovenous conduction. During cryoablation over the right PVs, a quadripolar catheter was used to continuously pace the phrenic nerve adjacent to the superior vena cava. In order to avoid right phrenic nerve palsy, cryoablation was discontinued immediately if there was loss of diaphragmatic contraction.

Radiofrequency ablation procedure

Procedures were performed under general anaesthesia. Electro-anatomic maps were generated during AF or sinus rhythm (depending on the rhythm at the start of the procedure) using the Velocity™ system (until 2016) or the EnSite Precision™ system (between 2016 and 2020) (Abbott Laboratories, Abbott Park, IL, USA). Electro-anatomic activation maps were acquired for patients with LAT. A circular duodecapolar catheter (Inquiry Optima, Abbott) or an HD Grid catheter (Abbott) was used for mapping. RF lesions were created using a Tacticath™ ablation catheter (Abbott). The oesophageal temperature was monitored.

For all patients, repeat PVI was performed in the event of PV reconnection. For patients with persistent AF, the goal was to create a roof line, a mitral isthmus and/or septal line, and a cavotricuspid isthmus (CTI) line (Fig. 1). For patients with persistent LAT, the goal was to create at least the line that broke the circuit and terminated the LAT. CFAEs were not ablated.

For line completion, the power was set to 30W at the beginning of ablation and then increased to 40W if necessary. RF applications were always performed within the coronary sinus if the mitral isthmus line could not be completed using an endocardial approach. The shot power for ablation within the coronary sinus was 20–25 W. We used differential stimulation and electroanatomic mapping during left appendage pacing to check that each line had created a bidirectional block (Fig. 2). Patients with ATa at presentation were cardioverted at the end of the procedure if the ATa was not terminated by ablation.

For patients treated with a vitamin K antagonist, oral anticoagulation was maintained. For patients treated with a direct oral anticoagulant, oral anticoagulation was withdrawn 48 hours before the procedure (until October 2017) or maintained (from November 2017). For all patients, heparin was

administered as an initial bolus after the transeptal puncture and then administered continuously to maintain the target activated clotting time (> 300 seconds).

Data recorded during the procedure included the overall operating time, the total duration of RF delivery, the fluoroscopy time and the radiation dose delivered during fluoroscopy. All adverse events that occurred during the procedure or in the first 72 hours thereafter were recorded and described.

Follow-up

After ablation, antiarrhythmic drug treatment was maintained for at least the 3-month blanking period. Anticoagulants were continued for ≥ 3 months after ablation.

Patients had follow-up examinations in our institution 3, 6 and 12 months after the ablation; this included a physical check-up, screening for arrhythmia-related symptoms, a 12-lead electrocardiogram (ECG) and 24-hour Holter monitoring. After the first year, patients were followed up by their cardiologist at least once per year, with a 12-lead ECG and 24-hour Holter monitoring. The presence of any symptoms after ablation prompted an assessment with a 12-lead ECG and 24-h Holter monitoring. Previously implanted pacemakers or dual-chamber implantable cardioverter defibrillators were interrogated at each follow-up visit.

Endpoints

The primary endpoint was the recurrence of ATa, defined as a documented episode of AF, LA flutter or atrial tachycardia (whether symptomatic or not) lasting for ≥ 30 seconds on any cardiac rhythm recording made during a planned or symptom-driven consultation after the 3-month blanking period. The secondary endpoints were the frequency of complications of any type during the procedure or in the 72 hours thereafter, and the identification of predictors of ATa recurrence.

Statistical analysis

Continuous variables are expressed as means \pm standard deviations (SDs) or median (interquartile ranges [IQRs]) 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 frequencies (percentages) and were compared using a chi-squared test or Fisher's exact test.

The Prentice-William-Peterson lag-time model for recurrent events was used to evaluate prognostic factors for time to recurrence, as each patient (1) could have more than one recurrence event and (2) is expected to return to his/her initial cardiac rhythm state after a procedure. To account for the fact that a patient with ATa between two procedures is not at risk of the next episode of recurrence, the survival time was calculated from the end of the procedure to the next recurrence or to last follow-up (after accounting for the time interval between the two procedures). Variables with $P < 0.10$ in univariate analysis were introduced into a multivariable Prentice-William-Peterson lag-time model.

All tests were two-tailed, and the threshold for statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS for Windows software (version 22.0, SPSS Inc., Chicago, IL, USA). The only missing data concerned the LA area (23.3% of the patients), operating time (9.8%), RF duration (22.5%), fluoroscopy time (29.3%) and fluoroscopy exposure (30.0%).

Results

Characteristics of the study population

Overall, 715 patients underwent cryoballoon PVI between 2012 and 2019 (Fig. 3). ATa recurred in 299 patients (41.8%); 164 patients relapsed with persistent AF and 35 patients relapsed with LAT. During March 2013 to March 2020, 134 patients underwent repeat RF ablation and met the study's inclusion criteria. One patient was lost to follow-up immediately after the first repeat ablation and so was excluded. Hence, 133 patients (170 RF ablations) were included in the final analysis, of whom 103 relapsed with persistent AF and 30 relapsed with LAT. The mean \pm SD time interval between the index cryoballoon PVI and the first recurrence of ATa was 11 ± 13 months.

The mean \pm SD age of the study population was 60 ± 9 years, most (80.5%) were male, and the mean body mass index was 30 ± 5 kg/m² (Table 1). Most patients (85.7%) present with persistent or long-standing persistent AF before the index cryoballoon PVI, with a mean \pm SD diagnosis-to-ablation time of 18 ± 19 months. The mean \pm SD CHA₂DS₂-VASc score was 1.7 ± 1.4 and 55.6% of patients had hypertension. The mean \pm SD LA area was 27 ± 5 cm² and LA volume was 168 ± 42 mL. Twenty-two patients (16.5%) had LVEF \leq 40%. Forty-eight patients (36.1%) were being treated with

an antiarrhythmic drug at the time of the first ATa recurrence (33 amiodarone, 13 flecainide and two sotalol).

Characteristics and complications of the procedure

The mean \pm SD time interval between the cryoballoon PVI and the first repeat procedure was 15 ± 13 months. Of the 103 patients who relapsed with AF, 10 presented with sinus rhythm at the start of the procedure. Of the 30 patients who relapsed with LAT, five presented with sinus rhythm at the start of the procedure whereas the others were in LAT (Table 2). The 25 cases of LAT corresponded to 16 peri-mitral flutters, eight roof-dependent flutters and one left septal flutter. Reconnection of ≥ 1 PV was observed in 60 patients (45.1%). The 95 reconnected PVs were all successfully re-ablated. The right inferior PV was the most frequently reconnected PV; it accounted for 27.1% of the patients and 37.9% of the reconnected PVs. After the first repeat procedure, 119 patients (89.5%) had a roof line, 118 (88.7%) a mitral isthmus and/or septal line, and 118 (88.7%) a CTI line. The reasons for not implementing the three lines included the occurrence of a tamponade, LAT termination with just one or two lines, or that extension of the procedure would have been too time-consuming. ATa was terminated in 41/118 (34.7%) of patients who were in ATa at the beginning of the procedure. The mean \pm SD procedure time was 189 ± 49 minutes, and the RF time was 41 ± 24 minutes.

Twenty-one patients (15.8%) underwent two RF re-ablations, and eight (6.0%) underwent three. After 170 procedures, 122 patients (91.7%) had a roof line, 100 (75.2%) had a mitral isthmus line, 70 (52.6%) had a septal line, 121 (91.0%) had a mitral isthmus and/or septal line, and 122 (91.7%) had a CTI line. A block was achieved for 93.4% (114/122) of the roof lines, 89.0% (89/100) of the mitral isthmus lines, 94.3% (66/70) of the septal lines, and 100% (122/122) of the CTI lines.

After all 170 procedures, we observed three cases of tamponade (1.8%), three pericardial effusions (1.8%), three vascular complications (1.8%), one retroperitoneal bleeding (0.6%) and one circumflex occlusion (0.6%). There were no procedure-related deaths and no oesophageal complications. For the three patients who presented tamponade, the complication occurred just after completion of the roof line in two cases and after completion of the mitral isthmus line (with ablation within the coronary sinus) in the third. The circumflex artery became occluded after a large number of 30 W shots had been delivered to the coronary sinus. The left circumflex artery was reperused via immediate angioplasty and stenting.

Follow-up and predictors of recurrence

Overall, 122 patients (91.7%) attended the 6-month follow-up visit, and 104 patients (78.2%) attended the 12-month follow-up visit.

Ninety-two patients (69.2%) were in sinus rhythm after their last procedure. The median (IQR) length of follow-up for these patients was 36 (21–53) months since the index cryoballoon PVI and 22 (8–37) months since the last procedure. Forty-two patients (31.6%) were on antiarrhythmic drugs at their last follow-up (32 on amiodarone and 10 on flecainide). In the subgroup of 25 patients in LAT at the time of the first repeat procedure, 17 (68.0%) were in sinus rhythm at their last follow-up.

The results of the univariate analysis are summarized in Table 3. In multivariable analysis, the predictors of ATa recurrence were longer diagnosis-to-ablation time (hazard ratio [HR] 1.01, 95% confidence interval [CI] 1.00–1.02; $P = 0.050$) and larger LA area (HR 1.12, 95% CI 1.04–1.20; $P = 0.002$). The protective factors were higher body weight (HR 0.98, 95% CI 0.96–0.99; $P = 0.007$) and the use of an Advance short tip cryoballoon (HR 0.44, 95% CI 0.20–0.98; $P = 0.046$).

There were three late thromboembolic complications, i.e. events arising > 72 hours after the procedure. Two patients died of cardiogenic shock 4 and 60 months after the last procedure.

Impact of PV reconnection on outcome

Fig. 4 shows the ATa-recurrence-free survival rates after the first repeat procedure among patients who presented ≥ 1 PV reconnection and those who did not (Fig. 4A; $P = 0.32$) and as a function of the number of PV reconnections (Fig. 4A; $P = 0.58$). Moreover, univariate analysis showed that neither PV reconnection ($P = 0.11$) nor the number of PV reconnections ($P = 0.25$) predicted recurrence. Inclusion of PV reconnection in the multivariable model did not modify the results significantly.

Discussion

The current results demonstrate that the creation of linear lesions to treat the recurrence of persistent ATa after an index cryoballoon PVI is an effective and safe strategy. There were only three cases of tamponade (1.8%), and 92 patients (69.2%) were in sinus rhythm after their last procedure (a median of 36 months since the index cryoballoon PVI, and a median of 22 months since their last procedure).

The predictors of ATa recurrence after ≥ 1 repeat RF procedures included the diagnosis-to-ablation time and the LA area.

Repeat ablations after an index PVI ablation: strategy and results

There is no consensus on the optimal ablation strategy for persistent AF and for persistent recurrence after an initial procedure.

The well-known STAR AF II [2] demonstrated that the addition of lines or the ablation of CFAEs did not improve the outcome after persistent AF ablation. The 2018 meta-analysis by Clarnette et al. [1] showed that PVI is at least as effective as other contemporary ablation strategies for persistent and long-standing persistent AF. In 2019, a similar analysis by Sau et al. [3] gave the same results: linear ablation, PWI and CFAE ablation did not predict better long-term outcomes, even though they increased intraprocedural termination of AF.

Studies that are most similar to ours (i.e. those of patients who underwent repeat ablations after an index PVI) are summarized in Table A.1 [4,5,8-15]. We excluded studies that focused on paroxysmal AF rather than persistent ATa. To our knowledge, there are only three studies in which the index PVI was based on cryoballoon ablation. Coutiño et al. [4] and Heeger et al. [5] decided to ablate CFAEs and/or create linear lesions during the repeat procedure; the recurrence rates were 75.0% (15/20) and 65.6% (21/32), respectively, after mean follow-up periods of 11.8 and 35 months. Iacopino et al. [9] adopted a novel strategy (LA posterior box isolation using cryotherapy) for the repeat procedure. Twenty-eight of their 33 patients (84.8%) were in sinus rhythm after a mean \pm SD follow-up of 11.8 ± 3 months.

Seven studies [10-15] focused on repeat procedures after an RF-based index PVI. The patients also underwent other lesions of the LA (i.e. in addition to PVI) during the index procedure, except in the studies by Bhargava et al. [15] and Sugumar et al. [8]. For the repeat procedure(s), the initial strategy was pursued: CFAE ablation and/or creation of linear lesions. The proportion of patients in sinus rhythm at last follow-up ranged from 52.7% [8] to 75.2% [11].

Our study stands out from the above-mentioned studies in several respects. Firstly, it included a large number of patients with long-term follow-up. Secondly, the same treatment strategy was applied to all consecutive patients. After all procedures, > 90% of patients had undergone the creation of a roof line, a mitral isthmus and/or septal line, and a CTI line, in addition to repeat PVI. Our results

are in line with the literature data: 69.2% of our patients were in sinus rhythm after a median follow-up of 36 months after cryoballoon PVI, and 22 months after the last procedure.

At the time of the repeat procedure, PV reconnection was noted in 45.1% of the patients. This reconnection rate is lower than those reported in the literature (between 66% and 93% in the studies presented in Table A.1, 78% in the FIRE and ICE trial [16] and 92% in the Cryoballoon vs Irrigated Radiofrequency Catheter Ablation: Double Short vs Standard Exposure Duration (CIRCA-DOSE) study [17]). However, rates are lower in studies that looked at reconnections after cryoballoon ablation. Glowniak et al. [18] reported a reconnection rate of 51.5%, whereas Buist et al. [19] reported a rate of 36.8%, which is closest to the value observed in the current study. Given our focus on persistent ATa recurrence, the low incidence of reconnected PVs was not surprising.

As our repeat ablation procedure was based on the creation of three lines, this lengthened the operating time and, conceivably, might have increased the frequency of complications. Chun et al. [20] reported that tamponade occurred after 3.2% of repeat PVI plus additional ablation procedures. Our tamponade rate (1.8%) was similar to Chun et al.'s value and, as expected, was higher than for PVI-only procedures (0.8% [20]). Regarding other types of complication, we observed few vascular problems or strokes.

In summary, we found that a stepwise strategy based on cryoballoon PVI and then the creation of linear lesions (in the event of persistent ATa recurrence) was effective and safe. However, it should be noted that these results were not fully explained by linear lesion creation. Indeed, 45.1% of patients had PV disconnection, and 31.6% of the patients were still on antiarrhythmics at last follow-up. These factors account for part of the results. Furthermore, patients' risk factors were managed (incitement to lose weight, treatment of sleep apnoea, etc.), which might have improved the outcomes.

Predictors of recurrence after repeat ablations

Predictors of recurrence after persistent AF ablation have been extensively studied. Diagnosis-to-ablation time [21-25], LA dimensions [1,21,22,25-28] and relapse during the blanking period [24,27,29-32] have been found to be predictors of recurrence in many studies. Female sex [8,33], cardiomyopathy [29], PV abnormality [29], body mass index [32,34], the number of cardioversions [35] and the number of failed antiarrhythmic drugs [35] have also been described.

Studies that focused on repeat procedures found that persistent AF [15,18], female sex [15], arterial hypertension [15], LA dimensions [28], coronary artery disease [13], congestive heart failure [13] and relapse during the blanking period [18] were predictors of recurrence. However, Coutiño et al.'s study (which had the same design as ours) did not identify any significant predictors of recurrence [4].

In our study of repeat ablations, we were able to test all the known predictors by using a statistical method that took account of the alternation between periods of sinus rhythm and periods of ATa. In multivariable analysis, the diagnosis-to-ablation time and the LA area were predictive of recurrence; this finding is in line with the literature data on predictors after an index procedure.

In the present study, the use of an Advance short-tip balloon for cryoablation was associated with a better outcome after repeat RF procedures. This balloon is associated with more accurate assessment of the time to PVI and therefore facilitates the ablation strategy [36]. This explains how this balloon was associated with better outcomes in the present study.

Rostock et al. reported that termination of AF was predictive of a favourable outcome – even after the last procedure [13]. This finding was not confirmed in Sau et al.'s meta-analysis [3] or by our current results.

It is reasonable to assume that patients with PV reconnection could have had better outcomes than patients with no reconnected PVs. However, univariate analysis only showed a trend ($P = 0.11$) towards a more favourable outcome when patients had ≥ 1 reconnected PV. The non-significant difference was possibly due to a lack of power.

Limitations and strengths

The current study had a number of limitations. Firstly, the single-centre design means that our conclusions cannot be extrapolated to other centres. Secondly, the sample size might appear to be small in absolute terms, but it was larger than other studies of the same subject. However, consecutive patients were included and all received the same treatment (creation of linear lesions), giving a homogenous study population with long-term follow-up. Thirdly, our protocol for atrial arrhythmia monitoring did not include continuous monitoring, but it corresponded to that used in other studies and in real life; hence, our conclusions are likely to be applicable to routine clinical practice.

Echocardiographic measurements of the LA area are subject to inter-observer variability and so conclusions based on these data must be interpreted with caution. In fact, these data are readily available but are rarely mentioned in the literature. CT-based volume measurement has not been extensively studied but is more accurate. Ideally, we would have liked to present comparative data for similar patients treated with a different strategy. Unfortunately, all the patients in our centre underwent the linear lesion procedure.

Conclusions

The creation of linear lesions (using RF) for the recurrence of persistent ATa after an index cryoballoon PVI is a safe and effective strategy; 69.2% of the patients were in sinus rhythm after a median of 36 months since the index cryoballoon PVI. The diagnosis-to-ablation time and the LA area were predictive of recurrence.

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Disclosure of interest

Conflict of interest: none.

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Figure legends

Figure 1. Line completion. A. Roof and septal line completion (3D map – anterior view). B. Mitral isthmus line completion (3D map – left oblique anterior view).

Figure 2. Line validation. A. Roof and mitral isthmus lines (schema). B. Roof line (3D map – posterior view). C. Roof and septal lines (schema). D. Roof and septal lines (3D map – anterior view). LAA: left atrial appendage; LIPV: left inferior pulmonary vein; LSPV: left superior pulmonary vein; M: mitral annulus; PV: pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.

Figure 3. Study flow chart. AF: atrial fibrillation; ATa: atrial tachyarrhythmia; PVI: pulmonary vein isolation; RF: radiofrequency.

Figure 4. ATa-free survival after the first repeat procedure. A. Patients who presented at least one reconnected PV vs patients with no reconnected PVs. B. Patients who presented two or more reconnected PVs vs one reconnected PV vs no reconnected PVs.

Graphical abstract. Overall, 133 patients underwent 170 procedures for the treatment of persistent ATa following an index cryoballoon pulmonary vein isolation ($n = 715$). After all the procedures, > 90% of the patients had a roof line, a mitral isthmus and/or septal line, and a cavotricuspid isthmus line. Ninety-two patients (69.2%) were in sinus rhythm after a median of 36 months since the index cryoballoon PVI. ATa: atrial tachyarrhythmia; cryo: cryoballoon; CTI: cavotricuspid isthmus; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; PVI: pulmonary vein isolation; RF: radiofrequency; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein.

Table 1 Baseline characteristics of the study population.

	All patients (<i>n</i> = 133)
Demographic variables	
Age (years)	60 ± 9
Male sex	107 (80.5)
Medical history	
Height (m)	1.76 ± 0.08
Weight (kg)	90 ± 16
Body mass index (kg/m ²)	30 ± 5
Body surface area (m ²)	2.12 ± 0.21
Type of AF before the cryo-PVI	
Paroxysmal AF	19 (14.3)
Persistent AF	92 (69.2)
Long-standing persistent AF	22 (16.5)
Diagnosis-to-ablation time for paroxysmal AF (months)	51 ± 52
Diagnosis-to-ablation time for persistent AF (months)	18 ± 19
Number of cardioversions	0.9 ± 0.9
Number of failed antiarrhythmics	1.0 ± 0.6
Creatinine clearance rate (mL/min)	82 ± 20
Creatinine clearance rate < 60 mL/min	16 (12.0)
Hypertension	74 (55.6)
Diabetes	18 (13.5)
Stroke	8 (6.0)
Heart failure	19 (14)
Coronary artery disease	18 (13)
Absence of structural heart disease	92 (69)
CHA ₂ DS ₂ -VASc score	
0	31 (23.3)
1	36 (27.1)

2	31 (23.3)
3	18 (13.5)
4	11 (8.3)
5	5 (3.8)
6	1 (0.8)
Previous cavotricuspid isthmus ablation	12 (9.0)
LA and LV parameters	
LA area (cm ²)	27 ± 5 (n=102)
LA volume (mL)	168 ± 42
LA volume index (mL/m ²)	80 ± 21
LVEF (%)	55 ± 12
LVEF ≤ 40%	22 (16.5)
PV anatomy	
LCT	16 (12.0)
Accessory vein	21 (15.8)

Data are expressed as mean ± standard deviation or number (%). AF: atrial fibrillation; LA: left atrial; LCT: left common trunk of the pulmonary veins; LV: left ventricular; LVEF: left ventricular ejection fraction; PV: pulmonary vein; PVI: pulmonary vein isolation.

Table 2 Characteristics of the procedure (first repeat procedure).

	First repeat procedure (<i>n</i> = 133 procedures)
Rhythm at presentation for repeat ablation	
Sinus rhythm	15 (11.3)
AF	93 (69.9)
LAT	25 (18.8)
PV reconnection	
≥ 1 reconnected PV	60 (45.1)
Total number of reconnected PVs	95/532
Number of reconnected PVs per patient	0.7 ± 0.9
0	73 (54.9)
1	35 (26.3)
2	17 (12.8)
3	6 (4.4)
4	2 (1.5)
Left superior PV reconnection	19/95 (20.0)
Left inferior PV reconnection	23/95 (24.2)
Right superior PV reconnection	17/95 (17.9)
Right inferior PV reconnection	36/95 (37.9)
Lesions	
Repeat PVI	60/60 (100)
Roof line	119 (89.5)
Mitral isthmus line	96 (72.2)
Septal line	64 (48.1)
Mitral isthmus and/or septal line	118 (88.7)
CTI line (including prior CTI ablation)	118 (88.7)
Termination of AF	22/93 (23.7)
Termination of LAT	19/25 (76.0)
Procedure time (min)	189 ± 49 (<i>n</i> =120)

RF time (min)	41 ± 24 (<i>n</i> = 103)
Fluoroscopy time (min)	36 ± 12 (<i>n</i> = 94)
Fluoroscopy exposure (mGy)	374 ± 404 (<i>n</i> = 93)
Fluoroscopy exposure (Gy.cm ²)	54 ± 70 (<i>n</i> = 93)

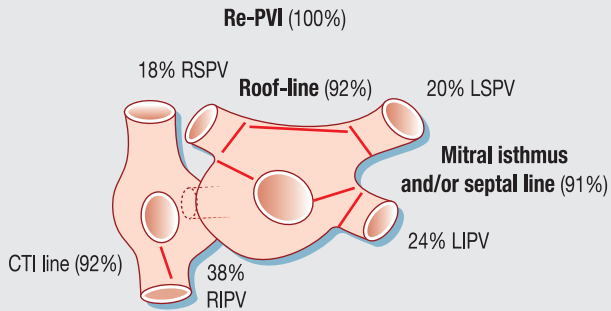
AF: atrial fibrillation; LAT: left atrial tachycardia; CTI: cavotricuspid isthmus; PV: pulmonary vein; PVI: pulmonary vein isolation; RF: radiofrequency.

Table 3 Predictive factors for ATa recurrence in a univariate analysis.

	No ATa recurrence (<i>n</i> = 92)	ATa recurrence (<i>n</i> = 41)	HR (95% CI) in univariate analysis	<i>P</i>
Age (years)	60 ± 9	60 ± 8	1.01 (0.98–1.03)	0.90
Female	13 (14.1)	13 (31.7)	0.99 (0.57–1.72)	0.98
Height (m)	1.76 ± 0.08	1.73 ± 0.10	0.22 (0.01–3.41)	0.28
Weight (kg)	92 ± 16	87 ± 17	0.98 (0.97–1.00)	0.026
Body mass index (kg/m ²)	30 ± 5	29 ± 5	0.96 (0.92–1.01)	0.11
Body surface area (m ²)	2.11 ± 0.21	2.07 ± 0.24	0.29 (0.11–0.81)	0.019
Persistent or long-standing persistent AF before the cryoballoon PVI	80 (87.0)	34 (82.9)	1.14 (0.56–2.31)	0.31
Long-standing persistent AF before the cryoballoon PVI	9 (9.8)	13 (31.7)	2.25 (1.40–3.41)	0.001
Diagnosis-to-ablation-time (for persistent AF) (months)	16 ± 18	23 ± 19	1.02 (1.01–1.03)	< 0.001
Creatinine clearance rate (mL/min)	81 ± 19	87 ± 22	1.01 (1.00–1.02)	0.023
Creatinine clearance rate ≤ 60 ml/min	11 (12.0)	5 (12.2)	0.84 (0.46–1.55)	0.58
Hypertension	51 (55.4)	23 (56.1)	0.84 (0.53–1.34)	0.47
Diabetes	15 (16.3)	3 (7.3)	0.40 (0.14–1.12)	0.08
Heart failure	8 (8.7)	11 (26.8)	1.13 (0.64–1.99)	0.67
Coronary artery disease	13 (14.1)	5 (12.2)	0.87 (0.45–1.71)	0.69
Absence of structural heart disease	66 (71.7)	26 (63.4)	0.97 (0.60–1.57)	0.89
CHA ₂ DS ₂ -VASc score	1.4 ± 1.3	1.8 ± 1.4	0.97 (0.83–1.13)	0.66
Previous CTI ablation	5 (5.4)	7 (17.1)	0.87 (0.50–1.54)	0.64
LA area (cm ²)	26 ± 4 (<i>n</i> = 70)	29 ± 5 (<i>n</i> = 32)	1.10 (1.01–1.19)	0.027
LA volume (mL)	167 ± 38	190 ± 40	1.01 (1.00–1.01)	0.011
LA volume index (mL/m ²)	78 ± 18	91 ± 21	1.02 (1.01–1.03)	< 0.001
LVEF (%)	55 ± 11	50 ± 14	1.00 (0.98–1.01)	0.66

LVEF < 50%	18 (19.6)	11 (26.8)	1.05 (0.61–1.80)	0.87
LVEF ≤ 40%	12 (13.0)	10 (24.4)	1.42 (0.82–2.45)	0.21
LCT	11 (12.0)	5 (12.2)	1.15 (0.57–2.33)	0.69
Accessory vein	17 (18.5)	4 (9.8)	1.05 (0.59–1.88)	0.86
Advance short tip	22 (23.9)	5 (12.2)	0.44 (0.22–0.89)	0.023
First recurrence during blanking period	40 (43.5)	19 (46.3)	1.18 (0.76–1.84)	0.46
LAT at recurrence	21 (22.8)	9 (22.0)	1.06 (0.62–1.81)	0.83
Mean time to first recurrence (months)	10 ± 12	8 ± 11	0.98 (0.96–1.00)	0.11
Sinus rhythm at the first repeat procedure	10 (10.9)	5 (12.2)	1.29 (0.65–2.54)	0.46
LAT at the first repeat procedure	17 (18.5)	8 (19)	0.99 (0.56–1.76)	0.96
≥ 1 reconnected PV at the first repeat procedure	48 (52.2)	12 (29)	0.68 (0.42–1.09)	0.11
Number of reconnected PVs at the first repeat procedure	0.9 ± 0.9	0.3±0.7	0.85 (0.64–1.12)	0.25
AF termination during the first repeat procedure	30/82 (36.6)	11/36 (30.5)	1.11 (0.69–1.81)	0.66
Roof + mitral isthmus lines vs roof + septal lines (after the last procedure)	28/42 (66.7)	14/21 (66.7)	0.80 (0.41–1.55)	0.51
Roof + mitral isthmus + septal lines vs Roof + mitral isthmus lines or roof + septal lines (after the last procedure)	36/78 (46.2)	13/34 (38.2)	1.13 (0.71–1.79)	0.608

AF: atrial fibrillation; AT: atrial tachycardia; CI: confidence interval; CTI: cavotricuspid isthmus; HR: hazard ratio; LA: left atrial; LAT: left atrial tachycardia; LCT: left common trunk; LVEF: left ventricular ejection fraction; PV: pulmonary vein; PVI: pulmonary vein isolation.

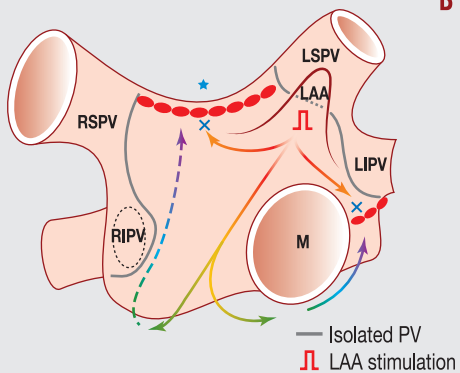
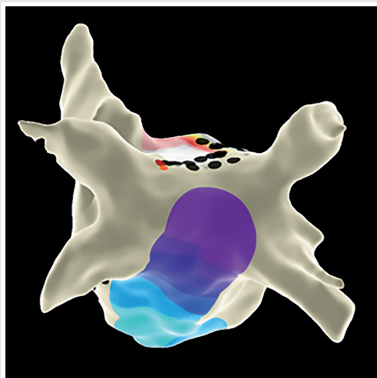
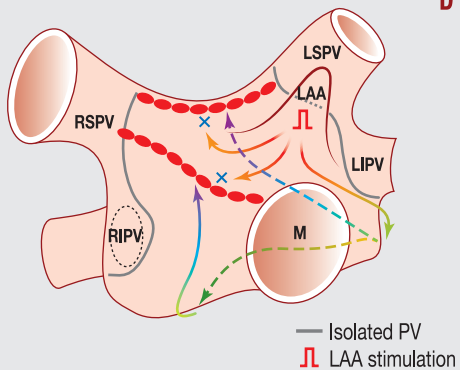
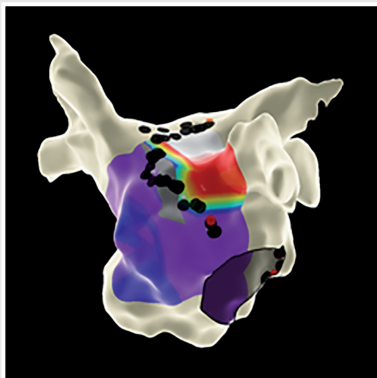


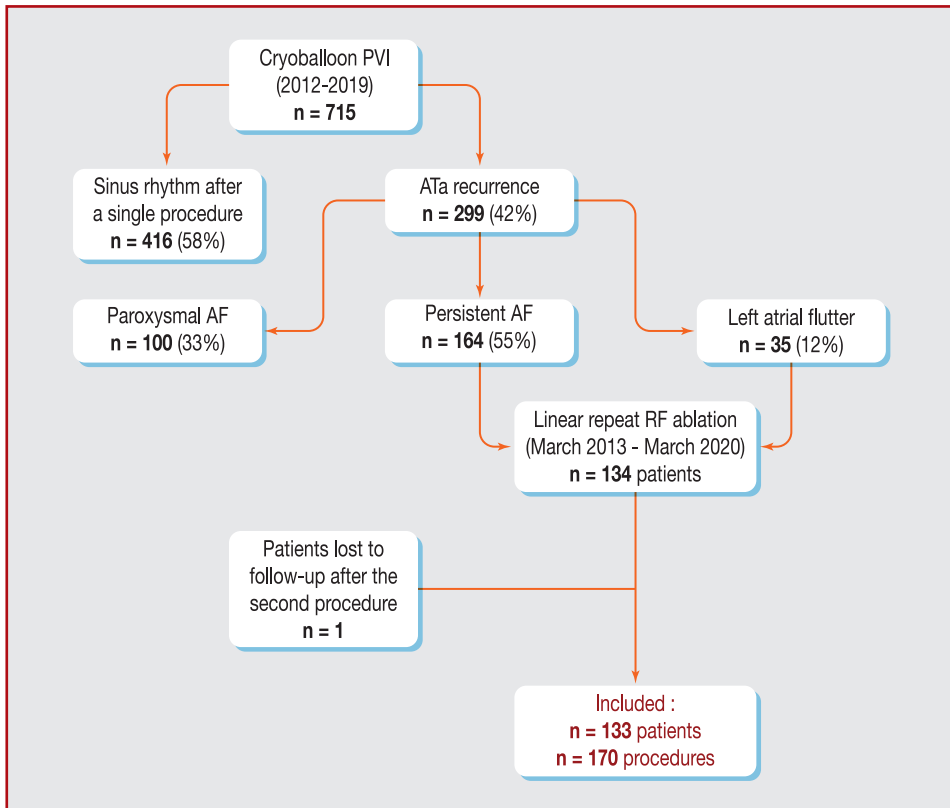
715 patients
index cryo-PVI

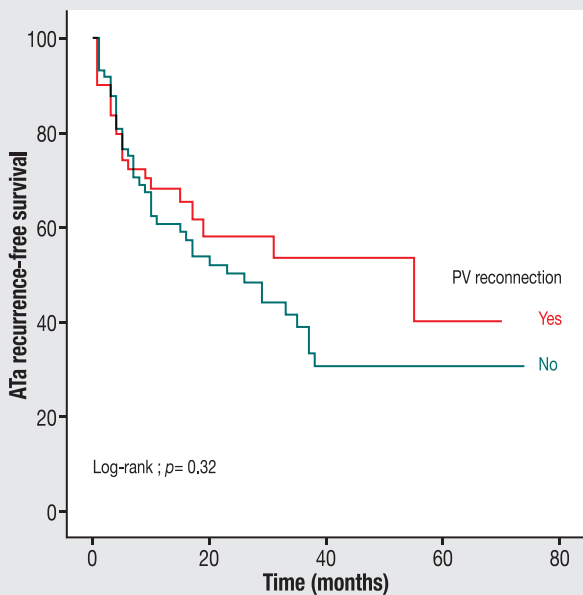
Persistent ATa recurrence

170 RF repeat ablations (**133** patients)
(Re-PVI, roof-line, mitral isthmus and/or septal line, CTI line)

69% (n = 92) in sinus rhythm **36** months after index cryo-PVI

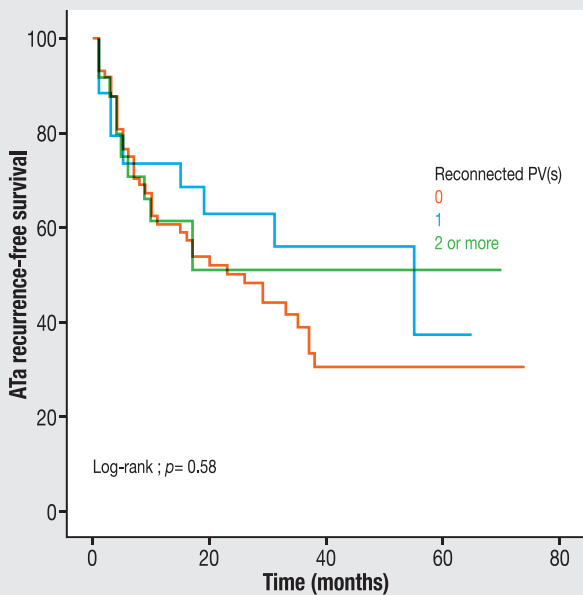
A**B****C****D**



A

Number at risk

No	73	29	9	2	0
Yes	60	16	7	2	0

B

Number at risk

0	73	29	9	2	0
1	35	11	4	1	0
2+	25	5	3	1	0

