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CLINICAL RESEARCH

Catheter ablation of atrial fibrillation and atrial tachycardia in patients with pulmonary hypertension: a randomized study

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Aims Atrial fibrillation (AF), typical atrial flutter (AFL), and other atrial tachycardias (ATs) are common in patients with pulmonary hypertension. Frequently, several supraventricular arrhythmias are successively observed in individual patients. We investigated the hypothesis of whether more extensive radiofrequency catheter ablation of the bi-atrial arrhythmogenic substrate instead of clinical arrhythmia ablation alone results in superior clinical outcomes in patients with pulmonary arterial hypertension (PH) and supraventricular arrhythmias.

Methods and results Patients with combined post- and pre-capillary or isolated pre-capillary PH and supraventricular arrhythmia indicated to catheter ablation were enrolled in three centres and randomized 1:1 into two parallel treatment arms. Patients underwent either clinical arrhythmia ablation only (Limited ablation group) or clinical arrhythmia plus substrate-based ablation (Extended ablation group). The primary endpoint was arrhythmia recurrence >30 s without antiarrhythmic drugs after the 3-month blanking period. A total of 77 patients (mean age 67 ± 10 years; 41 males) were enrolled. The presumable clinical arrhythmia was AF in 38 and AT in 36 patients, including typical AFL in 23 patients. During the median follow-up period of 13 (interquartile range: 12; 19) months, the primary endpoint occurred in 15 patients (42%) vs. 17 patients (45%) in the Extended vs. Limited ablation group (hazard ratio: 0.97, 95% confidence interval: 0.49–2.0). There was no excess of procedural complications and clinical follow-up events including an all-cause death in the Extended ablation group.

Conclusion Extensive ablation, compared with a limited approach, was not beneficial in terms of arrhythmia recurrence in patients with AF/AT and PH.

Clinical Trials Registration ClinicalTrials.gov; NCT04053361.

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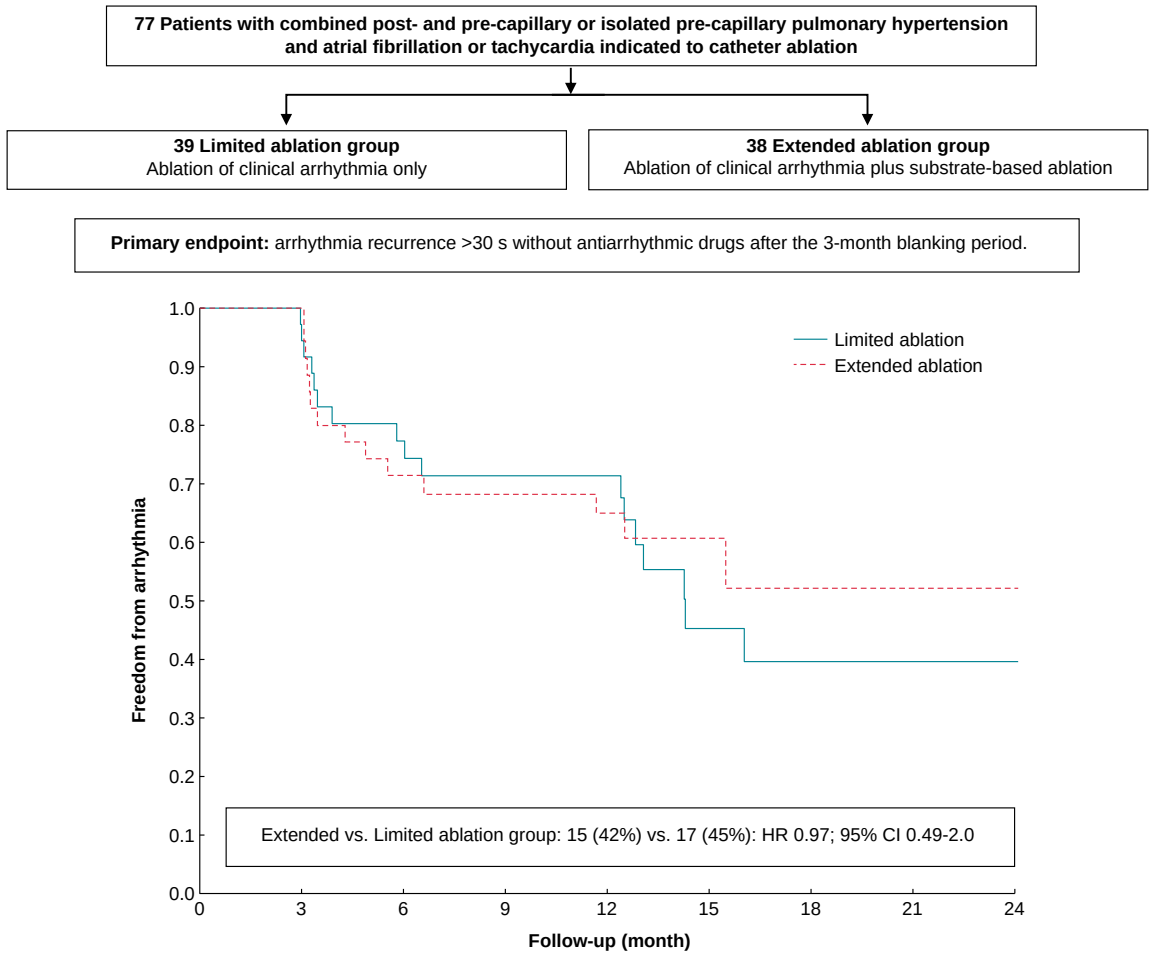
Graphical Abstract



Keywords Atrial fibrillation • Atrial tachycardia • Catheter ablation • Pulmonary hypertension

What's New?

- Extensive catheter ablation does not reduce arrhythmia recurrence in patients with pulmonary hypertension and atrial fibrillation/tachycardia.
- Despite enormous right atrial enlargement, regions with low-voltage and/or abnormal atrial electrograms are rare in patients with pulmonary hypertension.

Introduction

Various treatment strategies have been established in patients with pulmonary arterial hypertension (PH) that improve haemodynamics, exercise capacity, and quality of life.[1,2] Despite those advancements, PH is still a progressive disease with a generally inauspicious prognosis.

Supraventricular tachycardias (SVTs) have been frequently observed with a cumulative incidence of 10–29% in patients with both idiopathic[3] and secondary PH,[4–7] including chronic thromboembolic pulmonary hypertension, either inoperable[4,6] or treated with pulmonary endarterectomy.[8] The SVTs are associated with clinical deterioration and adversely impact the prognosis.[3,4,6,9] Conversely, maintenance of sinus rhythm (SR) appeared to improve the clinical outcome.[3,6,10] However, antiarrhythmic drugs may not be a feasible option because of their negative inotropic properties and interaction with specific therapy for PH.[11,12]

Radiofrequency catheter ablation (RFCA) of typical atrial flutter (AFL), atrioventricular nodal re-entrant tachycardia (AVNRT), and other focal or macroreentrant atrial tachycardias (AT) was reported to be effective (acute success rate of 86–100%) and safe in patients with PH according to retrospective studies with a limited number of patients.[5,10,13–16] However, the long-term results were much less favourable with freedom from arrhythmia in only 50–78% of patients.[13,14,16] Importantly, new-onset arrhythmias (different than their index SVT) were observed in 30–48% of recurrent cases.[13,14]

Although typical AFL can frequently be found as the first manifestation of SVT in patients with PH, atrial fibrillation (AF) is even more prevalent.[3–6] In this respect, data on the optimum rhythm control strategy of AF/AT, including RFCA, is lacking. Given the knowledge of the sequential manifestation of different SVTs in individual patients, it was plausible to hypothesize that first-line bi-atrial RFCA of all potentially arrhythmogenic substrates (i.e. not only ablation for index arrhythmia) could reduce the risk of arrhythmia recurrence and improve the clinical

outcomes compared to procedure targeting the clinical arrhythmia only. We investigated this hypothesis in a randomized fashion.

Methods

The study was a multicentre, parallel-group, open-label, randomized trial. It was performed according to good clinical practice and in compliance with the Helsinki declaration. The multicentric and local Ethics committees at all centres approved the study protocol. Individual written consent was obtained from each patient. The trial protocol is available in Supplementary material online, *Appendix S1*.

Patients

Participants were men or women, 18 years of age or older, who had pre-capillary or combined post- and pre-capillary PH of any aetiology, and documented symptomatic AF (paroxysmal, persistent, or long-standing persistent) or AT (typical AFL included) who were indicated for RFCA according to clinical practice guidelines.[17] Patients were excluded if they had any condition that might jeopardize patient safety or limit their participation in the study. The key exclusion criteria were complex congenital heart defects (corrected or uncorrected), isolated post-capillary PH, previous RFCA for AF, AT or AFL, NYHA Class IV, and life expectancy <1 year.

Study procedures and follow-up

Covariate adaptive 1:1 randomization was used to allocate enrolled patients into two parallel treatment arms to undergo clinical arrhythmia ablation only (Limited ablation group) or clinical arrhythmia plus substrate-based ablation (Extended ablation group). Covariates were applied as follows: age, gender, type of PH, and clinical arrhythmia.

Electrophysiological study

Patients were treated under conscious sedation or general anaesthesia at the discretion of the operator. The procedure was done on uninterrupted oral anticoagulation with the international normalized ratio between two and three in patients on vitamin K antagonists. In patients on direct oral anticoagulants, only the morning dose on the day of the procedure was omitted. All procedures were done under visual control of intracardiac echocardiography. Heparin was administered before transseptal puncture, and the doses were adjusted to achieve an activation clotting time of >300 s during the procedure.

In patients with SR at baseline, arrhythmia was induced by programmed, incremental, or burst atrial pacing. If present or induced arrhythmia differed from an arrhythmia that was documented non-invasively before the enrollment, the decision on what is 'clinical' arrhythmia was made by the operator. Point-by-point electroanatomical maps of both right (RA) and left (LA) atrium, each with a minimum of 100 mapping points, were acquired in consistent rhythm (SR/AF/AT) for meaningful assessment of low-voltage zones (CARTO 3, Biosense-Webster). Two-level quantification (bipolar voltages either <0.1 or <0.5 mV in SR; and either <0.04 or <0.2 mV in AF/AT) of low-voltage zones was applied separately for RA and LA.

Catheter ablation

Initial treatment was identical in both study arms. If clinical arrhythmia was fairly documented AF or typical AFL, pulmonary vein isolation (PVI) or cavotricuspid isthmus (CTI) ablation was performed. If AF persisted after PVI, electrical cardioversion was performed. When clinical arrhythmia was AT, it was induced (if not persistent), identified using activation and/or entrainment mapping, and ablated.

In patients in the Limited ablation group, no ablation was performed if AT was not inducible or if incidental (or induced) ATs were considered non-clinical. After clinical arrhythmia ablation, no induction protocols were attempted unless the non-inducibility was the principal endpoint of arrhythmia ablation, like in the case of AVNRT or microreentrant AT.

In patients in the Extended ablation group, substrate-based ablation continued after the initial ablation steps described above. This consisted of empirical lesion set within RA: superior vena cava (SVC) isolation, posteroseptal intercaval line, and CTI ablation (if not already done) and homogenization of low-voltage zones (if any) in LA/RA defined by bipolar voltage <0.5 mV in SR or <0.2 mV in AF/AT. These cut-off voltages were adapted (set lower) in severely diseased atria to identify reasonably smaller zones (<20% of the atrial surface) that were feasible to ablate. Arrhythmia induction protocol was performed consisting of 10-s burst atrial pacing with a cycle length of 300 ms decremented by 10 ms up to 1:1 atrial capture or cycle length of 200 ms. Induced ATs were mapped and ablated if feasible. In the case of inducible AF with a duration of >5 min, PVI was performed if not previously done as per protocol.

Follow-up and study objectives

During regular follow-up visits at 3-month intervals, symptoms and relevant clinical events were collected, and standard ECG was recorded. All class Ic or III antiarrhythmic drugs were discontinued at Month 3. Persistent arrhythmia (if observed at Month 3) was electrically cardioverted. Seven-day ECG monitoring was done 6 and 12 months after RFCA, and additional ECG monitoring was scheduled in patients with symptoms suggestive of non-documented arrhythmia. In case of arrhythmia recurrence, antiarrhythmic drugs were initiated and a repeated RFCA was considered.

The primary endpoint of the study was documented arrhythmia recurrence >30 s without antiarrhythmic drugs after the 3-month blanking period after the index ablation. Secondary endpoints were set up as follows: documented on-drugs arrhythmia recurrence, symptoms of arrhythmia, number of emergency visits, number of hospitalizations, mortality, procedure-related major complication rate, antiarrhythmic drugs, re-ablation, pacemaker implantation, and atrioventricular junction ablation. Major procedural complications were defined as events that occurred within 30 days of the ablation, were clearly or could probably be related to the procedure, and resulted in long-term disability, requiring intervention or prolonging hospitalization.

Statistical analysis

An independent statistician replicated and verified the analyses. All study objectives were analysed by standard statistical methods (*t*-test or Mann–Whitney U test for continuous variables or a Chi-square or two-tailed Fisher exact test for categorical variables). Time-to-event data were investigated by Kaplan–Meier analysis with log-rank statistics and by multivariate Cox regression models. A *P*-value <0.05 was considered significant. All analyses were performed using the STATISTICA vers.12 software (StatSoft, Inc., Tulsa, USA).

Results

From May 2018 to August 2021, a total of 77 patients (42 males) with a median age of 70 [interquartile range (IQR): 61; 75] years were enrolled at three sites in the Czech Republic. Thirty-nine patients were treated in the Limited ablation group, and 38 patients were treated in the Extended ablation group. At the time of randomization, the presumable clinical arrhythmia was AF in 38 and AT in 36 patients, including typical AFL in 23 patients (*Table 1*). One patient in the Limited ablation group (with left atrial appendage thrombosis) and two patients in the Extended ablation group (one with severe mitral regurgitation, and one who declined to participate) were later excluded (consort diagram, *Figure 1*). The baseline characteristics of the 74 patients who were scheduled for RFCA are shown in *Table 1*.

At the beginning of the index RFCA, arrhythmia different from that during the screening was seen in 5 of 38 and 8 of 36 patients from the Limited and Extended ablation groups, respectively. During the procedure, multiple distinct SVTs were observed in 5 and 4 patients from the Limited and Extended ablation groups, respectively.

In the Limited ablation arm, the RFCA procedure was completed per protocol in 36 (95%) out of the 38 patients. In one patient with enormous RA dilatation, transseptal puncture failed and CTI ablation only was performed. In another patient, extreme venous tortuosity prevented catheter insertion from the groin access. The RFCA was extended beyond assumed clinical arrhythmia in eight (21%) patients. This was done mainly because of conversion of the initial arrhythmia to a different one (three cases), spontaneous onset or induction of

Table 1 Baseline characteristics

	All patients $n = 74$	Limited ablation group $n = 38$	Extended ablation group $n = 36$	P
Age (years)	71 (61; 75)	70 (61; 75)	71 (60; 74)	NS
Males	41 (55%)	24 (63%)	17 (47%)	NS
Aetiology of PH				
– Idiopathic	41 (55%)	23 (61%)	18 (50%)	NS
– Chronic thromboembolic	22 (30%)	10 (26%)	12 (33%)	NS
– Lung disease/hypoxia	11 (15%)	5 (13%)	6 (17%)	NS
Index arrhythmia				
– Atrial fibrillation	38 (51%)	19 (50%)	19 (53%)	NS
– Paroxysmal	11 (15%)	6 (16%)	5 (14%)	NS
– Persistent	22 (30%)	10 (26%)	12 (33%)	NS
– Long-standing persistent	5 (7%)	3 (8%)	2 (6%)	NS
– Atrial tachycardia	36 (49%)	19 (50%)	17 (47%)	NS
– Typical atrial flutter	23 (31%)	12 (32%)	11 (31%)	NS
Symptoms of arrhythmia				
– Palpitation	28 (38%)	13 (34%)	15 (42%)	NS
– Dyspnea	47 (64%)	24 (63%)	23 (64%)	NS
– Peripheral oedema	26 (35%)	12 (32%)	14 (39%)	NS
Comorbidities				
– Arterial hypertension	59 (80%)	31 (82%)	28 (78%)	NS
– Diabetes mellitus	26 (35%)	12 (32%)	14 (39%)	NS
– Coronary artery disease	14 (19%)	5 (13%)	9 (25%)	NS
– Stroke/transient ischaemic attack	6 (8%)	4 (11%)	2 (6%)	NS
CHA_2DS_2-VASc score	3 (2; 4)	3 (2; 4)	3 (2; 4)	NS
HAS-BLED score	1 (0; 1)	1 (0; 1)	1 (0.5; 1)	NS
Treatment				
– Amiodarone	14 (19%)	8 (21%)	6 (17%)	NS
– Propafenone	3 (4%)	2 (5%)	1 (3%)	NS
– Sotalol	2 (3%)	1 (3%)	1 (3%)	NS
– Beta-blockers	27 (36%)	13 (34%)	14 (38%)	NS
– Warfarin	37 (50%)	18 (47%)	19 (53%)	NS
– Direct oral anticoagulants	31 (42%)	18 (47%)	13 (36%)	NS
– Specific therapy for PH	26 (35%)	14 (37%)	12 (33%)	NS
Functional status				
– NYHA I	0	0	0	NS
– NYHA II	17 (23%)	9 (24%)	8 (22%)	NS
– NYHA III	57 (77%)	29 (76%)	28 (78%)	NS
– NYHA IV	0	0	0	NS
– 6-minute walking test (m)	369 (280; 422)	363 (280; 413)	376 (300; 436)	NS
EQ-VAS	58 (40; 72)	56 (34; 74)	60 (42; 70)	NS
Laboratory				
– NT-proBNP (pg/mL)	1267 (732; 2317)	903 (724; 1979)	1587 (922; 3182)	NS
– Haemoglobin (g/L)	138 (128; 148)	145 (135; 148)	131 (117; 147)	NS
– Creatinine (μmol/L)	94 (80; 113)	95 (81; 112)	94 (73; 114)	NS
Echocardiography				
– LV end-diastolic diameter in PLAX (mm)	49 (44; 54)	49 (45; 54)	49 (44; 54)	NS
– LV ejection fraction (%)	60 (55; 63)	60 (55; 62)	60 (56; 64)	NS

Continued

Table 1 *Continued*

	All patients $n = 74$	Limited ablation group $n = 38$	Extended ablation group $n = 36$	P
– LA indexed volume (mL/m^2)	41 (31; 50)	39 (28; 51)	43 (32; 50)	NS
– RA diameter in A4C (mm)	53 (46; 59)	51 (46; 59)	54 (47; 59)	NS
– RV diameter in A4C (mm)	48 (41; 53)	49 (41; 52)	48 (42; 56)	NS
– Tricuspid annular plane systolic excursion (mm)	18 (14; 20)	17 (14; 20)	19 (14; 20)	NS
– Pulmonary artery systolic pressure (mmHg)	69 (50; 84)	72 (55; 87)	64 (48; 82)	NS
– LA appendage emptying velocity (m/s)	0.45 (0.34; 0.70)	0.49 (0.38; 0.70)	0.40 (0.30; 0.70)	NS
Haemodynamics				
– RA mean pressure (mmHg)	11 (6; 16)	13 (8; 18)	9 (5; 12)	0.02
– Pulmonary artery mean pressure (mmHg)	46 (38; 55)	47 (38; 54)	45 (36; 55)	NS
– Pulmonary capillary wedge pressure (mmHg)	11 (9; 15)	12 (10; 19)	11 (9; 13)	NS
– Cardiac index (L/min/m^2)	2.4 (2.0; 2.9)	2.35 (2.0; 2.8)	2.4 (2.0; 2.9)	NS

Data represent the number of cases (percentage) or median (interquartile range).
A4C, apical four-chamber view; EQ-VAS, European Quality of Life Group instrument self-report questionnaire visual analogue scale; NS, not significant; LA, left atrium; LV, left ventricle; PH, pulmonary hypertension; PLAX, parasternal long axis view; RA, right atrium; RV, right ventricle.

>1 arrhythmia during the procedure (two cases), and history of two clinically relevant arrhythmias in three cases, more details are in Supplementary material online, *Table S1*.

In the Extended ablation group, the RFCA procedure was completed per protocol in 33 (92%) out of 36 patients. Despite being assigned to extensive ablation, no RFCA was done in one patient without inducibility of any clinically relevant arrhythmia and lack of clear arrhythmogenic substrate. In two more patients, CTI block was not unequivocally demonstratable.

The RA lesions were significantly less frequently done in the Limited than in the Extended ablation group [22 (58%) vs. 33 (92%); $P < 0.001$]. The difference was mainly driven by the completion of per-protocol lesion set on top of CTI ablation (SVC isolation, posteroseptal intercaval line, and homogenization of low-voltage zones). On the other hand, the extent of LA lesions was comparable between the study groups. Electrical cardioversion for AF during the procedure was performed more often in the Limited than in the Extended ablation group [10 (26%) vs. 4 (11%) patients; $P = 0.04$]. Compared to patients in the Limited ablation group, procedural time and radiofrequency time were significantly prolonged in the Extended ablation group. The procedural details including performed lesions in both groups are provided in *Table 2* and Supplementary material online, *Table S1*.

The median duration of the follow-up period was 13 (IQR: 12; 18) months in the Limited ablation group and 14 (IQR: 12; 21) months in the Extended ablation group. The primary endpoint occurred comparably in 15 patients (42%) vs. 17 patients (45%) in the Extended vs. Limited ablation group [hazard ratio (HR): 0.97, 95% confidence interval (CI): 0.49–2.0], *Table 3*, *Figure 2*.

The secondary endpoints analysis is shown in *Table 3*. There were no other significant differences between the study groups except for the antiarrhythmic medication after the blanking period that was more frequently used in the Limited ablation group. There were 10 (28%) vs. 9 (24%) deaths in the Extended vs. Limited ablation group (HR: 0.92, 95% CI: 0.36–2.32). Corresponding Kaplan–Meier curves are presented in *Figure 3*.

Manifestation of new arrhythmia (different from all arrhythmias previously noticed) was seen in 9/31 patients with arrhythmia recurrence during the follow-up: 6 and 3 patients in Extended and Limited ablation groups, respectively. Typical AFL did not reoccur during the follow-up. Out of four patients with documented arrhythmia after CTI ablation, two had AF and two patients manifested atypical AFL (see Supplementary material online, *Table S2*).

Clear procedure-related complications were recognized in three patients: a prolonged severe vagal reaction during sheath removal at the end of the procedure with the necessity of short cardiopulmonary resuscitation, periprocedural progression of conservatively treated pericardial effusion, and surgically treated arteriovenous fistula. Three more adverse events could probably be related to RFCA. Of them, two patients manifested low cardiac output after RFCA, which led to prolonged hospitalization in one patient and slow progression to terminal heart failure and death in the second patient. One patient died suddenly (pulseless electrical activity) 1 day after the ablation of AVNRT without evidence of any periprocedural complication as assessed by autopsy. Hypoxia and end-stage heart failure were most likely responsible for this event. The other three patients manifested severe sinus bradycardia and sinus arrest episodes after the termination of persistent arrhythmia; however, ablation in these patients was not done in proximity to the sinus node. Major procedural complications and serious adverse events in the study are in more detail shown in Supplementary material online, *Table S3*.

Discussion

In this first multicentre randomized trial in a patient population with AF/AT and PH, extensive RFCA, compared with a limited approach, did not significantly reduce the recurrence of arrhythmia, symptoms, cardiovascular hospitalizations, and mortality.

Several retrospective studies with a limited number of patients have reported that RFCA of typical AFL or other less complex SVT was feasible, acutely effective, and safe in patients with PH.[5,6,10,13–16] Long-term clinical outcome after RFCA, however, was found to be less optimistic and more divergent. Bradfield *et al.*[13] reported that only 5 of 10 patients with acutely successful CTI ablation were completely arrhythmia-free at 3 months and three patients had recurrent arrhythmias different from their initial typical AFL. In 23 patients ablated for typical AFL and other organized SVTs, arrhythmia occurred in 12 patients during a 5-year follow-up, of whom the new onset of arrhythmia was seen in 10 cases.[14] On the contrary, a more favourable outcome was found in the recent retrospective study in 32 patients with successful ablation of typical AFL, who had a recurrence rate of ~20% during a follow-up of 3–108 months. However, the proportion of recurrence of index arrhythmia and onset of new arrhythmias was not provided.[16]

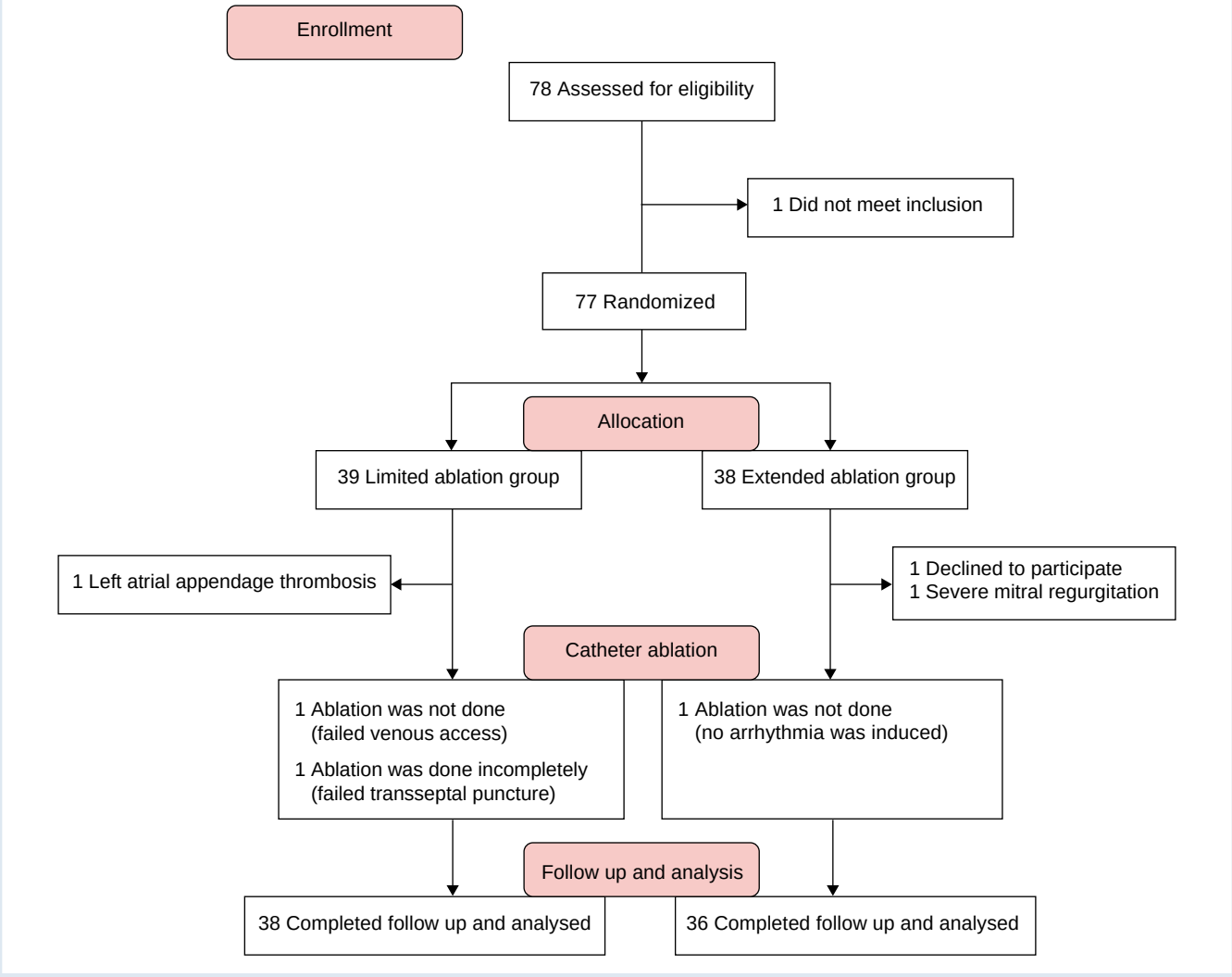


Figure 1 CONSORT flow diagram.

In our study, we prospectively evaluated the clinical outcome of two ablation strategies in PH patients with various types of supraventricular arrhythmia. The extensive ablation was intended to reduce a long-term arrhythmia recurrence rate by ablation of all inducible arrhythmias, including those that did not manifest clinically prior to the procedure, and by preventative modification of arrhythmogenic substrate for potentially new and currently non-inducible arrhythmias. Unlike previous studies, we also enrolled patients with AF.

The relatively high arrhythmia recurrence rate after the RFCA for AF/AT in patients with PH in both study arms was comparable to that in non-paroxysmal AF in non-PH patients with a low prevalence of structural heart disease.[18–20] A recent meta-analysis reported a pooled median success rate of 66.7% (95% CI 60.8–72.2%) after the single RFCA for non-paroxysmal AF.[18] Beyond PVI, a range of trigger and left atrial substrate modification ablation strategies have been proposed to improve success in non-paroxysmal AF. However, the randomized controlled trial STAR AF II indicated that adjunctive RF ablation strategies did not improve outcomes over PVI alone but were associated with higher fluoroscopy and procedure times.[19] Our study investigated different population of patients with highly suspected right over left atrial arrhythmogenic substrate because of right-sided pressure and volume overload, so tailored targeting of right atrial arrhythmogenic substrate seemed justified. Our study also included patients with paroxysmal AF (30% of all AF cases) and patients with AT including typical AFL.

No recurrence of typical AFL was observed in our cohort. This finding is far more favourable than previously reported long-term data.[13,14] We speculate that RFCA with 3D-electroanatomical mapping and direct visual control using intracardiac echocardiography could be responsible for such an outcome. Significant elimination of triggers (PVI in 62% of patients) may also play a role. The data overall indicate that CTI ablation in PH could be effective in patients with documented or highly suspected typical AFL. However, the reoccurrence of different arrhythmias in AFL patients in both study arms was noticed during follow-up, which is in concordance with previous results.[13,14]

Apart from the well-known reasons for the failure of additional substrate ablation in the general AF population, several other explanations for what is behind the lack of benefit from an extensive ablation in this trial can be offered. Although enlargement of RA, conduction slowing, reduced tissue voltage, and regions of electrical silence in RA were described in patients with PH,[21,22] we were not able, however, to detect a significant prevalence and extent of regions with low-voltage and/or abnormal atrial electrograms in our population despite expectedly dilated RA. We cannot exclude that our bipolar cut-off voltage for low-voltage zones was not sensitive and specific enough to identify RA arrhythmogenic substrate. We can

Table 2 Procedural characteristics

	All patients $n = 74$	Limited ablation group $n = 38$	Extended ablation group $n = 36$	*P*
Clinical arrhythmia present at baseline	28 (38%)	17 (45%)	11 (31%)	NS
SR present at baseline, clinical arrhythmia inducible	19 (26%)	11 (29%)	8 (22%)	NS
SR present at baseline, clinical arrhythmia non-inducible or not induced	14 (19%)	5 (13%)	9 (25%)	NS
Other than clinical arrhythmia present/induced at baseline	9 (12%)/4 (5%)	3 (8%)/2 (5%)	6 (17%)/2 (6%)	NS
>1 arrhythmia in the history	10 (14%)	6 (16%)	4 (11%)	NS
>1 arrhythmia during the procedure	9 (12%)	5 (13%)	4 (11%)	NS
RA mapping time (min)	18 (13; 24)	20 (13; 27)	16 (13; 22)	NS
LA mapping time (min)	18 (13; 23)	18 (13; 24)	17 (12; 22)	NS
Total procedure time (min)	173 (135; 210)	155 (130; 180)	205 (150; 225)	0.004
General anaesthesia	9 (12%)	4 (11%)	5 (14%)	NS
Fluoroscopy time (min)	2.4 (1.4; 5.1)	2.2 (1.4; 5)	3.3 (1.7; 7.3)	NS
Radiofrequency time (min)	39 (24; 56)	26 (14; 42)	49 (32; 65)	<0.0001
CARTO RA volume (mL)	196 (159; 250)	206 (155; 260)	191 (162; 249)	NS
CARTO LA volume (mL)	122 (99; 143)	122 (104; 142)	116 (62; 153)	NS
CARTO RA surface (cm^2)	198 (172; 228)	201 (173; 230)	182 (171; 213)	NS
CARTO LA surface (cm^2)	135 (120; 154)	137 (125; 156)	134 (119; 153)	NS
RA LVAs (% of the surface)	5 (1;12)	4 (1; 11)	5 (2; 13)	NS
LA LVAs (% of the surface)	2 (0; 10)	4 (1; 11)	2 (0; 22)	NS
Acute success of ablation	69 (93%)	36 (95%)	33 (92%)	NS
Ablation not done	3 (4%)	2 (5%)	1 (3%)	NS
Procedural ECV	16 (22%)	11 (29%)	5 (13%)	NS
Procedural ECV in AF patients	14/38 (37%)	10/19 (53%)	4/19 (21%)	0.04
LA ablation	48 (65%)	21 (55%)	27 (75%)	NS
– PVI alone	24 (32%)	10 (26%)	14 (39%)	NS
– PVI + additional lesions	22 (30%)	9 (24%)	13 (36%)	NS
– LA ablation without PVI	2 (3%)	2 (5%)	0 (0%)	NS
– LA foci	5 (7%)	3 (8%)	2 (3%)	NS
– CFAE	8 (11%)	3 (8%)	5 (14%)	NS
– LVAs	14 (19%)	4 (11%)	10 (28%)	NS
– CS	7 (9%)	4 (11%)	3 (8%)	NS
– Linear lesions	16 (%)	6 (16%)	10 (28%)	NS
RA ablation	55 (74%)	22 (58%)	33 (92%)	0.0009
– CTI alone	17 (23%)	14 (37%)	3 (8%)	0.004
– CTI + additional lesions	31 (42%)	2 (5%)	29 (81%)	<0.0001
– RA ablation without CTI	7 (9%)	6 (16%)	1 (3%)	NS
– SVC isolation	27 (36%)	1 (3%)	26 (72%)	<0.0001
– CFAE/LVA	14 (19%)	1 (3%)	13 (36%)	0.0002
– Intercaval line	26 (35%)	1 (3%)	25 (69%)	<0.0001
– RA/CS focal activity	4 (5%)	2 (5%)	2 (6%)	NS
– AVN slow pathway	3 (4%)	3 (8%)	0 (0%)	NS

Data represent the number of cases (percentage) or median (interquartile range).
AF, atrial fibrillation; AVN, atrioventricular node; CFAE, complex fragmented atrial electrograms; CS, coronary sinus; CTI, cavotricuspid isthmus; ECV, electrical cardioversion; LA, left atrium; LVA, low voltage area; NS, not significant; PVI, pulmonary vein isolation; RA, right atrium; SR, sinus rhythm; SVC—superior vena cava.

also speculate that elevated right-sided filling pressure with associated RA hypertrophy could mask the voltage-attenuation effects of spontaneous atrial scarring and dilatation. When abnormal myocardium could not be found, mainly empirical lesions (i.e. CTI block, SVC isolation, or intercaval line) constituted an extension of ablation, and such lesions alone might not be the most efficacious ablation targets in PH patients. We cannot also exclude the possibility that our strategy of extended ablation did not target sufficiently the uncommon type of ATs involving both atria and inter-atrial

Table 3 Study endpoints

	Limited ablation group $n = 38$	Extended ablation group $n = 36$	*P*
Primary endpoint			
– Documented arrhythmia recurrence >30 s without antiarrhythmic drugs after the 3-month blanking period	17 (45%)	15 (42%)	NS
Secondary endpoints			
– Documented on-drug arrhythmia recurrence	10 (26%)	7 (19%)	NS
– Symptoms of arrhythmia	13 (34%)	10 (28%)	NS
– Patients with emergency visits/number of emergency visits per patient	11 (29%)/2 (1; 3)	9 (25%)/2 (1; 2)	NS/NS
– Patients with hospitalization/number of hospitalizations per patient	14 (37%)/1 (1; 2)	13 (36%)/2 (1; 2)	NS/NS
– Patients with cardiovascular emergency visits or hospitalization/number of events per patient	13 (24%)/1 (1; 3)	11 (31%)/1 (1; 2)	NS/NS
– Mortality	9 (24%)	10 (28%)	NS
– Antiarrhythmic drugs (post-blanking period)	16 (42%)	7 (19%)	0.046
– Antiarrhythmic drugs (at the end of follow-up)	11 (29%)	7 (19%)	NS
– Reablation rate	5 (13%)	3 (8%)	NS
– Pacemaker implantation	3 (8%)	1 (3%)	NS
– AV junction ablation	0	1 (3%)	NS
Other objectives (12-month visit—baseline difference)			
– 6-minute walking test (m)	−10 (−27; 55)	9 (−28; 163)	NS
– EQ-VAS	−4 (−12; 14)	0 (−18; 22)	NS
– NT-proBNP (pg/mL)	239 (−312; 1120)	98 (−512; 695)	NS
Major procedural complications	5 (13%)	4 (11%)	NS

Data represent the number of cases (percentage) or median (interquartile range).
Details on major procedural complications are provided in Supplementary material online, *Table S3*.
EQ-VAS, European Quality of Life Group instrument self-report questionnaire visual analogue scale; NS, not significant.

connections.[23] Abnormal modulation of the intrinsic cardiac autonomic system has been identified as an arrhythmogenic mechanism in patients with PH.[24,25] The arrhythmia sources because of this mechanism are difficult to identify and modify by conventional ablation strategies. The high recurrence rate of arrhythmia in combination with PH, as a severely limiting underlying condition, was likely responsible for the absence of improvement in quality of life, functional capacity, and natriuretic peptides.

The results may be also biased by post-randomization deviations from protocol-specified care that could attenuate the difference in clinical outcome between study arms. For example, ablation on top of limited selective RFCA was done in eight (21%) patients in the Limited ablation group with more than one documented type of arrhythmias or when other arrhythmias were seen during the index procedure. This was done at the investigator's discretion if believed to be beneficial for the subject's welfare. Similarly, the investigators tended to perform more complex LA ablation in non-paroxysmal AF irrespective of the study treatment allocation, which finally resulted in a small difference in the LA lesion set between study arms. On the contrary, in the Extended ablation group, the lesion set was not completed in several patients. In one case with AT, ablation was not done when no arrhythmia was induced. Moreover, in two patients with AFL and two patients with AF, the full lesion set in RA was not completed mainly because of a prolonged and poorly tolerated procedure in combination with extreme enlargement of the right atrium preventing successful ablation.

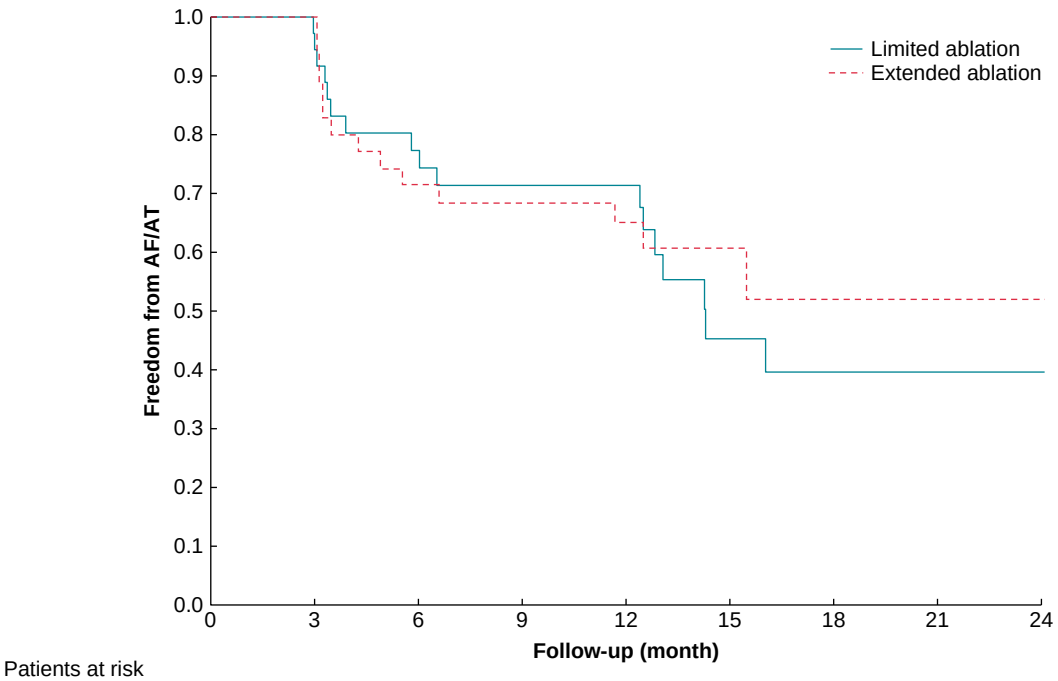
It has been shown that the use of general anaesthesia could increase the single procedure success rate of RFCA of complex atrial arrhythmia, and shorten fluoroscopy and procedural time without increasing procedural complications.[26] However, the concern about severe complications related to general anaesthesia in PH patients exists. The PH is a serious condition, and the induction of general anaesthesia can incur additional sudden haemodynamic stress.[27] It is also known that patients with severe PH have increased rates of delayed extubating, heart failure, and mortality after non-cardiac surgery.[28] On the other hand, conscious sedation may result in inadvertent hypoventilation episodes with their consequences. Operators preferred to use conscious sedation, which is a common way of performing RFCA even for complex arrhythmias in our country.

Importantly, a considerable number of adverse events were recorded during the follow-up. There was no excess of clinical events including all-cause death in the Extended ablation group, and only a few events were directly procedure-related while all others could be considered the natural course of the underlying disease. Therefore, RFCA appeared safe even in the population of frailty PH patients when performed by experienced operators.

The left atrial stiff syndrome is a plausible long-term side effect of extensive complex RFCA in LA resulting in pulmonary venous hypertension[29,30] that can aggravate PH. The potentially higher risk of left atrial stiff syndrome with its consequences in PH patients is one of the arguments against routine extensive ablation in the left atrium in that population. This risk was not, however, investigated in our study.

Limitations

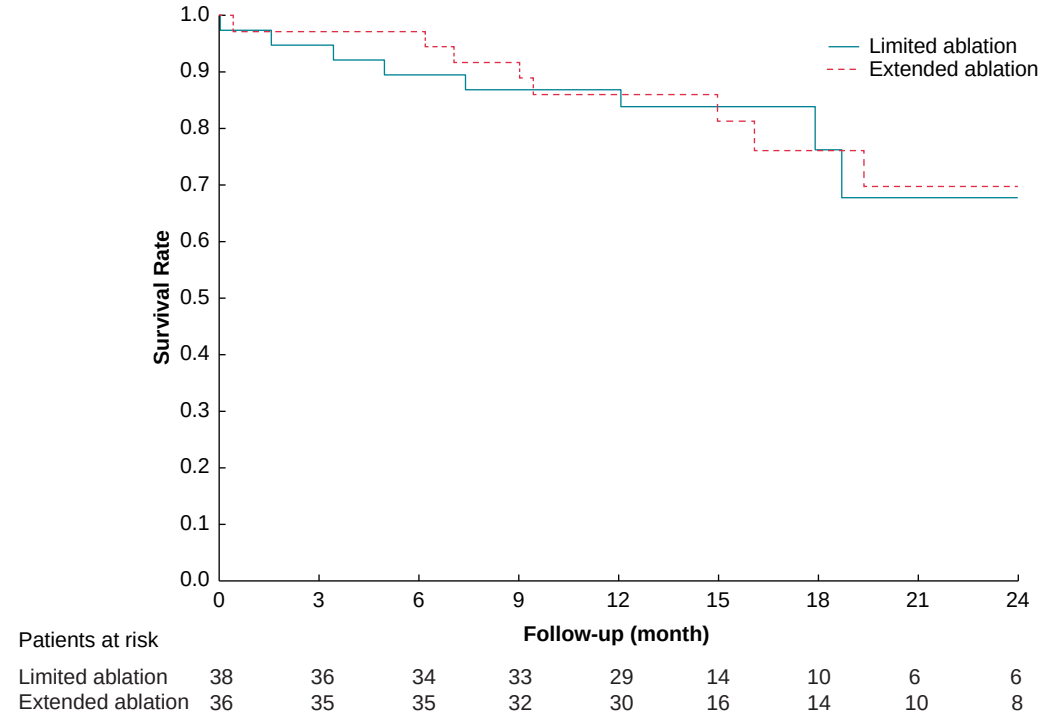
The study has several limitations. First, the patient population was heterogeneous in terms of the type and aetiology of PH. Second, high-



Patients at risk

Limited ablation	38	35	26	23	21	8	6	4	4
Extended ablation	36	34	24	21	19	7	6	5	3

Figure 2 Event-free survival for arrhythmia recurrence (primary endpoint). Kaplan–Meier curves: solid blue for the Limited ablation group; dashed red for the Extended ablation group.



Patients at risk

Limited ablation	38	36	34	33	29	14	10	6	6
Extended ablation	36	35	35	32	30	16	14	10	8

Figure 3 Event-free survival for all-cause mortality. Kaplan–Meier curves: solid blue for the Limited ablation group; dashed red for the Extended ablation group.

density mapping was not used to identify an arrhythmogenic substrate. Third, operators tended to deviate from the protocol (by performing more than simply PVI) in patients with persistent AF who were randomized to a limited ablation strategy. Fourth, pulsed electrical field ablation technology was not available during the study enrollment period. Fifth, the arrhythmia burden that would be a better procedural endpoint than the first arrhythmia recurrence was not assessed.

Conclusions

Extensive RFCA, compared with a limited approach, was not beneficial in terms of arrhythmia recurrence in patients with AF/AT and PH. The absence of clear advance in the context of the prolonged procedural time in the PH population warrants the conclusion that performing additional, and perhaps unnecessary, ablation lesions should be generally avoided.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: None declared.

Data availability

All relevant data are in the manuscript. Relevant dataset is available on request.

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