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The impact of right atrial volume on ablation outcomes in patients with pulmonary hypertension and atrial flutter

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Abstract

Background Catheter ablation has evolved as a safe treatment for atrial flutter (AFL) in patients with pulmonary hypertension (PH), and the recurrence of AFL may accelerate clinical decompensation. The aim of this study was to determine the recurrence rate and risk factors for recurrent AFL in PH patients after ablation.

Methods All PH patients who underwent AFL ablation at Fuwai Hospital between May 2015 and December 2020 were followed up. The recurrence rate and risk factors for recurrence were analyzed.

Results A total of 68 PH patients (mean age 44.0 ± 13.0 years, 36.8% male) were enrolled. The majority patients diagnosed PH had congenital heart disease-associated PH (63.2%), and 30.9% had idiopathic pulmonary arterial hypertension. At baseline, most patients (80.9%) had only cavotricuspid isthmus (CTI)-related AFL; the occurrence of non-CTI-related AFL among patients was 8.8%, and 10.3% of the patients had both types of AFL. During a median follow-up of 17.5 months, 22 patients developed at least one recurrent AFL episode (AFL-free survival: 76.5% at 1 year). The immediate success of ablation (HR 0.061, 95% CI 0.009 to 0.438; $P=0.005$) and the right atrial volume index (RAVi, per 10 ml/m^2; HR 1.064, 95% CI 1.011 to 1.120; $P=0.018$) were associated with long-term ablation outcomes in PH patients. With 166.64 ml/m^2 as a cutoff value, AFL-free survival was significantly greater in patients whose RAVi was < 166.64 ml/m^2 (log-rank $P=0.024$).

Conclusion The immediate success of ablation and the RAVi are associated with recurrent AFL. Patients with a RAVi ≥ 166.64 ml/m^2 are likely experience recurrence.

Keywords Pulmonary hypertension, Atrial flutter, Catheter ablation, Recurrence, Risk factors

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Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, as assessed by right heart catheterization; PH is characterized by progressively increased pulmonary pressure and can lead to heart failure as well as death if not effectively treated [1]. PH significantly affects the quality of life and life expectancy of patients [2]. As pulmonary pressure increases and cardiac remodeling occurs, dilation of the right atrium and right ventricle with subsequent valvular regurgitation may trigger arrhythmias [3].

In a series of 317 consecutive PH patients followed by Mercurio and colleagues [4], 5.8% had documented atrial flutter (AFL), which was the second most common type of supraventricular arrhythmia (SVA) after atrial fibrillation (AF). Prospective studies suggest that the development of SVAs is related to the worsening of hemodynamic and functional parameters as well as adverse prognoses [5, 6]. In recent years, radiofrequency catheter ablation (RFCA) has become a safe and feasible method to restore sinus rhythm and reverse clinical decompensation [7, 8]. However, the predictors and incidence of recurrence in PH patients with AFL after RFCA have not been systematically evaluated. In this study, we sought to assess the incidence and risk factors associated with the recurrence of AFL in patients with PH who underwent ablation.

Methods

Study population

This was a retrospective, single-center study enrolling all consecutive patients with PH aged ≥ 18 years with AFL ablation at Fuwai Hospital between May 2015 and December 2020. The inclusion criteria were as follows: (1) a diagnosis of PH according to current guidelines (previous right heart catheterization demonstrating a mean pulmonary arterial pressure [mPAP] of ≥25 mmHg)[1] and (2) a diagnosis of AFL according to an electrophysiology study (EPS) and an ablation procedure. The exclusion criteria included acute cardiovascular or cerebrovascular events within 3 months before the procedure, any major trauma, or known malignancy. Clinical data, standard 12-lead surface electrocardiograms (ECGs) in sinus rhythm after and during ablation, echocardiographic data, intracardiac electrograms, three-dimensional (3D) electroanatomic mapping data, imaging data, and follow-up outcomes were documented in the study. The types of PH were defined according to the ESC/ERS guidelines for the diagnosis and treatment of PH [1]. All patients provided general informed consent before the procedure. The study protocols were approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (No. 2021−1522), and were in accordance with the Declaration of Helsinki.

Electrophysiology study and catheter ablation

For all patients, antiarrhythmic medications were discontinued for at least five half-lives. All patients underwent contrast-enhanced cardiac computed tomography (CT) before the procedure. Atrial volume was obtained by drawing free-hand ROIs on each slice of the atria in the axial plane and automatically calculated by post processing software (Siemens, Erlangen, Germany). The atrial volume index was calculated by dividing the volume by the body surface area and was interpreted as the LA volume index (LAVi) and the RA volume index (RAVi). The CT data of all patients were measured by two experienced CT observers. All catheters were inserted percutaneously via the Seldinger technique and advanced into position under fluoroscopic guidance. Coronary sinus cannulation was completed via an inferior or superior approach (6-F steerable decapolar catheter; Triguy; APT Medical, CHN). A multichannel electrophysiology recorder (Bard Electrophysiology) was used to record the 12-lead surface electrocardiogram (ECG) and intracardiac electrogram. Navigation, activation mapping and ablation were performed via three-dimensional electroanatomic mapping systems (CARTO 3, Biosense Webster, Inc., Diamond Bar, CA). Electroanatomical maps were created via fast anatomic mapping, point-by-point mapping, or intracardiac echocardiography (ICE) reconstruction (SOUNDSTAR, Biosense Webster, Inc., Diamond Bar, CA). We used a multielectrodes mapping catheter (PENTARAY; Biosense Webster), which was advanced via an SL1 or SR0 long sheath to conduct electroanatomical activation mapping (EAM). When the EAM indicated an AFL related to the left atrium, a transeptal puncture was performed. Intravenous heparin was given after transseptal catheterization to maintain an activated clotting time of more than 250 s. For patients who were in sinus rhythm at the beginning of the procedure, atrial stimulation protocol was performed including programmed and progressive stimulation. In patients for whom tachycardia could not be induced via a regular procedure, isoproterenol was administered. The critical isthmus of the AFL was defined as the position where entrainment produced concealed fusion [9] and the postpacing interval was <30 ms greater than the tachycardia cycle length (TCL). RFCA with a maximum power of 40 W and a maximum temperature of 43 °C was delivered in the critical isthmus region via an irrigated catheter (Thermocool SmartTouch, Biosense Webster, Inc., Diamond Bar, CA). The endpoint of the RFCA was determined via a combination of documentation of bidirectional conduction block confirmed by differential pacing and atrial tachycardia noninducibility; the procedure was also terminated if the patient could not tolerate it for any reason. Endpoints had to be fulfilled after a waiting period of twenty minutes after the last ablation. Immediate success of ablation

was defined as the noninducibility of any kind of AFL. For patients with cavotricuspid isthmus (CTI)-related AFL, a line of bidirectional cavotricuspid conduction block was required for immediate success. Conduction across the ablation line was not checked in all patients with non-CTI-related AFL, whereas the voltage mapping of the ablation line to assure a voltage < 0.1 mV after ablation was required for immediate success [10]. Immediate failure was defined as the lack of the above criteria for immediate success.

Follow-up

Patients who underwent ablation were followed up by outpatient visits or telephone calls every 3–6 months, and the final census date was January 30, 2022. All arrhythmia-related symptoms, including palpitations, chest tightness, chest pain, dyspnea, and syncope, were recorded. Moreover, a 12-lead ECG was performed when patients reported any of the symptoms mentioned above and during follow-up. Two experienced clinicians independently evaluated the ECG-documented arrhythmia, and the final AFL diagnosis was made on the basis of the agreement between the clinicians. The diagnosis of typical AFL was characterized by an atrial rate between 250 and 350 beats/min, a sawtooth-like pattern in leads II, III and AVF, positive F waves in lead V1, and isoelectric or negative F waves in leads V5 to V6. The diagnosis of atypical AFL was made if the F-wave was not in accordance with typical AFL [11]. Recurrence was defined as symptomatic or asymptomatic ECG-documented AFL with a stable TCL (± 10 ms) longer than 30s in duration.

Statistical analysis

SPSS IBM 22 (IBM Co., Armonk, New York, USA), R V.4.0.5 (http://cran.r-project.org/), and GraphPad Prism 8.0 (GraphPad Software Inc., La Jolla, CA) were used for graphing, to perform the statistical analyses and create figures. For this analysis, only the first event was counted, even if patients had recurrent episodes during follow-up. Continuous data are presented as the means ± standard deviations (SDs) or medians and interquartile ranges, depending on the normality of the distribution. Categorical variables are described as frequency counts and percentages. For continuous variables, either Student's two-tailed *t*- test or the Mann-Whiney U-test was performed done for statistical comparisons. For comparisons of categorical data, Fisher's exact test was performed. A probability value of $p < 0.05$ indicated statistical significance. Univariable Cox regression analysis was used to identify the clinical and demographic variables associated with recurrent AFL during follow-up. Other variables believed to have clinical importance and those with $P < 0.05$ in the univariable analysis were considered confounders. Using a multivariate model, the risk factors for recurrence were analyzed by adjusting for other possible factors. The results of the analysis are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). X-tile (version 3.6.1; Yale University School of Medicine; New Haven, CT, USA) was used to generate the optimal RAVi cutoff points with minimum P values from chi-square tests [12]. Kaplan–Meier curves were plotted, and survival was compared between the different RAVi subgroups via the log-rank test.

Results

Sixty-eight PH patients (36.8% male) with AFL were included in the study (mean age 44.0 ± 13.0 years). The majority of PH patients (63.2%) had pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD), 30.9% had idiopathic PAH, and 5.9% had other PH etiologies (PH associated with connective tissue disease: 1.5%, chronic thromboembolic PH: 4.4%). Other comorbidities present at baseline were hypertension in 13.2% of patients, diabetes mellitus in 2.9%, hyperlipidemia in 7.4%, and thyroid disease in 19.1%. Approximately half of the patients (44.1%) had previously undergone cardiac surgery at baseline. Over half of the patients (44, 64.7%) had poor cardiac function, with Grade III/IV disease in the World Health Organization functional class. All patients were treated with PH targeted drugs: 37 (54.4%) with endothelin receptor antagonists, 37 (54.4%) with phosphodiesterase-5 inhibitors, and 20 (29.4%) combined with prostacyclin analogs. Other details are shown in Table 1.

Among the 68 patients, the TCL was 277.7 ± 74.0 ms. Most patients (64, 94.1%) were in AFL rhythm at the beginning of the procedure. The remaining four patients were in sinus rhythm at the time of RFCA, and in all of them, AFL was induced. In those patients, the induced arrhythmia was similar to clinical AFL according to the TCL and F wave morphology. Fifty-five patients (80.9%) had only CTI-related AFL, six patients (8.8%) had only non-CTI-related AFL, and the other seven patients (10.3%) had both types of AFL. Examples of both types of AFL are shown in Fig. 1. Immediate success was achieved in 57 (83.8%) patients, and heart beat in sinus rhythm after ablation was 75.1 ± 13.3 bpm.

During a median follow-up of 17.5 months, 22 patients (32.4%) developed at least one episode of recurrent AFL and 7 patients died before experiencing recurrence. Figure 2 shows the three-year AFL-free survival rate (AFL-free survival: 76.5% at 1 year, 64.1% at 2 years, and 60.3% at 3 years). The symptoms at the time of recurrent AFL detection were increasing dyspnea, palpitation, and worsening of cardiac function. Compared with patients who had a stable sinus rhythm throughout the entire follow-up period, patients who experienced a recurrence of AFL had significantly greater baseline values of

Table 1 Baseline demographic and clinical data

Variables	All (*n* = 68)	Recurrence		*P* values
		Yes (*n* = 22)	No (*n* = 46)	
Age, years	44.0 ± 13.0	42.5 ± 15.0	44.7 ± 12.1	0.524
Male gender, n (%)	25 (36.8)	9 (40.9)	16 (34.8)	0.624
BMI, kg/m^2	21.5 (19.2, 24.7)	21.2 (17.4, 22.5)	22.8 (19.8, 25.4)	0.095
BSA, m^2	1.6 ± 0.2	1.6 ± 0.2	1.7 ± 0.2	0.430
Hypertension, n (%)	9 (13.2)	1 (4.5)	8 (17.4)	0.144
Diabetes mellitus, n (%)	2 (2.9)	0	2 (4.3)	0.321
Hyperlipidemia, n (%)	5 (7.4)	0	5 (10.9)	0.108
Thyroid disease, n (%)	13 (19.1)	5 (22.7)	8 (17.4)	0.601
Diagnosis of PH, n (%)				
IPAH	21 (30.9)	6 (27.3)	15 (32.6)	0.656
PAH-CHD	43 (63.2)	16 (72.7)	27 (58.7)	0.262
PAH-CTD	1 (1.5)	0	1 (2.2)	0.486
CTEPH	3 (4.4)	0	3 (6.5)	0.221
Previous cardiac surgery, n (%)	30 (44.1)	11 (50.0)	19 (41.3)	0.499
WHO-FC III-IV, n (%)	44 (64.7)	15 (68.2)	29 (63.0)	0.678
NT-proBNP, ng/L	1592.0 (826.7, 2939.4)	2557.3 (1034.6, 3780.3)	1405.0 (683.4, 2332.3)	0.093
Uric acid, μmol/L	400.4 ± 137.3	372.9± 128.4	410.8 ± 141.6	0.371
Antiarrhythmic drug (class I), n (%)	5 (7.4)	2 (9.1)	3 (6.5)	0.704
Amiodarone, n (%)	21 (30.9)	6 (27.3)	15 (32.6)	0.656
Aldosterone, n (%)	40 (58.8)	12 (54.5)	28 (60.9)	0.620
Beta-blocker, n (%)	15 (22.1)	5 (22.7)	10 (21.7)	0.927
Diuretic, n (%)	61 (89.7)	21 (95.5)	40 (87.0)	0.281
ERA, n (%)	37 (54.4)	13 (59.1)	24 (52.2)	0.592
PDE-5i, n (%)	37 (54.4)	13 (59.1)	24 (52.2)	0.592
Prostacyclin analogue, n (%)	20 (29.4)	5 (22.7)	15 (32.6)	0.403

BMI = body mass index; BSA = body surface area; CTEPH = chronic thromboembolic pulmonary hypertension; ERA = Endothelin receptor antagonist; IPAH = idiopathic pulmonary arterial hypertension; PAH-CHD = PAH associated with congenital heart disease; PAH-CTD = PAH associated with connective tissue disease; PDE-5i = Phosphodiesterase type 5 inhibitor; PH = pulmonary hypertension; WHO-FC = World Health Organization functional class. *Variables with P value < 0.05

the RAVi, higher percentage of AFL differ from the CTI-related AFL and lower immediate success rate (Table 2). With respect to the hemodynamic data at baseline, there was no difference in the severity of PH between patients with and without recurrent AFL (right atrial pressure [RAP] 13.7 ± 4.4 versus 12.4 ± 5.7 mmHg, P=0.461; pulmonary vascular resistance [PVR] 14.5 ± 9.1 versus 18.3 ± 44.1 wood units, P=0.180; mPAP 58.8 ± 17.0 versus 52.3 ± 20.1 mmHg, P=0.227; and pulmonary artery wedge pressure [PAWP] 13.5 ± 7.5 versus 13.0 ± 5.0 mmHg, P=0.783). Additionally, most of the PH patients had pre-capillary PH and there was no significant difference between the groups (P=0.250).

Several factors were significant in the Cox univariate analysis (Fig. 3). Patients with higher BMI were more likely to develop recurrent AFL. Patients with larger RAVi and LAVi values were at greater risk of experiencing AFL recurrence at follow-up. Patients who were less likely to have recurrence included those who experienced immediate success and those who were diagnosed with isolated CTI-related AFL. In the Cox multivariate analysis including BMI, cardiac index, isolated CTI-related AFL, immediate success, the RAVi, and the LAVi, only immediate success (HR 0.061, 95% CI: 0.009–0.438, P=0.005) and the RAVi (HR 1.064, 95% CI: 1.010–1.120, P=0.018) remained in the model (Table 3).

The RAVi cutoff value with the maximum chi-square score and minimum P value was considered the optimal critical point of classification by the X-tile program [12]. As shown in Fig. 4, the RAVi cutoff value of 166.64 ml/m^2 had a statistically effect on AFL-free survival, which truncate in three years (logr-ank P=0.024).

Discussion

The main findings of the present study are as follows (i) AFL-free survival was 76.5% at 1 year, 64.1% at 2 years, and 60.3% at 3 years; (ii) immediate failure of ablation and an increased RAVi were independent predictors of recurrent AFL in PH patients; and (iii) a RAVi ≥ 166.64 ml/m^2 was associated with a high likelihood of AFL recurrence and lower AFL-free survival than patients with RAVi < 166.64ml/m^2.

Few studies have investigated the efficacy of ablation in the PH population. Those studies, have focused mainly on the immediate success and safety of RFCA [5, 8, 13]. In the supraventricular tachycardia (SVT) cohort of Zhou

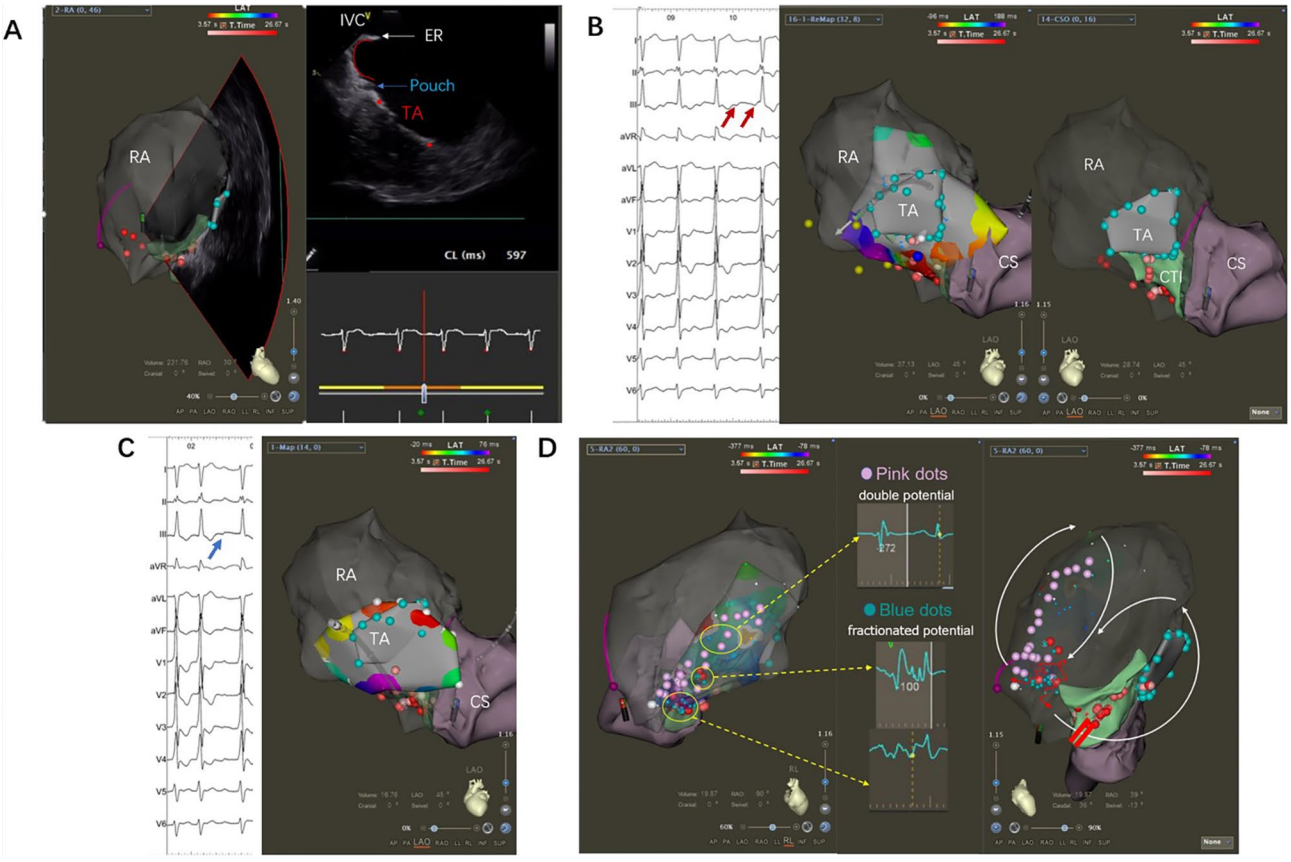

Fig. 1 Examples of both CTI- and non-CTI related types of AFL. (**A**): 3D reconstruction of the RA via ICE; (**B**): Activation mapping of a typical counter-clockwise AFL; note that red arrows represent a negative F wave in the inferior leads; (**C**): After ablation of the CTI, remapping indicated that the CL of the TA was insufficient; note that blue arrows represent a positive F wave; (**D**): Special electrograms recorded around the inferior lateral right atrium with potential reentry of figure-of-eight in this case. AFL, atrial flutter; CL, cycle length; CS, coronary sinus; CTI, cavotricuspid isthmus; ER, Eustachian ridge; ICE, intracardiac echocardiography; IVC, inferior vena cava; RA, right atrium; TA, tricuspid annulus

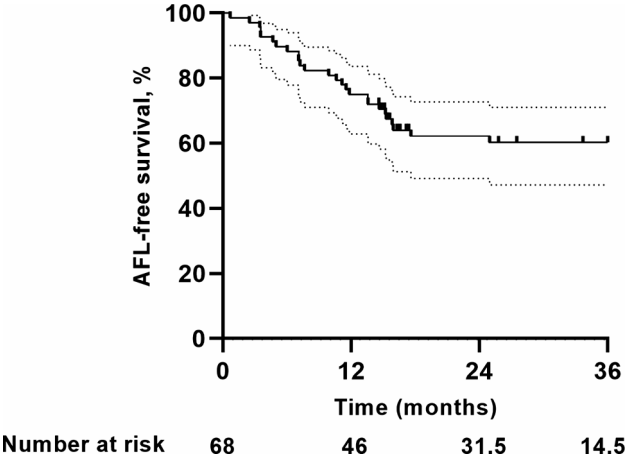

Fig. 2 AFL-free survival in a cohort of PH patients with a history of RFCA. AFL, atrial flutter; PH, pulmonary hypertension; RFCA, radiofrequency catheter ablation. The two dotted lines represent the 95% CI of AFL-free survival

and colleagues [14], 71 PH patients with 76 episodes of SVT were analyzed, and the 3-year success rate of RFCA was 78.3% for all SVTs and 70.7% for AFL. However, larger cohorts and predictors of AFL recurrence in PH patients are still lacking. In the present study, we enrolled a larger population of PH patients with AFL. During follow-up, 22 patients experienced a recurrence of the preablation AFL. The AFL-free survival rates at 1 year, 2 years, and 3 years were 76.5%, 64.1%, and 60.3%, respectively. The difference between the present study and Zhou's study may be due to the consideration of death in our study or the small sample size of both studies.

Furthermore, previous studies have indicated that SVT is associated with increased mortality. Wen et al. [15] reported an elevated risk for mortality in those who developed SVA (HR 4.757, 95% CI: 2.695–8.397, $P<0.001$). Olsson et al. [16] reported similar conclusions. Therefore, we suggest that preventing a recurrence of AFL is highly important in patients with PH. Currently, there is no evidence on how to predict or prevent the recurrence of AFL in PH patients. In the present study,

Table 2 Hemodynamic and procedural related data

Variables	All (*n* = 68)	Recurrence		*P* values
		Yes (*n* = 22)	No (*n* = 46)	
LA dimension (AP), mm	38.1 ± 7.6	37.0 ± 9.0	38.2 ± 6.9	0.975
LVEDD, mm	38.0 (36.0, 45.8)	38.0 (34.8, 47.5)	38.0 (36.0, 45.3)	0.599
Ejection fraction, %	60.0 (57.3, 66.4)	60.0 (55.0, 67.0)	60.0 (58.0, 66.0)	0.807
RV dimension (AP), mm	38.7 ± 9.7	41.0 ± 10.7	37.7 ± 9.2	0.211
Residual cardiac defect, n (%)	17 (25.0)	6 (27.3)	11 (23.9)	0.765
Intracardiac shunts, n (%)	18 (26.5)	7 (31.8)	11 (23.9)	0.489
Moderate-to-severe tricuspid regurgitation, n (%)	48 (70.6)	17 (77.3)	31 (67.4)	0.403
LA volume, ml	67.2 (46.6, 115.9)	71.0 (45.1, 166.8)	65.9 (48.9, 107.8)	0.295
RA volume, ml	285.6 ± 154.9	349.3 ± 176.8	253.8 ± 133.8	0.017*
LAVi, ml/m^2	55.9 ± 44.6	72.6 ± 66.9	47.6 ± 24.7	0.384
RAVi, ml/m^2	174.9 ± 88.8	212.5 ± 86.4	156.1 ± 84.8	0.014*
RAP, mmHg	12.8 ± 5.3	13.7 ± 4.4	12.4 ± 5.7	0.461
mPAP, mmHg	54.6 ± 19.2	58.8 ± 17.0	52.4 ± 20.1	0.227
CI, L/min/m^2	2.5 ± 1.0	2.3 ± 0.5	2.4 ± 1.2	0.624
PVR, wood	17.0 ± 36.0	14.5 ± 9.1	18.3 ± 44.1	0.180
PCWP, mmHg	13.5 ± 6.0	13.5 ± 7.5	13.0 ± 5.0	0.783
Mechanism of PH				0.250
Pre-capillary	61 (89.7)	20 (90.9)	41 (89.1)	
Post-capillary	1 (1.5)	1 (4.5)	0	
Mixed	6 (8.8)	1 (4.5)	5 (10.9)	
Coexistent atrial fibrillation, n (%)	4 (5.9)	1 (4.5)	3 (6.5)	0.746
Coexistent AVNRT, n (%)	3 (4.4)	0	3 (6.5)	0.221
Ablation during AFL, n (%)	61 (89.7)	19 (100.0)	42 (91.3)	0.154
Tachycardia cycle length, ms	277.7 ± 74.0	276.8 ± 90.3	277.2 ± 70.2	0.937
AFL type: CTI/both/non-CTI, n (%)	55 (80.9)/7 (10.3)/6 (8.8)	19 (86.4)/ 2 (9.1)/ 1 (4.5)	36 (78.3)/ 5 (10.9)/ 5 (10.9)	0.657
Isolated CTI AFL, n (%)	55 (80.9)	19 (86.4)	36 (78.3)	0.427
AFL different from isolated CTI-related, n (%)	13 (19.1)	3 (13.6)	10 (21.7)	0.427
Ibutilide during procedure, n (%)	7 (10.3)	3 (13.6)	4 (8.7)	0.531
Cardioversion during procedure, n (%)	3 (4.4)	0	3 (6.5)	0.221
Pacemaker, n (%)	8 (11.8)	4 (18,2)	4 (8.7)	0.256
Immediate success, n (%)	57 (83.8)	15 (68.2)	42 (91.3)	0.043*
Sinus rhythm after ablation, bpm	75.1 ± 13.3	71.5 ± 14.3	76.8 ± 12.6	0.124
PR interval, ms	194.1 ± 38.7	193.7 ± 46.1	194.3 ± 35.2	0.953
QRS duration, ms	122.0 (108.5, 155.5)	142.5 (115.8, 169.5)	121.5 (105.5, 150.3)	0.159
QTc interval, ms	462.2 (427.3, 501.8)	478.7 (428.8, 519.0)	456.3 (425.3, 496.5)	0.294
Right bundle branch block, n (%)	56 (82.4)	18 (81.8)	38 (82.6)	0.936

AFL = atrial flutter; AP = anteroposterior; AVNRT = atrioventricular nodal reentrant tachycardia; CI = cardiac index; CTI = cavotricuspid isthmus; LA = left atrial; LVEDD = left ventricular end-diastolic dimension; LAVi = left atrial volume index; NT-proBNP = N-terminal pro brain natriuretic peptide; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PPHTN = portopulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrial; RAP = right atrial pressure; pulmonary vascular resistance; RAVi = right atrial volume index; RV = right ventricle. *Variables with P value < 0.05

we propose that an increased RAVi and immediate failure of ablation are predictors of recurrent AFLs. Most of the AFL in our study were CTI-related AFLs, which are of RA origin in patients with PH. Indeed, RA size is an important factor in the risk stratification of PH in the current guidelines [1]. In addition, the RAVi is a readily available and generalizable measure of the RA size and extent of remodeling. Although several studies have illustrated the association of the RAVi and AFL after catheter ablation for atrial fibrillation in the general population [17] as well as the relationship between RA enlargement and SVT in the PAH population [18], there was no study to reported an association between the RAVi and recurrent AFL. In our study, we proposed that an increased RAVi promoting recurrence is likely to reflect the deterioration of PH and the underlying substrate as well as remodeling that serves for fixed reentry [17]. We also determined that the optimal cutoff value was 166.64 ml/m^2 and concluded that patients with a RAVi ≥ 166.64 ml/m^2 had significantly lower AFL-free survival. Under these circumstances, all PH patients with a greater RAVi should be monitored closely for recurrence. Our findings

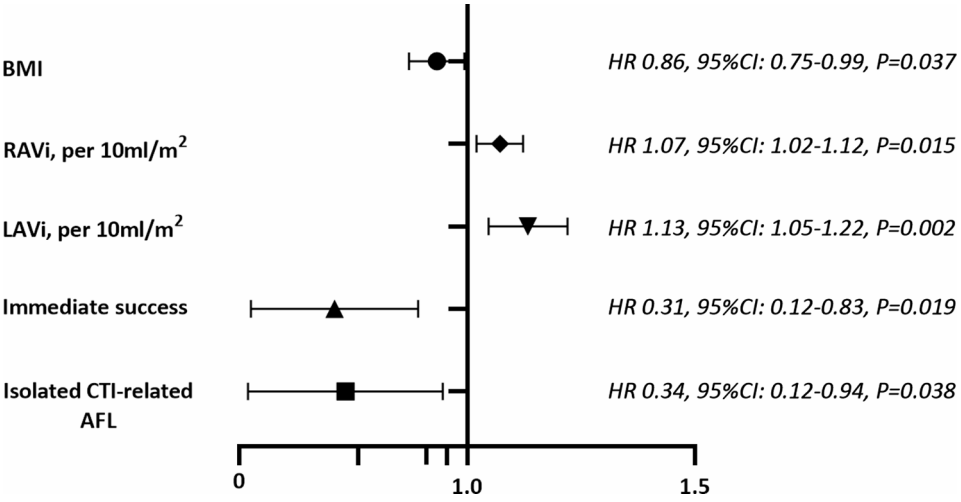

Fig. 3 Variables significant in the univariable Cox analysis. AFL, atrial flutter; BMI, body mass index; CI, confidence interval; CTI, cavotricuspid isthmus; HR, hazard ratio; LAVi, left atrial volume index; RAVi, right atrial volume index

Table 3 Multivariate models of factors related to recurrence of AFL

Variable	HR	95%CI	*P*
BMI, kg/m^2	0.939	0.781–1.128	0.500
CI, L/min/m^2	0.619	0.256–1.496	0.287
Isolated CTI AFL	4.279	0.417–43.915	0.221
Immediate success, n (%)	0.061	0.009–0.438	0.005*
LAVi, ml/m^2	0.997	0.861–1.155	0.970
RAVi, per 10 ml/m^2	1.064	1.011–1.120	0.018*

AFL=atrial flutter; BMI=body mass index; CI=confidence interval; CTI=cavotricuspid isthmus; LAVi=left atrial volume index; RAVi=right atrial volume index. *Variables with P value<0.05

may help identify high-risk patients, who may require closer follow-up and may need to do redo-ablation or add antiarrhythmic medications.

In our series, another factor related to recurrence in the multivariate analysis was the immediate success of ablation. Patients with immediate ablation failure tended to have a higher recurrence rate, as suggested by previous studies [19–21]. Initially, Schumacher et al. [19] reported that the recurrence rates of typical AFL were 100% and 54% in patients with only bidirectional conduction delay and unidirectional conduction block, respectively, which were significantly higher than those in patients with bidirectional block (9%). Wu et al. reported [20] that two of four patients with acute ablation failure experienced long-term AFL recurrence, which was greater than that reported in patients with acute ablation success. Several factors explain the high recurrence rate in this population. First, in our study, immediate success was defined as the termination of AFL and noninducibility of any kind of AFL. AFLs terminated by themselves did not complete the activation mapping; therefore, the operator could only detect the fractionated electrograms and ablate those abnormal electrograms by experience. Second, a bidirectional block of CTI was required for immediate

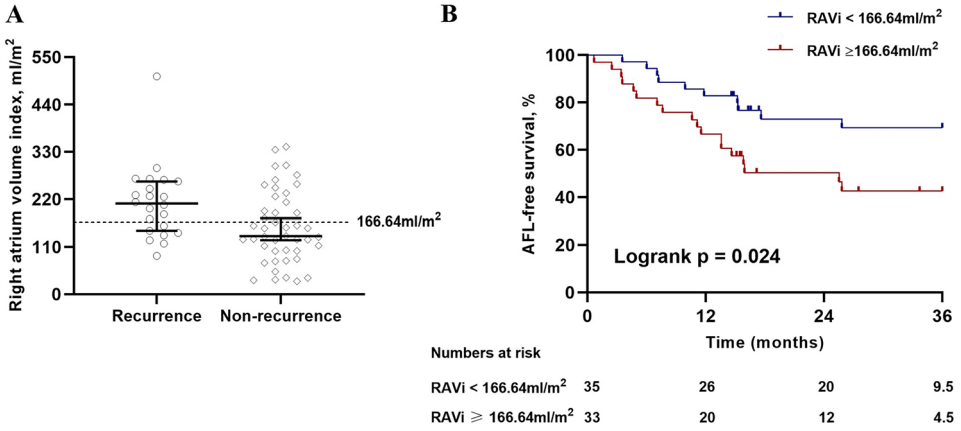

Fig. 4 (**A**) Comparison of the RAVi according to outcome (*P*=0.013). An RAVi of 166.64 ml/m^2 was the best predictor of recurrence. (**B**) AFL-free survival in the RAVi subgroup (log-rank *P*=0.024). AFL, atrial flutter; RAVi, right atrial volume index

success. For patients with a unidirectional conduction block or conduction delays, an improvement over time in bidirectional conduction across the isthmus was more common than in those with bidirectional conduction block [20]. Additionally, in our study, we checked the voltage of the ablation line to be less than <0.1 mV in patients with non-CTI-related AFL. However, to some extent, the low-voltage zone may still contain viable muscle with incomplete or inadequate lesion size and/or depth.

Limitations

Our study has several limitations. First, our study was a single-center study and included a relatively small number of patients. However, our Center of Pulmonary Vascular Disease is one of the largest centers in China, and this is the largest series on AFL ablation in patients with PH to date, which may allow for an accurate evaluation of the incidence and risk factors for recurrent AFL. Second, in cases of non-CTI-related AFL, although an ablation line has been performed between scars or scars and anatomical barriers, bidirectional conduction block was not systematically checked. Although voltage mapping has been performed, it could be related to immediate success. Finally, because of the heterogeneity of the population with different diagnoses of PH and the size of the population, the study was unable to find significant differences between specific types of PH as predictive factors of recurrence.

Conclusion

In our study, for PH patients with a history of AFL ablation, the AFL-free survival rate was 76.5% after 1 year, 64.1% after 2 years, and 60.3% after 3 years. Several clinical, electrophysiologic, and hemodynamic factors have been analyzed, and only factors related to the immediate failure of ablation and a larger RAVi have been related to recurrence according to multivariate Cox regression. The cutoff value of the RAVi was 166.64 ml/m^2, and patients with an RAVi ≥ 166.64 ml/m^2 had significantly lower AFL-free survival.

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Author contributions
Conceptualisation and formol analysis: Lei DING, Hong-Da ZHANG, Min TANG; Analysis and interpretation of data: Lei DING, Hong-Da ZHANG Writing-original draft: Lei DING, Hong-Da ZHANG Writing-review&editing: Lei DING, Hong-Da ZHANG, Feng-Yuan YU, Si-Xian WENG, Bin ZHOU, Cong DAI, Min TANG Final approval of the article: Lei DING, Hong-Da ZHANG, Feng-Yuan YU, Si-Xian WENG, Bin Zhou, Cong DAI, Min TANG Data curation and supervision: Min TANG Software: Lei DING, Si-Xian WENG, Min TANG Funding acquisition: Hong-Da ZHANG, Min TANG Methodology and project administration: Lei DING, Si-Xian WENG, Hong-Da ZHANG, Min TANG Investigation: Lei DING, Cong DAI, Hong-Da ZHANG.

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Data availability
The datasets presented in this article are not readily available because research data is confidential. Data sharing requests are required to meet the policies of the hospital and the funder. Requests to access the datasets should be directed to doctortangmin@yeah.net.

Declarations

Ethics approval and consent to participate
The study protocols were approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (No. 2021 – 1522), and were in accordance with the Declaration of Helsinki.

Consent for publication
We confirm that we have obtained written informed consent to publish.

Competing interests
The authors declare no competing interests.

Conflict of interest
All authors have no conflicts to disclose.

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