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Pre-Procedural Right Atrial Diameter May Predict the Development of Typical Atrial Flutter in Patients Undergoing Catheter Ablation for Atrial Fibrillation

ABSTRACT

Background: Some patients undergoing catheter ablation for atrial fibrillation may develop typical atrial flutter on follow-up, and a second procedure for typical atrial flutter is often required in such patients. In this study, we aimed to define the variables associated with the development of typical atrial flutter after ablation.

Methods: One hundred fifty-nine patients who underwent catheter ablation for the first time due to atrial fibrillation and who did not have a previously documented atrial flutter were included in the study. Before ablation, baseline clinical features and echocardiographic parameters were recorded. At the 1st, 3rd, 6th, and 12th months after the procedure, and then annually, the patients were followed up for typical atrial flutter development.

Results: At a mean follow-up of 34.0 (14.0-50.0) months, typical atrial flutter developed in 21 (13.2%) patients. During the follow-up, right atrial diameter was greater in those who developed typical atrial flutter than those who did not [39.0 (38.0-43.0) vs. 36.0 (34.0-39.0) mm, $P < .001$]. A multiple Cox regression analysis showed that the right atrial diameter was the only independent predictor of typical atrial flutter development (hazard ratio = 1.12, 95% CI: 1.02-1.23, $P = .021$). A receiver operating characteristic analysis showed that the best cutoff for the right atrial diameter was 38.5 mm to predict typical atrial flutter development (area under the curve = 0.77, 95% CI: 0.67-0.86, sensitivity = 62%, specificity = 75%, $P < .001$).

Conclusion: In patients undergoing catheter ablation for atrial fibrillation, a pre-procedural right atrial diameter measurement may predict typical atrial flutter development at follow-up. In particular, patients with a pre-procedural right atrial diameter ≥39 mm may be at a higher risk for developing typical atrial flutter in the future.

Keywords: Atrial fibrillation, atrial flutter, catheter ablation, right atrium

ORIGINAL INVESTIGATION

INTRODUCTION

When performed by experienced operators, catheter ablation is superior to antiarrhythmic drug therapy in terms of both maintenance of sinus rhythm and symptom control in patients with symptomatic paroxysmal or persistent atrial fibrillation (AF).[1] However, atrial tachyarrhythmia (ATa) recurrence can be seen in up to 50% of patients undergoing catheter ablation for AF. Cavotricuspid isthmus (CTI)-dependent typical or atypical atrial flutter (AFL) is responsible for some of these.[2] In these patients, rhythm control with antiarrhythmic drugs is difficult, and catheter ablation is usually required.[2] Ablation of the CTI is a well-established treatment modality in patients with typical AFL.[3]

Consensus reports recommend CTI ablation in the same session as pulmonary vein isolation (PVI), with a class I recommendation, in patients with a history of typical AFL or induced typical AFL during the procedure.[2] However, there is no consensus regarding CTI ablation during PVI in those who did not previously have typical AFL. A recently published meta-analysis reported that CTI ablation in addition to PVI did not reduce ATa recurrence in AF patients without pre-existing AFL.[4] Similarly,

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Lee et al[5] showed that performing CTI ablation in addition to PVI did not reduce the risk of ATa recurrence.[5]

However, some subgroups may still be at a higher risk for typical AFL development after PVI and may benefit from simultaneous CTI ablation. Today, with the greater use of 3-dimensional systems, the procedure and fluoroscopy times of typical AFL ablation have been shortened, and the complication rates have been greatly reduced. There are insufficient data on which patients undergoing AF ablation are at higher risk for developing typical AFL. In some studies on this subject, either the follow-up period was relatively short or the subgroup analyses had not been performed in sufficient detail.[5] In other studies, the patients had not been closely monitored after AF ablation, and the reported rate of typical AFL after AF ablation was relatively low (4.5%).[6]

Previous studies have shown that right atrial (RA) size measurements are predictive for typical AFL development after AF ablation.[6] In addition, they showed that persistent AF, linear lesions, and left atrial (LA) volume index (LAVI) were associated with atypical AFL development after AF ablation.[6] Cabrera et al[7] showed that angiographically measured RA dimensions were greater in patients with typical AFL than in controls.[7] In light of these findings, we aimed to define which patients who underwent AF ablation had a higher risk of developing typical AFL in long-term follow-up. We included parameters related to LA size, structure, and functions of the right chambers in the analyses. We also aimed to identify the variables associated with the development of atypical AFL during the follow-up.

METHODS

Patients who underwent catheter ablation for the first time due to symptomatic paroxysmal or persistent AF at Eskişehir Osmangazi University between 2016 and 2022 and who did not have a previously documented AFL were consecutively included in this retrospective study. The definitions of paroxysmal and persistent AF were made according to current guidelines.[1] Patients with missing follow-up data after AF ablation, the history of previous AFL ablation, AFL ablation in the same session with PVI, severe heart valve disease or prosthetic heart valve, severe LA enlargement (≥55 mm), a thrombus in the LA, AF due to thyroid disorder or infection, acute coronary syndrome or severe coronary heart disease at presentation, history of cardiac surgery in the last 3 months, pregnant patients, and patients with limited life expectancy due to serious comorbidities (<12 months) were excluded from the study. The flowchart of the study protocol is presented in Figure 1.

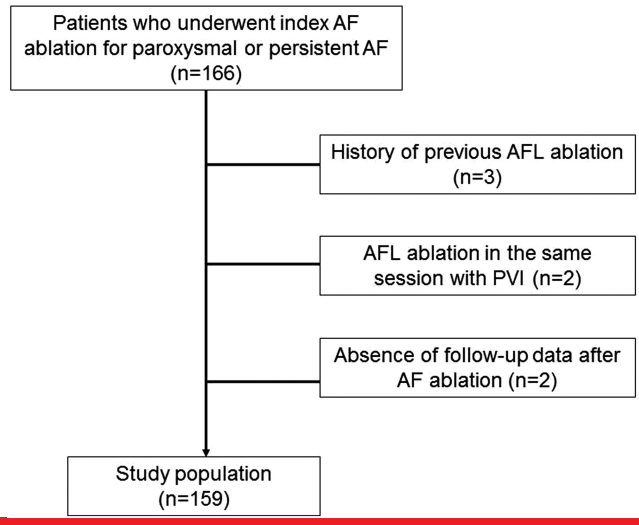

Figure 1. Flowchart of the study. AF, atrial fibrillation; AFL, atrial flutter; PVI, pulmonary vein isolation.

Pre-procedural clinical characteristics, baseline laboratory findings, 2-dimensional echocardiographic measurements, including LA diameter, RA diameter, LAVI, tricuspid annular plane systolic excursion (TAPSE), left ventricle (LV) mass index, and ablation-related features, such as energy type, procedural times, and complications, were recorded from the electronic database of Eskişehir Osmangazi University Hospital. Echocardiographic measurements were performed before AF ablation by 2 experienced echocardiographers. We measured the minor axis of the RA in the apical 4-chamber view as the distance between the lateral RA wall and the interatrial septum. Measurements were made at the mid-atrial level, defined by half of the RA long axis.[8] To test for interobserver reproducibility, RA size was measured in 30 patients by 2 unaware echocardiographers. Interobserver variability was assessed with an intraclass correlation coefficient (ICC), and the interobserver ICC of the RA dimension was 0.977. In addition, since RA diameters vary by gender, we categorized patients' RA diameters as dilated and non-dilated as previously defined, taking into account gender-specific normal values.[9] All echocardiographic measurements were performed according to current guidelines.[8] The Local Ethics Committee approval was obtained for the study (Decision date: 04.10.2022, Decision number: 40). The study complied with the Declaration of Helsinki.

Catheter Ablation

All antiarrhythmic drugs were discontinued at least 5 half-lives before the procedure. Transesophageal echocardiography was performed to evaluate the interatrial septum and exclude the presence of a thrombus in the LA within 24

HIGHLIGHTS

- Typical and atypical atrial flutter (AFL) usually develop within the first year after atrial fibrillation (AF) ablation.
- Male gender, persistent AF, right atrial (RA) diameter, and tricuspid annular plane systolic excursion are associated with typical AFL development after catheter ablation for AF.
- The RA diameter is an independent predictor of typical AFL development after AF ablation.
- In particular, patients with a pre-procedural RA diameter ≥39 mm may be at greater risk of developing typical AFL in the future.

hours before the procedure. All patients underwent multidetector computed tomographic angiography to evaluate LA and PV anatomy.

Either cryoballoon (CB) or radiofrequency (RF) ablation was used for catheter ablation. Cryoballoon and RF ablation procedures were performed as previously described.[10,11] If the patient's rhythm was AF, sinus rhythm was usually obtained with an electrical cardioversion before the procedure. A 6F decapolar catheter (St. Jude Medical, St Paul, Minn, USA) was placed in the coronary sinus, and a 6F pigtail catheter (Alvision™) was placed in the aortic root. Under fluoroscopy guidance, 1 transseptal (TS) puncture was performed for CB, and 2 TS punctures were performed for RF ablation. One TS needle (BRK-1™) and an 8.5F TS sheath (SL0 or SL1, St Jude Medical) were used for TS puncture. A 100 U/kg of unfractionated heparin was administered after entry into the LA, and then additional heparin boluses were administered throughout the procedure to maintain the activated clotting time of 300-350 seconds.

Cryoballoon ablation was performed under conscious sedation containing midazolam and fentanyl. The TS sheath was replaced with a 14F steerable sheath (FlexCath Advance, Medtronic Inc., Minneapolis, Minn, USA) over the wire. A 28-mm second-generation CB catheter was used for PVI (Arctic Front Advance™, Medtronic). A spiral mapping catheter delivered through the balloon was used to visualize the PV potentials (Achieve Advance™ mapping catheter 20 mm, Medtronic). After demonstrating complete occlusion of the PV ostia with 50% diluted contrast medium, CB was performed for 180-240 seconds in each PV antrum region. If the PV potentials did not disappear within 60 seconds or early reconnection was observed, a bonus freeze was applied for the relevant PV. While isolating the right-sided PVs, a decapolar catheter (St. Jude Medical) was introduced into the superior vena cava, and diaphragm contraction was followed by manual palpation.[10]

Radiofrequency ablation was performed under general anesthesia. After the double TS puncture, 1 steerable sheath (Agilis, St Jude Medical) and 1 8.5F TS sheath (SL1, St Jude Medical) were placed in the LA. The LA was mapped with multipolar catheters (Advisor HD Grid, Abbott or Pentaray, Biosense WebsterBiosense Webster, Irvine, CA 92618 USA) using a 3-dimensional mapping system (EnSite Precision, Abbott, or CARTO, Biosense Webster). Irrigated-type sensor-enabled ablation catheters were used for PVI (TactiCath, Abbott or SmartTouch Catheter, Biosense Webster). Meanwhile, the multipolar mapping catheter was parked in the ostium of each PV, and the isolation of a PV was monitored during ablation. Antral PVI was performed in all patients. Additional linear lesions were created according to operator preference.[11]

Acute procedural success was defined as the disappearance or dissociation of all visible PV potentials. Pulmonary vein isolation was confirmed with entry and exit block maneuvers by pacing the catheters in the coronary sinus and PV.[10,11]

Follow-up

Patients were followed up with a physical examination, 12-lead electrogram (ECG), and 24-hour Holter monitoring at the 1st, 3rd, 6th, and 12th months after ablation and then once a year. Antiarrhythmic drug therapy was continued for 3 months after catheter ablation. Patients were evaluated earlier if they had an ATa recurrence or symptoms suggestive of a procedure-related complication. The presence of ATa (AF, AFL, and atrial tachycardia) longer than 30 seconds after catheter ablation was defined as a recurrence. Recurrences within the first three months after catheter ablation were defined as early recurrence, and later recurrences were defined as late recurrence. A recurrence that developed more than 1 year after AF ablation was defined as a very late recurrence.[2,12] Patients with early recurrence sometimes returned to sinus rhythm spontaneously, and sometimes sinus rhythm was restored with electrical or pharmacological cardioversion.[13] In the first 3 months after ablation (blanking period), some patients with recurrent and very symptomatic AFL after cardioversion underwent catheter ablation. All patients with typical AFL underwent RF ablation, and the diagnosis was made by electrophysiological study (EPS). Except for 2 patients who developed early recurrence, all patients with atypical AFL underwent RF ablation, and the diagnosis was made with EPS. Two patients mentioned above did not accept the second procedure. In these patients, 2 expert reviewers evaluated the patients' ECGs, and the diagnosis of atypical AFL was made based on F-wave morphology inconsistent with typical AFL.[14]

Statistical Analysis

Continuous variables are presented as mean ± SD if they were normally distributed and as the median [25th and 75th percentiles] if they were not normally distributed. The Shapiro–Wilk test was used to determine whether the continuous variables were normally distributed. Differences between continuous variables were compared using the Student's *t*-test for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. Categorical variables are presented as numbers (percentages) and compared using the chi-square test. To evaluate the relationships between clinical variables and AFL development, univariate and multiple Cox regression analyses were performed, and hazard ratio (HR) and 95% CI were calculated. A receiver operating characteristic (ROC) analysis was performed to calculate the best cutoff value for a variable found to be an independent predictor for the development of typical AFL, and area under the curve (AUC), 95% CI, sensitivity, and specificity values were calculated. A Kaplan–Meier curve was used to evaluate the relationship between an independent variable and typical AFL. Analyses were performed using a software program (IBM Statistical Package for the Social Sciences Statistics for Windows, Version 23.0, IBM Corp., Armonk, NY, USA). A 2-tailed $P < .05$ was considered statistically significant.

RESULTS

The mean age of the patients was 58.0 (48.0-62.0), and 84 of them (52.8%) were male. Persistent AF was present in 32

Table 1. Baseline Characteristics of the Study Population Relative to Typical AFL Development

	All Patients (n = 159)	Typical AFL (−) (n = 138)	Typical AFL (+) (n = 21)	*P*
Age (years)	58.0 (48.0-62.0)	58.0 (49.5-63.0)	53.0 (44.0-60.5)	.061
Sex (male), n (%)	84 (52.8)	68 (49.3)	16 (76.2)	.021
Hypertension, n (%)	78 (49.1)	70 (50.7)	8 (38.1)	.281
Diabetes mellitus, n (%)	37 (23.3)	35 (25.4)	2 (9.5)	.165
BMI (kg/m^2)	28.1 (26.1-31.5)	28.0 (26.1-31.4)	28.3 (25.6-34.1)	.758
CVA/TIA, n (%)	13 (8.2)	12 (8.7)	1 (4.8)	.540
CAD, n (%)	15 (9.4)	13 (9.4)	2 (9.5)	.988
HF with reduced EF, n (%)	9 (5.7)	6 (4.3)	3 (14.3)	.099
COPD, n (%)	10 (6.3)	9 (6.5)	1 (4.8)	.757
OSAS, n (%)	11 (6.9)	10 (7.2)	1 (4.8)	.604
Smoking, n (%)	21 (13.2)	18 (13.0)	3 (14.3)	.876
Alcohol, n (%)	4 (2.5)	3 (2.2)	1 (4.8)	.436
CHA_2DS_2VASC score	2.0 (1.0-2.0)	2.0 (1.0-2.2)	1.0 (0.5-1.5)	.078
AF duration (months)	22.0 (14.0-30.0)	22.0 (14.0-30.0)	24.0 (15.0-26.0)	.895
Persistent AF, n (%)	32 (20.1)	24 (17.4)	8 (38.1)	.039
Early recurrence, n (%)	23 (14.5)	14 (10.1)	9 (42.9)	.001
Late recurrence, n (%)	53 (33.3)	39 (28.3)	14 (66.7)	.001
Linear lesions, n (%)	9 (5.7)	6 (4.3)	3 (14.3)	.099
Oral anticoagulant, n (%)	118 (74.2)	103 (74.6)	15 (71.4)	.754
Beta blocker, n (%)	106 (66.7)	90 (65.2)	16 (76.2)	.320
RAAS blocker, n (%)	63 (39.6)	53 (38.4)	10 (47.6)	.421
Amiodarone, n (%)	50 (31.4)	41 (29.7)	9 (42.9)	.339
Propafenone, n (%)	105 (66.0)	93 (67.4)	12 (57.1)	.499
Sotalol, n (%)	4 (2.9)	4 (2.9)	0 (0)	.429
LV EF (%)	62.0 (59.0-65.0)	62.0 (59.0-65.0)	60.0 (51.0-65.0)	.224
LA diameter (mm)	38.0 (36.0-42.0)	38.0 (36.0-41.2)	40.0 (37.5-42.5)	.135
LAVI (mL/m^2)	30.0 (25.0-40.0)	30.0 (25.0-40.0)	34.0 (26.0-47.5)	.374
RA diameter (mm)	37.0 (34.0-39.0)	36.0 (34.0-39.0)	39.0 (38.0-43.0)	<.001
Dilated RA, n (%)	84 (52.8)	67 (48.6)	17 (81.0)	.006
TAPSE (mm)	24.1 ± 3.9	24.4 ± 3.7	22.2 ± 4.8	.021
SPAP (mm Hg)	25.0 (20.0-30.0)	25.0 (20.0-30.0)	25.0 (20.0-29.5)	.800
LV mass index, n (%)	95.1 (82.7-108.9)	94.5 (81.8-106.3)	99.7 (85.7-119.4)	.181
Hemoglobin (g/dL)	14.1 (12.7-15.1)	14.1 (12.6-15.0)	13.9 (13.0-15.6)	.595
eGFR (mL/dk/1.73 m^2)	87.1 ± 19.9	87.0 ± 19.9	87.6 ± 20.5	.894
Follow-up (months)	34.0 (14.0-50.0)	34.5 (15.0-51.2)	27.0 (11.0-45.0)	.386

AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrium; LAVI, left atrium volume index; LV, left ventricle; OSAS, obstructive sleep apnea syndrome; RA, right atrium; RAAS, renin–angiotensin–aldosterone system; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischemic attack; CHA_2DS_2-VASC, Heart failure/ left ventricular ejection fraction < 40%, hypertension, history of stroke or systemic embolism, age ≥ 75 years, diabetes mellitus, vascular disease, age 65-74 years, female sex.

(20.1%) patients. During a mean follow-up of 34.0 (14.0-50.0) months, typical CTI-dependent AFL developed in 21 patients (13.2%), and atypical AFL developed in 11 patients (6.9%). The time to first documented typical AFL was 150 (77.5-232.5) days, and the time to first documented atypical AFL was 160 (108.0-380.0) days. The main characteristics of the patients are given in Table 1.

Procedural Characteristics and Follow-Up

A total of 630 (99.0%) of 636 PVs were acutely isolated during the procedure. Linear lesions were created in 9 patients (5.7%) at the initial ablation procedure. The localization of linear lesions and procedural features are presented in Table 2. Early recurrence was observed in 23 patients (14.5%), while late or very late recurrences developed in 53 patients (33.3%) during the follow-up period.

The causes in patients with early recurrences were as follows: AF in 15 patients (65.2%), typical AFL in 7 patients (30.4%), and atypical AFL in 2 patients (8.7%). One patient developed both AF and atypical AFL. Sinus rhythm was achieved spontaneously in 2 patients (8.7%), with pharmacological

Table 2. Procedural Features Associated with Catheter Ablation for AF

Energy type	
Cryoballoon ablation, n (%)	119 (74.8)
Radiofrequency ablation, n (%)	40 (25.2)
Procedure time (minutes)	85.0 (70.0-120.0)
Fluoroscopy time (minutes)	21.0 (17.0-25.0)
Linear lesions, n (%)	9 (5.7)
LA roof, n (%)	5 (3.1)
Mitral isthmus, n (%)	1 (0.6)
LA roof, posterior wall, n (%)	2 (1.3)
LA roof, mitral isthmus, n (%)	1 (0.6)
Common PV anatomy, n (%)	57 (35.8)
Left common, n (%)	45 (28.3)
Right common, n (%)	8 (5.0)
Left and right common, n (%)	4 (2.5)
Complications	
Pericardial effusion, n (%)	7 (4.4)
Cardiac tamponade, n (%)	4 (2.5)
Phrenic nerve paralysis, n (%)	1 (0.6)
PV stenosis, n (%)	0 (0)
Emboli/TIA, n (%)	2 (1.3)
Groin complications, n (%)	4 (2.5)*
Arrhythmia mechanisms in patients undergoing re-ablation due to late or very late recurrence**	25 (15.7)**
PV reconnection, n (%)	11 (40.0)
Typical AFL, n (%)	14 (56.0)
LA roof dependent atypical AFL, n (%)	5 (20.0)
Mitral isthmus-dependent atypical AFL, n (%)	3 (12.0)
LA posterior wall-dependent atypical AFL, n (%)	1 (4.0)

AF, atrial fibrillation; AFL, atrial flutter; LA, left atrium; PV, pulmonary vein; TIA, transient ischemic attack.

*One patient underwent surgical repair due to femoral arteriovenous fistula.

**Some patients had 2 mechanisms of arrhythmia.

cardioversion in 8 patients (34.8%) and with electrical cardioversion in 6 patients (26.1%). Catheter ablation was performed in 7 patients (30.4%) due to intolerable typical AFL during the blanking period.

The reasons for late or very late recurrences were as follows: AF in 40 patients (75.4%), typical AFL in 14 (26.4%), atypical AFL in 7 (13.2%), and supraventricular tachycardia in 1 person (1.8%). Some patients had more than 1 arrhythmia. Re-ablation was performed in 25 patients (15.7%) who developed late or very late recurrence (2 times in 22 patients, 3 times in 3 patients). Arrhythmia mechanisms in patients undergoing re-ablation due to late or very late recurrence are given in Table 2. For PV reconnection, PVI was performed with CB in 2 patients and with RF ablation in 9 patients. The number of patients who remained in sinus rhythm after multiple ablations was 126 (79.2%).

Predictors of Typical Atrial Flutter Development

The frequencies of male gender (76.2% vs. 49.3%), persistent AF (38.1% vs. 17.4%), early recurrence (42.9% vs. 10.1%), and late recurrence (66.7% vs. 28.3%) were higher in patients who developed typical AFL than in those who did not during the follow-up ($P = .021$, .039, .001, and .001, respectively). The RA diameter was higher [39.0 (38.0-43.0) vs. 36.0 (34.0-39.0) mm] and TAPSE was lower (22.2 ± 4.8 vs. 24.4 ± 3.7 mm) in patients who developed typical AFL than in those who did not ($P <$ .001 and .021, respectively). Typical AFL development was significantly higher in patients with dilated RA than in those without (81.0% vs. 48.6%, $P = .006$). The distribution of clinical and demographic characteristics of the patients according to typical AFL development are presented in Table 1.

Table 3A shows the results of Cox regression analysis for typical AFL development. Univariate analysis showed that male gender (HR = 3.21, 95% CI: 1.17-8.77), persistent AF (HR = 2.77, 95% CI: 1.14-6.71), RA diameter (HR = 1.16, 95% CI: 1.08-1.24), and TAPSE (HR = 0.88, 95% CI: 0.79-0.98) were predictors for typical AFL development ($P = .023$, .024, < .001, and .018, respectively). The RA diameter was found to be the only independent predictor of typical AFL development after AF ablation in the multiple analysis (HR = 1.12, 95% CI: 1.02-1.23, $P = .021$). An ROC analysis showed that the best cutoff value for RA diameter was 38.5 mm to predict typical AFL development (AUC = 0.77, 95% CI: 0.67-0.86, sensitivity = 62%, specificity = 75%, $P < .001$) (Figure 2A). When patients were divided into 2 groups based on this cutoff value, a Kaplan–Meier curve showed that survival without typical AFL was significantly lower in those with RA diameter of ≥38.5 mm than in those with <38.5 mm (92.3% vs. 71.8%, log rank $P =$ .001) (Figure 3A).

We also analyzed predictors of typical AFL development by gender. For male gender, RA diameter was significantly greater in those who developed typical AFL than those who

Table 3. Cox Regression Analysis to Predict Typical Atrial Flutter Development after AF Ablation (A) for all Patients, (B) for Male Gender, and (C) for Female Gender

	Univariate		Multiple	
	HR, 95% CI	P	HR, 95% CI	P
A				
Sex (male)	3.21 (1.17-8.77)	.023	2.70 (0.96-7.61)	.060
Persistent AF	2.77 (1.14-6.71)	.024	1.02 (0.32-3.22)	.966
RA diameter	1.16 (1.08-1.24)	<.001	1.12 (1.02-1.23)	.021
TAPSE	0.88 (0.79-0.98)	.018	0.95 (0.85-1.07)	.395
B				
Persistent AF	0.38 (0.14-1.04)	.061	0.86 (0.24-3.04)	.820
RA diameter	1.13 (1.04-1.24)	.003	1.10 (0.99-1.23)	.078
TAPSE	0.87 (0.76-0.99)	.038	0.93 (0.81-1.07)	.326
C				
Persistent AF	0.56 (0.06-5.09)	.614	1.78 (0.18-17.59)	.619
RA diameter	1.28 (1.06-1.55)	.010	1.26 (1.04-1.54)	.016
TAPSE	0.79 (0.62-1.01)	.067	0.81 (0.64-1.03)	.087

AF, atrial fibrillation; HR, hazard ratio; RA, right atrium; TAPSE, tricuspid annular plane systolic excursion.

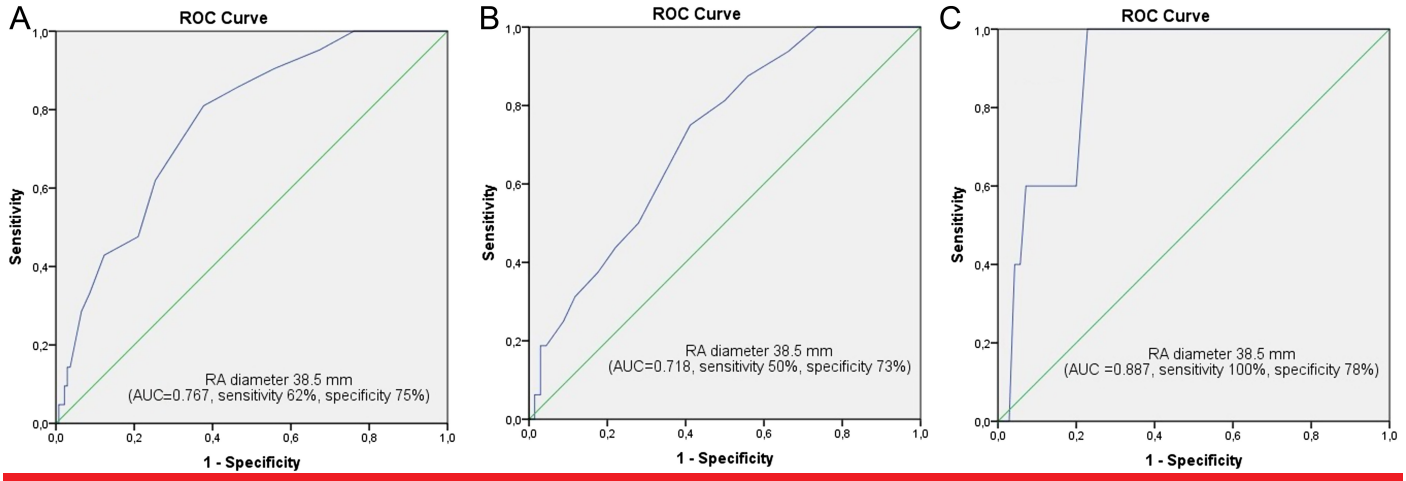

Figure 2. An ROC curve showing the optimal cutoff value of the RA diameter to predict the development of typical atrial flutter (A) for all patients, (B) for male gender, and (C) for female gender. AUC, area under the curve; RA, right atrium; ROC, receiver operating characteristic.

did not [38.5 (37.2-42.7) vs. 33.0 (36.5-39.0) mm, $P = .007$]. Univariate analysis showed that RA diameter (HR = 1.13, 95% CI: 1.04-1.24) and TAPSE (HR = 0.87, 95% CI: 0.76-0.99) were predictors for typical AFL development for male gender (P = .003 and .038, respectively). However, these variables were not independent predictors of typical AFL development in multiple analysis (Table 3B). An ROC analysis showed that the best cutoff value for RA diameter was 38.5 mm to predict typical AFL development (AUC = 0.72, 95% CI: 0.59-0.84, sensitivity = 50%, specificity = 73%, P = .007) (Figure 2B). A Kaplan–Meier curve showed that survival without typical AFL was lower in those with RA diameters of ≥38.5 mm than in those without it, but the difference was not statistically significant (83.8% vs. 66.7%, log rank P = .079) (Figure 3B).

For female gender, RA diameter was significantly greater in those who developed typical AFL than those who did not [41.0 (39.0-43.0) vs. 36.0 (34.0-38.0) mm, $P = .004$]. The RA diameter was found to be a predictor of typical AFL development in both univariate (HR = 1.28, 95% CI: 1.06-1.55, P = .010) and multiple analyses (HR = 1.26, 95% CI: 1.04-1.54, $P = .016$) (Table 3C). An ROC analysis showed that the best cutoff value for RA diameter was 38.5 mm to predict typical AFL development (AUC = 0.88, 95% CI: 0.79-0.98, sensitivity = 100%, specificity = 78%, P = .004) (Figure 2C). A Kaplan–Meier curve showed that survival without typical AFL was significantly lower in those with RA diameter of ≥38.5 mm than in those without it (100% vs. 74.3%, log rank $P < .001$) (Figure 3C).

Predictors of the Development of Atypical Atrial Flutter

The frequencies of persistent AF (54.5% vs. 17.6%) and late recurrence (90.9% vs. 29.1%) were higher in patients who developed atypical AFL than in those who did not during the follow-up (P = .009 and < .001, respectively). In addition, the frequency of linear lesions was higher (36.4% vs. 3.4%) and TAPSE was lower (21.8 ± 4.5 vs. 24.3 ± 3.8) in those who developed atypical AFL than in those without it (P = .001 and .043, respectively). The clinical and demographic characteristics of the patients according to the development of atypical AFL are given in Table 4.

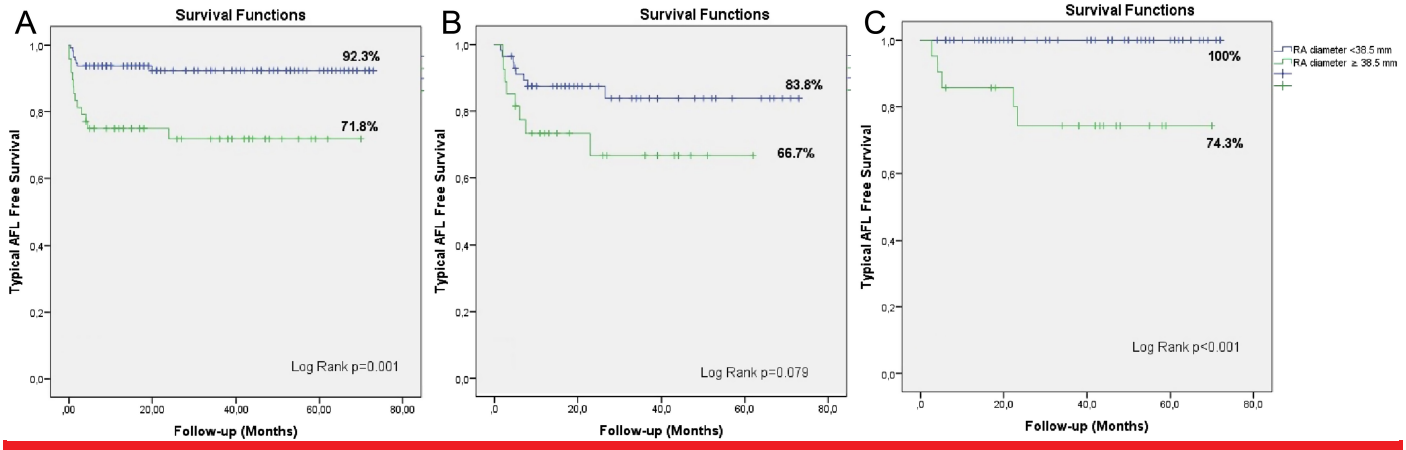

Figure 3. Kaplan–Meier curve showing typical AFL free survival according to the RA diameter during the follow-up period (A) for all patients, (B) for male gender, and (C) for female gender. AFL, atrial flutter; RA, right atrial diameter.

Table 4. Baseline Characteristics of the Study Population Relative to Atypical AFL Development

	Atypical AFL (−) (n = 148)	Atypical AFL (+) (n = 11)	P
Age (years)	58.0 (48.0-62.0)	58.0 (48.0-70.0)	.471
Sex (male), n (%)	78 (52.7)	6 (64.5)	.906
Hypertension, n (%)	73 (49.3)	5 (45.5)	.804
Diabetes mellitus, n (%)	34 (23.0)	3 (27.3)	.719
BMI (kg/m^2)	28.2 (26.1-31.2)	28.0 (22.6-34.7)	.831
CVA/TIA, n (%)	11 (7.4)	2 (18.2)	.223
CAD, n (%)	13 (8.8)	2 (18.2)	.278
HF with reduced EF, n (%)	8 (5.4)	1 (9.1)	.485
COPD, n (%)	10 (6.8)	0 (0)	.351
OSAS, n (%)	10 (6.8)	1 (9.1)	.558
Smoking, n (%)	20 (13.5)	1 (9.1)	.604
Alcohol, n (%)	4 (2.7)	0 (0)	.563
CHA_2DS_2VASC score	1.5 (1.0-2.0)	2.0 (1.0-3.0)	.328
AF duration (months)	22.0 (14.0-28.0)	24.0 (12.0-34.0)	.409
Persistent AF, n (%)	26 (17.6)	6 (54.5)	.009
Early recurrence, n (%)	19 (12.8)	4 (36.4)	.055
Late recurrence, n (%)	43 (29.1)	10 (90.9)	<.001
Linear lesions, n (%)	5 (3.4)	4 (36.4)	.001
Oral anticoagulant, n (%)	108 (73.0)	10 (90.9)	.291
Beta blocker, n (%)	97 (65.5)	9 (81.8)	.339
RAAS blocker, n (%)	61 (41.2)	2 (18.2)	.202
Amiodarone, n (%)	45 (30.4)	5 (45.5)	.324
Propafenone, n (%)	99 (66.9)	6 (54.5)	.511
Sotalol, n (%)	4 (2.7)	0 (0)	.563
LV EF (%)	62.0 (59.2-65.0)	61.0 (50.0-65.0)	.383
LA diameter (mm)	38.0 (36.0-41.7)	41.0 (38.0-43.0)	.150
LAVI (mL/m^2)	30.0 (25.0-40.0)	35.0 (28.0-44.0)	.354
RA diameter (mm)	37.0 (34.0-39.0)	38.0 (36.0-43.0)	.152
Dilated RA, n (%)	76 (51.4)	8 (72.7)	.171
TAPSE (mm)	24.3 ± 3.8	21.8 ± 4.5	.043
SPAP (mm Hg)	25.0 (20.0-29.7)	26.0 (25.0-30.0)	.181
LV mass index, n (%)	94.9 (83.6-107.0)	102.2 (77.4-123.0)	.689
Hemoglobin (g/dL)	13.9 (12.6-15.1)	14.4 (13.6-14.8)	.737
eGFR (mL/dk/1.73 m^2)	87.9 ± 19.4	76.1 ± 24.3	.058
Follow-up (months)	34.5 (15.0-50.7)	20.0 (12.0-36.0)	.158

AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrium; LAVI, left atrium volume index; LV, left ventricle; OSAS, obstructive sleep apnea syndrome; RA, right atrium; RAAS, renin–angiotensin–aldosterone system; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischemic attack; CHA_2DS_2-VASC, Heart failure/ left ventricular ejection fraction < 40%, hypertension, history of stroke or systemic embolism, age ≥ 75 years, diabetes mellitus, vascular disease, age 65-74 years, female sex.

DISCUSSION

In the current study, we investigated the predictors associated with the development of typical and atypical AFL in patients undergoing catheter ablation for AF. The main findings were as follows: (1) In long-term follow-up, the incidences of typical and atypical AFL after AF ablation were 13.2% and 6.9%, respectively; (2) typical and atypical AFL usually develop within the first year after AF ablation; (3) male gender, persistent AF, RA diameter, and TAPSE were associated with typical AFL development, whereas RA diameter was the only independent predictor of typical AFL development in the multiple analysis; (4) survival without typical AFL was significantly lower in patients with pre-procedural RA diameter ≥38.5 mm compared to the others; and (5) the parameters associated with the development of atypical AFL after AF ablation were persistent AF, linear lesions, and TAPSE.

The close relationship between AF and typical AFL has been known for a long time. Clinical AF may develop in 3 out of 4 AFL patients.[15] Hsieh et al[16] showed that 1/3 of patients without previous AF who underwent successful ablation for typical AFL developed manifest AF. The use of class IA, IC, or III antiarrhythmic drugs in patients with AF is associated with a significant increase in the frequency of conversion of AF to AFL.[17,18] Ortiz et al[19] showed that in a canine model, when AF continues for a sufficient period, the rhythm turns into AFL with the development of the functional block line.[19] Roithinger et al[20] showed that AF transforms into AFL in humans as a result of the fusion of fibrillatory waves around anatomical barriers such as the crista terminalis and Eustachian valve.[20] Wazni et al[21] suggested that PV triggers initiate AF, AF is organized by anatomical and electrical barriers, and AFL starts when RA is activated by a single organized wave.[21]

Previous studies have reported different rates of typical AFL development after AF ablation, depending on the methodology used. Scharf et al[22] showed that typical AFL developed in 1/3 of the patients who underwent AF ablation in the follow-up if CTI ablation was not performed during the procedure.[20] Moreira et al[23] reported this rate as 8.0%. Ipek et al[6] reported a lower typical AFL rate after AF ablation (4.5%). In this study, the fact that routine Holter was not requested during the controls after AF ablation and that the controls were usually performed by telephone after 3 months may explain this low rate. We found this rate to be 13.2%. In our study, the mean follow-up time was longer than in other studies, and the patients were followed more closely, including routine Holter.

In our study, we found that RA diameter was the only independent predictor of typical AFL development after AF ablation. Similarly, Ipek et al[6] also found that the RA volume index was an independent predictor for the development of typical AFL after AF ablation. Additionally, we found that TAPSE, although not an independent marker, was predictive for typical AFL development after AF ablation. The RA diameter and TAPSE are parameters related to the structure and

functions of the right heart chambers. Our results suggest that an increase in RA diameter and a decrease in TAPSE may facilitate the development of typical AFL by increasing the slow conduction areas in RA, and support previous results.[7,24]

When we analyzed by gender, we found that the RA diameter was significantly greater in both genders in those who developed typical AFL than in those who did not. In addition, when we divided the patients into dilated or non-dilated RA according to sex-specific cutoff values,[9] we found that typical AFL development was significantly higher in those with dilated RA than in those without. Our findings may indicate a gender-independent relationship between typical AFL development and RA diameter. In our study, the best cutoff value for RA diameter to predict typical AFL development was 38.5 mm for both genders. Therefore, patients with an RA diameter ≥ 39 mm are at higher risk for developing typical AFL. In such individuals, CTI ablation in the same session as PVI may be considered after the patient is informed. Thus, the increased cost and inguinal complications associated with the second procedure can be avoided.

For female gender, RA diameter was predictive for typical AFL development in both univariate and multiple analyses. For men, both RA diameter and TAPSE predicted typical AFL development in the univariate analysis. Both parameters are associated with right heart function, and a possible interaction between them may explain the fact that RA diameter was not an independent predictor for typical AFL development in male gender.

In our study, we found that the incidence of typical AFL development after AF ablation was higher in males. There could have been an interaction between the male gender and other variables associated with typical AFL development. In our study, we found that the frequency of persistent AF was higher in patients with typical AFL, which is consistent with previous findings.[6] However, none of these variables were independent predictors of typical AFL development.

The rate of development of atypical AFL after AF ablation was 6.9% in the study. This rate was 17% in another study.[6] The high rate of linear lesions (18.3%) formed during the procedure may explain the high rate of the development of atypical AFL in this study. Baman et al[25] reported this rate as 2.1%. Cryoballoon application in all patients and the absence of linear lesions in any patient may explain this low rate.[25] We found that linear lesions and persistent AF were associated with the development of atypical AFL. These findings are consistent with previous study results.[6] In our study, we found that TAPSE was also associated with the development of atypical AFL.

We found that typical or atypical AFL usually develops within the first year after AF ablation. This finding is in line with the results of a previous study (the median time to first documented typical AFL was 159.5 days, and the median time to first documented atypical AFL was 199 days).[6] Our finding highlights the importance of close follow-up within the first year after AF ablation in detecting typical or atypical AFL.

Study Limitations

There are also some important limitations of our study. It was a single-center, small, and retrospective study. A 24-hour Holter recording was performed during the controls, and some asymptomatic AFL attacks may have been overlooked. The RA diameters of our patients were in relatively normal ranges. For this reason, our results may not fully reflect patients with larger RA, and such patients may have higher RA cutoff values to predict the development of typical AFL. In addition, we measured only the minor axis of the RA; RA planimetric and volumetric measurements were not performed. Finally, the number of patients who developed atypical AFL after AF ablation was insufficient to draw definite conclusions.

CONCLUSION

Typical and atypical AFL usually develop within the first year after AF ablation, and it may be appropriate to monitor patients more closely for the development of AFL in this period. In patients undergoing PVI for AF, pre-procedural RA diameter measurement may help to predict typical AFL development in the long-term follow-up. In particular, patients with a pre-procedural RA diameter ≥39 mm may be at greater risk of developing typical AFL in the future. The CTI ablation in the same session as PVI may be considered after such patients have been informed before the procedure that they are at a higher risk for future development of typical AFL. The TAPSE is associated with an increased risk of developing both typical and atypical AFL in patients undergoing catheter ablation for AF. However, further studies are needed for more widespread use of these findings in clinical practice.

Ethics Committee Approval: The study complied with the Declaration of Helsinki. Eskişehir Osmangazi University Non-Invasive Clinical Research Ethics Committee approval was obtained (Decision Date: 04.10.2022, decision number: 40).

Informed Consent: Our study had retrospective design. The data were obtained retrospectively from electronic file records.

Peer-review: Externally peer-reviewed.

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