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CLINICAL RESEARCH

Incidence of atrial fibrillation during very long-term follow-up after radiofrequency ablation of typical atrial flutter

Incidence de la fibrillation atriale lors du suivi à très long terme de l'ablation par radiofréquence de flutter atrial typique

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KEYWORDS

Atrial fibrillation;
Atrial flutter;
Radiofrequency
ablation

Summary

Background. — Radiofrequency ablation is an effective treatment for typical atrial flutter (AFL) but long-term results may be hampered by atrial fibrillation (AF).

Aims. — To determine the incidence and predictors of AF during very long-term follow-up after radiofrequency ablation of typical AFL.

Methods. — From November 1998 to December 2000, patients who underwent successful radiofrequency ablation for cavotricuspid isthmus-dependent AFL in our centre were followed prospectively.

Results. — Of the 135 patients followed (mean age: 62 ± 11 years), 69 (51%) had structural heart disease. Mean left ventricular ejection fraction was $52 \pm 11\%$. Patients were analysed according

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; ECG, electrocardiogram; IQR, interquartile range; LA, left atrial/atrium; RF, radiofrequency.

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to preablation AF history: group 1 included patients with AFL ($N=71$); group 2 included patients with AFL and AF ($N=64$). During a median [interquartile range] follow-up of 7.8 [7.0–8.4] years, new-onset or recurrent AF was experienced by 99 (73%) patients: 44 (62%) in group 1 and 55 (86%) in group 2. Although most episodes occurred in the first 2 years postablation, AF prevalence increased continuously over time. Preablation AF history predicted AF occurrence (hazard ratio: 2.10, 95% confidence interval: 1.40–3.14; $p=0.001$), as did left atrial diameter (hazard ratio: 1.05 per 1 mm increase; 95% confidence interval: 1.02–1.08; $p<0.001$). AF evolved to become permanent in 24% of group 1 and 47% of group 2 patients ($p=0.005$).

Conclusion. – During long-term follow-up, most patients will experience AF after ablation of typical AFL. Preablation AF history and left atrial enlargement predict postablation AF occurrence.

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MOTS CLÉS

Fibrillation atriale ;
Flutter atrial ;
Ablation par
radiofréquence

Résumé

Contexte. – L'ablation par radiofréquence (RF) est un traitement efficace du flutter atrial typique mais la survenue de fibrillation atriale (FA) pourrait réduire le bénéfice de la procédure à long terme.

Objectifs. – Le but de cette étude était de déterminer l'incidence et les facteurs prédictifs de FA lors du suivi à très long terme après ablation par RF de flutter atrial typique.

Méthodes. – Les patients ayant bénéficié de l'ablation par RF de flutter atrial droit isthme-dépendant dans notre centre de novembre 1998 à décembre 2000 ont été suivis de manière prospective.

Résultats. – La population comprenait 135 patients (âge moyen: 62 ± 11 ans) dont 69 (51%) avaient une cardiopathie sous-jacente. La fraction d'éjection ventriculaire gauche était de 52 ± 11 %. Les patients ont été analysés en fonction de la présence éventuelle d'un antécédent de FA: le groupe 1 incluait des patients avec uniquement un flutter ($n=71$) et le groupe 2 des patients avec à la fois du flutter et de la FA ($n=64$). Au cours d'une durée médiane [intervalle interquartile] de suivi de 7.8 [7.0–8.4] ans, 99 patients (73%) ont présenté un épisode de FA: 44 (62%) dans le groupe 1 et 55 (86%) dans le groupe 2. Même si la plupart des épisodes sont survenus au cours des deux premières années suivant l'ablation, la prévalence de la FA n'a cessé d'augmenter par la suite. L'antécédent de FA avant l'ablation prédisait la survenue de FA après l'ablation (hazard ratio: 2,10; intervalle de confiance à 95%: 1,40–3,14; $p=0,001$), de même que le diamètre de l'oreillette gauche (hazard ratio: 1,05 par augmentation de 1 mm; intervalle de confiance à 95%: 1,02–1,08; $p<0,001$). La FA a évolué vers une forme permanente chez 24% des patients du groupe 1 et 47% des patients du groupe 2 ($p=0,005$).

Conclusion. – À long terme, la plupart des patients bénéficiant de l'ablation d'un flutter atrial typique présentent de la FA. L'antécédent de FA avant l'ablation et la dilatation de l'oreillette gauche prédisent la survenue de FA après l'ablation.

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Background

The incidence of AFL in the general population is 88/100,000 person-years [1]. Some risk factors for developing this condition, such as age, heart failure and chronic obstructive pulmonary disease, also predispose to AF. The two arrhythmias share common pathophysiological features [2–4] and often coexist. For instance, Halligan et al. reported that 56% of patients with lone AFL develop AF an average of 5 ± 6 years after the diagnosis of AFL [5]. Radiofrequency (RF) ablation of the cavotricuspid isthmus is now an established, safe and effective treatment for typical AFL with more than 90% success when complete bidirectional isthmus block is the sought procedural end-point [6–21]. However, the long-term result may be hampered by postablation AF, whether episodes of AF have been documented before the procedure or not. Although 17–22% of

patients experience a first episode of AF during the first 6 months after the procedure [9,12], the cumulative probability of developing postablation AF increases over time. Ellis et al. reported recently that 82% of patients with lone AFL developed drug-refractory AF after a mean follow-up of 39 ± 11 months [14]. All series published to date have a mean follow-up of less than 4 years. The purpose of this study was to determine the incidence and predictors of AF during very long-term follow-up after RF ablation of typical AFL.

Patients and methods

Study population

One hundred and thirty-nine consecutive patients underwent cavotricuspid isthmus ablation for typical AFL at our

tertiary care university hospital between November 1998 and December 2000. Cavotricuspid isthmus-dependence of AFL was diagnosed by the presence of a characteristic pattern on the surface ECG (negative sawtooth waves in inferior leads and usually positive waves in lead V1) and/or entrainment mapping during electrophysiological study. Immediate success of anatomically-guided linear ablation between the tricuspid annulus and the inferior vena cava was defined by complete bidirectional isthmus conduction block [22,23] persisting at least 30 min after the last RF energy application. Patients in whom the ablation was successful were eligible for prospective follow-up. The study patients were divided into two groups according to their arrhythmic history. Group 1 comprised patients with lone AFL (defined as AFL with no documented AF before ablation) and group 2 comprised patients with AFL and at least one documented episode of AF before ablation. Thus group 2 included patients in whom the clinically predominant arrhythmia was AFL (more episodes of AFL than AF, or same number with no more than two episodes of AF), patients in whom the clinically predominant arrhythmia was AF (more episodes of AF than AFL, or same number but at least three episodes of AF) and patients who developed AFL while receiving class IC or III AADs for AF.

All patients underwent transthoracic echocardiography before the ablation procedure for assessment of left ventricular function, cardiac chamber sizes and the presence of significant valvular heart disease. Left ventricular hypertrophy was defined by wall thickness of at least 13 mm. The left atrium (LA) was considered to be enlarged when its diameter in parasternal long-axis view was above 45 mm. Structural heart disease was defined by the presence of at least one of the following: left ventricular ejection fraction below 50%, left ventricular hypertrophy, significant valvulopathy, history of coronary artery disease or congenital heart disease.

Before ablation, all patients were treated with oral anti-coagulants aiming at a therapeutic international normalized ratio of 2 to 3 for at least 3 weeks. AADs were not discontinued before ablation. Study protocol was approved by the local ethics committee and all patients gave informed consent.

Follow-up

Oral anticoagulation was pursued for at least 1 month. Thereafter, the need for anticoagulation was assessed according to the presence of risk factors for thromboembolism [24]. Whenever possible, AADs were stopped after the procedure in patients with lone AFL. AADs were continued in patients with a history of preablation AF, if frequent or poorly-tolerated episodes of AF were documented recently before the ablation procedure. Subsequently, AAD prescription was left to the individual physician's discretion. Patients were scheduled for clinic visits at our institution at 1 month, and at 3, 6 and 12 months, with a 12-lead ECG recording. Thereafter, yearly evaluations were conducted either at our institution or at the referring cardiologist's practice. In the latter case, the cardiologist was reminded each year to monitor patient status. A 24-hour Holter recording was obtained when patients complained of symptoms suggestive of arrhythmias.

After a blanking period of 1 month, documented AF was considered to be significant if it was symptomatic or it was asymptomatic and discovered on a routine ECG recording (for 24-hour Holter ECG or pacemaker memory, total AF duration had to exceed 30 min). Hospital records were verified regularly to monitor hospitalizations in any department at our institution. At the end of the study, all patients' arrhythmic status and current drug prescriptions were obtained by contacting the patients or their relatives.

Statistical analysis

Statistical analysis was performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA). Continuous variables are reported as mean \pm standard deviation or median and IQR, and categorical variables are reported as number of patients in each category and corresponding percentage, as appropriate. Comparison of groups was performed with Student's *t*-test or the Wilcoxon's rank sum test for continuous variables and the Chi-square or Fischer's exact test for categorical variables, as appropriate. To identify risk factors associated independently with time to occurrence of AF, variables found to be significant in a univariate analysis were entered into a stepwise Cox model. Kaplan-Meier analysis was performed to determine the probability of AF-free survival. Survival curves were compared using the log-rank test. All values were considered to be statistically significant at *p* less than 0.05.

Results

Study population

Of the 139 patients undergoing RF ablation, immediate procedural success was achieved in 135 (97%). Baseline characteristics of the study population are summarized in Table 1. There were 122 men and 13 women. Mean age was 62 ± 11 years. Structural heart disease was present in 69 (51%) patients, hypertension in 56 (41%) and mitral regurgitation in 18 (13%). Mean left ventricular ejection fraction and left atrial (LA) diameter were $52 \pm 11\%$ and 42 ± 7 mm, respectively. Left ventricular ejection fraction was below 50% in 41 (30%) patients. Eleven patients (8%) had a history of ischaemic stroke or transient ischaemic attack. AFL was first documented at a median IQR time of 11 [3–48] months before the ablation procedure and patients had experienced a mean of 2.9 ± 1.7 episodes of AFL at the time of the procedure.

There were 71 (53%) patients in group 1 and 64 (47%) in group 2. Other than the fact that group 2 patients had been treated with more AAD regimens than group 1 patients (2.3 ± 1.2 and 1.4 ± 1.1 , respectively; $p < 0.001$), there were no baseline differences between the two groups. In group 2, the clinically predominant arrhythmia was AFL in 28 patients and AF in 20 patients. The remaining 16 patients developed AFL while receiving class IC or III AADs for AF. AF was first documented at a median IQR time of 30 [4–91] months before the procedure and a mean of 2.1 ± 1.2 episodes of AF had been recorded. Forty-five of these patients had an episode of AF in the year preceding the ablation.

Table 1 Baseline characteristics of the study population.

	All patients (N = 135)	Group 1 (N = 71)	Group 2 (N = 64)	p ^a
Age (years) ^b	62 ± 11	62 ± 12	62 ± 10	0.67
Men/women (N/N)	122/13	65/6	57/7	0.63
Structural heart disease (N [%])	69 (51)	38 (54)	31 (48)	0.56
Coronary artery disease (N [%])	13 (10)	10 (14)	3 (5)	0.07
Hypertension (N [%])	56 (4)	28 (39)	28 (44)	0.61
Diabetes mellitus (N [%])	15 (11)	8 (11)	7 (11)	0.95
Chronic obstructive pulmonary disease (N [%])	13 (10)	7 (10)	6 (9)	0.92
Number of failed AAD regimens ^b	1.8 ± 1.2	1.4 ± 1.1	2.3 ± 1.2	<0.001
LA diameter, mm ^b	42 ± 7	42 ± 7	43 ± 7	0.35
Left ventricular ejection fraction (% ^b)	52 ± 11	53 ± 12	52 ± 10	0.31
Mitral regurgitation of grade ≥ 2 (N [%])	18 (13)	12 (17)	6 (9)	0.20
Time since first documentation of AFL (months ^c)	11 [3–48]	11 [3–55]	12 [3–40]	0.53
Number of AFL episodes ^b	2.9 ± 1.7	3.0 ± 1.8	2.9 ± 1.5	0.87

AAD: antiarrhythmic drug; LA: left atrial; AFL: atrial flutter.

^a Group 1 versus group 2.

^b Mean ± standard deviation.

^c Median interquartile range.

Follow-up

AADs were maintained at discharge in 39 (29%) patients, more frequently in group 2 patients than in group 1 patients (48% versus 11%, respectively; $p < 0.001$). The median IQR follow-up was 7.8 [7.0–8.4] years and was similar in the two groups. Twenty-eight patients (21%) died at a median IQR of 4.9 [3.3–6.1] years after the RF ablation. Thirteen of these deaths were either sudden or distinctly attributable to a cardiovascular cause. Recurrences of AFL were documented in 11 (8%) patients, at a median IQR of 5.8 [3.1–8.9] months after the procedure. Six (55%) of these recurrences occurred within 6 months after the ablation and nine (82%) occurred within 1 year. All were typical AFLs, due to recovery of isthmus conduction, and were treated successfully with another RF ablation procedure, with no subsequent relapses. Of the 107 patients who were still alive at the end of follow-up in February 2008, 73 (68%) were treated with vitamin K antagonists, 17 (16%) with aspirin and 37 (35%) with AADs (amiodarone [$N = 15$], flecainide [$N = 14$], sotalol [$N = 6$], and cibenzoline [$N = 2$]).

Occurrence of AF after flutter ablation

Spontaneous AF occurred in 99 (73%) patients, at a median IQR of 11.4 [2.1–35.7] months after flutter ablation. AF incidence was 62% in group 1 and 86% in group 2 ($p = 0.002$). The first episode was documented earlier after the ablation procedure in group 2 than in group 1 (median IQR: 4.5 [1.4–28.0] months and 15.6 [7.0–55.7] months, respectively, $p = 0.011$). Nearly half of those first episodes of AF occurred in the first year after the ablation (in 51 patients) and two thirds occurred in the first 2 years (in 66 patients). Moreover, although 49% of all study patients had experienced AF within 2 years, the prevalence of AF continued to increase over time. After the first 2 years, the annual incidence of AF was 6.5% per year. The same trend was observed

in the two groups prespecified according to preablation history of AF. In particular, 19 patients (27%) in group 1 (lone AFL) experienced AF within 1 year of ablation and 27 (38%) within 2 years. The AF incidence rate then averaged 3.3% per year over the remainder of follow-up in this group. A Kaplan-Meier analysis estimating survival free of AF according to the presence or absence of preablation AF is shown on Fig. 1.

The initial pattern of presentation of AF was paroxysmal in 77 (78%) patients, persistent in 12 (12%) and permanent in 10 (10%). Ultimately, AF evolved to a permanent form in 47 (35%) patients, at a median IQR of 4.2 [1.6–5.3] years after the ablation procedure. Permanent AF was encountered more frequently in group 2 than in group 1 (47% versus 24%, respectively; $p = 0.005$).

Predictors of postablation AF

Univariate analysis showed that patients who experienced postablation AF were more likely to have a history of preablation AF, more episodes of preablation AF and more episodes of AF occurring in the year preceding the RF ablation procedure than patients who did not experience postablation AF (Table 2). They also had a larger LA diameter. Age, left ventricular ejection fraction, presence of structural heart disease, hypertension or mitral regurgitation was not associated with an increased risk of postablation AF. Multivariable analysis showed that two factors were associated significantly with time to occurrence of AF after RF ablation: history of preablation AF (hazard ratio: 2.10, 95% confidence interval: 1.40–3.14; $p = 0.001$), and LA diameter (hazard ratio: 1.05 per 1 mm increase, 95% confidence interval: 1.02–1.08; $p < 0.001$). Fig. 2 shows the Kaplan-Meier analysis of survival free of AF according to the presence or absence of LA enlargement (defined as LA diameter above 45 mm).

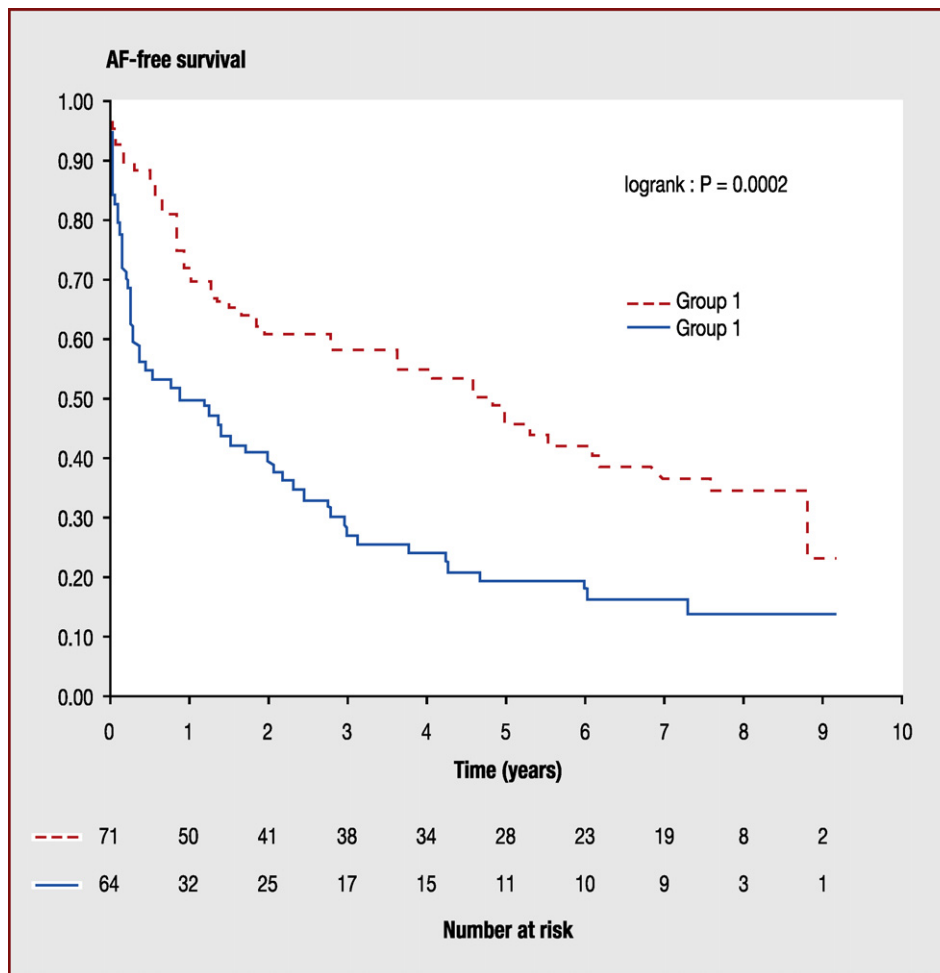


Figure 1. Probability of survival free from atrial fibrillation (AF) as a function of history of preablation AF. Patients with a history of preablation AF (group 2) have a higher risk of developing postablation AF than patients with lone atrial flutter (group 1) (log-rank: $p = 0.0002$).

Table 2 Predictors of postablation atrial fibrillation: univariate analysis.

	No postablation AF (N = 36)	Postablation AF (N = 99)	p
Age (years ^a)	61 ± 13	62 ± 10	0.97
Men/women (N/N)	30/6	92/7	0.11
Structural heart disease (N [%])	22 (61)	47 (47)	0.16
Coronary artery disease (N [%])	6 (17)	7 (7)	0.11
Hypertension (N [%])	14 (39)	42 (42)	0.71
Diabetes mellitus (N [%])	3 (8)	12 (12)	0.76
Chronic obstructive pulmonary disease (N [%])	4 (11)	9 (9)	0.75
Failed AAD regimens ^a	1.5 ± 1.2	1.9 ± 1.2	0.06
LA diameter (mm ^a)	39 ± 8	43 ± 7	0.004
Left ventricular ejection fraction (% ^a)	52 ± 13	53 ± 10	0.92
Mitral regurgitation of grade ≥ 2 (N [%])	5 (14)	13 (13)	1.00
P-wave duration (ms ^a)	123 ± 19	124 ± 19	0.82
Time since first documentation of AFL (months ^b)	12 [2–52]	11 [3–46]	0.82
Number of AFL episodes ^a	3.0 ± 2.0	2.9 ± 1.6	0.83
History of preablation AF (N [%])	9 (25)	55 (56)	0.002
Number of episodes of AF ^a	0.4 ± 0.9	1.2 ± 1.4	0.002
Episodes of AF occurring in the past year (N [%])	7 (19)	38 (38)	0.04

AAD: antiarrhythmic drug; LA: left atrial; AF: atrial fibrillation; AFL: atrial flutter.

^a Mean ± standard deviation.

^b Median interquartile range.

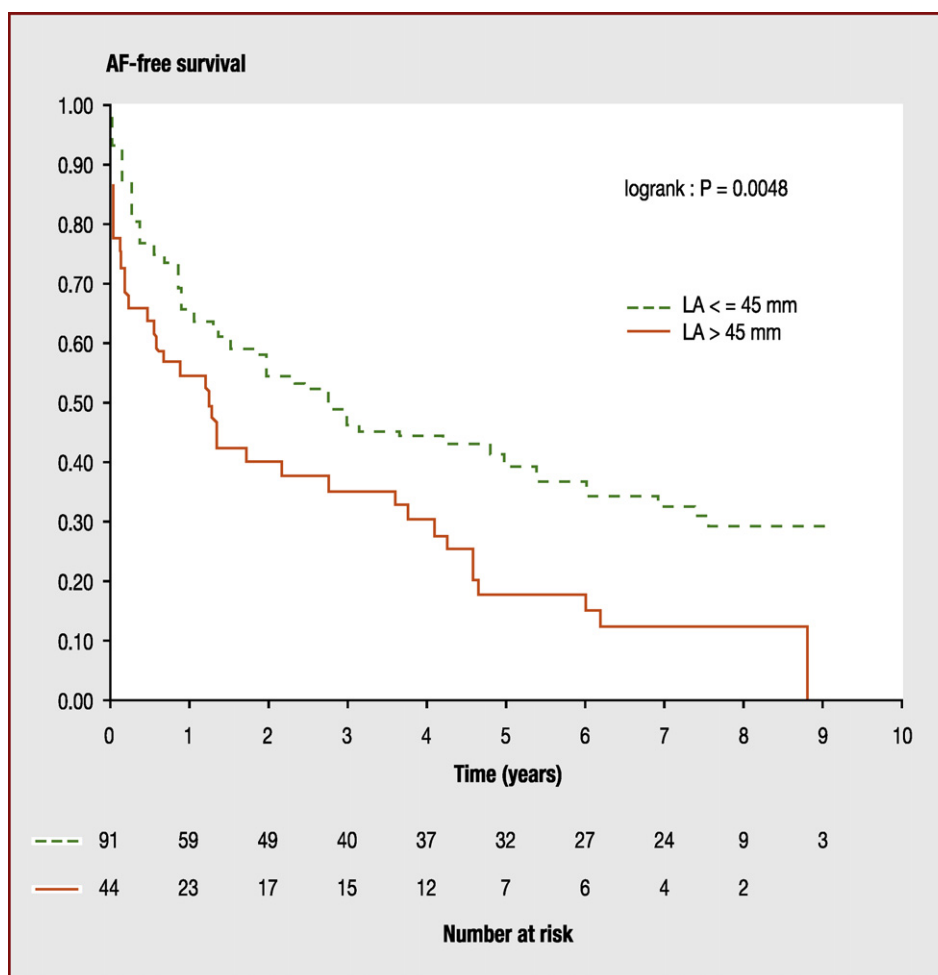


Figure 2. Probability of survival free from atrial fibrillation (AF) as a function of left atrial (LA) diameter. Patients with an enlarged LA diameter above 45 mm have a higher risk of developing postablation AF than patients with a normal LA diameter (log-rank: $p=0.0048$).

Discussion

To the best of our knowledge, the follow-up after RF ablation of typical AFL in this prospective study is the longest to be reported in literature. While only 8% of patients experienced AFL recurrence, AF occurred in 73% of them during a median follow-up of 7.8 years. The first AF episode was documented in the first year after the RF ablation in approximately half of the patients. A majority (62%) of patients without previously documented AF developed postablation AF. Nevertheless, history of preablation AF is an important predictor of postablation AF, as is LA enlargement.

Recurrence of AFL

Earlier studies of RF ablation of the cavotricuspid isthmus for typical AFL yielded unsatisfactory results, with an immediate procedural success rate as low as 78% and a recurrence rate as high as 42% during short follow-up [25]. Since complete bidirectional isthmus block was advocated as a procedural end-point, the rate of success has risen to more than 90% [6,7,9,10,12,13,16–18,20]. As in other reports, most recurrences in our study were discovered early

after the procedure and were due to recovery of isthmus conduction. Incomplete isthmus block has been described as a predictor for AFL recurrence [16] but such patients were not included in our study.

Interrelationship between AFL and AF

The two arrhythmias share common pathophysiological features. As in AF, electrical remodelling in both paroxysmal and chronic AFL is characterized by a spatially heterogeneous decrease in action potential duration and conduction velocity, contributing to a lengthening of the activation wavefront [2–4]. Thus, there is a continuum spanning from the single stable wavefront of AFL to the multiple nonstationary wavebreaks of AF, which is in part underlain by progressive shortening of action potential duration [26]. Another mechanism by which AFL leads to AF is when the AFL circuit has a very short cycle length, driving the atria so fast that some areas cannot follow in a 1:1 fashion, resulting in fibrillatory conduction [27,28].

Conversely, Waldo and Feld suggested that in most instances there cannot be AFL without preexisting AF [29]. Initiation and perpetuation of typical AFL, a

macro-reentrant circuit between natural endocardial barriers in the right atrium, depend on the existence of a line of block between the vena cavae in the region of the crista terminalis. In most patients, there is no physiological line of block and it is during transitional preceding AF that a functional line develops [30,31].

In clinical practice, this close interplay between the two arrhythmias also translates into a high incidence of AF following RF ablation of typical AFL, ranging from 17–58% after a follow-up of 6–36 months [6–10,12,13,15–17,19,20]. Few data regarding long-term follow-up are available. Bertaglia et al. reported a cumulative probability of AF of 63% at 4 years in their series with a mean follow-up of 20.5 ± 12.4 months [9]. Of note, their study protocol included routine Holter recordings at 1, 3 and 6 months thereafter, which may have documented episodes of AF in otherwise asymptomatic patients. Gilligan et al. reported a 33% rate of freedom from AF or atypical AFL at 5 years, with a mean follow-up of 17 ± 7 months [15]. In our study, which included fairly similar patients in terms of age, left ventricular function and LA diameter, nearly three out of four patients experienced postablation AF after an extended follow-up. After an initial phase consisting of the first 2 years after the ablation, during which most of the episodes occurred, AF prevalence increased continuously without seeming to reach a plateau.

In any case, it should be noted that in our study, as in others, a substantial number of patients received AADs and anticoagulants “in the long term”, highlighting the importance of the arrhythmic burden independent of the relapse of AFL [8].

Even in the subset of patients with lone AFL, postablation AF is a major concern. During 6–23 months of follow-up, 7–43% of such patients develop AF [6,8,12,17,18,21]. Recently, Chinitz et al. [11] reported a 50% incidence of postablation AF in patients followed for 29.6 ± 21.7 months and Ellis et al. [14] reported an even higher rate of 82% after a follow-up of 39 ± 11 months. In the latter study, patients have been treated unsuccessfully with at least two or more AADs to enter the study. Patients in their study might have been at higher arrhythmic risk than ours. Indeed, no restrictions were applied in our study, in which RF ablation was first-line therapy in 10 (14%) patients with lone AFL and second-line therapy after only one failed AAD in 34 (48%) patients.

Predictors of postablation AF

Studies with midterm follow-up have demonstrated that a history of preablation AF [6,9,12,13,15,16,19], LA enlargement [8,9] and left ventricular dysfunction [12,19] are related to the occurrence of AF after AFL ablation. Our study confirms the importance of the first two factors as predictors of postablation AF, but left ventricular dysfunction is no longer a risk factor for postablation AF in the long term. In the subset of patients with lone AFL, mitral regurgitation [12], LA size [14] and the number of previously used AADs [8] have been correlated with postablation AF in the literature. No predictors of subsequent AF were identified in this subset of patients in our study, probably because of an insufficient number of patients with lone AFL.

Study limitations

Recurrence of atrial arrhythmias was investigated by means of serial ECGs and Holter recordings if patients presented suggestive symptoms. Lack of routine monitoring may have missed asymptomatic and paroxysmal episodes of AFL and AF, which may account for a third to more than a half of total episodes of arrhythmias [9,32]. Consequently, the incidence of AF might have been underestimated. Furthermore, 29% of patients were maintained on AADs at hospital discharge and 35% were using AADs at the end of follow-up. Thus, in a certain number of patients the results should be interpreted as the consequence of the combination of RF ablation and AAD therapy rather than RF ablation alone.

In some cases, patients can experience clinical improvement despite a few relapses of AF [7,10]. In our series, 18 patients with postablation AF had a unique and self-terminating episode. Caution should be advised in the interpretation of the incidence of AF as it may not always reflect the clinical status of an individual patient.

Conclusions

Despite the efficacy of cavotricuspid isthmus RF ablation in the treatment of typical AFL, most patients cannot be considered definitely cured of all atrial tachyarrhythmias. Indeed, three out of four patients will potentially experience AF over time. Patients with a history of preablation AF or LA enlargement are at a higher risk of postablation AF and should be monitored closely. Clinicians should be aware of the risk of AF after the procedure, even after the first 2 years. Consequently, improvement of symptoms rather than complete freedom from arrhythmias should be of paramount importance when deciding whether to refer patients for ablation.

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None.

Conflicts of interest

None.

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