Atrial fibrillation recurrence after drug-induced typical atrial flutter ablation

Alberto Bandini, Paolo Golia, Denis Pantoli, Marcello Galvani, Franco Rusticali

Division of Cardiology, G.B. Morgagni Hospital, and Cardiovascular Research Unit, M.Z. Sacco Heart Foundation, Forlì, Italy

Key words:
Atrial fibrillation; Atrial flutter; Catheter ablation.

Background. **Catheter ablation of typical atrial flutter (AFL) occurring in patients who take antiarrhythmic drugs for atrial fibrillation (AF) has been proposed as a curative approach for AF. The aim of this study was to evaluate the efficacy of this technique.**

Methods. **Forty-six consecutive patients (30 males, 16 females, mean age 67 ± 9 years) with paroxysmal or persistent AF were submitted to right atrial isthmus ablation: 1) 33 patients (group 1) in whom typical AFL spontaneously occurred during oral treatment with propafenone (n = 19), flecainide (n = 9) or amiodarone (n = 6); 2) 13 patients (group 2) submitted to electrophysiological study while taking oral propafenone (n = 3), flecainide (n = 8) or amiodarone (n = 1), in whom sustained AFL was induced (n = 9) or AF was induced and AFL was obtained by intravenous administration of class IC drugs (n = 4). The same antiarrhythmic drug which induced the conversion of AF into AFL was administered after ablation.**

Results. **During a follow-up of 20 ± 18 months (range 1-78 months), 23 patients (50%) remained asymptomatic and free from AF recurrences. Fifteen patients (33%) with AF recurrences reported a reduction in arrhythmia-related symptoms. Eight patients (17%) did not show symptomatic improvement. These results did not significantly differ between group 1 and group 2. The duration of follow-up was significantly longer in patients with AF recurrence. Among several clinical, echocardiographic and electrophysiological parameters, only atrial enlargement and the absence of structural heart disease were independently associated with AF recurrence.**

Conclusions. **In selected patients with AF and drug-induced AFL, right atrial isthmus ablation and prosecution of the drug treatment is a safe and feasible approach, which totally eliminates or reduces symptomatic AF recurrences in one half and one third of patients, respectively. However, the number of AF-free patients tends to decrease over time.**

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Address:
Dr. Alberto Bandini
Viale Bologna, 329
47100 Forlì
E-mail:
abandini@ausl.fo.it

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice. Therapy is usually directed toward the restoration and maintenance of sinus rhythm, but the results obtained with pharmacological treatment are less than optimal.

Catheter ablation of AF has recently been proposed with different approaches[1-3] obtaining encouraging results[4], but it remains a complex procedure with possible serious complications, and therefore should be proposed only in carefully selected symptomatic patients.

It has been shown that atrial flutter (AFL) may occur in some patients receiving antiarrhythmic drugs (class I and III) for AF[5-8]. In these patients ablation of the right atrial isthmus associated with the prosecution of the antiarrhythmic therapy might eliminate both AFL and AF[9-18].

We report our experience in a population of 46 consecutive AF patients treated with right atrial isthmus ablation for drug-induced typical AFL.

Methods

Study population (Fig. 1). Between March 1997 and September 2003, 103 patients underwent right atrial isthmus ablation for the treatment of typical AFL at our Institution. During this recruitment period, 33 consecutive patients with paroxysmal or persistent AF and no previous documentation of AFL, but who developed typical AFL on class IC (propafenone or flecainide) or class III (amiodarone) antiarrhythmic drugs, underwent a successful right atrial isthmus ablation (group 1).

In the same period, 57 additional patients with paroxysmal of persistent AF and no previous documentation of AFL, symptomatic for palpitations in spite of drug therapy, but without any documentation of the arrhythmia, were submitted to electrophysiological study, performed on drug

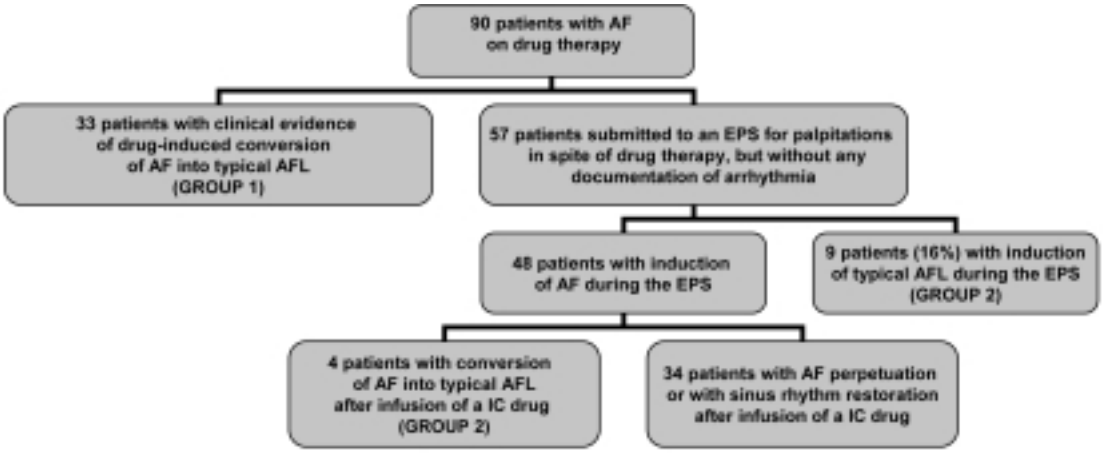

Figure 1. *Study population. AF = atrial fibrillation; AFL = atrial flutter; EPS = electrophysiological study.*

therapy. In 9 (16%) patients a sustained typical AFL was induced. In the remaining 48 patients, in whom AF was induced, flecainide (2 mg/kg body weight) in 20 and propafenone (2 mg/kg body weight) in 28 were infused; in 4 cases the drug converted the arrhythmia into a sustained typical AFL. All 13 patients in whom AFL was obtained were included in the study (group 2) and submitted to right atrial isthmus ablation during the same session.

Therefore 46 patients (30 males, 16 females, mean age 67 ± 9 years) who underwent AFL ablation (45% of total AFL ablations in the study period) were followed up as outpatients every 4 months by clinic visits and 12-lead ECG. Patients were also instructed to obtain a 12-lead ECG in case of palpitations. Regardless of the timing of the last visit, all patients were evaluated at the end of follow-up to confirm their clinical status.

The endpoint of the study was the recurrence of symptomatic, documented AF after right atrial isthmus ablation. When palpitations occurred, it was asked to the patients to compare their overall amount during the follow-up period to that in the pre-ablation period (during which the same antiarrhythmic drug was assumed), and to define it as lowered, unchanged or increased.

All the patients were discharged with the drug regimen which converted AF into AFL; such a therapy was administered during the follow-up at least until symptomatic palpitations or documented AF occurred.

The assessed variables included age, gender, left ventricular ejection fraction, left atrial diameter, presence of heart disease, associated antiarrhythmic drug therapy, typical AFL cycle length, and AF or atypical AFL occasional induction during the electrophysiological study. Also the duration of follow-up was considered with reference to AF recurrence. Left ventricular ejection fraction was determined by echocardiography in the apical long-axis view using the area-length method; the antero-posterior left atrial diameter was measured in the parasternal long-axis view.

Definitions. Typical AFL was defined as AFL exhibiting 1) a counterclockwise or clockwise activation sequence around the tricuspid annulus, 2) a proximal to distal coronary sinus activation sequence, 3) concealed entrainment at the pacing sites within the right atrial isthmus, with a post-pacing interval similar to the AFL cycle length.

An arrhythmia lasting > 1 min was considered as sustained.

Electrophysiological study. A duodecapolar catheter was placed around the tricuspid annulus to assess the activation sequence in the right atrial lateral wall. Another octapolar catheter was placed into the coronary sinus, with the proximal electrode pair located at the ostium site.

Induction on typical AFL was attempted by programmed atrial stimulation and atrial burst pacing from the distal electrode pair of the duodecapolar catheter and from the proximal electrode pair of the octapolar catheter.

Catheter ablation. A linear lesion between the tricuspid annulus and the inferior vena cava was performed by a combination of point-by-point ablations with an 8 mm-tipped ablation catheter (EP Technologies). Radiofrequency was delivered by a generator (EPT 1000XP, EP Technologies) to achieve a tip-tissue interface temperature of 70°C and an output of 100 W.

Successful ablation was defined as the achievement of bidirectional isthmus conduction block. Bidirectional isthmus block was present if 1) pacing from the proximal coronary sinus resulted in counterclockwise activation of the tricuspid annulus, with the latest activation at the infero-lateral tricuspid annulus, and 2) pacing from the infero-lateral tricuspid annulus resulted in clockwise activation of the tricuspid annulus, with the latest activation in the proximal coronary sinus.

Statistical analysis. Continuous variables were expressed as mean ± SD and compared using the unpaired Student's t-test. Nominal values were compared with

the χ^2 test. The Kaplan-Meier method was employed to analyze the timing of events during follow-up.

To identify independent predictors of AF recurrence, all variables included in the univariate comparison were tested in a Cox proportional hazard model using backward stepwise selection (likelihood ratio). Variables were entered if $p < 0.05$ and removed if $p > 0.10$.

A p value < 0.05 was considered as statistically significant.

All data analysis was performed using the Statistical Package for Social Sciences (SPSS 10.1) software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics. As shown in table I, clinical characteristics of group 1 and group 2 patients were similar, except for age which was significantly higher in group 1 patients.

During a follow-up of 20 ± 18 months (range 1-78 months), 23 of the 46 patients (50%) were asymptomatic and without any documentation of AF recurrence. Fifteen additional patients (33%) had documented AF recurrences, but reported an overall reduction of the arrhythmia-related symptoms compared to the pre-ablation period. The remaining 8 patients (17%) had documented AF recurrences and no symptomatic improvement. Among the 23 patients with documented recurrences, 3 patients had persistent AF, and one of them was submitted to electrical cardioversion; no patient had permanent AF.

As shown in table II there were no significant differences in any of the clinical characteristics of the patients with or without AF recurrence, except for gender (the recurrence rate was higher in males than in females) and the duration of follow-up, that was significantly longer in those with AF recurrences. In order to control for time-dependent exposure to the risk of AF recurrence, all the variables included in the univariate analysis were tested in a Cox regression model. The absence of heart disease (odds ratio 4.93, 95% confidence interval 1.21-20.05) and the increase in the left atrial diameter (odds ratio 1.24, 95% confidence interval 1.01-1.52) were found to be independent predictors of AF recurrence (Table III).

Figure 2 shows the Kaplan-Meier curve of AF recurrence in the study population. The median time to AF recurrence was 35 months (95% confidence interval 33-38 months). At the end of follow-up, 92% of patients had at least one recurrence of AF.

All patients underwent a successful cavo-tricuspid isthmus ablation with a single procedure; no patient had AFL recurrences during follow-up.

Associated antiarrhythmic drugs. The antiarrhythmic drugs prescribed at hospital discharge were

Table I. Clinical characteristics of the patients with spontaneous (group 1) and induced (group 2) atrial flutter (AFL).

	Group 1 (n=33)	Group 2 (n=13)	p
Age (years)	69 ± 8	62 ± 10	0.01
Sex (M/F)	20/13	10/3	NS
LVEF (%)	65 ± 9	62 ± 9	NS
LA diameter (mm)	39 ± 5	41 ± 4	NS
No heart disease	5 (15%)	4 (31%)	NS
Hypertensive heart disease	25 (76%)	7 (54%)	NS
Ischemic heart disease	3 (13%)	0	NS
Valvular heart disease	1 (3%)	2 (15%)	NS
Propafenone associated	19 (58%)	3 (23%)	NS
Flecainide associated	9 (27%)	8 (62%)	NS
Amiodarone associated	6 (18%)	1 (8%)	NS
AFL cycle length (ms)	287 ± 68	312 ± 38	NS
AF/atypical AFL induction	23 (70%)	10 (70%)	NS
AF recurrence	16 (48%)	7 (54%)	NS
Follow-up duration (months)	21 ± 20	16 ± 12	NS

AF = atrial fibrillation; LA = left atrial; LVEF = left ventricular ejection fraction.

Table II. Clinical characteristics of the patients with reference to univariate predictors of atrial fibrillation (AF) recurrence.

	AF (n=23)	No AF (n=23)	p
Age (years)	67 ± 8	67 ± 11	NS
Sex (M/F)	21/2	9/14	0.000
LVEF (%)	64 ± 9	65 ± 9	NS
LA diameter (mm)	40 ± 5	39 ± 5	NS
No heart disease	6 (26%)	3 (13%)	NS
Hypertensive heart disease	15 (65%)	17 (74%)	NS
Ischemic heart disease	3 (13%)	0	NS
Valvular heart disease	0	3 (13%)	NS
Propafenone associated	9 (39%)	13 (57%)	NS
Flecainide associated	10 (43%)	7 (30%)	NS
Amiodarone associated	4 (17%)	3 (13%)	NS
AFL cycle length (ms)	306 ± 47	297 ± 44	NS
AF/atypical AFL induction	18 (78%)	15 (65%)	NS
Follow-up duration (months)	28 ± 20	12 ± 12	0.002

AFL = atrial flutter; LA = left atrial; LVEF = left ventricular ejection fraction.

Table III. Independent predictors of atrial fibrillation (AF) recurrence (Cox regression).

	OR (95% CI)	p
Age (years)		0.82
Sex		0.82
LVEF (< 65%)		0.79
LA diameter (mm)	1.24 (1.01-1.52)	0.044
No heart disease	4.93 (1.21-20.05)	0.026
Associated drug therapy		0.26
AFL cycle length (ms)		0.66
AFL presentation (group 1 vs group 2)		0.41
AF/atypical AFL induction		0.58

AFL = atrial flutter; CI = confidence interval; LA = left atrial; LVEF = left ventricular ejection fraction; OR = odds ratio.

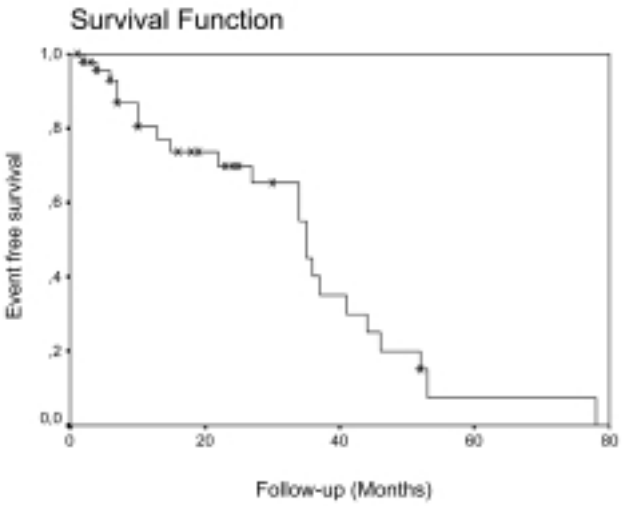

Figure 2. *Kaplan-Meier curve of atrial fibrillation recurrence in the study population.*

propafenone in 22 patients, flecainide in 17 patients, and amiodarone in 7 patients.

In all the 23 asymptomatic patients the antiarrhythmic drugs prescribed at hospital discharge were continued during the follow-up (propafenone in 13, flecainide in 7, and amiodarone in 3).

Discussion

It is well known that many patients experience episodes of both AFL and AF[12,13,19].

After catheter ablation of AFL the risk of developing AF is significant[20-25], being especially high in patients with left ventricular dysfunction, atrial enlargement, inducibility of AF after ablation, and previous history of AF[20,21,26].

In the setting of clinically predominant AF, AFL has been observed to occur spontaneously[27-29] or, more frequently, during treatment with antiarrhythmic drugs[5-8]. The probability to develop AFL appears to increase when AF prior to antiarrhythmic drug administration presented with an organized pattern (relatively long cycle lengths and high amplitude of the fibrillation waves) at the surface ECG[30].

Although we were not able to estimate the incidence of the conversion to AFL during antiarrhythmic drug therapy in our AF patients, it has previously been reported to occur in a variable percentage of cases[8-11,30,31], ranging up to about 25% when patients with exclusive paroxysmal AF episodes were considered[30,31].

The mechanisms by which antiarrhythmic drugs may induce AF termination or its conversion to AFL are not yet completely understood. Up to a few years ago the antifibrillatory action of class IC drugs and amiodarone was attributed to a prolongation of the atrial wavelength[32-34]. However, recent studies have shown that class IC drugs, although capable of prolonging refractoriness, principally induce conduction velocity slowing and consequently wavelength shortening[35,36]. At present, widening of the temporal excitable gap is thought to be the mechanism by which flecainide and other antiarrhythmic drugs may interrupt AF[36]; it might reduce wavelet formation and promote their fusion, leading to a decrease in the number of wandering wavelets and so favoring the chance of AF termination.

Maintenance of typical AFL circuit necessitates a posterior line of block between the venae cavae[37,38]. In experimental animal models it has been shown that the conversion of AF to typical AFL is preceded by the development of an area of slow conduction and unidirectional conduction block, mostly occurring in the region of the crista terminalis[39], with the formation of a functional line of block of a critical length[40].

Therefore, it may be hypothesized that when an antiarrhythmic drug converts AF into AFL it happens at least in part because it has facilitated the development of a stable line of functional block of a critical length between the venae cavae[41]. Moreover, the reduction in the number of circulating wavelets induced by antiarrhythmic drugs might increase the statistical chance that the descending activation front from the right atrial lateral wall could propagate to the right atrial isthmus and lower interatrial septum[42].

In patients who had AFL during drug prophylaxis for AF, right atrial isthmus ablation in combination with long-term prosecution of antiarrhythmic therapy has been proposed in order to eliminate both arrhythmias. Such a treatment has been shown to be effective in maintaining sinus rhythm in 36-93% of patients[9-18]. The results of such a therapy appear to be even more encouraging if we consider that many patients in whom AF was not completely eliminated reported a markedly lower recurrence of paroxysmal symptomatic AF and a significant improvement in quality of life[10,12,16-18].

In general, our results appear to be similar to those reported in the studies with a comparable follow-up, regarding both the number of patients who remained AF-free and those who improved clinically. Comparing the results of different studies regarding arrhythmia recurrence rate, the differences between endpoints must be taken into account. We and others[17] have considered only documented AF episodes as recurrences, whereas other authors preferred to directly address symptomatic events, regardless of ECG documentation[18].

We have observed that patients with a longer follow-up had a greater number of AF recurrences, i.e., the number of AF-free patients significantly reduces over time. This is also confirmed by the comparison between the percentage of AF-free patients in studies with a short-term[12,13] vs a more prolonged[14-18] follow-up.

Moreover, according to the Kaplan-Meier curve of AF recurrence in the population, we observed an important drop of the rate of AF-free patients nearly at 35 months of follow-up; afterwards, at the end of the observation time only 8% were in stable sinus rhythm.

Therefore it seems that the benefit of hybrid therapy tends to be lost over 35 months of follow-up. However, the number of patients with an adequately long follow-up time is too low to draw definitive conclusions. However, Bonso et al.[15] have shown that the percentage of AF-free patients tends to remain stable after the first year of follow-up.

In our study arrhythmic recurrences did not significantly differ between patients with clinical AFL and patients with "concealed" AFL. However, the number of group 2 patients was limited, and therefore additional investigations are needed before concluding that a similar efficacy may be observed in this group compared to group 1.

Some authors have reported that the rate of AF-free patients at follow-up was higher if AFL was the only arrhythmia documented during drug therapy[9,12,13,16-18]. In this regard, it should be observed that we have submitted to the same treatment patients with both spontaneous and induced AFL (group 1 and group 2 patients, respectively), assuming that the clinical significance of the two arrhythmias was similar: AFL induced at electrophysiological study in group 2 patients was hypothesized to be the cause of symptoms ("concealed" drug-induced AFL). However, whereas group 1 patients had exclusive documented AFL episodes on drug therapy, it could not be excluded that some of the non-documented arrhythmias in the group of patients with "concealed" AFL were short-lasting paroxysmal AF episodes. This appears even more likely if we consider that AFL is mainly a stable arrhythmia, manifesting persistent rather than paroxysmal episodes. Therefore, the incidence of AF episodes associated with AFL on drug therapy could have been underestimated in group 2 patients; on the basis of the available literature data[9,12,13,16-18], a longer follow-up might reveal in such patients a higher rate of AF recurrences.

The clinical characteristics of patients with and without AF recurrences have been compared. If it is well known that atrial enlargement predisposes to AF recurrences[43], the finding of a higher incidence of AF recurrences in patients without structural heart disease is more difficult to explain. It is possible that different mechanisms of the initial AF episodes may be involved in different patients; when a hypertensive, coronary or valvular disease was present, it might be hypothesized a relevant role of the substrate. On the other hand, in the absence of a significant structural heart disease the role of trigger would have been predominant at the time of AF occurrence. The latter patients, in whom after right atrial isthmus ablation the trigger probably emerges again, might be less sensitive to the antifibrillatory action of drugs that converted AF into AFL.

Bottoni et al.[18] have shown a higher AF recurrence rate in patients with a long history of AF. We did not evaluate the duration of AF history before ablation in our patients; however, the higher rate of recurrences in the patients who have a longer follow-up after ablation would have a similar significance.

Another factor that has been shown to be predictive of AF recurrence after ablation is the documentation of coexisting AF episodes on drug therapy before ablation[16,17]. None of our patients had such episodes; however, it might be observed that the rate of AF-free patients in our study appears to be high in comparison to that of studies with a low rate of patients with coexisting AF[17]. In this respect, it may be possible that some AF recurrences were missed before ablation in our patients.

Moreover, a lower number of patients were treated with amiodarone in our study, compared to that of Reithmann et al.[17]; the difference in the results between the two studies might be attributed to a trend that these authors found toward a higher efficacy of amiodarone.

The prevalent use of IC drugs over amiodarone in our study might also explain that none of our patients had the antiarrhythmic therapy prescribed upon hospital discharge discontinued due to side effects.

Study limitations. We have evaluated arrhythmic recurrences on the basis of symptoms; since many AF episodes may be asymptomatic[44], it is possible that the incidence of AF recurrence has been underestimated. Theoretically, antiarrhythmic therapy might have enhanced this problem by slowing ventricular rate during AF, thus rendering the arrhythmia less symptomatic[45]. We did not find asymptomatic paroxysmal AF episodes at ECG recordings in our patients; however, it is well-known that the prevalence of asymptomatic AF depends on the method used for documentation, being higher when external loop recorders or implantable devices are used[46]. The major concern with asymptomatic AF is about thromboembolic events after anticoagulation therapy withdrawal. In our patients we did not register thromboembolic events after suspension of anticoagulation in sinus rhythm patients without possibly arrhythmia-related symptoms. Nevertheless, according to current clinical data, it should be underlined that AF patients continue to be at increased risk for thromboembolic events after apparent stabilization in sinus rhythm, and therefore withdrawal of oral anticoagulation in such patients must be carefully evaluated[47]. Another limitation of our study is the lack of a control group; in particular, randomization of isthmus ablation vs non-ablation would be adequate to evaluate the additional long-term efficacy of ablation on the recurrences of AF in the subset of patients with inducible non-documented AFL (group 2).

In conclusion, drug-induced typical AFL ablation and prosecution of the antiarrhythmic therapy can be proposed only in a small subset of patients with AF (approximately 10-15%). Nevertheless, such a treatment appears to be safe and effective in reducing or totally eliminating symptomatic arrhythmia recurrences, and therefore should be considered as a first step in the ablative approach of AF.

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