Current perspective

Atrial flutter and atrial fibrillation: which relationship? New insights into the electrophysiological mechanisms and catheter ablation treatment

Leonardo Calò, Filippo Lamberti, Maria Luisa Loricchio, Ermenegildo De Ruvo, Leopoldo Bianconi, Claudio Pandozi, Massimo Santini

Department of Cardiac Diseases, San Filippo Neri Hospital, Rome, Italy

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Atrial fibrillation (AF) and atrial flutter (AFL) are two arrhythmias commonly associated in clinical practice. This association generally reflects a similar arrhythmogenic substrate. It has been observed that the development of isthmus-dependent AFL is often preceded by AF. The conversion from AF to AFL develops thanks to a line of functional block in the right atrial free wall. In this subset a particular condition is represented by typical AFL that occurs during the treatment with class IC or III antiarrhythmic drugs in patients with previous AF. A hybrid approach (antiarrhythmic drugs and catheter ablation) has been proposed as a possible treatment of drug-induced AFL. The conversion from AFL to AF is less frequent and may be due to several mechanisms: a shortening of the length of the line of functional block, atrial ectopic beats or rapid atrial rhythm, focal activation from the pulmonary veins, alternans of atrial action potentials. Also, atypical right and left AFL can determine AF. Finally, atypical AFL may occur after AF ablation, and could be prevented by associated cavotricuspid isthmus ablation.

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Address:

Dr. Leonardo Calò

Via della Pedica, 348
00046 Grottaferrata (RM)
E-mail:
leonardo.calo@tin.it

Electrophysiological mechanisms of conversion from atrial fibrillation to atrial flutter and from atrial flutter to atrial fibrillation

The relatively frequent association between atrial fibrillation (AF) and atrial flutter (AFL) has been well documented[1-6]. Indeed, AFL was present in 5-30% of patients with AF, and AF has been reported to occur in 12-60% of patients with AFL treated with transisthmic ablation[7-21]. These clinical associations are likely to reflect a similar arrhythmogenic substrate.

Usually, the conversion from AF to AFL is more frequent than the transition of AFL in AF. In fact, it has been observed that the development of isthmus-dependent AFL is very often preceded by a transitional rhythm of AF of variable duration[2-6]. Waldo[6] has hypothesized that this is due to a line of functional block in the right atrial free wall between the venae cavae. The lateral boundaries are crucial to the initiation and stability of AFL. One, the tricuspid annulus is anatomic. The other, the intercaval line of block in the right atrial free wall is usually functional. If this line of block does not form, isthmus-dependent AFL does not occur.

In humans, Roithinger et al.[2], using a 20-pole catheter in the right atrium and a multipolar catheter in the coronary sinus, have mapped 16 episodes of AF converting into AFL in 10 patients. They have observed the following temporal events: 1) a gradual prolongation of FF intervals; 2) an electrically silent period (267 ± 45 ms); 3) a progressive organization of AF probably due to coalescence and annihilation of wavelets (usually, the activation along the right lateral wall was craniocaudal); 4) another delay on the lateral right atrium (283 ± 52 ms); 5) typical AFL. The authors have hypothesized that, during the phase of organized AF, the orthodromic craniocaudal wavelets along the right lateral wall oppose with the antidromic wavelets coming from the septum and then both block in or near the sub-Eustachian isthmus, resulting in disorganized AF. Conversely, if the right lateral craniocaudal wavelets find both the sub-Eustachian isthmus and the septum excitable, statistically a rare event, the descending wave can activate the septum and the left atrium, thus initiating AFL. More-

over, they observed that the direction of the wavefront along the right atrial free wall during the organization of AF (craniocaudal in 70% and caudocranial in 30%) determines the direction of flutter rotation after its onset (craniocaudal → counterclockwise AFL; caudocranial → clockwise AFL). Tissue-specific determinants of anisotropic conduction and/or anatomic "funnelling" effect statistically favor the activation on the trabeculated right atrium in a counterclockwise rather than in a clockwise direction. Figure 1 shows an example of conversion of AF in AFL recorded in our laboratory.

Emori et al.[4] have mapped 12 episodes of conversion of AF in AFL in 7 patients. They found a prolongation of FF interval before conversion of AF in AFL, as Roithinger et al.[2] did. Most important, they observed in the right atrial septum fractionated electrograms with disorganized activation sequence up to the conversion in AFL, when the septal electrograms became separated by an isoelectric baseline, and the activation sequence organized. As also reported by Kumagai et al.[22], the authors suggested that unstable reentrant circuits with very short cycle lengths principally involving the atrial septum are critical for AF maintenance[22].

Regarding the conversion from AFL to AF several mechanisms can be considered (Table I). The group of Waldo[5] showed in a canine sterile pericarditis model, that conversion of AFL to AF was associated with a shortening in the length of the line of functional block from a mean of 24 ± 4 mm to a mean of 16 ± 3 mm. In fact, the decrease in the length of the functional line of block determines rapid unstable circuits and AF. This shortened line of block continued to change while migrating over the right atrial free wall during AF. AFL was re-established when a sufficiently long line of block developed to protect stable AFL through lateral boundaries. In humans with typical AFL, it has been reported by Narayan et al.[23] that alternans of monophasic action potentials occurs during progressive disorganization of AFL to AF. During AFL, they have found that the atrial action potential is longer and shortens less with increasing rate at the isthmus than at the other right atrial sites. With progressively faster pacing, this rate maladaptation lead to alternans of action potentials at the isthmus preceding transitions to AF, potentially via wavefront fractionation[23].

Table I. Electrophysiological mechanisms involved in the conversion of atrial flutter to atrial fibrillation.

Shortening in the length of intercaval line of functional block
Ectopic beats (pulmonary veins or extra pulmonary veins)
Right atrial reentry through break(s) over the crista terminalis
Rapid atrial rhythm (atrial tachycardia, atypical atrial flutter)
Alternans of action potentials at the isthmus
Electrical remodeling

In patients with lower loop reentry, it has been observed that atrial ectopic beats or rapid atrial rhythm can initiate AF either directly or by determining double-wave reentry or multiple breaks over the functional barriers[3]. As also suggested by Wu et al.[24], the authors

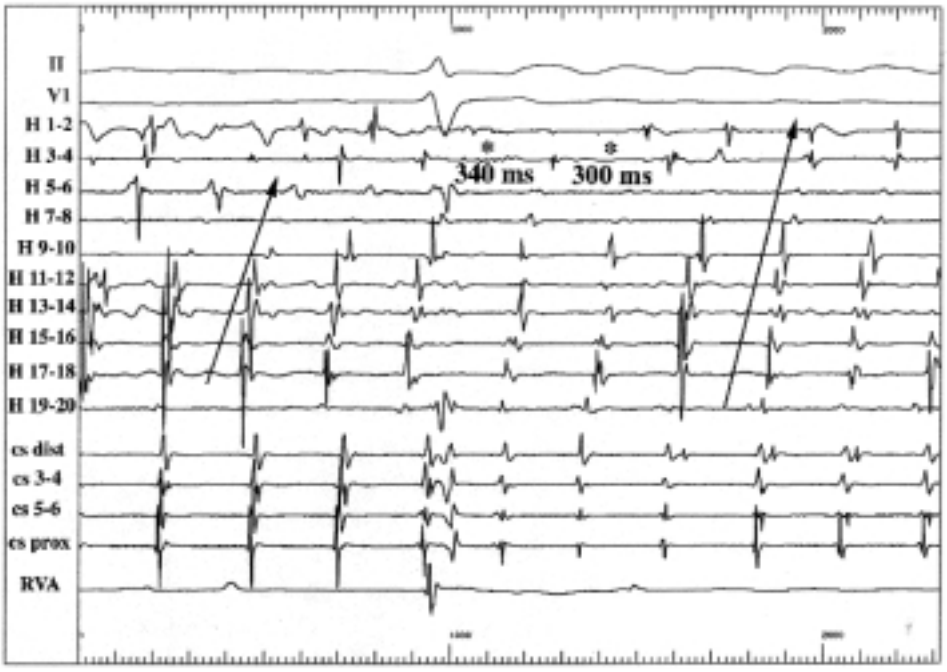

Figure 1. *Characteristic sequence of events in the conversion of atrial fibrillation to typical atrial flutter. After a period of partially organized atrial fibrillation with caudocranial activation* (arrows) *along the right free wall, two electrically silent periods* (*) *followed. Then, typical counterclockwise atrial flutter resumed. CS dist = distal coronary sinus; CS prox = proximal coronary sinus; H 1-2 = low lateral right atrium; H 19-20 = right septum; RVA = right ventricular apex.*

hypothesized that these multiple breaks or the double-wave reentry resulted in more rapid rates, which favor unstable circuits and AF.

Another mechanism of conversion from AFL to AF involved the role of focal activation from the pulmonary veins[1,25]. Hsieh et al.[1] found that the conversion from AFL to AF is induced by triggers from pulmonary vein foci in 85% of cases. In the remaining cases, the triggers were found in the right atrium. Morton et al.[26], in an ovine study of AFL with an Y-lesion anatomic barrier model, demonstrated that chronic AFL leads to a highly significant fall in atrial refractoriness and conduction velocity. Principally by way of these changes, AFL induced the substrate for development of sustained AF not present at baseline. However, despite the development of a very short atrial wavelength, spontaneous conversion of AFL to AF occurs infrequently, and the development of AF depended on appropriate triggers[26].

Atypical AFL can also determine AF. Atypical right and left AFL have both stable reentrant circuits. However, when the rate of these flutters is critically fast with very short cycle length, they will only activate small portions of the atria in a 1:1 manner and the rest of the atria will be activated irregularly favoring AF. AF can be actually initiated, and in some cases maintained, by short runs of AFL[6]. In dogs, Kumagai et al.[22,27] reported that unstable reentrant circuits, critical for AF induction and maintenance, involved mainly the septum. In fact, they were present in the septum in the 62% of the time, the right atrial free wall 21%, around the pulmonary veins 7%, and around the inferior and superior vena cava 5 and 5%, respectively. Three of these five reentrant circuit locations included Bachmann's bundle as part of the reentrant circuit for the 68% of the time. Catheter ablation of Bachmann's bundle terminates and prevents the induction of AF in all dogs. In humans, very rapid reentrant circuits, the so-called "mother rotors", can be the drivers of AF. These rotors generally anchor the musculature around the pulmonary veins or the base of left atrial appendage[28-31].

In other cases the circuit responsible for AF initiation is a stable macroreentry[32-34]. Nair et al.[34] in 17 patients with chronic AF and rheumatic heart disease have observed that induced AF begins as a rapid organized atrial arrhythmia. The earliest atrial activity during these atypical AFL circuits was localized near the coronary sinus ostium in 14 patients and along the left side of the interatrial septum in 3 patients. An ablation limited to these areas has been successful in most patients. Recently, the group of Chen[32,33] has reported that reentrant circuits (AFL) in the right atrium can determine AF. In 27 patients with AF, non-contact mapping showed right atrial reentry (2 patients with a single circuit, 23 patients > 2 reentry circuits) with conduction through the low right atrial isthmus (n = 22), crista terminalis gap (n = 24), or channel between low voltage zones (n = 12), all resulting in fibrillatory conduction. Short lines of ablation lesions on crista terminalis gap, channel between low-voltage zones, and low right atrial isthmus resulted in bidirectional conduction block. After a follow-up of 19 ± 3 months, 83% of patients were free of AF without antiarrhythmic drugs (AAD).

In summary, the conversion from AF to AFL develops thanks to a critically long line of functional block in the right atrial free wall. This conversion is characterized by a progressive organization of AF probably due to coalescence and annihilation of wavelets and by the disappearance of disorganized electrograms along the septum. The conversion from AFL to AF is less frequent. It may be due to several mechanisms, including a shortening of the length of the line of functional block, atrial remodeling, atrial ectopic beats or rapid atrial rhythm, focal activation from the pulmonary veins, alternans of atrial action potentials. Also, atypical right and left AFL can determine AF.

Cavo-tricuspid isthmus ablation in patients with atrial flutter and atrial fibrillation

Radiofrequency ablation of the cavo-tricuspid isthmus is a well established, safe and effective therapy for the treatment of typical AFL. Moreover, this approach can also reduce significantly the incidence of AF in those patients in whom the right AFL plays a critical role in the initiation and maintenance of AF. However, after ablation of AFL, AF can even occur as a result of different electrophysiological and/or clinical causes.

Philippon et al.[8] in patients ablated for AFL have observed that, among 11 different clinical variables, only the persistent inducibility of sustained AF after AFL ablation was independently associated with subsequent AF. Paydak et al.[9] have found that history of spontaneous AF and left ventricular dysfunction (left ventricular ejection fraction < 50%) both identify a subgroup of patients at high risk for AF recurrences (74%). These patients should be advised for continuation or initiation of AAD therapy and anticoagulation as well as additional ablation procedures. Those patients with neither risk factors were at lower risk of recurrent arrhythmia (10%) and necessitate a less aggressive treatment. Da Costa et al.[16] confirmed these data and found that also a significant mitral regurgitation (at least 2+) was associated with the risk of early post-ablation AF. As in the general population, post-ablation AF may occur as a consequence of end-stage mitral regurgitation or very large left atrium (diameter > 50 mm)[7]. Noteworthy, a recent retrospective study reported that the use of angiotensin converting enzyme inhibitors/angiotensin II receptor blockers and diuretics was significantly associated with less development of AF in patients who underwent isthmus ablation both in case of pre-ablation presence of only AFL and in case of coexisting AFL and AF[21].

A particular condition is represented by typical AFL that occurs for the first time during the treatment with class IC or III AAD in patients with previous AF. In this case the potential of a clinically dangerous drug-induced 1:1 atrioventricular conduction must be considered. In this subset of patients, a hybrid approach, consisting of ablation of the tricuspid annulus-inferior vena cava isthmus and continued pharmacological therapy, may be as effective in maintaining sinus rhythm as in patients with history of pure AFL. AAD treatment can in fact promote AF organization to a macroreentrant circuit, in which the inferior vena cava-tricuspid annulus plays a crucial role. AAD treatment, by depressing intra-atrial conduction velocity, progressively blocks more and more wavefronts until only a single AFL reentrant circuit survives.

An AFL incidence of 5-10% has been reported in safety studies, even though a higher incidence has been reported by Bianconi et al.[35]. These data have been confirmed by Stabile et al.[36], who tested the response to flecainide infusion in the hybrid pharmacological approach to AF. The infusion of flecainide 2 mg/kg intravenously determined the acute conversion of AF in AFL in 71/404 patients (17.5%). In this study the efficacy of the hybrid treatment of AF, acutely organized by flecainide into a stable typical AFL, was tested versus pharmacological or ablation alone treatment. It was reported that the effectiveness of the flecainide AFL induction was a reliable way to identify patients with AF who could benefit from hybrid therapy.

The long-term success rate of cavo-tricuspid isthmus ablation in patients with both AF and AFL widely ranges in different studies (Table II)[7-9,11-17,36]. The predominant clinical arrhythmia was clinical or drug-induced AFL. In most patients, the isthmus ablation reduces the recurrence of symptomatic episodes of AF and increases the quality of life. In patients with history of AF and drug-induced AFL, the group of Bri-gnole[19] has reported that even if symptomatic AF recurrence occurred in 64% of the patients, 89% improved clinically and hospitalizations were reduced from 53 to 11%.

It can be summarized that the efficacy of the hybrid therapy changes in relation to the clinical history of the patient and the beneficial effect is inversely proportion-

Table II. Incidence of atrial fibrillation and/or atypical atrial flutter after cavo-tricuspid isthmus ablation.

	No. patients	Patients with only AFL	Patients with AFL due to AAD	Patients with AFL and AF	Patients with only AF
Reithmann et al.[17]	92	25% (10 ± 6.2 m)	20% (8.3 ± 2.8 m)	76% (8.2 ± 5.6 m)	
Nabar et al.[10]	82	7% (18 ± 14 m)	27% (4 ± 2 m)	AFL > AF 38% [14%]* (20 ± 14 m) AFL < AF 86% [43%]* (13 ± 8 m)	
Schumacher et al.[13]	20		64% [20%]** (11 ± 4 m)		
Paydak et al.[9]	110	12% (18.3 ± 9 m)		45% (17.8 ± 10 m)	
Philippon et al.[8]	59	19.5% (13 ± 6.6 m)		50% (13 ± 6.6 m)	
Huang et al.[12]	9		11% (14.4 ± 6.9 m)		
Tai et al.[11]	15		7% (12.3 ± 4.2 m)		
Nabar et al.[14]	24		15% (13 ± 6 m)	Isthmus-dependent atypical AFL 50% (13 ± 6 m)	100% (13 ± 6 m)
Da Costa et al.[16]	96	8% (30 ± 46 days)		33.3% (30 ± 46 days)	
Stabile et al.[36]	24		41.7% (24 ± 7.2 m)		> 95% (24 ± 7.2 m)
Schmieder et al.[15]	343	33% (16.5 ± 11.1 m)			
Bertaglia et al.[7]	383	12% (2 years)	66% (2 years)		
		52% (4 years)	68% (4 years)		

AAD = antiarrhythmic drugs; AF = atrial fibrillation; AFL = atrial flutter; m = months. * on AAD; ** significant reduction of AF.

al to the prevalence of AF before isthmus ablation. In particular, radiofrequency ablation of AFL due to AAD treatment (transformation of AF in AFL by class I or III AAD) significantly reduces the recurrence of symptomatic episodes of AF and allows a better pharmacological control in previously drug-resistant arrhythmias with a lower need for rehospitalization.

Atrial fibrillation ablation in patients with atrial fibrillation and atrial flutter: conflicting reports

It is still not clear if AF ablation could eliminate also AFL without performing the cavo-tricuspid isthmus ablation. The group of Natale[37], in a clinical study performed in patients with both AFL and AF, concluded that pulmonary vein disconnection alone may be sufficient to control both arrhythmias. In fact, in 55% of these patients episodes of typical AFL were documented within 8 weeks after pulmonary vein ablation alone, only 5% of them continued to have recurrent sustained AFL after 8 weeks, without any clinical recurrence of AF. The authors concluded that pulmonary vein disconnection alone may be sufficient to control both arrhythmias. Thus, the cavo-tricuspid isthmus block would only reduce early post-ablation recurrence of AFL, which in the majority of patients reflects a short-term clinical problem. A main limitation of this study is that the follow-up is limited to 1 year.

Conversely, in a more recent study, Scharf et al.[38] suggested that during pulmonary vein isolation for AF ablation, right atrial isthmus ablation should be performed in all patients at risk for AFL. In fact, among the 133 patients undergoing AF ablation, a clinical episode of AFL was documented in 40 patients (30%) and inducible AFL in 86 patients (65%) including 32 with clinical AFL. Although the isthmus ablation was not randomized, of the 28 who underwent this procedure, none had AFL, whereas of the 105 patients who did not undergo isthmus ablation, 25 patients (24%) were documented to have symptomatic AFL during long-term follow-up (609 ± 252 days). Both a history of clinical AFL ($p = 0.05$) and inducible AFL during the ablation ($p = 0.01$) were independent predictors of symptomatic AFL during follow-up. Noteworthy, AF occurred in 21% of patients who underwent cavo-tricuspid isthmus ablation and in 40% of the patients who did not ($p = 0.07$) with a trend toward a lower incidence of recurrent AF.

In our experience[39], concordant with that of other groups[29,30], the right atrial isthmus is added to left atrial ablation, particularly in patients with a prevalent substrate-mediated AF and in all patients with clinical AFL. However, for patients undergoing AF ablation without clinical history of AFL but with inducible AFL during electrophysiological study, the data are not yet strong enough to recommend a combined AFL and AF ablation.

Conclusions

In clinical practice AF and AFL are two arrhythmias that often coexist. Cavo-tricuspid isthmus ablation may reduce the incidence of AF in the subset of patients in whom typical AFL has a role in the initiation or maintenance of AF. Left ventricular dysfunction, mitral regurgitation, left atrial enlargement, inducibility of AF or previous history of AF have been demonstrated to be independently associated with AF occurrence after a successful right isthmus ablation. In patients with prevalent common AFL but with clinical history of AF, we may suppose that the creation of other lesions in the right atrium apart from cavo-tricuspid isthmus line may reduce AF recurrences, whereas a hybrid approach (ablation of the tricuspid annulus-inferior vena cava plus pharmacological therapy) has been demonstrated to be effective in patients in whom AF is transformed in AFL by class IC or III AAD.

Otherwise it is still not clear if pulmonary vein ablation may eliminate AFL occurrence.

Hence cavo-tricuspid isthmus block is not yet performed systematically during all AF ablation procedures, even if it may be better to perform cavo-tricuspid isthmus ablation in specific subgroups of patients (previous history or inducibility of AFL, substrate mediated AF, AF in structural heart disease).

The knowledge of the mechanisms linking AF and AFL can help us to choose the best treatment for the patient in relation to the clinical prevalence of the arrhythmia substrate.

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