Lessons from catheter ablation: how a proarrhythmic effect has become a therapeutic chance. The case of class IC/III drugs in atrial flutter

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Introduction

Class IC or III antiarrhythmic drugs have been proven to be effective in almost 50% of the cases during long-term prophylaxis of atrial fibrillation (AF) episodes.

The conversion into atrial flutter (AFL), sometimes occurring with high ventricular response and more rarely even with catastrophic consequences, has long been regarded as an undesired proarrhythmic side effect. This phenomenon, with unfavorable hemodynamic effects, is particularly dreadful during emotional or exercise-induced activation of sympathetic tone, traditionally leading to the early interruption of the therapy.

The rate of this event ranges from 3.5 to 20% for class IC drugs[1,2] or amiodarone[2], although the clinical evaluation of only more symptomatic episodes probably underestimates the effective rate of conversion of AF into AFL.

Radiofrequency transcatheter ablation of the cavo-tricuspid isthmus in the right atrium has been shown to prevent typical AFL with high procedural safety and long-term success when based on the electrophysiological achievement of conduction block.

Thus the conversion of AF into a drug-induced AFL could theoretically represent a very desirable and favorable clinical outcome.

Since 1998, several peer-review papers have shown that radiofrequency ablation of typical AFL combined with the maintenance of antiarrhythmic drug therapy could prevent in many patients the recurrence of both AFL (secondary arrhythmia) and AF (primary arrhythmia)[3-14].

How can antiarrhythmic drugs convert atrial fibrillation into typical atrial flutter?

Drug-induced depression of excitability makes the rotors, spinning during AF, lose the ability to turn sharply, at the sites with high wavefront curvature (pivot point). This effect of drugs leads to larger turning radius and core of rotation of functional small circuits, widens the excitable gap, reduces the space to sustain the minimum critical number of rotors (or wavelets) necessary to maintain AF and causes the incorporation of anatomic obstacles within the circuit.

Such a shift from functional to larger anatomic reentrant pathways with excitable gap may exit in AF conversion into typical AFL, rotating around the tricuspid valve.

The accompanying induction of wide longitudinal conduction block in the posterior right atrium, limiting the transverse conduction, such as in the crista terminalis, is the other main requirement for this conversion of spontaneous or induced AF into AFL due to antiarrhythmic drugs[15-22].

Atrial macroreentry around the tricuspid valve is the most common form of stable (anatomical-functional) circuit of both spontaneous and drug-induced AFL (80-90% of the macroreentrant atrial tachycardias)[7].

Additional mechanisms may also be drug-induced suppression of factors promoting loss of synchronization such as biatrial triggers[21].

Results of drug-induced atrial flutter ablation

Class IC- and amiodarone-AFL ablation have shown to be effective in preventing AF recurrences in a variable proportion of patients ranging from 30 to 93%, and summarizing literature data in about 50% of these patients. A review of the literature results is reported in table I[3,4,6,8,9,11-14]. Some studies have compared patients with accompanying AF during the recruitment period on drug treatment before ablation versus patients with only drug-induced AFL before ablation. The AF recurrence rate is higher in AFL patients with coexisting AF.

In drug-induced AFL, the prognostic significance of accompanying AF before ablation in predicting AF relapses after ablation has been observed also in patients with AFL not induced by drugs[6]. Therefore, AF patients with drug-related AFL probably do not differ in their substrate from patients affected by spontaneous AFL.

The reported variability of clinical success of combined therapy (i.e. ablation + drug) is probably related to the small case series, patient selection and changing definition criteria of this syndrome (Table I).

Unsolved clinical issues

Definition. A more appropriate definition of ("class IC/amiodarone") drug-induced typical AFL concerns AF patients with recurrence(s) of *de novo* typical AFL after the beginning of oral antiarrhythmic drug therapy in the absence of AF.

Only in a broad sense we can also include patients with AF relapses after starting the antiarrhythmic therapy in association with predominant episodes of AFL.

It is arguable that patients with only or predominant episodes of drug-induced AFL might have a different clinical outcome during the follow-up in comparison with patients expressing both the two tachyarrhythmias before AFL ablation.

Inadequate run-in period. The absence of a control group in the published studies, due to the reasonable fear of maintaining a "proarrhythmic" drug therapy and of 1:1 atrioventricular response and/or widening of QRS complex risky phenomena, renders the evolution of drug-induced AFL during the follow-up unknown.

There are no available comparative data about combined therapy and antiarrhythmic drug therapy in order to evaluate the incremental role of ablation therapy in moderately symptomatic patients with class IC/III AFL and AF. The only available study concerns patients with acutely drug-induced AFL, and it showed a better response of combined therapy versus either only drug or ablation (or no therapy)[8].

A lead-in time period of some months should be considered to permit optimization of antiarrhythmic drug therapy, and adequate definition of arrhythmic burden before ablation.

Inadequate follow-up period. Drug therapy could channel AF into the forcing boundaries of stable AFL, rather than imply the replacement of arrhythmia.

In the first case, the drug would convert one arrhythmia into another one, and therefore ablative therapy could be a definite solution. However, in the second case, a substitution of a more erratic arrhythmia with another one more stable would occur leading to a modification or a delay of its clinical manifestation. A short follow-up, the inadequate analysis of clinical characteristics of patients or of the run-in period do not allow us to identify which is the more convincing hypothesis and in which patients it might work.

A longer follow-up can unmask the persistent propensity to AF if the prevention of an epiphenomenon (typical AFL) does not result in the eradication of the substrate.

Table I. Drug-induced atrial flutter (AFL): results according to accompanying atrial fibrillation (AF).

Author	AF + AFL* No AF recurrences (%) (no. pts)	Only AFL* No AF recurrences (%) (no. pts)	AFL* (AF not reported)	
			No AF recurrences (%) (no. pts)	Improvement (%)
Huang et al.[3], 1998		88% (9)		
Schumacher et al.[4], 1999			37% (19)	42%
Nabar et al.[6], 1999			68% (16)	13%
Stabile et al.[8], 2001			58% (24; all§)	
Reithmann et al.[9], 2003	42% (17)	84% (67)		
Delise et al.[11], 2003	48% (25)	75% (28)		
Bottoni et al.[12], 2004	37% (46)	30% (10)		
Bertaglia et al.[13], 2004			43 (IC)-69 (III)% (105)	
Bandini et al.[14], 2005			50% (46; 13§)	33%
Total	41% (88)	77% (114)	60% (174)	12%

* drug-induced AFL; § AFL induced by acute infusion of class IC antiarrhythmic drugs.

Clinical impact of class IC/III atrial flutter ablation

AF is currently classified as paroxysmal, persistent, or permanent. However, AF is an arrhythmic manifestation of a chronic and progressive disease that often gradually worsens and evolves over a lifetime. Thus, a more gradual transition of arrhythmia duration often occurs clinically, with short bursts of triggering atrial tachycardia at the beginning followed by short episodes of self-limited AF, then longer and even longer episodes of paroxysmal AF as time goes on, till finally many patients end with persistent or permanent AF.

Combined therapy could interfere in this process reducing the speed of progression of this arrhythmia although no related data are nowadays available. Slowing down of progression could be considered as a favorable result and a turning point in the clinical history of AF patients although in other perspectives it could also be regarded as only a delay of clinical corollaries of the disease. Longer follow-up tends to show a declining efficacy of combined therapy like other non-pharmacological approaches to AF[23,24].

Moreover it has not been sufficiently explored the role of AFL ablation by suppressing a "perpetuator" (such as AFL) either in the conversion of persistent AF into a self-limited form of AF or in the reduction of paroxysmal AF attacks.

Therefore the Kaplan-Meier curves analysis of efficacy currently constructed considering the first AF episode occurrence as the index event like in Bandini's et al. paper[14] and in the remaining literature on this topic, is an inadequate tool of analysis of the clinical impact of IC AFL ablation.

The mean interval time between the episodes, the mean duration of episodes, and the total arrhythmic "burden" can represent more stringent criteria for this purpose.

From this perspective, hybrid therapy could not be adequately evaluated in its clinical impact compared with other strategies targeting triggers and initiators when AF suppression is considered the endpoint rather than the duration of prolonged arrhythmic episodes due to the organization of AF into AFL and to the mutual influence on AF propensity[17].

Therefore an "all or none response" is probably an inadequate way to analyze the results of this not curing (but palliative) therapy addressed to the suppression of the clinically relevant symptoms rather than to the eradication of the arrhythmia. To this purpose, paroxysmal AF with rare episodes of persistent AF converted in short and tolerable palpitations may represent a favorable exit of ablation. So some "partially responder" patients could return to a satisfactory quality of life and to a limited symptomatic "arrhythmic burden".

This more lenient judgment of the clinical outcome of a therapy for drug-induced AFL patients is related to the essential role played by drugs in reducing the symptomatic "arrhythmic burden" and to a higher safety pro-

file of isthmus ablation in comparison to other more risky (even if more effective) procedures, such as left atrial ablation[25].

AF episodes are very frequently silent (in almost 50% of patients)[26-28]. A seeming cure of AF may simply represent the conversion of early symptomatic to subsequently asymptomatic disease. Adequate tools of the detection of asymptomatic arrhythmias (not limited to intermittent "snapshot" ECGs every month) could be relevant in coming to a decision on continuing drug therapy or performing long-term anticoagulation therapy.

Limits and perspectives of combined therapy

Potential limitations should be kept in mind in the management of patients by combined therapy.

Patients should be carefully evaluated for adverse side effects before initiation of therapy involving IC drugs or amiodarone[9].

The presence of significant structural heart disease or ventricular dysfunction for IC drugs and the development of hyperthyroidism or pulmonary toxicity for amiodarone should be carefully excluded. IC drug administration has to be combined with an adequate control of the ventricular rate, in case of recurrences of AFL, should either an atypical, not isthmus-dependent (and therefore not preventable by right isthmus ablation) AFL recur during follow-up (with its inherent risk of ventricular acceleration and hemodynamic or electrical instability).

New atrial selective antiarrhythmic agents (such as K_{ur}-channel blockers)[29] might selectively influence the atrial electrophysiology without any associated impact on ventricular proarrhythmia or ventricular function. This might render safer a combined therapy even at high doses, although it will require confirmation in ongoing large-scale clinical trials.

Another main limitation is that only a minority of AF patients tends to develop the organization of the arrhythmia into AFL and can eventually benefit from combined therapy.

Conclusions

Some patent clinical characteristics (such as conversion of AF into a typical AFL) identify a small subgroup of patients with AF probably related to the effects of drugs on conduction block lines in the posterior right atrium, chemical isolation of thoracic veins and suppression of small reentry functional circuits in the atria.

It would be desirable for other unidentified subgroups of patients (such as vagally or adrenergically induced, and so on) to discover some relevant electrophysiological mechanisms and consequent clinical characteristics for selecting the best and individualized therapeutic approach to the arrhythmia.

Combined therapy should be chosen as first-line therapy for patients with drug-induced AFL, when it is the only or predominant atrial arrhythmia on antiarrhythmic drugs, if undesirable drug effects have not been observed and are not expected to occur during long-term treatment.

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