Hybrid therapy for atrial fibrillation

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In some patients with atrial fibrillation stand-alone therapy with drugs, pacemaker or catheter ablation is not able to sufficiently suppress recurrences. Therefore, combined use of either strategies has been introduced using two or more therapeutic approaches in order to augment clinical benefit. Among these, the simultaneous use of antiarrhythmic agents and ablation has been shown to improve the atrial fibrillation burden by promotion of atrial fibrillation to atrial flutter with drugs and consecutive isthmus ablation. Other studies using preventive pacing could document a significant improvement of symptoms and AF burden with additional drugs.

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Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia, especially in the elderly, and has an important impact on morbidity, quality of life and health care costs. Furthermore, it is associated with an increased risk for arterial embolism, often leading to a significant degree of disability. The predominant therapies for patients with AF in its paroxysmal, persistent and permanent form are still antiarrhythmic drugs and electrical cardioversion. However, new approaches such as preventative pacing, the atrial defibrillator and focal or linear catheter ablation have been developed for a subgroup of patients, depending on the mechanism of AF initiation or refractoriness to drug therapy. Most of these therapies are still used as an adjunct and do not render drug treatment obsolete. The concomitant use of drugs and pacing or ablation has recently been named ‘hybrid treatment’. Primarily, this term indicates the combined use of, for example, bi-atrial or bifocal pacing and antiarrhythmic agents, or focal pulmonary vein ablation and drugs. The only true conceptional ‘hybrid approach’, however, is the modification of AF to atrial flutter with isthmus dependency and the subsequent ablation of the inferior right isthmus to reduce the incidence of AF (Fig. 1).

Class IC drug-induced atrial flutter in patients with atrial fibrillation

The concept of treating patients with AF by linear ablation of the inferior isthmus and a class IC drug was developed following observations in patients who received propafenone or flecainide intravenously and converted to atrial flutter with isthmus dependency, proven by right and left atrial activation mapping and entrainment pacing. Furthermore, patients treated permanently with oral propafenone or flecainide presented with typical atrial flutter as a subsequent arrhythmia recurrence. This led to systematic testing of patients in AF by several working groups...
(i.e. studying intravenous administration of a class IC drug during AF). The investigators reported varying percentages of responders. The concept behind this treatment is the hypothesis that, by using class IC drugs, transversal conduction blocks the crista terminalis, and the slowing of isthmus conduction and the change in wavelength of fibrillation cycles lead to an inability to maintain fibrillation. Numerous authors have consistently shown both conduction through the crista terminalis and complete conduction block after the use of, for example, disopyramide (Fig. 2).

According to the literature, approximately 5—20% of patients are responders to propafenone or flecainide and convert to atrial flutter. However, there are still no large, prospective investigations that have used continuous Holter or loop recordings to ensure reliable information on the true rate or character of arrhythmia recurrence after treatment with a class IC drug for AF.

Schumacher et al.1 reported on a series of 187 patients from an AF registry who were treated with either oral flecainide or propafenone. Of these patients, 12.8% developed atrial flutter during follow-up. Electrophysiological study then revealed typical atrial flutter in 20 patients (10.7%). All patients underwent right atrial linear isthmus ablation. The rate of recurrence of atrial flutter or AF was assessed with a serial questionnaire and Holter recordings. During a mean follow-up of 11 ± 4 months, the group treated with ablation and a class IC drug exhibited a significantly lower rate of recurrence of AF than that in the group of patients who were treated with an antiarrhythmic drug alone, or in comparison with the rate of recurrence before therapy.

These findings were supported by Nabar et al.,2 who studied the effect of additional isthmus ablation for atrial flutter in 24 consecutive patients presenting with AF who developed atrial flutter after intravenous administration of propafenone or flecainide. In these patients, 54% had typical atrial flutter, eight patients had atypical atrial flutter and three patients had coarse AF. Acute bidirectional block during the ablation procedure could be achieved in 23 of the 24 patients. During a mean follow-up of 13 months (6—26 months), improved control of AF was present in 11 of the 13 patients with typical atrial flutter and in four of the eight patients with atypical atrial flutter during initial propafenone or flecainide administration. It is interesting that the difference in clinical success between the two groups was not statistically significant.

In a larger study conducted in 82 consecutive patients, Nabar et al.3 studied patients with documented typical atrial flutter with or without concomitant AF. In their series, linear isthmus ablation was performed in all patients. The clinical success was assessed for four different groups: patients with atrial flutter only (n = 29), patients with more atrial flutter than AF (n = 22), patients with more AF than atrial flutter (n = 15) and ‘hybrid’ patients who developed atrial flutter with a class IC drug (n = 16). In general, a low rate of recurrence of AF was observed in this patient population, with the lowest rate in the ‘hybrid’ patient group. Of the ‘hybrid’ patients, 73% were free of any recurrence within a 4 ± 2 month follow-up period. First, the authors concluded that linear lesions in the inferior isthmus do not act pro-arrhythmically in terms of creating AF. Second, they stated a potentially beneficial impact of inferior isthmus ablation, because there seemed to be a subgroup of patients in whom the isthmus has a major role to play in the initiation or perpetuation of AF.

In a report by Huang and coworkers4 on 13 patients who converted to either typical or atypical atrial flutter following antiarrhythmic drug treatment, a total of 88.9% of the patients remained in sinus rhythm after successful ablation of the inferior isthmus.

In another very interesting report, Philippon et al.5 studied the risk for recurrence of AF in patients who had atrial flutter as the major clinical problem and AF as a concomitant arrhythmia. In their series of patients, after isthmus ablation of atrial flutter, they observed a recurrence of atrial flutter in 5.9% of the patients and recurrence of AF in 26.4%. According to those investigators, none of the patients were treated with any antiarrhythmic drug. They concluded that linear isthmus ablation does not reduce the risk for AF during follow-up. However, it would be of great interest to know the incidence of AF under drug treatment with propafenone or flecainide.

**Fig. 1** Concept of hybrid therapy for atrial fibrillation. After promotion of atrial fibrillation to isthmus-dependent atrial flutter, linear inferior isthmus ablation is performed to convert to sinus rhythm.
The above-mentioned experience in patients who convert to atrial flutter after administration of a class IC drug suggest that the hybrid approach is very promising for a subgroup of patients with AF. However, there has been only one prospective study in which the true percentage of responders was assessed using a prospective protocol. Stabile et al. tested whether long-term success of hybrid therapy may be predicted by response to flecainide infusion. In 71 consecutive patients with paroxysmal or persistent AF, they demonstrated that patients in whom fibrillation was promoted to atrial flutter by infusion of flecainide 2 mg/kg body weight and who underwent isthmus ablation and oral flecainide treatment have a significantly lower risk for AF during follow-up. Hybrid therapy was superior to oral flecainide only and ablation only. In a retrospective analysis conducted by Riva and coworkers in 305 patients with paroxysmal AF, 14.6% of the patients developed type I atrial flutter with antiarrhythmic drugs. There is a need for prospective studies to provide support for these findings and to add further information about the extent to which the acute effects of flecainide or propafenone, in terms of flutter induction, predicts the long-term behaviour of atrial electrophysiology.

**Pacing and drug treatment**

Pacing therapy for the prevention of AF has been used clinically and in numerous clinical trials, especially in patients with sick sinus syndrome. Newer studies using bifocal pacing at the coronary sinus orifice or Bachmann's bundle, or stimulation in the distal and proximal coronary sinus aimed at optimization of atrial repolarization and improvement in inter-atrial conduction times have not yet proven the clinical success of these approaches. In the Pa(3) study, a prospective randomized trial comparing the efficacy of DDDR pacing vs VDD pacing after atrioventricular node ablation in patients with paroxysmal AF, no benefit could be demonstrated for dual chamber rate adaptive (DDDR) pacing vs single chamber ventricular (VDD) pacing, but an increase in AF burden for both groups and a significant number of patients who developed persistent AF during follow-up was shown. This very stringently conducted study emphasizes that pacing alone is not sufficiently effective in reducing arrhythmia burden in patients with paroxysmal AF.

Delfaut et al. reported on a series of 30 consecutive patients with bifocal atrial pacing (right atrium and coronary sinus orifice) in whom...
AF recurrence could be reduced by pacing and additional antiarrhythmic drugs, predominantly class III agents. They stated that the combination of antiarrhythmic drugs and atrial single-site or dual-site pacing should be applied simultaneously to control AF. This is consistent with the experience from other trials, in which dual-chamber pacing was not superior to single-chamber pacing with respect to efficacy in preventing AF. There are further ongoing studies assessing the effect of overdrive suppression, anti-extrasystole pacing modes and antitachycardia pacing together with rate smoothing algorithms. Most of these studies are designed to assess the effect without any antiarrhythmic drug. The Atrial Tachyarrhythmia Prevention by Antitachycardia Pacing and Rate Smoothing Therapy (APART) study is an ongoing trial in which 200 patients with a class I pacemaker indication and paroxysmal atrial tachyarrhythmias are randomized to receive preventative pacing and atrial antitachycardia pacing with a beta-blocker (the only allowed concomitant antiarrhythmic drug) and dual chamber (DDD) pacing only. This study will show the effect of pacing alone on the recurrence of atrial arrhythmia and provide an answer as to how many patients need an additional specific antiarrhythmic drug to better control the recurrence of atrial tachyarrhythmia together with pacing features.

### Combined antiarrhythmic drug use

The most commonly used antiarrhythmic drugs for maintaining sinus rhythm in patients with AF are class IC drugs, class III drugs and beta-blockers. However, these drugs are almost always used as a stand-alone therapy. In patients with frequent recurrences of AF and increased sympathoadrenergic tone, the combination of a beta-blocker and a drug such as flecainide or propafenone may be useful to impact positively on heterotopy and repolarization, and reduce right and left atrial pressure and wall stress. There is no contraindication to combined use in the absence of structural heart disease or reduced left ventricular function, even though combined use is only rarely practiced. The same is true for amiodarone and beta-blockers, which is a combination that may safely be given to patients with an implantable defibrillator but not to patients with lone AF. In the literature there is limited information on the numbers of patients receiving more than one drug at a time for treatment of AF.

### Pulmonary vein ablation and drugs

The most recent approach to the treatment of AF in a subgroup of patients is focal radiofrequency ablation in patients with pulmonary vein ectopy triggering AF. The success rate with this new technique is reported to amount to a maximum of 50% in selected patients using different approaches such as focal radiofrequency ablation within the veins, encircling of the veins from within the left atrium, or segmental ablation at the venous orifice. However, Haissaguerre et al. stated that additional antiarrhythmic drug treatment is necessary in many of these patients to increase clinical success. This is attributed especially to extrapulmonary triggers within the left atrium, which are extremely difficult to ablate.

### Conclusion

Because anti-bradycardia pacing and ablation have not proven to be sufficiently effective when used as a stand-alone therapy in the prevention of AF on a larger scale, combined therapy using these non-pharmacological approaches and antiarrhythmic drugs may be the approach of choice for many patients. One possible way to achieve clinical and symptomatic improvement in a subgroup of patients with AF is a hybrid therapy with a class IC drug and linear isthmus ablation. However, further studies in larger patient populations using this therapeutic approach must be performed to assess the potential benefit of right atrial lesions and antiarrhythmic drugs. Finally, concomitant use of beta-blockers and class IC drugs must be tested with respect to tolerability and safety, because they may represent a promising combination of agents aimed at atrial haemodynamics, excitability and refractoriness, and thus address both initiation and perpetuation of AF.

### References


