The complementary role of drug, ablation and device in the electrical therapy of atrial fibrillation

A. Capucci, G. Q. Villani, N. Marrazzo and M. Piepoli

Divisione di Cardiologia, Ospedale Civile, Piacenza, Italy

Atrial fibrillation (AF) is the most common sustained arrhythmia. Current therapies, including pharmacological treatment, radiofrequency ablation and implantable devices, showed significant limitation when used alone. Recently a number of combined therapies (hybrid therapy approach) were suggested. Radiofrequency ablation may improve the efficacy of drugs, pacing and automatic internal defibrillators. Antiarrhythmic drugs may play a similar role, enhancing preventive atrial pacing effectiveness as well as sinus rhythm restoration capabilities of cardioversion shocks and antitachycardia pacing. The availability of a wide range of therapeutic options suggests that the approach to the treatment of AF needs to be selected on an individual basis.

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Introduction

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia, and is often associated with heart failure and thromboembolism. Preventive treatment would avoid progression of AF and would reduce the incidence of complications; therefore, in patients with recurrent and symptomatic AF episodes, or who are otherwise significantly disabled by AF, the maintenance of normal sinus rhythm should be the primary aim. Even once AF is established, it is well known that the shorter the duration, the easier it becomes to restore normal electrophysiological properties.

Clinical experience indicates that monotherapeutic approaches (drug, ablation or device) are often associated with unsatisfactory results in the treatment of AF patients. Because all therapies have poor efficacy when considered alone, interest in the role of combinations of therapies (hybrid therapy) has recently increased. The rationale underlying hybrid therapy is that a combination of modalities of intervention in AF might have a synergistic effect, with the efficacy of each intervention building upon that of the others. At present this concept is considered particularly in the prevention of AF recurrence, but hybrid therapy has also been utilized both in facilitating restoration to sinus rhythm and in control of heart rate.

The present overview summarizes the indications and preliminary findings with several different hybrid therapy approaches in different AF clinical settings.

Limitations of monotherapy

Drug therapy has poor long-term efficacy when used alone, with 50–70% of patients eventually progressing to chronic AF. It also carries a risk for proarrhythmia and may increase mortality, especially in patients with left ventricular dysfunction.

Catheter-based radiofrequency ablation procedures, which are aimed at curing chronic AF, with the exception of focal, paroxysmal AF originating in pulmonary veins, have limited application because of excessive procedure time, the need for left atrial ablation (which carries the potential risk for major complications including stroke) and limited long-term success. Limited right atrial ablation is a safe and technically simpler procedure, but (with occasional exceptions) it is ineffective in curing AF.

Single-site permanent atrial pacing has a positive therapeutic outcome in the case of AF that appears after sinus pauses. Unfortunately, this type of AF is uncommon. Taking a wider view of the antiarrhythmic effect of atrial pacing in the paced population as a whole, it is clear that the benefits are not rigorously established and that the common perception until recently was based on retrospective, observational studies that were of low statistical power.
rationale for biatrial pacing, and for dual-site right atrial pacing, derives from the fact that intra-atrial and inter-atrial delays are essential to the initiation and maintenance of the intra-atrial re-entrant mechanisms that underlie AF. The validity of this has been tested in acute studies of inducible arrhythmia, but primary verification by long-term, prospective, properly randomized trials is still awaited.

Although the implantable atrial defibrillator appears to be highly effective in restoring sinus rhythm, many unresolved issues remain\[15,16\]. Because the shocks for atrial defibrillation are delivered to conscious, ambulatory patients, tolerance is poor. In addition, the ideal candidate for this therapy and whether anticoagulation is needed have not yet been established.

**Hybrid therapy in preventing recurrences of atrial fibrillation**

Radiofrequency ablation and pacing or drugs

Radiofrequency ablation may be used to modify the electrophysiological pattern of AF by improving the efficacy of pacing or drug therapy in preventing arrhythmia recurrence. The first demonstration of this was provided by Warman et al.\[18\] in 1999. In an animal model, a ‘Y’ lesion created by limited radiofrequency ablation restricted to the right atrium changed the pattern of AF to a ‘flutter-like’ one, with a consequent improvement in the ability of atrial pacing to terminate arrhythmias.

Few data are available in humans regarding the combination of radiofrequency ablation with pacing. Prakash et al.\[19\], in a small clinical study involving 12 patients with refractory AF, observed that the combination of atrial pacing (single- and dual-site) and radiofrequency ablation (linear lesion) in the right atrium prevented recurrences in 10 out of 12 patients after a 31-month follow up.

More data are available on the effects of the combination of radiofrequency ablation with drug therapy, particularly in those patients with AF in whom atrial flutter develops after administration of class IC or III antiarrhythmic drugs (Fig. 1). In an abstract, Schumaker et al.\[20\] reported on 190 patients who had AF and were treated with intra-coronary antiarrhythmic drugs, approximately 13% of whom had recurrences of flutter. After radiofrequency ablation, 40% of the patients did not experience symptomatic recurrence and a further 40% had a marked reduction in AF recurrences, suggesting that in some cases atrial flutter may precipitate AF. However, approximately 15–20% of the patients did not benefit from this approach. Reithmann et al.\[21\] described their experience with radiofrequency catheter ablation of the isthmus in patients with atrial flutter after amiodarone therapy for treatment of paroxysmal AF. Those investigators compared their findings in those patients with the results of isthmus ablation in patients with isolated atrial flutter and in patients with both atrial flutter and AF before isthmus ablation.

More recently, Stabile et al.\[22\] tested the hypothesis that isthmus radiofrequency ablation would reduce AF recurrence in patients in whom acute flecainide infusion promotes the transformation of AF to atrial flutter. In a population of 71 patients, those investigators created a complete bidirectional conduction block at the inferior caval vein (i.e. tricuspid anulus isthmus). The combination of the intervention with flecainide therapy in this group of patients significantly reduced the recurrence of AF as compared with the antiarrhythmic treatment alone.

In conclusion, radiofrequency ablation of the right atrial isthmus may result in clinical improvement in the majority of patients, and may represent an alternative management strategy for a subset of patients with therapy-resistant AF.

**Ablation and internal atrial defibrillation**

The effect of radiofrequency ablation on the atrial defibrillation threshold was recently investigated. Lesh et al.\[23\] tested the hypothesis that linear atrial lesions, by increasing the ‘organization’ of AF, would decrease the atrial defibrillation thresholds in dogs with AF induced by
rapid atrial pacing. In this animal model creation of linear right atrial lesions led to a greater degree of global spatio-temporal organization, as indicated by an increase in AF cycle length and decrease in dispersion of cycle lengths in both atria, despite lesions being present in the right atrium alone. Those investigators did not observe any change in the effective refractory period and suggested that the slower, more organized AF was presumably the result of fixed barriers forcing a longer path length. Furthermore, there was also a significant reduction in atrial defibrillation threshold, presumably as a result of this improved organization. This hybrid therapy approach could thus be an option in the future for those patients implanted with an automatic internal defibrillator.

Drugs and pacing

It has been suggested that the antiarrhythmic drugs may improve the efficacy of cardiac pacing in preventing AF, by increasing the percentage of paced beats and by impacting on the factors that initiate AF. Several non-controlled studies of this hybrid therapy approach have been reported.

Defaut et al.,[24] conducted a crossover study in 30 patients with drug-refractory AF. They compared dual-site and single-site right atrial pacing, and examined the efficacy of two right atrial lead implantation sites (high right atrium and coronary sinus ostium) in long-term cardioversion, and of antithrombotic and antiarrhythmic drug therapies (classes I and III) during dual-site atrial pacing. Those investigators observed that atrial pacing in combination with antiarrhythmic drugs eliminated or markedly reduced AF recurrence, and that dual-site right atrial pacing enhanced prevention of AF. Saksena et al.,[25] investigated the feasibility, safety and efficacy of multisite right atrial pacing for preventing AF, and the ability of single-site and dual-site atrial pacing to increase arrhythmia-free intervals in patients with drug-refractory AF. Atrial pacing resulted in a marked decline in AF recurrences (P < 0·001). There were no AF recurrences in any patient during dual-site pacing with an optimal drug regimen, as compared with five recurrences in 12 patients during single-site pacing (P = 0·03). The mean arrhythmia-free interval before pacing (14 ± 14 days) was prolonged with dual-site (89 ± 7 days; P < 0·0001) and single-site pacing (76 ± 27 days; P < 0·0001). Symptomatic AF episodes exhibited a declining trend during dual-site and single-site pacing as compared with those during the pre-implantation period (P = 0·10).

Mean antiarrhythmic drug use (classes I and III) for all causes declined from 4 ± 1·9 drugs before implantation to 1·5 ± 0·5 (P < 0·01) drugs after implantation. Twelve (80%) out of 15 patients remained in atrial paced rhythm at 13 ± 3 months.

Because of the lack of prospective studies on the efficacy of this hybrid therapy, the Drug and Pace Health Clinical Evaluation (DAPHNE) study was initiated and is ongoing. This is a prospective, multicentre, randomized study to evaluate long-term results with an antiarrhythmic therapy (beta-blocker versus sotalol) in AF patients with a single-site DDDRP device, with prevention algorithms and automated antitachycardia pacing therapies (Medtronic AT500; Medtronic Inc., Minneapolis, MN, U.S.A.).

In conclusion, the combination of antiarrhythmic drugs with cardiac pacing may be considered a valid hybrid approach in patients with AF that is refractory to drug therapy alone.

Hybrid therapy in sinus rhythm restoration

Drugs and external or internal cardioversion

Antiarrhythmic drugs have been tested in order to improve the efficacy of external or internal electrical cardioversion, reducing the atrial defibrillation threshold.

Oral et al.,[26] examined the effect of ibutilide (a class III antiarrhythmic agent) on the energy requirement for external atrial defibrillation, and assessed the value of this agent in facilitating cardioversion in patients with AF that is resistant to conventional transthoracic cardioversion. In 100 patients with persistent AF, pre-treatment with ibutilide (1 mg) was associated with an efficacy of 100% in sinus rhythm restoration; also, in all 14 patients in whom transthoracic cardioversion alone failed, sinus rhythm was restored when cardioversion was repeated after administration of ibutilide. Furthermore, pre-treatment with ibutilide was associated with a reduction in the mean energy required for defibrillation (166 ± 80 vs 228 ± 93) without pre-treatment; P < 0·001.

Boriani et al.,[27] evaluated the effects of intravenous flecainide on defibrillation energy requirements in patients treated with low-energy internal atrial cardioversion. They observed a favourable effect of flecainide both in persistent (13 patients) and in paroxysmal AF (five patients), with significant reductions in energy requirements for effective defibrillation (persistent AF, from 4·42 ± 1·37 to 3·50 ± 1·51 [P < 0·005]; paroxysmal AF, from 1·68 ± 0·29 to 0·84 ± 0·26 [P < 0·01]). This resulted in a significant reduction in scores for shock-induced discomfort (3·71 ± 0·83 versus 4·29 ± 0·61 [P < 0·005]).

Capucci et al.,[28] in a controlled randomized study, assessed the effectiveness of electrical cardioversion in patients with persistent AF after pre-treatment with amiodarone as compared with potassium infusion. In that study, conducted in a population of 92 patients, electrical cardioversion was more successful after amiodarone pre-treatment (88% versus 56%), but pre-treatment had no influence on electrical threshold.

In conclusion, the combination of specific antiarrhythmic drugs with electrical cardioversion may improve the chance of sinus rhythm restoration in patients with persistent AF, either with external monophasic or internal biphasic shocks.
Drugs and internal automatic defibrillator

In patients implanted with an atrial defibrillator, antiarrhythmic drugs are employed in order to limit patient exposure to high-energy shocks (to make shock therapy more tolerable). They achieve this primarily by reducing the number of arrhythmia recurrences (fewer shocks), by suppressing coexisting arrhythmias, by affecting rate and organization of tachycardias (in order to improve the effectiveness of atrial pacing therapies), and by increasing the efficacy of painless pacing therapies.

Recently, Santini et al.[29], for the Medtronic 7250 Italian Registry, reported experience in a population of 91 patients treated with antiarrhythmic drugs and implanted with a dual-chamber implantable defibrillator (model 7250, Medtronic Inc.). The device is able to detect and treat atrial tachycardia and AF automatically by antitachycardia pacing (featuring ramp, burst+ and 50-Hz burst) and low-energy cardioversion. The painless antitachycardia pacing therapies were highly effective in terminating atrial tachycardia, but had only a mild effect on AF. It was possible to convert AF to sinus rhythm by high-frequency atrial pacing (50 Hz) in only 15% of cases, whereas the efficacy in the case of atrial tachycardia was 72%. It is possible that antiarrhythmic drugs may slow and regularize the AF cycle, improving the efficacy of atrial pacing therapies.

Pacing and electrical cardioversion

Lesh et al.[23] reported the ability of pacing to entrain AF regionally, resulting in a more organized atrial arrhythmia. Those authors suggested that, in the case of a ‘regular’ AF, a lower threshold for endocardial defibrillating shocks might be anticipated, and they had occasionally observed this.

More recently, Villani et al.[30] evaluated the impact of atrial entrainment in induced AF on defibrillation threshold, and reported a significant decrease in energy requirement for restoration of sinus rhythm associated with stable atrial capture. Synchronization of energy delivery to both the ventricular and atrial complexes could potentially result in a lower defibrillation threshold.

Further work is needed in order to confirm whether single-site or multisite regional entrainment may be considered an effective hybrid therapy to lower the atrial defibrillation threshold.

Hybrid therapy in rate control

The ‘ablate and pace’ strategy may be considered a viable hybrid viable strategy in the palliative management of patients with medically refractory, highly symptomatic AF (Table 1).[31-38] The clinical efficacy of ablate and pace therapy in controlling arrhythmia symptoms and improving overall quality of life is well established in patients with paroxysmal AF, although not yet for patients with persistent and permanent AF because of the limited number of clinical studies. Several authors have reported that ablate and pace therapy is associated with a significant improvement in quality of life and left ventricular function, particularly for those patients with left ventricular ejection fraction below 45% at baseline.

At present, class I indications for this hybrid strategy include drug-refractory paroxysmal AF that is associated with significant symptoms, bradycardia-tachycardia syndrome that has already been treated with a pacemaker, and continued paroxysmal AF. The recommended pacing mode in these patients is DDDR with mode switching,[39,40].

Table 1  Ablate and pace strategy results

<table>
<thead>
<tr>
<th>Authors [reference]</th>
<th>Year</th>
<th>Patients</th>
<th>QoL</th>
<th>LVEF</th>
<th>NYHA</th>
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<tr>
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<td>23</td>
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<tr>
<td>Edner et al.[32]</td>
<td>1995</td>
<td>29</td>
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<td>+</td>
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<tr>
<td>Natale et al.[34]</td>
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<td>14</td>
<td>+</td>
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<tr>
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<tr>
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<td>156</td>
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<td>155</td>
<td></td>
<td>+</td>
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</tr>
</tbody>
</table>

Improvement in a parameter is denoted by ‘+’, whereas deterioration is denoted by ‘-’. *Baseline ejection fraction <45%. LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; QoL=quality of life.

Conclusion

At present, clinical use of hybrid approaches is mainly limited to the prevention of AF recurrence.

We have developed a stepwise strategy based on our own experience, because no data from prospective studies of the efficacy of hybrid therapy are available. In case of a first AF episode, we propose that in-hospital pharmacological conversion should be performed as soon as possible. After restoration of sinus rhythm (spontaneous or with electrical cardioversion), a blood sample should be drawn and echocardiography, Holter ECG and stress test (if older than 50 years) performed; no antiarrhythmic therapy should be administered at this stage. After a second AF episode within 4 months, a first-choice antiarrhythmic drug should be considered (Table 2); a second-choice antiarrhythmic drug should be considered if a third episode of AF occurs within the following 4 months. In patients with recurrent AF despite antiarrhythmic drug therapy, we suggest an electrophysiological study to guide selection of hybrid therapy for treatment of AF (Fig. 2).

In conclusion, we believe that sinus rhythm, in AF patients, should probably be maintained in order to prevent stroke, eliminate need for warfarin, improve haemodynamics and relieve symptoms. There is no single approach to the treatment of AF, and its management needs to be individually selected.
The mainstay of managing AF is drug therapy. In patients in whom AF cannot be adequately managed by pharmacological therapy, the most appropriate type of non-pharmacological therapy must be selected on an individual basis. In a patient who requires an implantable cardioverter-defibrillator and who experiences occasional episodes of AF, implantation of a device that is capable of both atrial and ventricular defibrillation should be considered. Only if all reasonable attempts to maintain sinus rhythm have failed would we accept the final option - anticoagulation and rate control.

Table 2  Currently available drugs for maintenance of sinus rhythm

<table>
<thead>
<tr>
<th></th>
<th>No structural heart disease</th>
<th>Left ventricular hypertrophy (mild to moderate)</th>
<th>Ischaemic heart disease</th>
<th>Congestive heart failure</th>
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<tbody>
<tr>
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<td>Propafenone</td>
<td>Propafenone</td>
<td>Sotalol</td>
<td>Amodarone</td>
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<tr>
<td></td>
<td>Flecainide</td>
<td>Flecainide</td>
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<td></td>
<td>Sotalol</td>
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<td>Second choice</td>
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Figure 2  Electrophysiological study guided management of atrial fibrillation refractory to drug therapy alone. First column shows possible study findings leading to different hybrid approaches. IAD=implantable atrial defibrillator; RA=right atrium.

References


