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Management of patients with atrial fibrillation: different therapeutic options and role of electrophysiology-guided approaches

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Summary. - At present the approach to atrial fibrillation treatment is based on the electrophysiological patterns of atrial fibrillation (on the basis of multiple intra-atrial recordings or sophisticated new mapping techniques) only in a restricted minority of patients, those who are candidate to ablation of the substrate and/or of the triggers. Atrial fibrillation has a broad spectrum of clinical presentations and a heterogeneous electrophysiological pattern. The treatment of this arrhythmia, both with drugs and non pharmacological treatments, has been based, classically, on empirical basis and on a clinically-guided staged-approach. The limitations of pharmacological treatment led in recent years to the development of a wide spectrum of non pharmacological treatments. This implies a change in the approach to atrial fibrillation and the need to identify potentially ideal candidates to complex and expensive treatments. In this view it is currently under investigation the possibility to identify potential responders to a definitive treatment or a combination of treatments (both pharmacological and non-pharmacological) on the basis of the electrophysiological pattern.

Key words: atrial fibrillation, atrial defibrillation, electrophysiology, endocardial mapping, remodeling.

Riassunto *(Trattamento dei pazienti con fibrillazione atriale: opzioni terapeutiche e ruolo di un approccio elettrofisiologico).* - Attualmente, il trattamento della fibrillazione atriale si basa sull'analisi del pattern elettrofisiologico solo in una ristretta popolazione di pazienti, i candidati a procedure di ablazione del substrato e/o dei trigger. La fibrillazione atriale ha un ampio spettro di presentazioni cliniche e un eterogeneo pattern elettrofisiologico. Il trattamento farmacologico e non farmacologico di questa aritmia è stato impostato classicamente su basi empiriche e su un approccio clinico a gradini. La limitata efficacia dei trattamenti farmacologici ha condotto, negli ultimi anni, allo sviluppo di una ampia gamma di trattamenti non farmacologici. Tutto ciò implica un cambiamento nell'approccio alla fibrillazione atriale e la necessità di identificare a priori i potenziali responder a trattamenti complessi e costosi. In quest'ottica è attualmente oggetto di studio la possibilità di identificare, sulla base del pattern elettrofisiologico, i potenziali responder a un trattamento curativo o a una combinazione di trattamenti (farmacologici e non farmacologici).

Parole chiave: fibrillazione atriale, defibrillazione atriale, elettrofisiologia, mappaggio endocardico, rimodellamento.

Introduction

Apart atrial and ventricular ectopic beats, atrial fibrillation (AF) is the most frequently occurring cardiac rhythm disturbance. Its prevalence in the population increases with age: it is 2 to 3 per 1000 between 25 and 35 years, 30 to 40 per 1000 between 50 and 64 years, and 50 to 90 per 1000 between 62 and 90 years [1]. In the Framingham study, in a 22 to 30-year follow-up, the incidence of AF was observed to increase progressively with age, with a modest male predominance, and overall the chance of developing this arrhythmia over two decades was 2% [2].

The social costs caused by AF are relevant: in the United States AF caused far more hospital admissions than any other arrhythmia, accounting for almost a million days spent in hospital per year [3].

AF may occur in different clinical forms, referred as paroxysmal, persistent and permanent AF (Table 1) [4, 5]. For the treatment of AF three main goals have to be considered: 1) maintenance of sinus rhythm by preventing AF recurrences; 2) rate control during AF; 3) prevention of AF-related thromboembolic risk.

For the first two goals both pharmacological and non pharmacological treatments can be used, alone or in combination. The choice about the most appropriate

Table 1. - Options for AF treatment in different types of AF. (Modified from [3]).

	Paroxysmal AF	Persistent AF	Permanent AF
Arrhythmia characteristics	Terminates spontaneously	Will not terminate spontaneously but can be converted to SR	Will not terminate spontaneously, cannot be converted to SR
Short-term treatment goal	Rate control	Cardioversion to SR Rate control	Rate control
Long-term treatment goal	Prophylaxis of AF recurrences	Prophylaxis of AF recurrences Rate control	Rate control
Potential treatments	AA drugs for prophylaxis Preventive pacing Ablation Atrial defibrillator	AA drugs for conversion External CV Internal CV Atrial defibrillator AA drugs for rate control AA drugs for prophylaxis Preventive pacing Pacing to stop AF	AA drugs for rate control AV node modification AV node ablation + pacing Ablation

AF: atrial fibrillation; AA drugs: antiarrhythmic drugs; AV: atrioventricular; CV: cardioversion; SR: sinus rhythm.

treatment depends on several factors including arrhythmia characteristics, AF related symptoms, impairment of quality of life due to AF and concomitant heart disease. In Table 1 a summary of currently available therapeutic options is shown. Persistent AF may be a difficult field for patients' management. Indeed, the decision to try to maintain sinus rhythm or, alternatively, to limit treatment to rate control and prevention of thromboembolic risk, should be individualised for each patient, trying to assess the risk-benefit ratio in each clinical case.

The complexity of AF electrophysiology: its heterogeneity, dynamics and plasticity

AF is a heterogeneous disease and its heterogeneity is related to its clinical presentation (paroxysmal, persistent, permanent), its clinical evolution (ranging from a single episode to frequently recurrent episodes evolving to persistent AF) and its clinical relevance (ranging from none to acute hemodynamic impairment or development of tachycardiomyopathy with congestive heart failure).

Heterogeneity involves also the electrophysiological pattern. In order to analyse the degree of electrical organisation of AF, this arrhythmia was initially divided, on the basis of the pattern at surface electrocardiogram, into "coarse" and "fine" AF [6, 7]. Later Wells *et al.* [8] in a study based on recordings from unipolar epicardial electrodes positioned surgically in the right atrium, described 4 patterns of AF, with a variable degree of organisation of the signals and with possible transitions from one pattern to another even in a short time.

According to these preliminary observations, AF in humans resulted to have a heterogeneous patterns among different patients or ad seriatim in the same patient. A series of more accurate mapping studies in humans [9] showed that AF is sustained by different patterns of atrial activation correspondent to different types of re-entry or to focal activation [10].

A series of studies analysed intra-atrial recordings during AF for evaluating the patterns of spontaneous or pharmacologically induced AF termination [11-15] or the pattern of spontaneous or electrically induced AF onset [16].

Heterogeneity increases when mapping at multiple sites is performed [9, 17] and this finding may offer some insights into AF electrophysiological mechanisms. Indeed, multiple types of circuit may sustain AF perpetuation [10]: random reentry, leading circle reentry or repetitive focal activation [18]. The key question is how to assess easily, in the single patient, the electrophysiological mechanism sustaining AF persistence in order to guide the treatment (drugs, ablation, electrical treatment) with the aim to improve the efficacy in AF management.

Apart heterogeneity, also dynamics characterises the electrophysiological characteristics of AF with changes of its patterns occurring in a short time. Evaluation of atrial endocardial recordings shows that intracardiac organisation exists at AF onset but may evolve into new activation patterns in few beats, with arrhythmia perpetuation [16], and that the atrial cycles lengthens before termination in self-terminating paroxysmal AF [13].

Other changes in the electrophysiological pattern of AF occur at long term and this phenomenon is the expression of the plasticity of AF. The term "remodeling"

was initially introduced by Allessie's group [19] to indicate long term changes in atrial refractoriness resulting from prolonged changes in atrial rate. Today, remodeling indicates a complex series of electrophysiological and structural changes (Table 2) that induce a vicious circle leading to perpetuation of the arrhythmia ("AF begets AF") [20]. This phenomenon has been confirmed in humans [21, 22]. The electrophysiological changes are potentially reversible with restoration and maintenance of sinus rhythm but it is unknown how long the complete spectrum of electrophysiological/structural changes is fully reversible. Remodeling influences deeply the efficacy of our approach to AF management and improved knowledge of this complex phenomenon may provide new targets for prevention and treatment of AF [20].

The possibility to guide the treatment of AF on the basis of trigger/initiation pattern is critically challenged by the observation of the AF therapy trial, where a diagnostic pacemaker programmed at low rate was used to assess the pattern of onset of paroxysmal AF. In this study [23] multiple triggers were identified with important inter-individual and intra-individual variability of the onset pattern (a mean of 4.1 ± 2.5 different triggers per patient were observed).

Atrial fibrillation termination *versus* prevention of recurrences by antiarrhythmic drugs

Different antiarrhythmic agents, with disparate electrophysiologic effects, have been used for terminating AF episodes or for preventing AF recurrences [24-30]. For most patients it is prevention of AF recurrences rather than restoration of sinus rhythm that is the most difficult problem to solve.

A series of antiarrhythmic agents was demonstrated to be highly effective in terminating recent onset AF, with class 1C agents being the most effective [31, 32]. In contrast with the high efficacy in recent-onset AF, the results obtained in prophylaxis of AF recurrences are scanty [20, 33-35].

Different experimental models have been adopted for studying the effects of antiarrhythmic drugs in terminating experimental AF. According to the leading circle model [20] and the multiple wavelet theory [36], termination of AF was initially considered to be related to the ability to increase the wavelength of reentry circuits, by an increase in the size of individual reentry circuits and a decrease in their number. According to this hypothesis, when the number of reentry circuits is critically low, fibrillation can't maintain itself and stops by block in a single macroreentry circuit, by short-circuiting of reentry or by collision of wave fronts [36]. This hypothesis was recently questioned by new experimental observations of the same group [37]. Pharmacological cardioversion of AF with a series of class I or class III antiarrhythmic agents could not be explained by prolongation of the wavelength, meanwhile it was possible to interpret the data on the basis of a widening of the temporal excitable gap [37].

Reduction of inhomogeneity in atrial refractoriness is another important factor involved in the pharmacological effects leading to arrhythmia termination. Antiarrhythmic agents may exert frequency-dependent effects on conduction and refractoriness: flecainide and propafenone cause a rate-dependent increase in refractoriness, whereas sotalol has a reverse-rate dependent effect on refractoriness. It is of interest to consider that the efficacies of these drugs were correlated to the changes in refractoriness and wavelength produced at the rapid rates of AF and sotalol resulted less effective than flecainide and propafenone [36]. These experimental evidences suggest that class III antiarrhythmic agents with reverse rate-dependent effect on refractoriness would be of limited efficacy in terminating AF and this is in accordance with clinical

Table 2. - Time course of atrial alectrical remodeling and mechanisms involved

Time	Remodeling	Mechanism
Short-term (s/min)	Metabolic	Ionic gradient fluxes Ion pump activities Phosphorilation of ion channels
Medium-term (hours/days)	Electrical	Altered gene expression Altered protein synthesis Altered channel assembly
Long-term (weeks)	Contractile	Hibernation Stunning
Very long-term (months/years)	Anatomical	Irreversible structural damage Fibrosis Fatty degeneration Atrial dilation

observations [32]. The mechanism of AF prevention is partly different from arrhythmia termination; as known, atrial premature beats initiate AF by blocking in an area of longer refractoriness, resulting in a single macroreentry circuit followed by multiple focal zones of reentry causing AF [36]. The ability to lengthen atrial refractoriness during sinus rhythm may prevent atrial premature beats from initiating AF. Therefore, while class III antiarrhythmic agents with reverse rate-dependence may have limited efficacy in terminating AF, they may nonetheless be effective in preventing arrhythmia recurrences due to premature beats during sinus rhythm at normal slow rate. Indeed, a recent prospective trial [38] showed that amiodarone is more effective than sotalol or propafenone for the preventions of AF.

Maintenance of sinus rhythm *versus* control of ventricular response

In patients with AF, restoration of sinus rhythm by electrical or pharmacological cardioversion may eliminate palpitations, fatigue and dyspnea, may prevent left ventricular dysfunction and may significantly reduce thromboembolic complications. Unfortunately, because of the high recurrence rate, only 30% of the patients, without antiarrhythmic drug prophylaxis, maintain sinus rhythm for 6 months or more [39]. Therefore, attempts to maintain sinus rhythm by pharmacological prophylaxis of arrhythmia recurrences is required. Antiarrhythmic drugs may cause proarrhythmic effects or other adverse effects and for this reason this prophylactic strategy has to be considered as an alternative to another therapeutic strategy which is based only on ventricular rate control by appropriate drugs associated with antithromboembolic prophylaxis. Advantages and disadvantages of each therapeutic option are reported in Table 3.

The impact of these two different approaches to AF management is currently under evaluation in a controlled trial, named AFFIRM (AF follow-up investigation of rhythm management) [40].

Non-pharmacological treatments for AF

The limited efficacy of antiarrhythmic agents and the evidence that adverse effects including proarrhythmic effects may be caused by antiarrhythmic treatment led to the development of non-pharmacological treatments, whose cost-benefit profile is in most cases still under evaluation. Non pharmacological treatments developed in recent years for management of AF include atrial pacing, internal atrial cardioversion and catheter or surgical ablation procedures.

Atrial pacing for AF prevention

The effects of conventional atrial pacing in preventing AF recurrences need to be evaluated in patients with sick sinus syndrome at low risk of AF, in patients with brady-tachy syndrome at high risk of AF, and in patients with paroxysmal AF without significant bradycardia.

In the last 10 years a series of retrospective studies [41-46] showed that there was a higher risk of developing AF in patients with sick sinus syndrome paced in the VVI mode than in those paced in AAI or DDD. Sgarbossa *et al.* [47] in a retrospective study found that VVI pacing was associated to risk of developing chronic AF in patients with preimplant AF but not in those without it. The prospective randomised study reported by Andersen *et al.* [48], involving 225 patients, showed that more patients (23%) randomised to VVI pacing developed AF over a 40-month period than patients randomised to AAI pacing (14%). This difference, however, did not reach statistical significance.

In patients with sick sinus syndrome with an high risk of AF (brady-tachy syndrome) DDDR pacing achieved a significant reduction of AF episodes both in comparison to baseline and to DDD pacing [49]. In patients with AF, without symptomatic bradycardia, the possible mechanisms supporting a beneficial effect of pacing in AF prevention are: 1) prevention of bradycardia,

Table 3. - Alternative therapeutic strategies for atrial fibrillation management: advantages and disadvantages of each therapeutic option

Maintenance of sinus rhythm by antiarrhythmic drugs	**Control of ventricular rate + antithromboembolic prophylaxis**
Advantages	**Advantages**
Better hemodynamics	"Natural history"
Reduction in thromboembolic risk	Absence of relevant proarrhythmic effects
Disadvantages	**Disadvantages**
Risk of drug-related proarrhythmic effects	Worse hemodynamics
Risk of other drug-related adverse effects	Hemorragic risk due to anticoagulants
Need for repeated cardioversions (if partial efficacy)	Residual embolic risk

2) better adaptation of heart rate to exercise, 3) overdrive suppression of ectopic beats, 4) shortening of prolonged interatrial conduction due to atrial ectopic beats.

The ways to positively influence the risk of AF are related to: 1) pacing mode, 2) pacing rate, 3) pacing site (single site or multisite), 4) use of novel, dedicated pacing algorithms - consistent atrial pacing (CAP), atrial rate stabilization (ARS) or dynamic atrial overdrive (DAO) - and, finally, 5) use of pacing to stop AF episodes.

A great interest was developed in recent years on the effects of pacing site on the risk of AF. Indeed, the site of atrial pacing can impact on the development of AF in pacemaker patients. Multisite atrial pacing may favourably modify the atrial electrophysiological substrate in patients with paroxysmal AF [50, 51] or in animal studies [52]. These findings had important implications for applying, in the clinical setting, pacing techniques aimed to reduce inhomogeneities in atrial conduction and refractoriness and normalise atrial activation.

The incidence of AF appears to be higher with pacing from the right auricular lateral wall compared with pacing from the right auricular appendage [53], whereas pacing from the interatrial septum can reduce the interatrial conduction time and possibly prevent AF [54]. Intra and interatrial conduction delays are frequent in patients with AF. In this regard, right auricular appendage pacing appears to be more effective in preventing AF in patients with sick sinus syndrome without marked atrial conduction delay [55].

The search for better clinical results in terms of AF prevention led to test pacing in alternative sites (coronary sinus, coronary sinus os, interatrial septum) or to test dual/multi-site atrial pacing. Clinically, multisite atrial pacing has been achieved via biatrial pacing (one lead in the right auricular appendage and the other in the coronary sinus to pace the left atrium [56]) or via dual-site right atrial pacing (one lead in the appendage and the other in the interatrial septum just outside the coronary sinus ostium [57]). Pacing from the distal coronary sinus [50, 51] or its ostium [58] prevents the induction of AF by high right auricular premature depolarisations by limiting their prematurity at the posterior triangle of Koch and by not allowing local conduction delay and local re-entry to occur.

At present the translation of these observations into the clinical setting showed that multisite atrial pacing or pacing from alternative sites was more effective than single-site right auricular pacing when AF was associated to bradycardia [54, 59] but disappointing results were found in controlled studies when AF was not associated to bradycardia [60]. This finding stresses the need for further knowledge on the complex interaction between atrial pacing and the electrophysiological substrate favouring AF onset in specific subgroups of patients.

New pacing modalities for preventing AF recurrences include special algorithms to increase the rate of atrial pacing, thus leading to continuous overdrive pacing or for suppressing the pauses that follow an atrial ectopic beat [61]. These algorithms (CAP, ARS, DAO) are currently under evaluation and preliminary data seem promising [62]. Unfortunately the wide variability in AF onset pattern, also in the same patient [23] create some difficulties in identifying the most appropriate algorithm.

A new perspective of atrial pacing is related to the possibility to capture locally the atrium by high frequency stimulations [63]. These observations raise the possibility in the next future of rapid termination of AF through multi-site pacing. In this perspective, it is really interesting to consider the preliminary experience on the use of 50 Hz burst stimulation. In patients implanted with a dual chamber atrial defibrillator able to deliver antitachycardia pacing, 50 Hz bursts were able to terminate 33% of episodes classified by the device as AF episodes [64].

Internal atrial cardioversion

Atrial cardioversion (CV) can be performed by delivering biphasic shocks between transvenous catheters positioned within the cardiac chambers or great vessels.

Low energy internal atrial CV can be performed by two approaches: by placing the leads in right atrium (RA) and coronary sinus (CS), or left polmonary artery, in order to obtain defibrillating currents that preferentially encompass the atrial tissue or by placing the leads in RA and right ventricle (RV) with the same configuration used for ventricular defibrillation. The efficacy for terminating AF is very high, 92-100% for paroxysmal AF [65] and 77-100% for chronic persistent AF [66] with relatively low energy requirements, especially when dealing with paroxysmal AF. Delivery of shocks results in effective CV at energies below 6-10 joule and the procedure can be effective even when external CV has failed. Shock induced discomfort shows wide variability from patient to patient but the procedure can be performed without general anaesthesia, under sedation. Nevertheless, tolerability has to be improved by obtaining a substantial reduction in defibrillation thresholds. Atrial defibrillation threshold is usually evaluated in clinical studies by using a step up protocol and this implies some approximation in comparison with the methodology used for defibrillation threshold evaluation in animal studies. Apart clinical issues, atrial defibrillation threshold seems to be dependent on some technical issues such as electrode size [67], electrode positioning [68], electrode coil length [69, 70]; moreover atrial defibrillation threshold is more favourable when biphasic versus monophasic shock waveforms are delivered, when asymmetrical waveforms with the second phase shorter than the first phase are used [69] and when sequential shocks are delivered trough dual current pathways [71].

Atrial electrophysiological substrate is obviously important in conditioning the atrial defibrillation threshold during internal cardioversion. In transvenous cardioversion the atrial defibrillation threshold was higher in chronic AF than in paroxysmal AF [72]. In a recent study evaluating the predictors of atrial defibrillation threshold among a series of clinical, electrophysiological and echocardiographic parameters, only AF duration resulted to be an independent predictor of the atrial defibrillation threshold [73].

In an experimental model of AF, the remodeling of the atrial electrophysiological substrate that occurred after 8 hours of pacing-induced AF was associated with a significant increase in atrial defibrillation threshold [74]. Moreover, reverse remodeling of atrial refractoriness following internal conversion of AF was associated wiht a significant decrease of atrial defibrillation threshold [75].

Tolerability of shock induced discomfort is an intriguing problem because patients perception of pain is probably dependent on several factors: psychological status and patient conditioning, number of shocks delivered, energy delivered, shock waveform, leads positioning [69, 76, 77]. A great interindividual variability exists in shock induced discomfort and some patients report severe discomfort even after delivery of shocks at 0.1 joule of energy [71]. On the other hand, our group and others [76, 77] reported the feasibility of the procedure with no or mild sedation in a substantial proportion of patients.

Delivery of shocks for defibrillating the atria implies a potential risk of inducing ventricular fibrillation and cases of ventricular fibrillation following internal atrial CV have been reported [78]. To minimise this problem, delivery of the shocks in synchronous with the QRS is mandatory and moreover it's important to avoid shock delivery during rapid RR cycles (< 300 ms) because of tachycardia dependent inhomogeneity of repolarisation [79].

Following cardioversion of a chronic persistent AF, recurrences have a typical time course, with an early or very early phase of increased vulnerability [69]. Different electrophysiological, structural, clinical, autonomic and neurohormonal factors condition the risk of AF relapses following CV, but for recurrences occurring in an early phase (few hours) or in a very early phase (seconds, minutes) post-cardioversion, the electrophysiological factors may have a predominant role.

An electrical remodeling of atrial refractoriness has been described both in animal and human studies [19] and this phenomenon may condition an high vulnerability to AF recurrences immediately following CV. Immediate reinitiation of AF, defined as recurrence within 1 minute, has been described to occur in 13-36% of patients submitted to low energy internal atrial CV [69] and it had a substantial impact also on initial experiences with implantable atrial defibrillators [80]. A key point is therefore to define the effects of antiarrhytmic agents in reducing AF recurrences at short and long term and of pre-treatment with calcium antagonist, to reduce electrophysiological remodeling and, indirectly, AF recurrences. Evaluation of the effects of antiarrythmics drugs on atrial defibrillation threshold is at present possible for evaluating the effects of drugs in patients submitted to low energy atrial CV [78].

Although, at present time, transvenous low energy CV is still an investigational procedure, a widening of indications is expected in the near future [72]. Low energy internal CV allowed development of devices for atrial defibrillation. The first experience on a stand-alone atrial defibrillator was published by Wellens *et al.* [80] and included in 51 patients. During the follow up 96% of the episodes was succesfully converted to sinus rhythm but early recurrence of AF (within 1 minute) was observed in 27% of the episodes and in 51% of the patients, thus supporting the need for concurrent antiarrhytmic therapy. A dual chamber defibrillator has been also tested [64, 68]. In this system addition of an atrial lead to a cardioverter-defibrillator allows diagnostic informations in combination with atrial pacing capability (delivery of different antitachycardia pacing therapies, including 50 Hz stimulation) and with possibility of R wave synchronous shock therapy. In this system a coronary sinus lead is not required. Mean atrial defibrillation threshold resulted to be 4.8 ± 2.7 joule [68].

The possibility to include in an electrical defibrillator a drug delivery system able to deliver a bolus of an antiarrhyhtmic drug in order to painless terminate AF is currently under evaluation [65].

Catheter ablation

Two different approaches can be used in patients with AF using radiofrequency catheter ablation: 1) atrio-ventricular (AV) junction ablation or AV node modification for rate control in patients with chronic persistent AF; 2) ablation of the atrial substrate by creating linear lesions in the right and/or the left atrium or by ablating atrial foci in cases of AF of focal origin [18, 81, 82]. Atrio-ventricular junction ablation combined with pacemaker insertion is a purely palliative treatment [26, 82]; however, it is a safe and effective procedure to be used in poorly tolerated chronic permanent AF with high ventricular rate. With these selected indications, this procedure may have a favourable cost-benefit. Its use in paroxysmal AF need to be limited, in our view, to very selected cases.

Atrioventricular node modification is aimed to reduce ventricular rate during AF avoiding pacemaker implantation. Effective modification of AV node can be obtained in 65-75% of patients but inadvertent complete heart block may occur in up to 16% of patients at the time of the procedure or later during the follow-up [26].

The possibility to cure AF by catheter ablation has created a growing enthusiasm. The first application of radiofrequency catheter ablation was related to the creation of linear barriers to prevent intra-atrial reentry and to reply surgical Maze procedure. Different techniques were used [81] (right atrial and/or left atrial linear ablation) with a rate of acute success ranging from 33% to 100% and a rate of long-term success ranging from 33% to 80%. The difficulties in performing the procedure, the evidence of procedure-related complications and the need for technological improvements in catheter and mapping techniques [83] have limited the possibility to consider this procedure as a therapeutic option to be adopted in daily clinical practice.

Haissaguerre *et al.* [18] on the basis of elegant mapping of the pulmonary veins demonstrated the importance of the regions around and inside the pulmonary veins for initiating and maintaining AF. These observations led to focal ablation of pulmonary veins foci as a curative treatment for AF. Indeed, in selected cases of AF without underlying heart disease, a focal origin of AF was described by Haissaguerre *et al.* [18], more frequently at the origin of left pulmonary veins. These Authors showed that ablation of atrial foci was able to cure AF in 62% of treated patients. At present time it is not known how many patients with lone AF have this kind of focal substrate.

The frequent existence of multiple foci and the problem of pulmonary veins stenosis inspired an alternative approach [83]. This approach is based on non-fluoroscopic electroanatomic mapping with creation, by radiofrequency, of circumferential lines of conduction block around the ostia of each pulmonary vein.

Table 4. - Possible combined or hybrid therapies that can be used in selected cases of drug-refractory AF

AA drugs + atrial pacing (at interatrial septum/ biatrial/ dual site)
AA drugs + atrial pacing + algorithms to suppress PAC
AA drugs + atrial pacing + algorithms to suppress PAC + atrial defibrillator
AA drugs + atrial ablation
AA drugs + atrial pacing + atrial ablation

AF: atrial fibrillation; AA drugs: antiarrhythmic drugs; PAC: premature atrial complexes.

Combined or hybrid treatments

The awareness of the limitations of pharmacological treatment led in recent years to the development of a wide spectrum of electrical, non pharmacological treatments [26]. Despite a series of limitations, non pharmacological techniques may convey significant advantages to AF treatment in appropriately selected groups of patients. However, up to now, a single procedure able to cure drug refractory AF in a large percentage of patients with the best guaranties for safety and efficacy could not be identified.

The limitations, in terms of efficacy rate, of AF management based on a single treatment has led to the concept of combined or hybrid treatments (Table 4). The rationale of combined or hybrid treatments is to combine different therapeutic modalities in an attempt to achieve a synergetic effect, to improve efficacy over single approaches by acting on different targets (the electrophysiological substrate, the anatomical substrate, the triggers, the modulating factors), having also a rescue treatment in case of failure (Table 5). In view of the potential effects on different targets (AF terminations, atrial conduction and refractoriness, atrial premature beats frequency, atrial electrophysiological remodeling,

Table 5. - Rationale for hybrid treatments: ability of different treatments to modify a series of variables facilitating AF initiation/maintenance

	AF termination	Atrial conduction and refractoriness	PAC frequency	Reversal of electrophysiological remodeling	Atrial size
Antiarrhythmic drugs	+	+ +	+	+ / ?	-
Atrial pacing	- / ?	+	+	?	-
Internal cardioversion	+ +	-	-	+ / ?	+ / ?
Focal ablation	+ / -	+	+ / -	?	+ +
Linear ablation	+ / -	+	+ / -	?	+ +

AF: atrial fibrillation; PAC: premature atrial complexes; +: clinically relevant effect; ++: strong clinical effect; - : lack of clinical effect; ?: unknown effect.

atrial size) a series of treatments (antiarrhythmic drugs, internal cardioversion, atrial pacing with/without specific pacing algorithms, focal ablation, linear ablation) may be combined with the aim to achieve a synergetic effect (Tables 4 and 5).

This approach is therefore justified by two expectations: 1) some of non pharmacological treatments may render AF responsive to previously ineffective drugs; and 2) the combined use of more than one non pharmacological treatment is expected to be required, alone or in combination to drugs, in some patients, in order to obtain a synergetic effect [84, 85].

Prospective studies are required to evaluated the risk-benefit profile of these strategies in appropriately selected patients [26, 84, 85].

Conclusions. The role of electrophysiological approaches in AF treatment

At present the approach to AF treatment is guided by a careful analysis of the electrophysiological patterns of AF (on the basis of multiple intra-atrial recordings or sophisticated new mapping techniques) only in a restricted minority of patients, those who are candidates to ablation of the substrate and/or the triggers.

Indeed, AF has a broad spectrum of clinical presentations and a heterogeneous electrophysiological pattern and its treatment, both with drugs and non pharmacological treatments, has been based, classically, on empiric basis and on a clinically-guided staged-approach. The limitations of pharmacological treatments led in recent years to the development of a wide spectrum of electrical, non pharmacological treatments. This implies a change in the approach to AF and the need to identify potentially ideal candidates to complex and expensive treatments.

It is matter of investigation to evaluate if the analysis of the electrophysiological pattern may be helpful for identifying a priori potential responders to a definitive treatment or a combination of treatments (both pharmacological and non-pharmacological). This approach could be advantageous both in term of risk-benefit ratio and cost-effectiveness but requires a series of controlled trials to be validated and a standardisation of mapping techniques coupled with further advances into the knowledge of AF electrophysiology.

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