New advances in nonpharmacologic therapy for atrial fibrillation

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Atrial fibrillation (AF) is the most commonly occurring cardiac arrhythmia. Due to the low clinical efficacy of current antiarrhythmic agents, various nonpharmacologic approaches including catheter ablation, permanent cardiac pacing and surgical procedure alone or in combination, have been developed for treatment of AF. Except in patients who require open heart surgery, surgical procedures have very limited role in the treatment of AF. Pacing therapy alone, except in patients with concomitant bradycardia, has a very limited role for the treatment of AF. The incremental benefit of alternate or multiple site pacing and different pacing algorithms remains to be defined. Catheter ablation procedures may prove to provide curative therapy for AF in selected but widening patient populations. However, issues concerning the optimal ablation technique and safety of the procedure remain to be resolved. Currently, most of the nonpharmacologic methods of AF treatment are more or less experimental and need to be proven by randomized control before they can be considered as routine therapy for AF.

Keywords: antiarrhythmic agents, atrial fibrillation, nonpharmalogic therapy

Atrial fibrillation (AF) is the most commonly occurring cardiac arrhythmia. Epidemiologic data from the Framingham Heart Study indicates that the cumulative incidence of AF over 22 years of follow up is 2.1% in men and 1.7% in women. The prevalence of AF increases with age, doubling with each successive decade, and 70% of people with AF are between the ages of 65 and 85 years [1]. Even in an ethical group with a low incidence of coronary artery disease, AF occurs in 1.3% of the population over the age of 60 years [2]. Furthermore, recent data suggest that the prevalence of AF is increasing, even after adjusting for age and other risk factors [1]. In conjunction with congestive heart failure, AF has been described as one of the two emerging epidemics of cardiovascular disease due to the ageing population [3].

For many years, AF has attached less research interest than ventricular arrhythmias, which typically have a more dramatic clinical presentation. This is because the symptomatic impact of AF can be subtle and nonspecific, and because the deleterious effects occur insidiously or remote from the time of onset of the arrhythmia. However, AF is associated with a three- to fivefold increased risk of stroke, a threefold increase risk of congestive heart failure, and a significant 1.5- to threefold increase in the risk of death [1]. In addition to the lack of awareness of the adverse effects of AF, another feature which has encouraged the tacit acceptance of this arrhythmia is a paucity of effective therapies, due to a poor understanding of its mechanism.

With regards to the treatment of AF, successful restoration and maintenance of sinus rhythm are conceptually expected to improve quality of life, reduce the incidence of stroke, heart failure, and mortality, and avoid the use of lifelong anticoagulation. However, recent randomized trials have failed to show any superiority of rhythm control strategy – primarily pharmacologic – over rate control plus anticoagulation strategy in term of quality of life, stroke and mortality [4–7]. These studies highlighted the low clinical efficacy of current antiarrhythmic agents to maintain sinus rhythm, which probably contributes to the risk of stroke associated with rhythm control. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, the presence of sinus rhythm (with or without antiarrhythmic agents) was associated with a significant reduction in the risk of death, but the use of antiarrhythmic agents is associated with increased mortality [8]. These observations have prompted the development of new and safer methods to maintain sinus rhythm in patients with AF.

Mechanisms of AF

Recent experimental and clinical studies have provided new insight into the mechanisms of AF. These mechanisms are heterogeneous and likely to vary in different clinical circumstances. However,

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three basic components are required for the occurrence of AF – a specific trigger, a suitable substrate and modifying factors.

Experimental AF could be induced by a single source of very rapid impulses or by multiple re-entering wavelets that continuously travel randomly through the available myocardium [10,11]. If the cycle length of the firing focus is shorter than the refractory period in other parts of the atria, a rate-dependent functional conduction block and nonuniform excitation will result. This type of AF is actually represented as 'fibrillatory conduction.' Haissagurere and colleagues have demonstrated that a single source of rapid impulses, mainly originating from the pulmonary veins, is the majority source of trigger for the initiation and maintenance of AF in patients with paroxysmal AF [12]. Furthermore, atrial flutter or any supraventricular tachycardia may also serve to trigger AF.

In contrast, established AF often consists of multiple wavelets and was thought to be caused by multiple re-entries. Allessie and colleagues provided the first experimental evidence to support the presence of a multiple re-entering wavelet during AF by using a mapping technique. They postulated that perpetuation of AF depends on a critical number – 4 to 6 – of simultaneously circulating wavelets [13]. Subsequently, Cox and colleagues documented the presence of multiple wave fronts, nonuniform conduction, bidirectional block and complete re-entrant circuits during AF in human atria using intraoperative electrophysiologic mapping [14]. This type of AF requires the presence of appropriate atrial substrates which include an adequate atrial mass and the occurrence of a short wavelength. Wavelength is a product of the atrial refractory period and atrial conduction velocity. Thus, any atrial structural and electrophysiologic changes that resulted in a shortening of atrial refractoriness or slowing of conduction can facilitate the maintenance of AF [11]. Both animal and human studies have shown that the occurrence of AF leads to changes in the atrial refractory period which favors the maintenance of AF [15,16]. Furthermore, heterogeneous changes of regional dispersion in atrial effective periods in the right and left atria also contribute to the chronicity of AF. These changes occurred in parallel with progressive increase in P-wave duration, sinus node dysfunction and left atrial dilatation from paroxysmal to persistent AF, suggesting a progressive electromechanical remodelling process [17]. In addition, dispersion of conduction velocities when atrial dilatation occurred in heart failure may also be an alternative mechanism for, persistence of AF [18]. This electromechanical remodeling is associated with cellular hypertrophy, atrial fibrosis and calcium overloading, which increases the propensity to AF [19,20]. Thus, a vicious cycle of progression to long-standing AF occurs once the process begins. Therefore, aggressive treatment of AF, if initiated early, may potentially prevent these progressive atrial electromechanical remodeling.

A variety of modifying factors appears to be of importance in the initiation and maintenance of AF. In experimental models for AF, stimulation of the parasympathetic system or applying acetylcholine directly onto atrial tissue is required to produce sustained AF [13]. A change in autonomic tone with either parasympathetic or sympathetic stimulation directly affects atrial refractoriness to contribute to both multiple wavelets of re-entry and focal mechanisms with fibrillatory conduction [21,22]. In animal models, catheter ablation of cardiac autonomic nerves by radiofrequency energy successfully abolished AF mediated by vagal stimulation [23]. Other modifying factors appear to be of importance in the initiation and maintenance of AF including effects of drugs such as adensoine, inflammation and electrolytes, may affect the onset of the atrial trigger and the atrial susceptibility for AF.

Nonpharmalogic therapy for AF

The observations on the mechanisms of AF have resulted in the development of a new electrical therapy that directed to eliminate the triggers and to modify the electrophysiologic substrate for the prevention and treatment of AF.

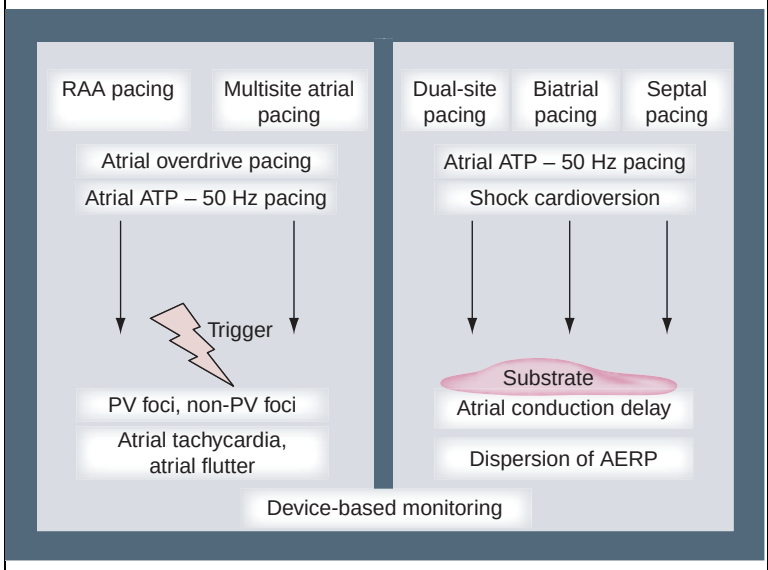
Pacing for prevention of AF

There are multiple potential mechanisms by which atrial pacing can theoretically prevent AF [24]

- Suppression of atrial premature beats
- Preventing bradycardia-induced dispersion of repolarization by atrial overdrive pacing
- Shortening of atrial conduction time by multiple or alternative atrial pacing
- Preserving atrioventricular (AV) synchrony to avoid stretch-induced changes in atrial repolarization

Pacing can be delivered either in a passive or an active manner at a variety of sites (Figure 1). 'Passive pacing' is conventional pacing to prevent or alter the response to AF. 'Active pacing' involves either fixed or dynamic (based on the current sinus or a sensor-mediated rate) atrial overdrive of the sinus

Figure 1. Pacing therapy for atrial fibrillation.



Potential mechanisms and approaches for pacing for prevention of AF.
AERP: Atrial effective refractory period; P: Pulmonary vein; PV: Pulmonary vein; RAA: Right atrial appendage.

rhythm. Furthermore, active pacing intervention using algorithms to counteract the mode of atrial premature beats onset and antitachycardia pacing for AF termination have been developed [24].

Conventional atrial pacing for prevention of AF

In patients with sick sinus syndrome, several randomized control trials [25–27] have confirmed that atrial-based pacing (either atrium–atrium-inhibited [AAI] or dual–dual-dual [DDD]) is superior to ventricular pacing alone in the prevention of AF. However, patients with a history of paroxysmal AF but no history of sinus node disease did not benefit from atrial pacing for prevention of AF [28–30].

Alternative & multiple-site atrial pacing

Alternative or multiple-site atrial pacing may prevent AF by abbreviating critical areas of slow conduction and decreasing the atrial conduction time. These include biatrial pacing (right atrial appendage and distal coronary sinus), dual-site atrial pacing (right atrial appendage and low atrial septum) and Bachmann's bundle region/interatrial septal pacing (Figure 1).

In patients with interatrial conduction block and drug-refractory atrial tachyarrhythmias, biatrial pacing was shown to have some benefits in terms of reduced AF episodes and duration of AF [31,32] but of no significant prolongation of time to first AF recurrence and atrial tachyarrhythmia burden [33]. Similarly, dual-site right atrial pacing in patients with or without bradycardia has only a modest effect in preventing AF compared with single-site atrial pacing or no pacing [34–36].

Alternative atrial pacing at Bachmann's bundle/interatrial septal locations appears to be safe and feasible as conventional right atrial site. Over an intermediate period of follow-up, pacing at these sites may prevent progression of AF in patients with bradycardia and AF who have conventional pacing indications [37–39]. Furthermore, the additional use of atrial overdirve pacing algorithms appears to further enhance the beneficial effect of septal pacing. Compared with multiple sites atrial pacing, these alternative pacing sites require less hardware and may achieve similar results in terms of AF reduction. The relative efficacy of high versus low right atrial septal pacing for AF prevention remains unknown however, the use of high septal pacing is associated with a lower risk of ventricular far-field sensing.

Preventive & antitachycardia pacing algorithm

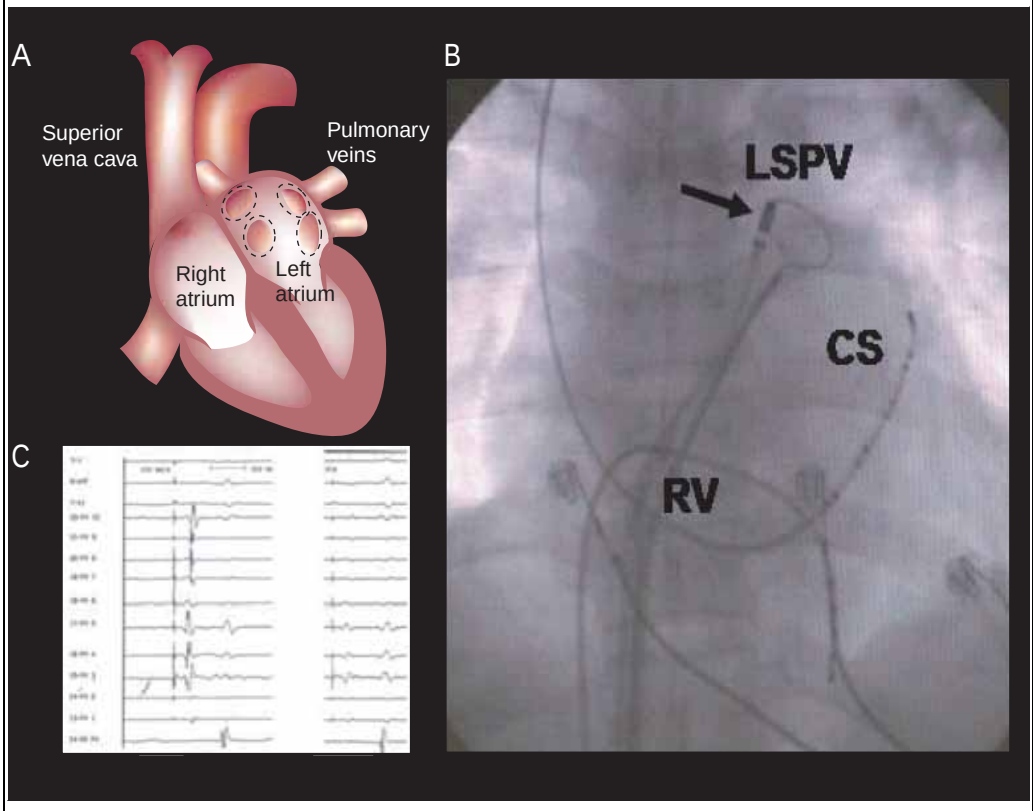
Various pacing algorithm approaches have been developed for AF prevention, including algorithms for atrial overdrive and algorithms triggered by atrial premature beat, AF termination or exercise [24]. These algorithms increase the frequency of atrial pacing compared with conventional rate responsive pacing with minimum change in overall heart rate. Except for the atrial overdrive algorithm which can provide a modest adjunctive role in arrhythmia control [40], there is limited data on the role of other additional pacing algorithms for AF prevention [30].

Antitachycardia pacing algorithms are available in some implantable pacemakers and defibrillators. These algorithms successfully terminated about half of a device-defined atrial tachyarrhythmias but did not reduce the overall AT/AF burden or frequency [41]. However, in combination with atrial shock therapy, antitachycardia pacing has been shown to reduce arrhythmia burden [42]. Currently, there is no convincing evidence to prove that antitachycardia pacing can terminate or reduce AF [30].

Surgical treatment

Based on the theory that the coexistence of several re-entrant wavelets in a critical mass of atrial tissue is responsible for the perpetuation of AF [13], Cox and colleagues described a surgical procedure that involved multiple linear atrial incisions over both atria (Maze procedure), which proved to restore sinus rhythm [14]. It consisted

Figure 2. Segmental pulmonary vein isolation procedure.



(A) Diagrammatic representation of the segmental pulmonary vein isolation procedure. **(B)** Anteroposterior view of fluoroscopic image during segmental pulmonary vein isolation procedure. A circular mapping catheter and ablation catheter are positioned at the ostium of left superior pulmonary vein. **(C)** Electrogram recording by the circular mapping catheter at the left superior pulmonary vein before and after segmental pulmonary vein isolation to show complete electrical isolation of the pulmonary vein after ablation.
CS: Coronary sinus; LSPV: Load-sensing proportioning valve; RV: Right ventricle.

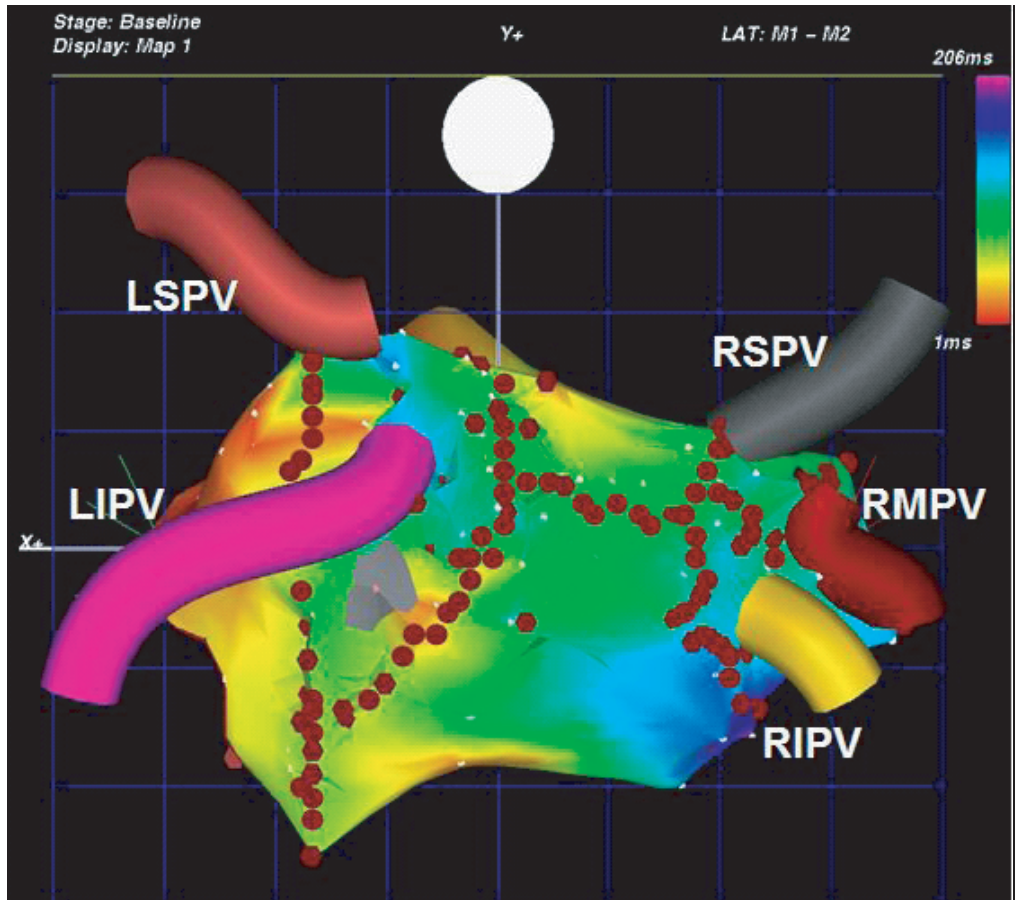
of extensive incisions in both atria in order to create anatomic barriers to reduce the number of circulating wavelets below the critical number required to sustain AF (compartmentalization). In a recent series of patients with lone paroxysmal AF, the success rate was as high as 95% [43]. However, because of associated impairment of sinus node function and atrial mechanical function, as well as the operative risk and long hospital stay, surgical therapy for AF remains an unattractive option for patients without another indication for open heart surgery. Conversely, in patients with AF undergoing concomitant open heart surgery, such as mitral valve surgery or bypass surgery, the Maze procedure is a viable option for treatment of AF [44,45]. Furthermore, recent developments in the use of different energy sources, such as ultrasound, microwave and cryoablation for epicardial ablation, have also facilitated the surgical procedure for AF [46].

Catheter ablation

Catheter ablation techniques for ventricular rate control (AV junction ablation and AV nodal modification) have been shown to be effective in reducing symptoms, improving left ventricular function, exercise capacity and quality of life [47]. However, the requirement for life-long pacemaker therapy, the development of persistent AF, and in some rare cases, sudden death, poses significant disadvantages for AV junction ablation. Although AV nodal modification may provide rate control without permanent pacing, substantial proportions of patients have failed in controlling their symptoms through the development of late-onset AV block and resumption of rapid AV conduction [48].

To prevent AF, it is logical to remove the triggering atrial ectopics in patients who are susceptible. Pioneering by Haissagurere and colleagues, percutaneous application of lesions

Figure 3. Posterior view of electroanatomical mapping (CARTO) of the left atrium and pulmonary veins after the circumferential PV ablation procedure.



Please noted additional linear ablations have been performed between the left (LSPV) and right superior PV (RSPV), and between the left inferior PV (LIPV) and mitral valve annulus.
RIPV: Right inferior PV; Pulmonary vein; RMPV: Right middle PV.

around the ostia of the pulmonary veins is increasingly used as a therapeutic option for treatment of AF [12]. Initially, the ablation strategy was mainly targeted to the triggering focus within the pulmonary veins [12,49,50]. However, due to the difficulty in mapping these arrhythmogenic foci with high recurrence rate, and the potential risk of pulmonary vein stenosis with ablation inside the veins, segmental ostial isolation of pulmonary veins as guided by a circular mapping catheter is currently been used [51–53] (Figure 2).

Encouraged by the success of the Maze procedure, electrophysiologists started to employ catheter-based ablation to create linear ablation lines to compartmentalize the atria, mimicking the Maze operation [54,55]. However, it is still very difficult with the currently available catheter technology to create linear left and right atrial lesions rapidly or safely. Another ablation strategy is to perform circumferential ablation lesions at the ostia of pulmonary veins under 3D electroanatomic nonfluoroscopic mapping system guidance [56,57]. Instead of chasing the electrical focus of the pulmonary vein muscle potential, this technique consists of anatomically encircling the ostia of each pulmonary vein with radiofrequency lesions delivered at the left atrial side of the left atrio–pulmonary vein junction. Furthermore, in addition to pulmonary vein encircling, additional linear ablation at the posterior left atrium connecting both encircling lesions and a line connecting the left encircling lesions with the mitral valve annulus (Figure 3). Therefore, this approach also provides additional substrate modification to segmental pulmonary vein isolation.

The clinical efficacy of the pulmonary vein ablation procedure for AF vary with regard to technique used, patient population studied,

Executive summary

- Current nonpharmacologic therapies are aimed at eliminating the triggers and modifying the electrophysiological substrate for the prevention and treatment of atrial fibrillation (AF).
- Atrial-based pacing only prevents AF in patients with concomitant bradycardia. The incremental benefit of alternate- or multiple-site pacing and different pacing algorithms remains to be defined.
- In patients with AF undergoing concomitant open heart surgery, such as mitral valve surgery or bypass surgery, the surgical Maze procedure is a viable option for treatment of AF.
- Catheter ablation procedure with segmental pulmonary vein or circumferential pulmonary vein ablation may prove to provide curative therapy for AF in selected but widening patient population. However, issues regarding the optimal ablation technique and safety of the procedure remain to be resolved.
- Currently, most of the nonpharmacologic methods of AF treatment are more or less experimental, and need to be proven by randomized control before considering them as routine therapy for AF.

operators experience, concomitant use of antiarrhythmic drugs, and duration and method of follow-up [51–53,56,57]. Currently, the most appropriate candidates for AF catheter ablation are those with symptomatic paroxysmal AF resistant to antiarrhythmic drugs. The results of AF catheter ablation in this population have varied from 60 to 90%, and second procedure is required in 20 to 30% of patients because of the recurrence of pulmonary vein potential and gaps in the linear ablation lesion sets. Furthermore, successful curative ablation for AF was associated with a lower rate of cardiovascular deaths, primarily heart failure, stroke and sudden death, and better quality of life than medical therapy [56]. Consistent with this initial observation, a recent study evaluating the effects of catheter ablation for AF in patients with heart failure also demonstrated that restoration and maintenance of sinus rhythm by catheter ablation significantly improve cardiac function, symptoms, exercise capacity and quality of life [58].

However, serious complications related to this ablation procedure do occur, including pericardial effusion and tamponade (<2%), pulmonary vein stenosis (1.5%), ischemic stroke (<2%), cardiac perforation, phrenic nerve injury, and even fatal esophageal fistula [50–57,59,60].

Even though radiofrequency currently remains the most widely used energy, alternative sources such as and ultrasound and cryoenergy have gained increasing attention in an attempt to overcome certain limitations associated with this technology. For pulmonary vein isolation, cryoablation appears promising because of a lower risk of pulmonary vein stenosis, cardiac perforation and thrombogenesis [61,62]. Although cryothermy historically has been employed predominately in the surgical suite, the advent of percutaneous catheter cryoablation, which avoids the risks associated with open heart surgery, provides an important alternative to radiofrequency ablation for the treatment of cardiac arrhythmias. Recent clinical studies have demonstrated that percutaneous catheter cryoablation is a safe and effective method for pulmonary vein ablation [63]. In a series of 52 patients with paroxysmal or persistent AF undergoing pulmonary vein isolation with this system, both primary (97%) and long-term (56%) success rates were comparable with previous studies using radiofrequency energy. However, this procedure is limited by a long procedure time. Further refinement in catheter design and the mode of cryoablation are required to address this limitation. Furthermore, various imaging, mapping and navigation tools have been introduced aimed at reducing fluoroscopy time and improving catheter steering. It is expected that the efficacy and safety of catheter ablation procedures for AF will improve with future development of catheter mapping and ablation technology.

Percutaneous left atrial appendage occlusion device

Oral anticoagulation therapy reduces the risk of thromboembolism in patients with AF. However, some patients are not candidates for oral anticoagulation therapy. In the majority of patients with AF left atrial appendage is thought to be the source of thrombi in the majority of patients with non-valvular AF. Recent studies have demonstrated the safety and feasibility of using a percutaneous left atrial appendage occlusion device for interventionally occluding the left atrial appendage [64,65]. Future prospective studies are needed to clarify the long-term treatment clinical efficacy of this new technique.

Expert opinion

Due to the significant limitations of current pharmacological therapies for AF, we are now well on the way to the development of nonpharmacologic

therapies. Recent advances in pacing and ablation technologies, either alone or in combination with antiarrhythmic agents, may provide new therapeutic options. Pacing therapy alone, except in patients with concomitant bradycardia, has a very limited role in the treatment of AF. Catheter ablation procedures may prove to provide a curative therapy for AF in selected but widening patient populations. However, issues regarding the optimal ablation technique and safety of the procedure remain to be resolved. Currently, most of the nonpharmacologic methods of AF treatment are more or less experimental and need to be proven by randomized controls before being considered as a routine therapy for AF.

Outlook

Recent advances in various imaging, mapping and navigation tools and ablation technologies will further improve the efficacy and safety of catheter ablation procedures for treatment of AF.

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