Novel non-pharmacological approaches for antiarrhythmic therapy of atrial fibrillation

Julia Koebe¹ and Paulus Kirchhof²*

¹Department of Cardiology and Angiology, University Hospital Münster, Albert-Schweitzer-Str. 33, 48149 Muenster, Germany; and ²Atrial Fibrillation Competence NETwork (AFNET), Domagstr-5, 48149 Muenster

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Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. Its prevalence is increasing in our ageing population, and it has a soaring impact on health systems. It can cause thrombo-embolism, heart failure, and hospitalizations, and is associated with a two-fold increase in all-cause mortality. There have been great advances in understanding the mechanism of AF that are currently being translated into new therapeutic concepts. Experimental studies demonstrated that AF-induced electrical and structural remodelling of the fibrillating atria perpetuates AF ('AF begets AF'). Furthermore, there is growing understanding that the atria are an endocrine organ expressing angiotensin and thrombogenic substances. Clinical, electrophysiological studies have identified automatic triggers, often in the pulmonary veins, that initiate paroxysmal AF. Electrical isolation of the pulmonary veins by circular ablation abolishes these triggers. Whereas isolation of the pulmonary veins often maintains sinus rhythm in patients with paroxysmal AF, additional ablation strategies are used in persistent and permanent AF to modify the more complex electrical and structural atrial changes. The 'role model' for extensive ablation in the left atrium is the surgical MAZE procedure that abolishes long-standing AF by cutting and sewing the atria into complex pieces. New surgical approaches of AF therapy use radio-frequency or other sources for an easy ablation during open-heart surgery. A lot of effort has also been put in the development of device therapy for the treatment of AF, with mixed effects on maintenance of sinus rhythm, but unexpected insights into the development of asymptomatic AF recurrences. This review aims to provide an overview of these non-pharmacological treatment options of AF in the context of potential pathophysiological processes.

KEYWORDS
Atrial fibrillation; Catheter ablation; Rhythm control; Pacemaker therapy; Antithrombotic therapy

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. Its prevalence increases with age and affects several million people in Europe.¹ AF is of major importance for health professionals and systems in ageing populations and hence in all almost European countries. The presence of AF is often associated with symptoms, reduces quality of life, and increases hospitalizations. AF causes approximately every 5th stroke and increases the risk for stroke more than any other risk factor for ischaemic strokes. Furthermore, AF is associated with heart failure and all-cause mortality. Atrial fibrillation is usually the consequence of several complementary pathophysiological processes. Some of these processes have been delineated as ‘electrical remodelling’, ‘structural remodelling’, ‘atrial cardiomyopathy’,² and ‘atrial automaticity’. Many of these processes interact (Figure 1). Electrical remodelling is a ‘survival reflex’ of the cardiomyocyte to reduce rate-induced calcium overload: repolarization and refractoriness are shortened within a few hours after the onset of AF. This process shortens atrial wave length and thereby facilitates re-induction and perpetuation of AF.³ ‘Structural remodelling’ can be caused by pressure or volume overload in the atria, e.g. as a consequence of ventricular heart failure or arterial hypertension, but can also be a consequence of AF itself that may lead to premature atrial cardiomyocyte death and to increased production of interstitial proteins. A major signalling pathway inflicted in structural remodelling is activation of the rennin–angiotensin–aldosterone system which increases extracellular fibrosis. These processes are accelerated when AF is accompanied by ventricular heart failure, e.g. due to high ventricular rate or structural heart disease (Figure 1).

A milestone in understanding the initiation of AF was the identification of electrical foci in the junction of the posterior left atrium and the pulmonary veins that often initiate
and perpetuate AF. The pathophysiological changes that provoke abnormal automaticity in the pulmonary vein–left atrial (LA–PV) junction and thereby initiate AF have not been fully understood, but acute atrial stretch and partial isolation and/or anisotropy of cardiomyocytes at the LA–PV junction may play a role. Catheter-based or intraoperative isolation of the pulmonary veins abolishes this trigger for AF and can ‘prevent recurrent AF’ for several years in patients with paroxysmal AF. In patients with long-lasting (persistent or permanent) AF, structural remodelling and ‘atrial cardiomyopathy’ are usually more advanced. This may explain why PV isolation is often not sufficient in such patients to maintain sinus rhythm. The fact that ‘subclinical’ heart disease, e.g. slight atrial dilatation, arterial hypertension, or valvular heart disease, is often found in patients with paroxysmal AF suggests that electrical and structural remodelling also contribute to earlier-stages of the arrhythmia, albeit probably to a lesser extent.

‘Reversal’ of electrical remodelling, i.e. prolongation of the shortened action potential duration and refractory period, is a mainstay of antiarrhythmic action potential-prolonging drug therapy. Although acute pharmacological cardioversion rates are ~60–80%, efficacy rates in preventing AF recurrences are lower (40–60% at 1 year).

New approaches for antiarrhythmic drug therapy are discussed elsewhere. The present review will focus on novel non-pharmacological approaches for the treatment of AF. A major treatment option for patients with AF is the catheter ablation which has evolved to a relatively safe and effective procedure. Besides this, surgical strategies and pacemaker therapy or the combination of those are discussed (Table 1).

Pulmonary vein isolation (catheter based or operative)—trigger elimination

The observation that foci in the ostia of the PVs act as triggers for paroxysmal AF started a new era of catheter-based AF ablation procedures. The PV foci are characterized by sharp PV potentials preceding the left atrial activity. The initial approach of ablating foci within the PV resulted in high rates of PV stenosis. Currently, the PVs are electrically isolated from the atria by ablating the anatomical junction of the PV and the left atrium by either circular lines outside the pulmonary vein antrum, or segmental PV ablation. Complete PV isolation is the first and most important step of any AF ablation procedure.

PV isolation may require several ablation procedures in 20–40% of the patients, but maintains sinus rhythm in 60–80% of patients at 1–3 years of follow-up. Recovery of PV conduction in the LA can occur and results in early recurrence of AF. Additive antiarrhythmic therapy after PV isolation has higher success rates than ablation alone. This appears reasonable given the fact that antiarrhythmic drugs mainly target electrical remodelling, whereas catheter ablation mainly eliminates the trigger for AF (Figure 1). Early after PV isolation, left atrial tachycardias may occur in up to 10% of patients. Their underlying mechanism is often a macro-reentrant circuit around lesions set or anatomical boundaries.

In patients with persistent or permanent AF, PV isolation alone does not have sufficient success rates (20–45% with single procedures). Several more extensive catheter ablation strategies have been proposed in these
patients: following the ‘role model’ of the MAZE procedure, several sets of linear lesions in the atrium (roof line, mitral annulus line) have been used and improve the outcome in patients with non-paroxysmal AF in single-centre studies. Targeted ablation of areas with low-amplitude, fractionated potentials in the left atrium has been associated with acceptable success rates in some studies. Those areas may represent areas of slow conduction or small re-entrant circuits. Other experimental observations suggest that fractionated potentials may identify areas close to ganglionated plexus (see below). While catheter ablation in the form of pulmonary vein isolation is a recommended therapy for drug-resistant, symptomatic AF, there is no generally accepted consensus on a ‘second step’ for catheter ablation is PV isolation fails to prevent AF.

Ablation in the left atrium for AF is a long and at times difficult procedure, and major complications occur in ~5% of the procedures. Risks of AF ablation include thrombo-embolic events (0–7%), atrioesophageal fistula (<0.25%), pericardial effusion, and pulmonary vein stenosis (1–3%). Rare complications comprise damage to the phrenic nerve and gastric hypomotility.5 PV isolation outside of the pulmonary veins can probably reduce pulmonary vein stenosis. Modern catheter visualization and mapping systems [e.g. the CARTO® (Biosense Webster, CA, USA) and the NavX® system (St. Jude Medical, Endocardial Solutions, MN, USA)] provide non-fluoroscopic, three-dimensional catheter localization and a superimposed three-dimensional reconstruction of the left atria and adjacent anatomical structures (e.g. oesophagus) from CT or MRI images. Besides this, CT or MRI scan is a precise tool to detect PV stenosis in repeat procedures. The systems have the potential to reduce complications and fluoroscopy times. In the future, robotic or remote catheter navigation may improve outcome of AF and other complex ablations.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of non-pharmacological approaches for the treatment of AF</th>
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<tbody>
<tr>
<td><strong>Indications</strong></td>
<td><strong>Comments</strong></td>
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<tr>
<td>Surgical AF ablation</td>
<td>In combination with a surgical procedure (e.g. bypass graft, valve replacement).</td>
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<tr>
<td>Catheter ablation</td>
<td>Symptomatic patients refractory to at least one antiarrhythmic treatment.</td>
</tr>
<tr>
<td>Pacemaker with AF prevention algorithms</td>
<td>Patients with AF and an indication for a pacemaker. Possibly with algorithms to reduce ventricular pacing.</td>
</tr>
<tr>
<td>Atrial defibrillator</td>
<td>No indication</td>
</tr>
<tr>
<td>AV-node ablation and pacing</td>
<td>Patients in whom rate and rhythm control failed. Possibly in combination with a biventricular device in patients with reduced LV function.</td>
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- Requires open-heart surgery
- Small increase in perioperative risk
- Additional LAA excision may reduce thrombo-embolic risk
- Complications: rare (sinus node dysfunction in the original MAZE procedure)
- Optimal energy source and lesion design strategy not known
- Stroke and transient ischaemia (1%)
- Pulmonary vein stenosis, atrioesophageal fistula (rare)
- Repeat procedures
- Proarrhythmia (left atrial flutter)
- More effective in paroxysmal AF and patients with normal atrial size and normal ventricular function
- Valuable diagnostic tool
- Probably little additional effect on AF with preventive pacing algorithms
- Painful, not very accepted
- Unexpectedly high early recurrence rate
- No reduction of total AF burden
- Proarrhythmia early after ablation (rare)
- Lifelong pacemaker dependency
- Negative effect of right-ventricular pacing on left ventricular function

Non-pharmacological approaches for antiarrhythmic therapy of AF
**MAZE procedure and linear lesions—elimination of 'structurally remodeled' atrial myocardi um**

The original MAZE procedure was introduced by James Cox in 1987. Currently, a modified version (MAZE III) is used. This procedure isolates PVs and creates multiple areas of electrical transmural conduction block in both atria by cutting and sewing. It was designed to interrupt re-entrant circuits in the left and right atrium. 90% of patients are free of symptomatic AF 10 years after the MAZE procedure, but the monitoring for AF recurrences was certainly insufficient for today's standards. The original MAZE III procedure requires considerable surgical skill and operation time. Therefore, cardiac surgeons often deploy a reduced set of scars in the left atrium, and, similar to the interventional electrophysiologist, use radio frequency, microwave, laser, or cryogenic sources to create endocardial or epicardial lesions. Common lesions sets involve pulmonary vein isolation and linear lesions that extend to the mitral annulus and to the left atrial appendage (LAA). Sinus rhythm maintenance rates vary between 65 and 95% after surgical ablation for AF, although patients receiving this treatment often suffer from long-standing AF. The success of surgical treatment of AF may rely on the higher rate of transmural lesions and true 'compartmentalization' of the atria compared with catheter-based linear lesions. The risk of adding AF ablation to a conventional surgical procedure is low. This type of treatment should, hence, be considered in all patients with AF undergoing open-heart surgery. The type and extent of the procedure should be tailored to local surgical routine and potentially to the extent of 'structural remodeling' and atrial dilatation in a given patient.

**Ganglionated plexus—ablation of autonomic innervation**

In addition to the above-mentioned pathophysiological aspects of AF (Figure 1), an autonomic imbalance and a possibly inadequate firing of sympathetic and parasympathetic fibres can initiate AF. Stimulation of the ganglionated plexus in the LA induces firing of the PV with consecutive AF in the experimental models. The close anatomic relation of epicardial autonomic plexus and the PV ostia have spurred speculations that catheter ablation could in part prevent AF by eliminating autonomic innervation of the left atrium. The clinical relevance of these concepts remains to be studied prospectively.

**Left atrial appendage occlusion or excision—elimination of prothrombotic endocardium**

Another aspect of surgical treatment of AF is the removal of the LAA. The LAA is the main area for clot formation in the atria. Stasis and thrombus development in the LAA is the main source for cardio-embolic events in patients with AF. Oral anticoagulation is a very effective and safe therapy to prevent AF-related strokes. After the MAZE procedure, strokes are rare. This may be a result of the excision of the LAA. This 'antithrombotic effect' may either be due to the marked stasis in the fibrillating LAA compared with other areas of the left atrium or due to the endocrine activity of the LAA endocardium ('endocardial remodelling'). Presently, there are two devices available that close the LAA via a percutaneous access (PLAATO and WATCHMAN). They might be considered in patients with a high risk of stroke and contraindications for oral anticoagulation. The efficacy of stroke prevention is presently under investigation.

**Atrioventricular (AV)-nodal ablation and pacemaker implantation for rate control**

Left ventricular failure is one of the main causes of symptoms in AF, and can in addition accelerate structural remodelling in the atria. Therefore, adequate rate control is an important therapeutic modality to prevent AF-related symptoms, and potentially—yet unproven—to prevent recurrent AF. Drugs that slow AV nodal conduction can achieve adequate rate control in the vast majority of patients. In patients with suboptimal medical rate control or intolerance of medication, AV nodal ablation and pacemaker implantation are a valid therapeutic option to control ventricular rate. The procedure of AV-node ablation has high success rates (>90%). In patients with paroxysmal AF, a dual-chamber pacemaker should be implanted, while patients with permanent AF require a ventricular pacemaker with adequate rate response algorithms. There is a small risk of ventricular proarhythmia (<0.1%) in the first week after AV-node ablation that may be reduced by high basal pacing rates. Patients with markedly reduced left ventricular function may require biventricular pacing to prevent deterioration of left ventricular function secondary to asynchronous activation of the left ventricle. This reasonable concept requires prospective testing in controlled trials. Biventricular pacing can also reduce AF recurrences in selected patients with heart failure.

**Internal atrial defibrillation and pacing to prevent atrial fibrillation**

Pacemakers with atrial leads are at present the most reliable technology to detect asymptomatic AF. In addition, pacemakers have been used to prevent AF, with mixed effects.

Dual-chamber pacing reduces the incidence of AF in patients with and without prior episodes of AF compared with single-chamber ventricular pacing. Asynchronous atrial and ventricular activation can cause acute dilatation of the atria and may thereby initiate AF or accentuate structural atrial remodelling. Intrinsic activation of the ventricles via the AV node may lower the incidence of AF in patients with dual-chamber pacemakers because right ventricular pacing is recognized as inducing ventricular atrial cardiomyopathy in some patients. It appears reasonable to use pacemakers that avoid ventricular pacing in patients with paroxysmal AF.

Several 'antitachycardia' pacing algorithms have been designed to terminate AF early after its initiation. In practice, pacing does often not terminate AF, and the effects of preventive atrial pacing on AF recurrence are unequivocal. Slow and regular atrial tachycardias can, in contrast, at times be terminated by antitachycardic pacing, possibly due to the macro-reentrant nature of these tachycardias.
Prevention of low heart rates can partly prevent paroxysmal AF. Other algorithms attempt ‘rate smoothing’ in the atria by continuous atrial pacing slightly faster than the intrinsic sinus rhythm, or by increased (paced) atrial rates after premature atrial complexes. These types of algorithms can only prevent a small portion of AF recurrences.

Atrial defibrillators can consistently terminate AF early after its initiation. Conceptually, early atrial defibrillation could reduce electrical remodelling by early termination of AF. These devices did not find broad acceptance because internal cardioversion is uncomfortable for AF patients. Furthermore, immediate cardioversions predisposes to recurrent AF. The reasons for these early recurrences are not well understood.

In theory, alternative (e.g. septal) pacing sites in the atrium may reduce AF by activating the atrium more simultaneously and thereby preventing re-entry. Besides a higher dislocation rate in alternative lead positions (septal, coronary sinus, or biatrial pacing), this strategy has not proved to be beneficial on reduction of AF episodes in clinical trials. In summary, prevention of bradyarrhythmia and maintenance of ‘natural’ ventricular activation via the AV node may have the potential to contribute to prevention of AF. Antitachycardic pacing can terminate macro-reentrant tachycardias without much effect on AF. Pacemakers are the most reliable monitors to detect asymptomatic AF recurrences at present.

Future therapies

Controlled prospective clinical trials are needed to further evaluate non-pharmacological treatments of AF. Although mortality studies require a long time for completion, large multi-centre studies on the impact of catheter ablation on the mortality are under way (Kirchhof et al., see Table 3). Standardized outcome parameters have to be applied in any study concerning AF, and possibly also in clinical trials. Owing to the high amount of symptomatic episodes, symptomatic AF recurrence is not sufficient to assess recurrent AF.

New technical tools to facilitate AF ablation are needed. Presently, the recovery of conduction across ablation lines is a major problem of catheter-based AF ablation. New energy sources and technical equipment that ensures single and highly effective procedures have to be developed. Concepts for rhythm control therapy when pulmonary vein isolation fails are needed.

Many non-pharmacological therapies for AF have been developed without a clear understanding of their pathophysiological target. A better understanding of the causes of AF in individual patients may help to select such therapies appropriately. In addition to non-pharmacological therapies, new antiarrhythmic drugs and a better understanding of the atria as endocrine organs will probably increase the treatment options of AF patients. The multifold causes and consequences of AF suggest that a successful rhythm control strategy may require early and multimodal therapeutic interventions, i.e. a combination of life-style changes, pharmacological therapies, and non-pharmacological therapies. Such a therapeutic strategy requires a careful individual balance of benefit and risk. Slowing down the progression of AF rather than ‘curing AF’ may be a reasonable treatment goal for many patients in the foreseeable future.

References