What's new in diagnosis and therapy of atrial fibrillation?
New drugs, new ablation techniques and new devices

Isabel Deisenhofer

Deutsches Herzzentrum München, Technische Universität München, Munich, Germany

Abstract

Management of atrial fibrillation (AF) regarding new diagnostic and therapeutic tools has constantly evolved over the last years.

For paroxysmal AF, implantable loop recorders offer new options for better assessment of AF burden. For treatment, pulmonary vein (PV) isolation has evolved an accepted, effective treatment with ~75-85% of patients in stable sinus rhythm. Since the rate of major complications of 2.5% is relatively low, PV isolation is nowadays the first choice therapy for symptomatic patients with drug-resistant paroxysmal AF. To reduce the most frequent reason for AF recurrence after PV isolation, i.e. reconnection of formerly isolated PV, new techniques including pharmacological testing for dormant PV connection and more precise testing for incomplete ablation lines by pacing manoeuvres have been introduced. New ablation tools include contact force measuring catheters for larger and more durable lesions by better catheter tip to tissue contact, and balloon-shaped ablation catheters providing single shot PV isolation using cryo-energy or laser applications.

For persistent AF, assessment of the atrial substrate maintaining AF by 3-dimensional magnetic resonance imaging (3D MRI) has the potential to predict ablation outcome. For the treatment of symptomatic persistent AF, the best ablation approach is a matter of debate, with linear ablation concepts competing with the ablation of complex fractionated atrial electrograms (CFAE). The combination of both techniques seems to provide the best results, with 65-80% of patients in stable sinus rhythm. These favourable results, however, are only reached after 2-3 ablation procedures.

For new antiarrhythmic drugs, dronedarone has widely deceived the high hopes, revealing considerable liver toxicity, increased mortality for some AF patients' subgroups and sobering antiarrhythmic effect when compared to amiodarone for the suppression of AF. New oral anticoagulants which act by direct inhibition of thrombin or factor X are promising and are expected to facilitate considerably future clinical practice. In large trials, they were found to be comparable or better than warfarin regarding the incidence of ischemic stroke and major bleedings including intracranial bleeding.

Key words: atrial fibrillation, medical treatment, pulmonary vein isolation

Introduction

Atrial fibrillation (AF) is the most common human arrhythmia and associated with significant morbidity and mortality. The incidence increases dramatically with age and approximately 10% of patients older than 70 years suffer from AF prompting a constant search for new diagnostic and therapeutic options for AF [1-3].

In this review we try to give an overview of new developments in the field of AF diagnosis and treatment.

AF is not AF

While it is not completely new, the classification of AF into the "3 P" classification scheme introduced in 2006 allows differentiating AF into pathophysiologically different entities [4, 5]:
- Paroxysmal AF is defined as AF lasting not longer than 7 days, with spontaneous restoration of sinus rhythm (SR)
- Persistent AF is defined as AF lasting longer than 7 days requiring electrical or pharmacological cardioversion to SR
- Long-lasting persistent AF is the subgroup of persistent AF patients with an episode lasting longer than 1 year
- Permanent AF is defined as AF which cannot be converted to SR or where there is general consent that conversion to SR is not desired or thought to be impossible.

Pathophysiologically, episodes of paroxysmal AF are thought to be initiated by triggering foci inside the pulmonary veins (PV) generating atrial extrasystolics and atrial bursts. The atria are driven into AF by these foci, but there is only small if any atrial remodelling, so that AF stops spontaneously after a short time. Consequently, the electrical isolation of the PV, first described by Haissaguerre et al. [6], remains the cornerstone of all ablation approaches for paroxysmal AF. With this ablation approach, elimination of AF can be achieved in approximately 60-75% of patients (75-85% when more than 1 ablation procedure is performed) [7, 8].

In persistent, long-lasting persistent and permanent AF the progressive electrical, structural and finally anatomical remodelling of the atria leads to the persistence of AF. Thus, initiating triggers are less important than the maintaining substrate of AF in these patients. There are diverging opinions how to correctly identify this substrate maintaining AF, leading to a disparity of ablation approaches. The isolation of PV, however, remains the first step of ablation also in these patients.

According to their distinct pathophysiology, new diagnostic and therapeutic strategies are divergent in paroxysmal and persistent AF.

Paroxysmal AF

New diagnostics

In patients suffering from paroxysmal AF, correct rhythm monitoring is clinically extremely important in the view of potential thrombembolic complications caused by non-detected AF and stopped oral anticoagulation. In the last years, it has become increasingly evident that paroxysmal AF is frequently under-diagnosed: even in symptomatic patients, 30% of episodes are asymptomatic and this percentage increases to up to 50% after initiation of a specific AF treatment [9-12]. Thus, assessment of AF burden or of AF treatment efficacy based on symptoms only is widely insufficient. There have been several studies comparing different modalities of rhythm monitoring including 24h Holter, 7 days Holter-ECG and trans-telephonic ECG monitoring [9-11]. The diagnostic value of 24h Holter ECG was found to be very limited, whereas it appeared that trans-telephonic ECG monitoring and 7 days Holter ECG provide the best approximation to real AF burden, with a striking loss of accuracy to only 67% detected AF episodes if the 7 day Holter ECG duration was reduced to less than 5 days [12].

A new tool to monitor for AF episodes are implantable loop recorders (ILR, e.g. the Reveal XT™ device) providing a continuous rhythm assessment. In the XPECT trial, where the Reveal XT ILR recordings were compared to a continuous 48h recording via conventional Holter ECG in 247 patients with paroxysmal AF, the overall diagnostic accuracy of the ILR was 98.5%, with a sensitivity of 96.1% and a specificity of 85.4% [13]. There remain problems to be solved, e.g. the correct automatic detection of AF in the presence of frequent atrial and ventricular extrasystolics or pseudo-regularized AF, but compared to the gold-standard of 7 days Holter ECG, the ILR has the advantage of a continuous, long-lasting recording, faster rhythm evaluation and the automatic arrhythmia detection. It requires, however, the invasive implantation (and possibly explantation), which is a drawback for this tool.

New ablation techniques

Pulmonary vein isolation and the problem of reconnection

The isolation of the PV is since 2000 with the seminal work of Haissaguerre et al. from Bordeaux the cornerstone of any paroxysmal AF ablation approach [6]. Since then, the level of isolation has moved more and more from the ostium to the antrum of the PV and most operators prefer a circumferential PV isolation with two common isolating ablation rings around the ipsilateral veins [7, 8]. The lesions are usually placed with an open irrigated tip ablation catheter applying radiofrequency energy (RF) in a point-by-point manner. For this, 3 dimensional (3D) mapping systems, mainly the NavX system (St. Jude Medical, St. Paul, MN, USA) and the Carto3 system (Biosense-Webster, Diamond bar, CA, USA), are widely used. In the newest version of both systems, the simultaneous display of all intracardially placed catheters with their spatial relation to each other and to a reconstructed anatomic shell of the left atrium and the PV is possible. Additionally, the left atrial anatomy as segmented from a preprocedural CT or MR scan can be fused with the reconstructed anatomy, allowing optimal anatomic guidance for placement of the ablation lesions [14-16]. With this approach, elimination of AF can be achieved in 65-85% of patients, with approximately 2.4% of periprocedural complications and approximately 20% of patients necessitating a repeat PV isolation [17-18].

While the acute isolation of all PV is nowadays reached in >98%, the durability of the applied lesions has emerged to be a crucial problem: in a recent study by Willems et al. [19], where 40 patients after PV isolation were re-studied invasively irrespective of AF relapse, 40% of PV were reconnected 3 months after initially successful isolation. Even more importantly, all patients without any reconnected PV were free from AF, whereas patients with 2 reconnected PV experienced relapse of the arrhythmia. These results and abundant data from repeat ablation procedures for arrhythmia recurrence strongly suggest, that relapse of paroxysmal AF is caused mainly by reconnection of the PV [19-23]. Even late arrhythmia recurrence more than one year after ablation, which occurs approximately in 2-6% of patients, seems to be caused by the reconnection of the PV-left atrial conduction [21]. To improve the durability of PV isolation some operators suggest an intra-procedural waiting period of up to 1.5 hours with recurrent re-isolation of reconnecting PV. Another approach is to test apparently isolated PV for dormant residual conduction by injecting adenosine and to re-isolate the respective PV, if such a residual, but masked conduction can be demonstrated during adenosine administration [24-26].

Since recurrence of conduction is thought to be caused by incomplete, non-transmural lesions, new ablation catheters were designed, allowing measuring the contact force of the catheter tip to tissue interface during ablation. In animal models it could be shown that lesion depth and volume will increase with higher contact force (CF), providing better transmurality and thus

less reconduction [27, 28]. In the recently published "Toccata" study, safety and efficacy of the Tacticath™ (Endosense, Geneva, CH) CF ablation catheter system was demonstrated in human right atrial tachycardia and in AF ablations [29].

Alternative ablation systems for pulmonary vein isolation

In the last years, a variety of innovative catheter designs have been tested with the aim of applying a circular, linear ablation lesion avoiding thus the cumbersome alignment of RF point lesions to a (hopefully complete) line. All these catheters share the concept of a balloon shaped device that is advanced to the ostium of the vein. Thereafter, ablation energy is delivered via the catheter in a circumferential manner.

The **pulmonary vein ablation catheter** (PVAC; Ablation Frontiers, Medtronic, Minneapolis, MN, USA) is a distally circular shaped catheter with 10 electrodes mounted on the distal ring. These electrodes are used for mapping of PV activation as well as for the isolation of the PV using duty-cycled RF energy. Thus, only one catheter (for PV mapping and PV isolation) is necessary and a completely circumferential lesion can be delivered with one energy application. First results show a similar success rate regarding acute achievement of PV isolation and regarding mid-term elimination of AF with 60-81% [30]. However, in a randomized study comparing RF energy ablation, cryo balloon ablation and PVAC ablation, significantly more patients after PVAC ablation than after RF or cryo ablation showed new embolic cerebral lesions in post-ablation MR scans (37.5% vs. 7.4% vs. 4.3%) [31]. The MR detected lesions were not associated with major neurological symptoms, but it is recommended that in future patients treated with PVAC should undergo further neuro-psychological examinations.

The most commonly used of these devices is the **cryo balloon tool** (Arctic Front™, CryoCath, Medtronic, Minneapolis, MN, USA). In several medium scale studies, a suc-

cess rate of 68-74% regarding AF elimination could be documented in 6-12 months follow-up [32-36]. This is very similar to the published results for RF ablation, which ranges between 60-80%. Regarding periprocedural complications, it seems that the Cryo balloon causes less (but not zero) moderate PV stenosis, whereas phrenic nerve palsy occurs in 3-12% of patients [36]. The latter is a complication that is almost uniquely reported with balloon shaped ablation devices, with a high incidence during cryo ablation. The majority of these phrenic nerve palsies resolves after <12 months, but can lead to shortness of breath in the meantime.

A new balloon like tool is the **endoscopic laser ablation system** (EAS). It consists of a DO2 filled compliant balloon and a catheter shaft containing a fibre connected to a 980nm laser diode source and a 2F fiberoptic endoscope. The balloon is placed at the PV antrum and the laser beam can be directed circumferentially to the ostium with constant visualization via the fiberoptic endoscope. First results of ablation with this tool are encouraging, with 60% of patients free from AF after 1 year of follow-up [37].

Persistent atrial fibrillation

It has to be stated that in contrast to paroxysmal AF, where PV isolation is a highly effective treatment option, the ablation of persistent AF is associated with a significantly lower efficacy of 35-45% if only one ablation procedure is performed. This percentage increases significantly to 65-75% of AF free patients, if additional ablation procedures are accepted. However, ablation still remains the best option for elimination of persistent AF, because the treatment alternative of cardioversion with additional drug administration to avoid AF relapse has an overall efficacy of only 10-30%.

New diagnostics

As pointed out above, the key feature of persistent AF is the so-called atrial substrate maintaining AF. While the existence of atrial substrate is widely accepted, it is a matter of intensive debate what the patho-physiological or anatomical correlate of substrate exactly is. Hypotheses include remodelled atrial tissue with lost gap junctions and atrial fibrosis, but also autonomic dysbalance with overactive mixed ganglionated plexi causing changed excitability and refractory periods of atrial myocytes or anatomically fixed areas of larger re-entrant waves which promote AF by producing a "mother wave" reentry. A newly emerged method to measure the extent of atrial fibrosis and by this the putative extent of AF maintaining substrate is high density cardiac MR. Oakes et al. [38] could show that late gadolinium enhancement (LGE) areas in the atrial wall detected by 3 dimensional magnetic resonance imaging (3D-MRI) correspond to scarred or fibrotic atrial tissue. Thus, 3D-MRI could offer a possibility for pre-procedural quantification of atrial substrate, allowing forecasting the possible outcome of AF ablation in a specific patient. The after-processing of the 3D MRI scans, however, to obtain information on atrial wall scarring is extremely time-consuming and expensive and its wide-spread applicability in clinical practice seems at least questionable.

New ablation techniques

Due to the debate regarding the nature of the atrial substrate, there is no "standard" ablation technique for persistent and long-lasting persistent AF. The isolation of PV, though, is in most ablation approaches the first step of the procedure. Thereafter different techniques are applied to eliminate or reduce the AF substrate.

In the linear ablation approach, left atrial ablation lines are deployed to compartmentalize the left atrium, leading to a reduction of multiple micro-reentries present during AF

to larger re-entrant waves. These larger (and slower) re-entrant waves eventually stop at the ablation lines which serve as wave front breakers [39, 40]. This approach follows the example of the surgically deployed MAZE procedure, in which surgeons apply under direct view a set of linear ablation lesions during concomitant cardiac surgery. To copy this approach by catheter ablation is challenging, since complete lines by applying point-by-point lesions are hard to achieve in a trabeculated left atrium in the beating heart of a breathing patient without direct view of the lesions.

A completely different approach has been introduced in 2004 by Nademanee et al. with the ablation of complex fractionated atrial electrograms (CFAE). CFAE are supposed to reflect zones of slow conduction and heterogeneous de- and re-polarization, i.e. electrophysiological properties of the "substrate" [41]. By ablating focally areas showing CFAE, a gradual reduction of the number of atrial micro-reentries during AF can be achieved leading to a gradual prolongation of the AF cycle length until only one macro-reentry, i.e. one singular atrial tachycardia (AT) instead of AF, is left. Subsequently, sinus rhythm can then be restored by ablating these AT [42].

Data from a randomized study from our centre suggest, that the results after a single ablation procedure regarding freedom of any arrhythmia are similar for the linear and the CFAE ablation approach (~35%), but it seems that CFAE ablation causes significantly more often AT as a relapse arrhythmia than the linear ablation approach [43]. However, if the repeat ablation is performed for AT and not for AF, results are significantly better with 75% of patients in SR after AT ablation compared to 42% after repeat ablation for AF [44]. Thus, the ablation technique used for the first ablation has a significant impact on the success of the repeat ablation.

Haissaguerre et al. were the first to perform a combined ablation approach (the so-called stepwise ablation) applying in one procedure first CFAE ablation and then lines

[45]. The results of a single ablation procedure (approximately 35%) are more or less the same as for the single ablation approach, but again the success rate after more than one ablation reaches as high as 82% of patients in stable SR with 80% of the recurrent arrhythmias being AT and not AF any more [46,47].

New drugs

New antiarrhythmics

It has to be stated, that antiarrhythmic drugs (AAD) for rhythm control in AF have been studied extensively in a multitude of studies, as well in randomized comparisons to placebo, in comparisons to other AAD as in comparison to catheter ablation. In all these studies, irrespective of the drug, AAD proved to be of low to moderate efficacy with only 10-30% of patients in stable SR in a follow-up of minimum one year. In the series of randomized trials comparing AAD to ablation in paroxysmal AF, ablation proved to be significantly more effective in all of these studies as well as in a meta-analysis of the published trials [8].

Vernakalant

Vernakalant is a new antiarrhythmic agent acting selectively on atrial ion channels which can be used for rapid pharmacological cardioversion of AF. It has been evaluated in the AVRO trial, where vernakalant (intravenously) was randomly compared to amiodarone [48]. Vernakalant proved to be significantly more effective in cardioversion of new onset AF than amiodarone i.v. (51.7% vs. 5.2% of patients). As anticipated, due to its atrial selectiveness, vernakalant proved to be safe with no ventricular arrhythmia observed. While these are encouraging results, the limitations of vernakalant are its availability only for i.v. use, and its high costs as well as the fact that with external electrical cardioversion, more than 95% of patients can be cardioverted successfully.

Dronedarone

The class III potassium channel blocker dronedarone has been introduced in the last years for the treatment of paroxysmal and persistent AF. It was supposed to have a similar antiarrhythmic effect than amiodarone but significant less side effects, including no hypo- or hyperthyroidism. However, reports about a significant hepatotoxicity which necessitated in singular cases even liver transplant and only moderate effectiveness calmed down the initial enthusiasm [49]. In the Dionysos study, where AF patients were randomly assigned to amiodarone or dronedarone for suppression of AF in a short term follow-up of 7 months, amiodarone proved to be significantly more effective (58% of patients free from AF) than dronedarone (26.5% free from AF) [50]. The PALLAS trial, published recently, where persistent AF patients were included, was even preliminary stopped due to an excess mortality in the group of patients treated with dronedarone [51]. Thus, it has to be stated that dronedarone has a limited efficacy while it has not negligible side-effects and its use should be restricted to patients with paroxysmal AF in whom regular liver markers controls should take place.

New anticoagulants

The most feared complication of AF are thrombembolic complications and the indications for oral anticoagulation for AF patients have been recently extended to patients according to the new CHADSVASC score. In this score, age between 65-76 years, female gender and any vascular disease have been added as risk factors. On the other hand, the use of ASS instead of oral anticoagulation in low risk (score 1) patients has been discouraged.

Regarding the low percentage of patients who are actually in the therapeutic INR range (in general, it is only approximately 60%), search for new, easier to use oral anticoagulants has been intensive. In the last 4 years, three new oral anticoagulants have emerged, that could replace in long term the nowadays

used warfarin or phenprocoumon. First approved for AF due to the RELY study was dabigatran (Pradaxa™, 2x110mg or 2x150mg), followed by rivaroxaban (Xarelto™, 1x20mg; following the ROCKET trial), whereas apixaban is awaiting the approval after the successful ARISTOTLE trial [52-54]. While dabigatran is a direct thrombin inhibitor, rivaroxaban and apixaban are activated factor X antagonists. The results for all three in the respective trials can be summarized as follows: the efficacy in suppression of thrombembolic events was comparable or superior to warfarin, whereas major and/or intracranial bleedings were reduced or similar.

All of them have the advantages of fixed dosage independent of nutrition (especially vitamin K intake) with no INR controls necessary, as well as short half-time duration of less than 24h. Thus, they will be especially useful in patients with varying liver functionality as well as in patients with instable INR values or in patients unable or not willing to undergo regular INR measurements. Furthermore, due to their short half-time, peri-operative management of anticoagulated patients will be much simpler. Future studies have to be conducted to verify the so far positive impression, especially regarding potential drug-drug interactions or rare, but severe, side-effects. Additionally, the so far still high treatment costs should come down significantly.

Conclusion

The management of atrial fibrillation has evolved significantly over the last 5-10 years. For paroxysmal AF, isolation of the pulmonary veins has proven to be the most effective treatment option to achieve freedom of arrhythmia. New ablation tools and strategies have the potential to increase even further the success rate and to improve the durability of the ablation effect in long-term follow-up. For persistent AF, ablation techniques are still evolving, mainly due to competing concepts of the pathophysiology of

this arrhythmia. Regarding freedom of arrhythmia, catheter ablation is still the most effective treatment, but results have to improve, especially regarding results of a single ablation procedure. New antiarrhythmic drugs have been developed to treat AF, but it has to be stated that dronedarone, the most prominent of these new drugs, has failed to stand the test of time and studies. Its indication should be carefully evaluated. New oral anticoagulants yielded promising results in the first large multicentric randomized trials and could replace vitamin K antagonists in the near future.

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Address for correspondence:
Isabel Deisenhofer, M.D., Ph.D.
Deutsches Herzzentrum München
Technische Universität München
Lazarettstr. 36
80636 München
Germany
deisenhofer@dhm.mhn.de