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SUPPLEMENT PAPER

Innovations and paradigm shifts in atrial fibrillation ablation

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Abstract

Treatment of symptomatic atrial fibrillation has seen important changes in the past decades. Advancements have especially been made in the field of non-pharmacological treatment of this disease. Patients in whom a rhythm control strategy is chosen the place of catheter ablation has become more frontline therapy in the past years. The procedure itself has also seen changes in technologies that can be used, either using point-by-point radiofrequency or one of the single-shot techniques. One of the major limitations that remain is that re-do procedures are often necessary due to incomplete pulmonary vein isolation and/or atrial fibrillation being initiated by other mechanisms than pulmonary vein triggers. Therefore, there is further need for developing ablation tools that reproducibly isolate the pulmonary vein transmurally. Furthermore, addressing the underlying conditions before and after catheter ablation has been shown to be of great importance. In this review, we will give an overview of the evolution of catheter ablation, highlight the latest technologies and their future endeavours, and lifestyle modifications are being discussed as part of the catheter ablation strategy.

Keywords Atrial fibrillation • Pulmonary vein isolation • Technology • Innovations • Review

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased morbidity and mortality.[1] Recent AF guidelines consider pulmonary vein isolation (PVI) as first-choice treatment for maintenance of sinus rhythm and symptom improvement, especially in patients with paroxysmal AF.[1] Unfortunately, a significant proportion of patients experience AF recurrences following PVI (10–35% in the first year).[2,3] This is of importance as repeat procedures are associated with substantial costs and potential complications. The explanation for AF recurrences following PVI is complex and multifactorial. First, with the current ablation modalities transmurality of ablation lesions is often not obtained and as a consequence reconduction of one or more of the pulmonary veins occurs.[4] Secondly, many patients with AF have underlying cardiac conditions such as hypertension, heart failure, or valvular disease and in these patients marked atrial dilatation and atrial fibrosis is often present.[5] Elimination of potentials triggers by PVI will not be sufficient to restore and maintain long-term sinus rhythm. Consequently, if a patient experiences a recurrence of AF following ablation this could be explained by incomplete PV isolation and/or initiation and maintenance of AF by other mechanisms than PV triggers. For this reason, there is a need for further development of ablation tools that reproducibly isolate the PV with durable transmural ablation lesions. In addition, optimal patient selection based on clinical characteristics might aid in the decision whether or not the patient may benefit from PVI and ideally should guide the lesion set/ablation approach.

Ablation tools for pulmonary vein isolation

In 1998, Haissaguerre *et al.*[6] described the role of focal drivers within the atrial muscular extensions of the pulmonary veins for initiation of AF. This pivotal paper laid the foundation of our current

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understanding of AF with respect to invasive endocardial or epicardial ablation strategies. Although much remained unknown, for example, which electrophysiological and pathophysiological processes underlie these focal triggers, this hallmark paper with only 45 patients marked the beginning of a new era of invasive AF management. Currently, the cornerstone of AF ablation is PVI.[1] Especially in patients with paroxysmal AF PVI is as first-line therapy very effective with regard to AF recurrence.[7,8] Besides eliminating PV triggers, PVI may also have anti-arrhythmic effects due to atrial debulking or to interruption of microre-entry at the PV ostium/antrum.[7–9] Over the years, the importance of achieving durable PVI for maintaining sinus rhythm was supported by several observations. For example, in the GAP-AF trial, it was demonstrated that patients with incomplete PV isolation had a higher recurrence rate of AF than patients with complete PV isolation.[4] Since there is a large number of patients referred for AF ablation there is a great need for a safe, effective ablation tool that is easy to use with short procedure times. The most widely used ablation approach is point by point circumferential ablation of the PVs using a single tip catheter with radiofrequency as energy source. The past decade several single-shot technologies have also been developed. These have the advantage of isolating the PV in one ablation attempt, rather than performing a point-by-point isolation. Examples of widely used single-shot devices are the multi-electrode circular ablation catheter, the cryoballoon catheter, and laserballoon technology (*Figure 1*). In the FIRE and ICE trial, a head to head comparison was evaluated between radiofrequency 'point by point' ablation vs. cryoballoon ablation in patients with paroxysmal AF.[2] This trial showed less PV reconnection at redo procedures in the cryoballoon-treated patients, and therefore needed fewer additional lesions to achieve success.[10] Still, major progress is made in the understanding of lesion formation for the different ablation tools. To move the outcome of radiofrequency point-by-point, ablation forward improvements in incorporation of impedance information, tissue contact, catheter stability, ablation time, and catheter tip temperature have been introduced.[11] Shorter procedure times can be achieved by high power, short duration radiofrequency point-by-point ablation (*Figure 1*).[12] In contrast to longer application of 60 s and 35 W, shorter application of 5–10 s with 45–50 W is being performed.[13] Long-term follow-up is promising, however, this technique has not yet been investigated in a large randomized trial.[13] Subsequent steps in this field are already underway which is called very high-power short duration. This strategy allows applications of 70 or 90 W.[14,15] In the field of single-shot device, a promising technique is pulsed field ablation. Pulsed field ablation is a technique which rapidly gained interest as it has been shown to be effective in creating myocardial lesions while reducing the risk of collateral damage (*Figure 1*).[16] It is a non-thermal ablation technique that preferentially targets myocardial tissue (in contrast to other currently used ablation tools). At present, only a small patient series has been reported: in patients with persistent AF, it appears to be feasible to perform PVI in combination with posterior wall isolation with excellent acute success.[16] It is particularly reassuring that in these first attempts with pulsed field ablation it appears that no oesophageal, phrenic nerve, or pulmonary vein stenosis was encountered. Also, the lesions (both PVI and the posterior wall) appear to sustain over a short period of follow-up as assessed with a remapping procedure.[16] Further studies into this novel single-shot device are definitely needed, as well as larger series, long-term follow-up, and comparison with other single-shot or point-by-point strategies. PVI can also be performed by the cardiothoracic surgeon either via a thoracoscopic approach as stand-alone procedure or concomitantly during open chest cardiac surgery.[17] The PVs are addressed by epicardial application of a bipolar radiofrequency clamping device. The surgeon has direct visibility of the PVs and after clamping of the two jaws there is no blood flow anymore at the site

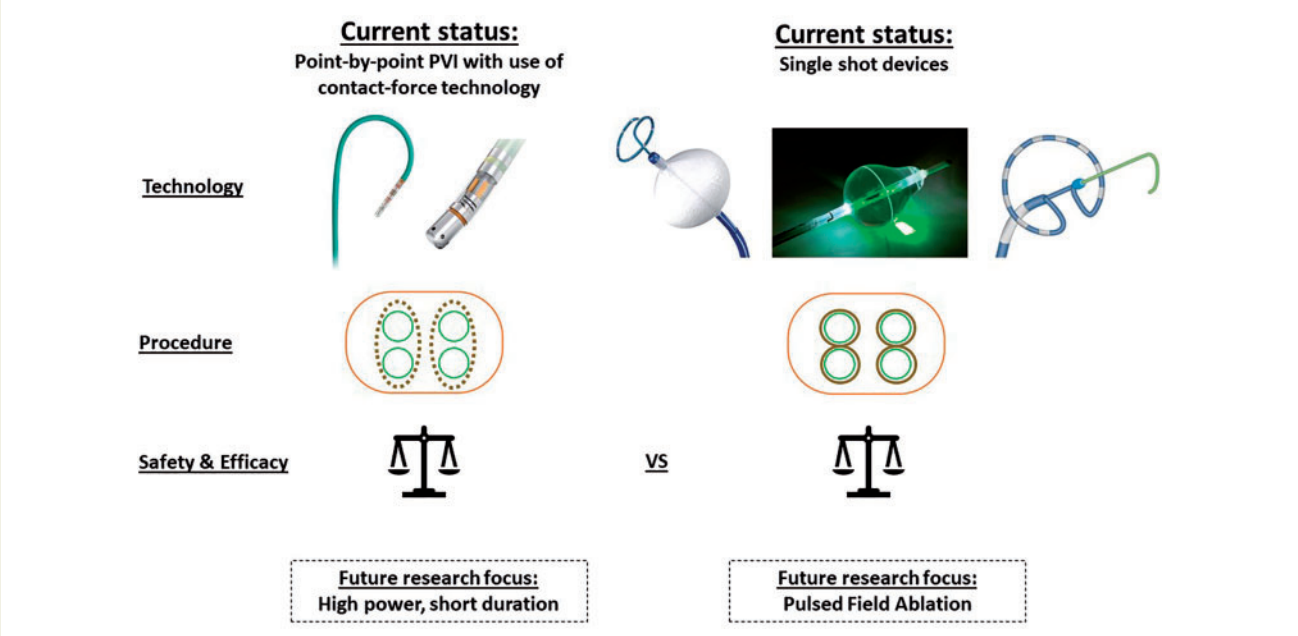

Figure 1 Current status and future prospects of point-by-point ablation and single-shot devices. PVI, pulmonary vein isolation.

of ablation. This eliminates the heat-sink cooling effect to the tissue during ablation. This result in transmural ablation lesions with excellent durable isolation of the PVs.[18]

Patient selection and ablation strategy

Despite the advancements that have been made in the technological aspects of PVI in the past two decades, the success rates in patients with persistent forms of AF remain limited.[19] Apart from the durability and transmurality of the ablation lesion set, the outcome after PVI is affected by factors associated with the extent of the AF substrate or atrial remodelling, such as the AF type, the size of the left atrium, and relevant underlying conditions.[1] A hypothetical treatment strategy is shown in *Figure 2* where additional extensive ablation options are shown with relation to a larger left atrial volume, higher AF burden, or more underlying conditions. Of course, any of these steps might be used when deemed necessary (e.g. performing a mitral isthmus line). The development of atrial disease or atrial myopathy may start years before the first initiation of AF.[20] This interplay between atrial myopathy and AF is based on complex interactions accelerated by risk factors as aging, inflammation, oxidative stress, and stretching of the atria.[20] These myopathic changes may consequently lead to disturbances in the properties of myocardial electrophysiology and the cardiac autonomic nervous system, structural changes (characterized by fibrosis), and may result in endothelial dysfunction leading to increase in pro-thrombotic state.[20] Therefore, it is of importance to treat the underlying conditions in as early stadium as possible to slow down the progression of AF. Several trials have shown improvement in outcome when underlying conditions are aggressively treated. In RACE 3, this was performed in an early stadium (history of AF less than a year) and showed an improvement in sinus rhythm maintenance at one year when compared with conventional therapy.[21] Or this may be introduced as an integral part of (pre or post) PVI management as was performed in two pivotal trials.[22,23] In these two studies, patients received, regardless whether there was a clinical history, an aggressive risk factor management including weight management and exercise, treatment of hyperlipidaemia, obstructive sleep apnoea, hypertension, diabetes, and cessation of alcohol and smoking. These types of intervention may reverse the severity of atrial myopathy and should therefore be implement early on.[1,20,22,23] Optimal patient selection before PVI could potentially increase the effectiveness of AF ablation. Several clinical risk scores have been introduced in the past years to predict AF recurrences after PVI.[24,25] The APPLE score includes underlying conditions as age, AF type, renal function, LA diameter, and left ventricular ejection fraction and has been associated with AF recurrences after a single PVI.[25] The DR-FLASH score has been associated with left atrial low voltage areas.[24] The presence of these areas, as a measure of AF substrate, has been shown to be a powerful predictor of arrhythmia recurrence after catheter ablation.[26] Biomarkers, like NT-proANP, have been incorporated in risk scores as well and have demonstrated good prediction of low voltage areas.[27] Moreover, additional imaging of the left atrium may be used to assess the left atrial substrate. An interesting study in this field was the Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF) trial.[28] All patients underwent a delayed enhancement MRI scan of the left atrium prior to PVI. Atrial tissue fibrosis identified by MRI was associated with increased risk for recurrent AF. Concerning optimal patient selection, the factors described above might be able to identify patients who may not benefit from

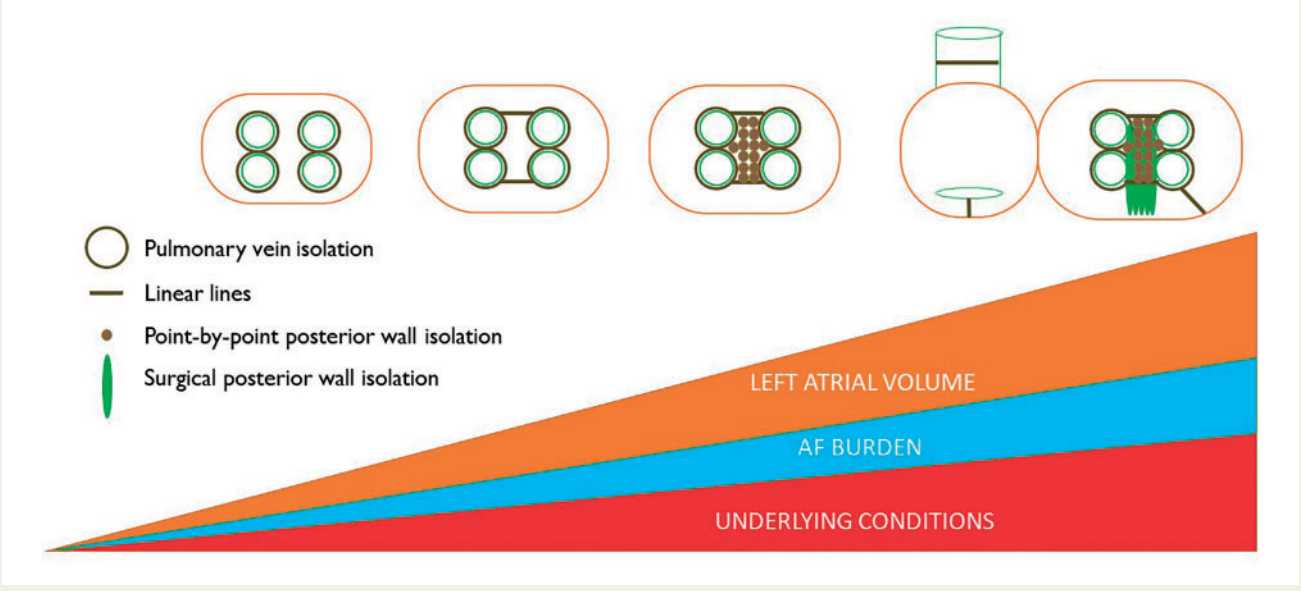

Figure 2 Hypothetical illustration of the different steps in ablation strategy in relation to underlying atrial volume, AF burden, and underlying conditions. Due to advanced disease or clinical judgement (e.g. mitral isthmus-dependent flutter) one of these steps may be performed in an earlier stadium.

PVI. Often a PVI only approach is not sufficient to maintain long-term sinus rhythm in patients with persistent forms of AF and therefore more extensive ablation has been advocated. This may include linear lesions in the atria, isolation of the LAA or of the superior vena cava, coronary sinus, ablation of complex fractionated electrograms, rotors, non-pulmonary foci, or ganglionated plexi, fibrosis-guided voltage and/or MRI-mapping, or ablation of high dominant frequency sites.[1,29,30] However, many of these additional ablations techniques have not been investigated in a randomized fashion. Recently, it was shown that PVI in combination with ethanol infusion in the vein of Marshall, as compared with PVI alone, increased the likelihood of remaining free of AF or atrial tachycardia for 12 months.[31] In the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II (STAR AF II), the issue of additional substrate modification was addressed. This trial showed that patients with persistent AF did not benefit from linear ablation or ablation of complex fractioned electrograms if this was performed in addition to PVI.[32] An issue that remains after this trial is whether the ablation techniques used were sufficient enough to create transmural lesions. It could be that in some patients with extensive underlying conditions or increased left atrial size the primary approach should be to perform a thoracoscopic surgical ablation as higher success rates may be reached by creating transmural lesions (*Figure 2*).[33] Moreover, a more tailored and individualized approach might be the preferred strategy instead of creating 'one size fits all' lesions indiscriminately. Kircher *et al.*[34] demonstrated that an individually tailored substrate modification guided by voltage mapping was associated with a significantly higher arrhythmia-free survival rate compared with a conventional approach of applying linear ablation according to AF type. Comparably, one could use MRI data to incorporate into an optimal ablation strategy for any individual patient. In the Efficacy of DE-MRI-Guided Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II; URL: https://www.clinical-trials.gov. Unique identifier: NCT02529319), patients are randomized to PVI or PVI and additional fibrosis-guided ablation. Recently, a randomized trial including 155 patients randomized to MRI-guided atrial fibrosis PVI vs. conventional PVI and showed no improvement in outcome for MRI-guided PVI.[35] Therefore, the results of the larger DECAAF II will provide further insights whether there will remain a role for substrate ablation targeting atrial fibrosis in AF. Besides careful patient selection and an individualized AF ablation strategy, upstream therapy might improve the outcomes of AF ablation. Risk factor-driven upstream therapy refers to interventions that aim to modify the atrial substrate and also have a favourable effect on risk factors and diseases underlying AF. This was addressed in the beforementioned LEGACY and ARREST-AF studies were aggressive risk factor management conferred greater AF-free survival following catheter ablation compared with usual care.[22]

Paradigm shift in the treatment of atrial fibrillation

While looking back on the innovations and paradigm shifts in AF ablation it is important to realize that treatment of AF has been focused for a long time on rate vs. rhythm control.[36] Since both strategies showed similar morbidity and mortality the primary goal of rhythm control management was alleviation of AF symptoms. Recently, two contemporary rhythm control trials were published.[37,38] In The Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, 2204 patients with symptomatic AF were randomized to catheter ablation or medical therapy. The primary composite Endpoint of death, disabling stroke, serious bleeding was not different despite significantly fewer AF recurrences in the ablation arm.[37] The negative results of the intention-to-treat analysis of this study have been explained in several ways. First, high patient crossovers and event rates that were much lower than expected dampened the study's statistical power. Secondly, more than half of patients in this trial suffered persistent AF. Of note, per-protocol analyses suggested that catheter ablation-treated patients had reduced mortality compared with drug therapy. The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial EAST-AFNET 4, investigated a true early rhythm control strategy as opposed to the CABANA trial. Patients ($n = 2789$) with a short history of AF (<1 year) were randomized to early rhythm control consisting of AF ablation and AADs vs. usual care. After 2 years patients randomized to the early rhythm control had a lower risk of the primary composite outcome.[38] Similar to CABANA, EAST-AFNET 4 showed low event rates and the incidence of stroke was very low (0.6% early group vs. 0.9% in usual care group). Although data on AF burden are eagerly awaited, the trial showed that longer periods of sinus rhythm are associated with improved outcome. Based on these recent trials it appears that early intervention in the course of the disease by striving for sinus rhythm has prognostic benefit. As subsequently ablation is more effective in maintaining sinus rhythm compared with AAD, ablation may even move further forward towards first-line therapy.[7,8]

Conclusion

During the past two decades, catheter-based ablation of the pulmonary veins has become standard of care for rhythm control management of symptomatic AF. Recent large randomized trial data suggest that PVI not only reduces AF burden but may also have prognostic implications. Progress is made in ablation techniques that create durable transmural ablation lesions, advancements should now be made in the appraisal and treatment of the underlying substrate of AF. Combined this may potentially lead to an individualized pre- and post-ablation approach that will improve the outcome of AF ablation.

Conflict of interest: none declared.

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