European Heart Journal Supplements (2023) **25** (Supplement C), C249–C252
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad024

How the new technologies and tools will change the electrophysiology of the future

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KEYWORDS
Atrial fibrillation;
Ablation;
Radiofrequency current;
Cryo energy;
Laser;
Pulse field ablation

Novel technologies and therapies are evolving rapidly in the field of electrophysiology and cardiac ablation, particularly with the aim of improving the management of atrial fibrillation (AF) where pharmacologic treatment fails. High-power short-duration radiofrequency (RF) ablation, in association with the optimized cooling process of the electrode-tissue interface, is one of the most promising approaches for treating durable lesions and pulmonary vein isolation (PVI). Cryo energy, laser, and RF current are examples of novel tools used by competitive balloon catheter platforms and these tools are specifically created to properly promote an effective PVI. Specific mention deserves to be made on the linear array ablation with ultra-low temperature cryoablation that appears promising for durable lesions. It is needless to remind here about the novel evolving energy source in the form of pulsed electrical field (PFA), which results in an irreversible electroporation of myocardial tissue, sparing the surrounding tissue, and thus, apparently with a significant reduction of potential untoward effects. Furthermore, intensive research is in place to specifically investigate the activation pattern of AF so as to devise a patient-('tailored') target ablation, although with inhomogeneous results. Overall, it seems that technologies and therapies are evolving so rapidly than ever with the hope of achieving better long-term clinical results and an improved quality of life for our patients.

General considerations

Atrial fibrillation (AF) has become a challenging medical emergency worldwide because of its epidemic proportions leading to a significant increase in morbidity and mortality. Moreover, this clinical scenario poses critical logistical and economic challenges for healthcare systems across several countries. Over the last few decades, enormous efforts have been put in place by several basic and clinical investigators to better explore the pathophysiologic mechanisms of AF, proposing modalities and approaches of catheter and surgical ablation to treat arrhythmia and reduce its burden for patients. Since the seminal work of Haissaguerre *et al.*,[1] which showed triggering activity from the pulmonary veins (PVs) as one of the main mechanisms of AF, other investigational studies have followed in the attempt to devise effective methods to tackle arrhythmia. Radiofrequency catheter ablation (RFCA) has been the main energy source to be employed from the beginning of this journey. Despite the evolution of this technique over the years, including current contact-force sensing, which is the use of 3D navigation systems, it remains a time-consuming procedure in which the operator's experience and skill become paramount for defining the clinical outcome. This has led to the development of alternative modalities of ablation, especially relying on balloon-based catheter design, so as to overcome the time-consuming point-by-point radiofrequency (RF) technique. In this regard, the most widely used technology is cryoballoon,[2] which has been demonstrated to be equally effective but faster and easier to be employed. Equally effective and safe can be the balloon-based laser approach. In the perspective of improving the clinical outcome of catheter ablation of AF, the search for new tools and energy sources continues. The scope of this brief review is to give an update of the technology advancements in the field of AF ablation.

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Point-by-point radiofrequency ablation

This approach with a power setting between 25 and 35 W to create the so-called 'wide area of catheter ablation' (WACA) for achieving PVI has been in vogue for many years and several improvements have been suggested over time, such as a contact force (CF) between 10 and 30 g and the reaching of lesion size index values of 5–5.5 for each application with contiguous lesions not being apart by more than 5 mm. This can promote long-term freedom from AF in roughly 80–85% of patients.[3] Undoubtedly, this requires skills and highly experienced operators that lead to unlikely clinical outcomes across several EP laboratories. Moreover, concerns about the potential oesophageal damage and nerve injury causing gastroparesis limit the use of a higher RF power, especially in the posterior left atrial wall. A better understanding of the mechanisms leading to lesion formation by RF energy has given birth to the concept of high-power short-duration (HP-SD), in which the stability of the catheter is a less critical factor, and short applications with rapid energy guarantee lesion creation. The basic idea behind this concept is based on the creation of a homogeneous transmural '*resistive*' heating lesion, avoiding the fact that the '*conductive*' heating occurs with the creation of lesions that could reach the surrounding structures.[4] In this regard, a recent review and meta-analysis[5] showed a significantly shorter procedure, fluoroscopy exposure time, and RF ablation time for HP-SD and with no difference in safety outcomes. Interestingly, the rate of the 12-month freedom from any atrial arrhythmias was reported to be higher for paroxysmal AF patients in whom the HP-SD approach with protocols using >50 W was followed. Moreover, combining HP-SD with CF sensing seems to yield better outcomes. Theoretically, this approach should be more reproducible among operators, since it facilitates to overcome problems related to catheter stability and ensures safety and effectiveness. A novel high-power ablation catheter with a diamond tip has been introduced in clinical practice (DiamondTemp, Medtronic) that provides rapid energy transfer to the tissue in a few seconds. The catheter employs low-flow irrigated RF in a temperature control mode by using six thermocouples at its tip so as to achieve a target tissue temperature of 60°C with a maximum of 50 W. The diamond tip with higher heat dissipation allows rapid cooling and reduces the risk of thrombus formation and charring. A recent RCT in more than 400 patients showed similar procedure time and efficacy to achieve PVI but a significantly shorter RF duration when compared with conventional CF + RF. At 12 months, the rate of freedom from any atrial arrhythmias of Class I and III antiarrhythmic drugs was 59.4% for the diamond tip approach group of patients vs. 49.4% ($P = 0.03$) for the control group.[6]

Balloon-based catheter ablation

Cryoballoon catheter ablation represents the main alternative and widely used technology, introduced several years ago to overcome the challenge of creating contiguous lesions with RF application in point-by-point fashion. Initially, the imperfect design of the balloon and the potential phrenic nerve damage were important limitations of this technology. Over the years, an improvement of the balloon characteristics has provided better clinical outcomes along with higher safety profiles. The purpose of cryoballoon ablation is to create a more homogeneous freezing effect around the PVs. In the first RCT FIRE&ICE trial,[2] the cryoballoon (Arctic Front Advance, Medtronic, Inc., USA) was found to be as effective as the 3D-guided irrigated tip electrode ablation catheter for helping paroxysmal atrial fibrillation (PAF) patients to gain freedom from atrial arrhythmias. Furthermore, a more recent CIRCA-DOSE RCT comparing CF + RF with cryoballoon (Arctic Front Advance generation) showed that there were no differences in clinical outcomes after 4 or 2 min cryoballon ablation (success rates between 54 and 52%) with a 98% reduction of AF burden. Again, there were no significant differences between the two strategies in terms of effectiveness and safety profile, even though cryoballoon ablation required longer fluoro exposure times. The same results have been reported with the latest cryoballoon generation (Arctic Front Advance Pro, Medtronic, Inc., USA) when compared with HP-SD RFCA in patients with PAF.[7] Cryoballoon ablation therapy is also offered in the form of a novel Polarx balloon (Boston Scientific Inc., Minneapolis, MN, USA), which shows a different compliance profile and a different workflow. The first studies comparing the two cryoballoons currently available showed similar procedural profiles in terms of length of procedure, fluoro time, and the achievement of acute PVI. The long-term clinical outcome of this novel-designed cryoballoon is still awaited. The other balloon-based platform technology that is available is the HeartLight balloon that uses laser energy guided by an endoscopic camera to visualize the target tissue of the PVs ostia so as to properly create lesions that overlap with each other. The goal of this technology is to provide a continuous ring around PVs' ostia aided by the camera embedded into the system so as to reduce the likelihood of leaving gaps behind. The system emits 980 nm laser energy with a power ranging between 5.5 W for 30 s and 12 W for 20 s. Several studies have been published in the last few years showing a rate of 98% of acute PVI, and a 3-month remapping study showed a rate of 86%. A more recent multi-centre European randomized clinical trial comparing laser technology with cryoballoon ablation showed an efficacy rate of ~80% for both technologies, with cryoballoon having slightly higher rates of phrenic nerve transient injury.[8] Quite promising is the first generation of multi-electrode RF balloon, the Heliostar (Biosense Webster), which is a 13F-compliant balloon catheter delivering RF energy at 15 W through 10 gold-irrigated surface electrodes. The Heliostar is highly effective in promoting acute PVI (100% in the RADIANCE trial) with 80% isolation with single application.[9] The design of the catheter has been recently changed with an improved workflow. The system will be commercially available soon.

New insights into the pathophysiology of atrial fibrillation

One system has been designed to investigate and analyse the fibrillatory process of AF. The ACUTUS is constituted of a basket-array catheter (AqQMap) consisting of electrodes and microcrystals on multiple spines that emits ultrasound while rotating in the left atrium to construct the atrial chamber shell. Non-contact dipole-density charge mapping detects the electrical activation pattern during

AF ablation. The aim of the system is to identify the different activation patterns through rotational activity or focal drives that are considered potential targets for ablation. The results of two multi-centre studies[10,11] have shown a 56% success rate at 1 year and 67% after two procedures. Interestingly, when posterior wall index was linked to PVI, AF terminated in 73% of patients when compared with 10% in the control group patients.

New energy sources

The need to optimize AF therapies by improving clinical outcomes has, in the last few years, prompted a search for better energy sources. We still consider RF energy the main energy source used for AF catheter ablation, but its variable tissue destruction process does not allow us to properly predict lesion depth and width. This factor explains its unpredictable effectiveness, with the potential occurrence of damaging effects in the organs surrounding the heart. Needless to mention that thrombus formation can still occur when a high-power setting is used. Cryo-thermal energy has also been introduced in clinical practice to overcome some of the drawbacks of RF, but due to the limits of the balloon design, it can be effectively employed only for PVI, with no proper use for patients with persistent AF. In order to improve the efficacy of cryo-thermal use and also for the treatment of persistent AF, a novel ultra-low-temperature cryoablation system (ADAGIO, PaloAlto, CA, USA) has been recently introduced. This system can deliver a freezing temperature of −196°C, which avoids gaseous expansion with the creation of deeper lesions.[12] The advantage of ADAGIO is related to the 8Fr catheter that can be modulated in several shapes through a dedicated stylet, and thus it can be used in the lasso-like catheter for PVI and/or also for the creation of linear lesions. It is recommended to position an oesophageal warming balloon with circulating saline at 37°C to protect the oesophagus from any potential injury. The cumulative acute success rate for PVI has been reported to be 97% with freedom from atrial arrhythmias at a 1-year follow-up of 82%. The value of this technology in terms of safely providing the isolation of the left posterior wall in patients with persistent AF has yet to be estimated.

Another intriguing technology is the low-intensity collimated ultrasound system that includes a 3D ultrasound-guided anatomical mapping system with a robotic single-tip ablation. The catheter emits ultrasound at a frequency of 10 MHz to produce non-contact lesions within a 16 mm distance to perform PVI. The initial results in humans (value trial) have shown a 98% efficacy rate for acute PVI and 80% freedom from atrial arrhythmias at a 12-month follow-up.

Needless to say that the most investigated new technology and, probably, the most promising is pulse field ablation (PFA) ('Irreversible Electroporation'), which determines a high voltage field for destroying the target myocardial cells[13] (*Figure 1*). Briefly, electroporation is a technique favouring the exposure of a tissue to a high-voltage electrical field either by direct current or by alternate current (500–1000 V/cm range) penetrating the cell membrane with the creation of pores ('holes'). Immediate cell death occurs with subsequent fibrosis, since the cell membrane cannot be repaired.[14] Importantly, the effect on the cells is extended to all tissues within the electrical field and, therefore, it is more dependent on tissue proximity than direct tissue contact. One of the most significant features of PFA is the so-called 'tissue specific', which denotes that the electrical field threshold is quite low for the myocardium and may vary among tissues. In fact, animal studies have shown preservation of the extracellular matrix, nerves, blood vessels, and more importantly for cardiac ablation, the sparing of oesophagus. This ablation technology can be delivered in different ways such as monophasic, biphasic waveform, unipolar, bipolar with different pulse trains, pulse width, voltage gradient, and catheter design. Several attempts have been made to optimize the delivery of electroporation. For example, the most known system, Farapulse (Boston Scientific, Inc., Minneapolis, MN, USA), consists of a basket-type over-the-wire catheter deployed in the left atrium through a 13F deflectable sheath that can change its shape into a flower to deliver eight applications per vein at the PV's ostium (basket shape) and at the PV's antrum (flower shape).[15] The biphasic waveform delivering (1800–200 V) has been demonstrated to be effective to increase PVI durability from 45 to 98% at a 3-month remap. At a 12-month follow-up, 79% of patients were free

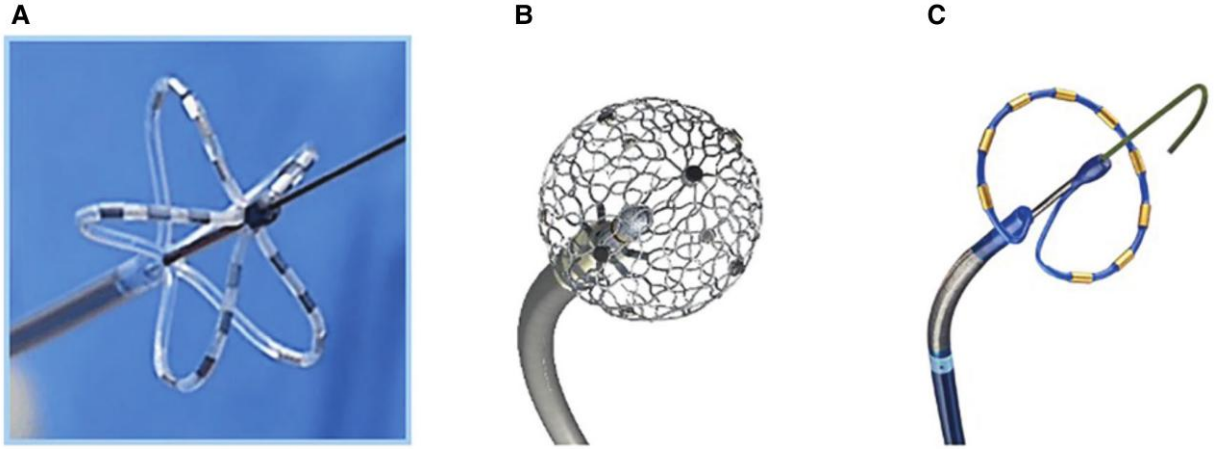

Figure 1 Pulsed field ablation. (*A*) Farawave micro-electrode basket catheter. (*B*) Sphere-9 lattice tip catheter. (*C*) PulseSelect multi-electrode array.

of any atrial arrhythmias. Most importantly, no PV stenosis, phrenic nerve injury, and oesophageal damage have been detected. Based on these preliminary clinical results, it appears that the Farapulse system can represent a very promising modality of AF ablation with a high safety profile. There is much enthusiasm about PFA and several investigators are actively exploring this technology. Another system that has been recently tested is the AFFERA, which consists of a 7.5F bidirectional catheter with an expandable nitinol lattice electrode tip with nine mini electrodes on the spherical surface.[16] The main characteristic of the system is the ability to deliver high-power RF current (73–75 W for 3–7 s) and PFA (monophasic waveform for 3–5 s (total current 24–32 A) with two generators (HexaGen and HexaPulse). A 3D electroanatomic mapping system is also linked to visualize the catheter and guide ablation. The first results in humans,[17] by using PFA alone or alternating with RF, showed successful PVI in all patients (76 patients), and PFA + RF was used for caval-tricuspidal isthmus and mitral isthmus. What was intriguing was the notion that a minor oesophageal erythema was detected in a few patients, but not when PFA was used alone. In the field of electroporation, another technology deserves to be mentioned, and this is the PulseSelect PFA system (Medtronic, Inc., Minneapolis, MN, USA), which uses a biphasic, bipolar waveform through a 9F PVAC GOLD catheter, a loop-shaped ablation once used for RF applications. This is an over-the-wire circular catheter that can deliver PFA from 500 to 1500 V, with each application of four consecutive R-wave synchronized pulse trains of milliseconds. In the experimental setting context, acute PV isolation was achieved and a histologic examination revealed dense fibrosis after a 4-week tissue examination. It was confirmed that no PV stenosis was detected, and the oesophagus was spared of damage even during energy applications in close proximity to the oesophagus[18] Therefore, there is confirmation of the excellent safety profile of this technology.

Final remarks

This is a time of unprecedented improvements in the field of AF ablation where creative, technical, and huge efforts are being put in place so as to devise new tools and strategies to achieve better clinical outcomes for patients suffering from AF. It seems that the search for novel energy sources has shifted from conventional RF ablation to new ultra-low-temperature cryoablation, and more intriguingly to non-thermal electroporation by applying high-power electrical fields. In addition, the attempts to investigate the electrophysiologic patterns underlying the most complicated forms of AF are becoming crucial for the identification of specific targets of ablation beyond PVs. Therefore, we need to make all efforts to transform these new energy sources and technologies into constantly performing entities in clinical practice so as to improve the quality of life of patients.

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

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