Recent advances in the tools available for atrial fibrillation ablation
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\textbf{ABSTRACT}

\textbf{Introduction:} Atrial fibrillation (AF) is the commonest arrhythmia in clinical practice with significant detrimental health impacts. Much effort has been spent in mapping AF, determine its triggers and drivers, and how to develop tools to eliminate these triggers.

\textbf{Areas Covered:} In this state-of-the-art review article, we aim to highlight the recent techniques in catheter-based management of Atrial Fibrillation; including new advancements either in the catheter design or the software used. This includes a comprehensive summary of the most recent tools used in AF mapping and subsequent ablation.

\textbf{Expert opinion:} Electrical isolation of the pulmonary veins has been developed and established as the cornerstone in AF ablation with good results in patients with paroxysmal AF (PAF) whilst new ablation tools are aimed at streamlining the procedure. However, the quest for persistent AF (PeAF) remains. The future of AF ablation, we believe, lies in identifying AF drivers by means of the new developing mapping tools and altering their electrical properties in a safe, reproducible, and effective manner.

1. Introduction

Atrial fibrillation (AF) remains a huge challenge to modern medicine with a major impact on public health. It is the most common sustained cardiac arrhythmia with more than 40 million worldwide living with the condition [1]. It is estimated that one in four adults over the age of 40 will present with AF at some point during their lifetime [2]. Catheter ablation for atrial fibrillation has progressed significantly over the years, from an investigational procedure to mainstream therapy in patients with symptomatic atrial fibrillation [1].

Catheter ablation for atrial fibrillation has been shown to be beneficial in patients with heart failure with reduced ejection fraction [3,4] and to some degree, those with heart failure with preserved or minimally reduced systolic function [5]. In these patients, the positive impact on all-cause mortality, heart failure admissions, quality of life, and symptomatic AF recurrence has led to guideline changes proposing catheter ablation as first-line therapy in patients with AF and heart failure with reduced ejection fraction (class IIA [1] or IIB [6] recommendation).

Historically, the pulmonary veins have been recognized as the primary source of atrial triggers [7]. Electrically isolating the pulmonary veins has become the cornerstone of AF ablation for Paroxysmal AF with a success rate of 70–75% in maintaining rhythm control. The effectiveness of catheter ablation becomes somewhat suboptimal and variable for persistent or long-standing persistent AF where the success rate is estimated to be around 40–50% requiring repeat procedures [8].

The arrhythmic pathophysiological mechanism of AF is thought to comprise a trigger that initiates and a substrate that maintains the arrhythmia with most ectopic discharges emerging from the pulmonary vein sleeves [7]. This may be due to new impulses triggered by different mechanisms as a result of abnormalities in pulmonary vein tissues [9]. Beyond the pulmonary veins, the posterior left atrial (LA) wall, with its extremely heterogeneous and anisotropic fiber bundle arrangements and sudden changes in thickness, also provides an ideal substrate for arrhythmia and impulse propagation [10]. Catheter ablation is therefore set out to remove the trigger by means of pulmonary vein isolation (PVI), or modify the substrate, or both.

Although it is generally hypothesized that going ‘beyond PVI’ in patients with persistent AF is recommended to achieve better outcomes and success rate, no randomized clinical trial has proven a significant benefit from additional ablations [11]. The STAR AF II trial showed that ablation of empiric linear lesions and complex fractionated electrograms did not show a significant benefit or add long-term success over PVI alone among patients with persistent atrial fibrillation [11].

Despite promising advances in catheter technologies to improve AF ablation outcome over the last few decades, there remains many challenges especially in patients at the advanced stages of the arrhythmia development manifesting as persistent AF. Different energy sources and ablation strategies have been tried and tested over the years and many advances have been made in the mapping of focal, rotational, and other drivers during persistent AF. In some cases, these drivers may co-locate with regions of LA scars that are prone to reentrant atrial arrhythmias [12–14].

In this review, we summarize recent advances in the tools developed for mapping and ablation of AF (Figure 1).
2. Novel mapping strategies and tools for atrial fibrillation

The commonly used three-dimensional mapping systems CARTO 3 (Biosense Webster, Irvine, Ca.) and Ensite Precision (St. Jude Medical, St. Paul, Min) allow three dimensional anatomical mapping which in turn allows better catheter localization and processing of local electrograms [15]. A recently released Advisor HD Grid Mapping Catheter (GMC; Abbott, St. Paul, MN) has been used with the Ensite Precision mapping system, allowing better electrode tissue-contact and also bipolar signal recording from multiple wavefront directions (omnipolar mapping). It also showed favorable outcomes when compared with the circular mapping catheters (CMC) for voltage mapping and identification of low voltage areas (LVAs) [16].

The Rhythmia Boston Scientific mapping system is a 3D electro-anatomical mapping system that utilizes a 64-electrode roving catheter with a mechanism for bidirectional tip deflection and includes a hybrid of magnetic field and impedance location technology [17]. It allows rapid and ultra-high resolution electro-anatomical and activation mapping [18]. This was one of the early approaches to high-density mapping, yet it is more relevant for regular arrhythmia (e.g. macro-reentrant atrial tachycardia) than AF mapping per se.

Beyond the established understanding of electrical triggers arising from pulmonary veins, there is now considerable evidence that localized rotational or focal drivers play an important role in sustaining AF using optical mapping in preclinical and clinical studies [19]. In particular, mapping studies in humans have recognized the presence of tempo-spatial periodic activity originating in the PV region, capable of maintaining AF by having either short cycle length reentrant sources and/or focal automatic activity [20]. The implication of other AF drivers has been described but not proven as an effective therapeutic target in randomized clinical trials [21].

The complex nature of the pathogenesis of AF and the interaction between the electrical triggers and structural substrate constitute a major challenge in localizing the ideal targets for ablation. Recently, several advances in mapping technology have allowed activation and/or wavefront mapping of both right and left atria during AF [22,23]. Many of the new mapping technologies for persistent AF ablation consist of systems that can map the entire chamber during AF and using specific electrogram patterns and/or mathematical transformations to identify AF drivers. Preliminary clinical studies have also suggested that ablation of these organized activation patterns could improve outcomes in persistent AF [24]. However, the role of such mapping in the approach to persistent AF is yet to be tested in large, randomized trials [25].

2.1. Focal impulse and rotor modulation

Focal impulse and rotor modulation (FIRM) utilizes a computerized algorithm that analyses the atrial activation acquired with a 64-pole basket catheter and creates 2D focal impulse and ‘rotor’ modulation maps. The system converts raw electrogram data into more organized wavefronts using phase mapping to visualize the rotational activations [26].

The CONFIRM trial (Conventional Ablation for Atrial Fibrillation with or Without Focal Impulse and Rotor Modulation), enrolled 92 patients with PAF or persistent AF and randomized them to either ablation of AF sources (Focal Impulse and Rotor Modulation [FIRM]-guided) followed by conventional ablation, mainly PVI (n = 36), or conventional ablation alone (n = 71; FIRM-blinded). Results from this study showed that FIRM ablation at patientspecific sources acutely terminated or slowed AF and improved outcome [27]. However, this promising acute procedure outcome was not reproduced or translate into long-term clinical outcome with the OASIS trial failing to show any benefit of adjunctive rotor ablation in patients with non-paroxysmal AF at 2 years follow-up [21] [28].

Technical challenges in attaining adequate tissue contact with basket and issues with electrogram processing have been highlighted as limitations to this technology. There was also a questionable lack of a conventional PVI-alone control group in the OASIS randomized trial.

In the most recent REAFFIRM trial, FIRM + PVI was compared to PVI+ any additional ablation strategies of operator’s discretion. Most patients in this latter arm ended up receiving linear ablations, posterior wall isolation and electrogram-guided ablation. The trial failed to prove any benefit from the FIRM-guided ablation vs the ‘conventional’ strategy. Single procedure 12-month freedom of AF/AT recurrence was 69.3% (115/166) in the FIRM group and 67.5% in the conventional group [29].

2.2. Electrocardiographic imaging (ECGi)

Electrocardiographic imaging is a mapping technique that aims to characterize cardiac electrical activity using signals collected from the body surface to reconstruct epicardial potentials.

A 252-electrode vest is applied to the patient’s torso and connected to the system (ECVue, Cardioinsight Technologies Inc, Cleveland, OH). A high-resolution non-contrast computed tomography scan is then performed, allowing the definition of cardiac anatomy and the position of each electrode on the torso. Atrial and/or ventricular geometry are then reconstructed to obtain a three-dimensional mesh (Figure 2). This model serves to project unipolar signals represented by virtual nodes of the epicardial surface. The collected signals are post processed using mathematical reconstruction algorithms to create different maps, including activation maps, voltage maps, isopotential maps, and phase maps [30].
The AFACART trial was a nonrandomized multicenter trial evaluating ECGi with driver ablation followed by PVI, with 4.9 ± 1.0 driver sites mapped per patient. Driver-only ablation resulted in AF termination in 75 of the 118 patients (64%). At 1-year follow-up, 78% of the patients were off antiarrhythmic drugs and 77% of the patients were free from AF recurrence. At follow-up, 49% had recurrent atrial tachycardia which required further management [22].

Of relevance, AF complexity (defined as the number of stable AF reentrant sites) tended to be concordant between invasive and noninvasive mapping methods and correlated with ablation result [31], suggesting its clinical utility as a tentatively reliable noninvasive mapping tool.

2.3. Cartofinder
Recent mapping systems such as Cartofinder have allowed demonstration of focal and rotational activations during AF without the need for phase mapping.

CARTOFINDER uses the CARTO platform (Biosense Webster, Inc., Baldwin Park, California) as its foundation. Carto 3 is an electroanatomical mapping system from Biosense Webster which involves a locator pad placed under the procedure table (this contains 3 low-level magnetic field emitting coils), 6 body patches, a mapping catheter and a magnetic location sensor. The movement of the mapping catheter across the three magnetic fields allows the orientation of the catheter position to be detected and subsequently a 3D map to be drawn [32]. It typically requires multipolar catheters that either maps the atrium simultaneously such as a basket catheter (64 poles, or 192 poles) [33] or more recently, mapping catheters that allow sequential collection (e.g. Pentaray, Biosense Webster Inc), with the aim of mapping wavefront propagation and determining activation patterns suggestive of localized AF drivers. Activation maps are generated during a 250-ms window referencing each electrogram relative to all the others in the LA. This time window then moves through the 30-s recording to show a changing activation map over time. The system has a built-in automated algorithm that uses QS signal patterns to identify focal activations and sequential electrogram activation gradients occupying most of the cycle length to identify rotational activations (Figure 3).

In one study, CARTOFINDER was able to identify focal and rotational activations the ablation of which led to a high rate of AF termination during the procedures [34]. This, however, was challenged by Hemam et al. where CARTOFINDER was used to create activation map to detect fibrillatory electrograms created in dogs by rapid left atrial pacing with or without AF induction. Surprisingly, the mapping algorithm detected rotational and focal activation sites unrelated to AF induction or maintenance and was unable to detect pacing sites as true drivers for fibrillatory conduction [35]. This warrants continued search for patient-specific mapping tools.

Data from Verma et al also suggested that focal activations may be more important than rotational targets since AF termination was significantly increased when targeting foci (not so for rotations). Furthermore, most rotations occurred only in the presence of accompanying foci while foci may occur without rotations. This might suggest that the foci drive the rotations and might be the more important target [36].
Figure 2. ECGI work flow.
A→ Vest applied to the patient’s chest, B→ CT scan performed, C&D→ definition of cardiac anatomy and electrode positions, E&F→ Signal Processing, G→ Activation projected on the surface of 3D cardiac model. (From Cheniti G, et al. Noninvasive Mapping and Electrocardiographic Imaging in Atrial and Ventricular Arrhythmias (CardioInsight). Card Electrophysiol Clin. 2019 Sep;11(3):459–471. With permission)

Figure 3. CARTOFINDER maps showing rotational activity along the anterior wall with the corresponding unipolar electrograms obtained from a basket catheter. (From Honarbakhsh S, et al. A Novel Mapping System for Panoramic Mapping of the Left Atrium: Application to Detect and Characterize Localized Sources Maintaining Atrial Fibrillation. JACC Clin Electrophysiol. 2018 Jan;4(1):124–134. No permission required)
2.4. Non-contact intracardiac mapping

The AcQMap (Acutus Medical, Inc) is another mapping system which reconstructs the endocardial anatomic surface and then overlays the former with a high resolution charge density maps of electrical activation. It is a noncontact mapping system that uses a catheter that has 6 splines, each populated with eight ultrasound transducers and interspersed with eight electrodes for anatomical and electrical mapping Figure 4. Similar to other noncontact mapping systems, the electrodes gather unipolar signals, which are then used to generate thousands of noncontact unipolar electrograms using the inverse solution. The device not only shows transient focal and rotational activations, but it also detects narrow isthmuses of slow conduction within the atrium through which conductor wavefronts pass [37].

The UNCOVER AF trial showed that this combined ultrasound imaging and charge density mapping system identified non-PV ablation targets in patients with persistent AF and ablation achieved freedom from AF at 12 months of 73% after single procedure and 93% after second procedure [38].

2.5. Stochastic trajectory analysis of ranked signals (STAR)

The STAR mapping method is a novel method that uses data on multiple individual wavefront trajectories to characterize and locate regions with earliest activation to try and identify potential drivers [39]. For a specific region to be labeled as ‘earliest activation site,’ it had to be leading for at least 75% of the time. These sites were subsequently targeted with RF ablation and showed a promising outcome in terms of freedom from AF/AT [40] Another study found that PVI plus STAR mapping guided ablation for persistent AF was superior to PVI alone or in combination with liner/CFAE ablation [41]. A randomized controlled trial of STAR mapping guided ablation of AF (ROC-STAR) is currently ongoing (NCT04442113).

2.6. Dominant frequency (DF) mapping

Ng et al. proposed that record plot analysis would identify sites of stable and repeatable electrocardiogram patterns. Their work showed checkerboard patterns of alternating high and low cross-correlation values, indicating periodic recurrences in morphologies of atrial activation [42].

High density non-contact mapping was previously used to map the left atrium, demonstrating that Dominant frequencies (DFS) of intracardiac electrograms(EGMs) lacks spatio-temporal stability. However, there was evidence of cyclic irregular pattern which is somewhat organized toward the core of the high dominant frequency areas (HDFAs), with the organization significantly reduced toward the periphery, suggesting that this may be due to wavefront collisions. This has been suggested to play a significant role in driving

Figure 4. Fluoroscopic image of the AcQMap catheter positioned during simultaneous biatrial noncontact mapping.
(From Pope, MT, Kuklik, P, Briosa e Gala, A, et al. Spatial and temporal variability of rotational, focal, and irregular activity: Practical implications for mapping of atrial fibrillation. J Cardiovasc Electrophysiol. 2021; 1–11. No permission required)
AF and a 3D DF mapping graphic user interface (GUI) platform has been created to enable DF-guided catheter ablation [43].

Atrial areas of high dominant frequency have been previously hypothesized as AF drivers. In a study of 10 patients (USURP AF Phase I study [Understanding the electrophysiological substrate of persistent AF]) undergoing index ablation for persistent AF ablation, noncontact Ensite Array catheter was used to map AF and High dominant frequency (HDF) sites identified using MATLAB (MathWorks programming and numeric computing platform) were targeted for ablation before PVI. Four patients out of the 10 had their AF terminated before PVI. It also found that baseline regional DF and OI (organization index) were significantly associated, suggesting that lower and more organized DF areas may be more clinically significant and thus utilizing mean DF and OIs may improve specificity [44-46].

2.7. Wide-band dielectric mapping

THE KODEX-EPD is a new cardiac imaging mapping system that does not involve electrical mapping. It utilizes seven external reference patches on the body surface and any diagnostic/ablation catheter electrode to use distinct electrical signals and sense the ‘bending of the electrical field’ to generate high-resolution imaging with the potential to create CT like images without requiring additional peri-procedural fluoroscopy.

The movement of any catheter electrodes inside the cardiac chambers causes electrical field transmission and reflection with the different endocardial structures lying in between the electrodes and the surface patches leading to different gradients across the electrical field, to which the term ‘bending of the electrical field’ refers to. The relative position of different electrodes inside the left atrium allows the Kodex system to create detailed 3D anatomy without contact [47].

The Kodex system can also be used with cryoablation where dielectric sensing gives information on whether there is good balloon occlusion without the use of contrast or fluoroscopy, thereby reducing radiation. The workflow is as follows; baseline impedance of the targeted PV is recorded (using a circular catheter) then the balloon is inflated and advanced into the pulmonary vein ostium, the eight electrodes on the mapping catheter are then used for voltage comparison to estimate the dielectric coefficient change in the adjacent tissue and thus, confirming the degree of occlusion in real time [48].

This allows quick adjustments in the cryoballoon position without gross movements, it also minimizes the use of contrast, radiation and fluoroscopy during the procedure and provides the potential of delivering real-time data. There is the aim and ongoing development in using dielectric mapping for real-time tissue interrogation with assessment of wall thickness (i.e. advantage of titrating regional ablation) and lesion integrity (i.e. efficacy of ablation) [49].

3. Novel ablation tools for atrial fibrillation

It is worth noting that the outcomes of the aforementioned mapping techniques are yet to be confirmed in larger prospective studies. When it comes to ablation, PVI remains the only established procedure with definite beneficial outcome for patients with AF (either Paroxysmal or persistent AF) [11,50]. Historically, the success rate of AF ablation can be variable due to heterogeneity in ablation technique, energy source as well as the definition of ‘procedural success’ and post-ablation rhythm monitoring. However, the success rate of PVI (after multiple procedures) in patients with PAF after 5 years of follow up has been found to be around 79% [51], and 62% after 10 years [52] whereas there was a 25% single and 68% multiprocedural success in patients with persistent AF after 7 years of follow-up [53].

The durability of Pulmonary vein isolation is one of the most crucial factors in long-term outcome post PVI. It has previously been shown that most patients with recurrent AF had at least one reconnected vein at a redo procedure [54]. For RF ablation, it is acknowledged that in addition to power and duration of RF delivery, adequate and consistent tissue contact is necessary for good quality and durable RF lesions. With the advent of force-sensing catheter, it is possible to integrate power, force and ablation duration in a weighted formula to provide real time information regarding lesion depth and size. Lesion size index (LSI) [55]

and ablation index (AI) [56] in the Ensite and CARTO platforms, respectively, have been developed as surrogate markers of radiofrequency lesion quality. AI has been found to be predictive of PV reconnection [56] in addition to helping to reduce ablation times [57]. Nonlinear AI has also been shown to provide more comprehensive information during PVI compared to Force-time integral [58]. Evaluation of local impedance (LI) drop (DIRECTSENSE™, Boston Scientific) which can be measured using the previously mentioned Rhythmia HDx™, Boston Scientific mapping system has also been shown to reflect tissue heating and lesion characteristics with LI-guided ablation showing promising safety and efficacy outcomes in a recent preclinical study [59].

3.1. Cryoballoon

Cryoballoon ablation has also been used for PVI as a ‘single shot’ ablation modality rather than the point by point RF ablation technique, and has proven to be noninferior to RF ablation in patients with paroxysmal AF, as reported by the Fire and Ice trial [60] with less incidence of major complications [61].

The ICE-ReMap study evaluated the durability of PVI using the ICE-T [62] time-to-isolation (TTI) dosing protocol and managed to provide interesting insights. 788 patients with AF underwent ablation using the ICE-T dosing concept and in a subset of patients (n = 184), the target freeze duration was reduced to 180 s instead of 240 s. PV remapping was done in patients who had a clinical indication for a repeat procedure (n = 106). This included a total of 424 PVs mapped (320 in the 240 s group and 106 in the 180 s group). This showed an overall PV reconnection rate of 17%, demonstrating a high rate of durable PVI following single shot cryoballoon freezing approach using the ICE-T protocol, with significantly higher rate of lesion durability associated with a target freeze.
duration of 240 s compared to 180 s (61.3% vs. 34.6% of patients; \( p < 0.02 \)) [63]. Despite it being a retrospective analysis, that’s further limited by remapping only done in patients with a clinical indication for a redo procedure, this study managed to provide valuable remapping insights for CB based AF ablation.

A recent prospective trial randomized 200 AF patients in a 1:1 manner to either receive Cryoballoon or Laser balloon PVI. The ICE-T protocol was followed for cryoballoon and a high dose protocol for Laser balloon. Both achieved comparable safety and efficacy in terms of the primary end point (freedom from atrial arrhythmias between 3 and 12 months postprocedure off AADs). Cryoballoon, however, was associated with a much shorter procedure time but not fluoroscopy time (50.9 ± 21.0 versus 96.0 ± 20.4 minutes; \( P < 0.0001 \) and 7.4 ± 4.4 versus 8.4 ± 3.2 minutes, \( P = 0.083 \)) [64].

There is widespread adoption of the technology due to its relative ease of use, and favorable learning curve with less operator skill dependence. Results can still be variable with redo procedures demonstrating reconnected PVs due to anatomical factors with different sizes of PV ostia and challenging anatomy (especially with right inferior PV). Phrenic nerve palsy is a more prominent complication from this technology (which requires online monitoring of diaphragmatic contraction during ablation) and it is subject to usual complications expected of the procedure including cardiac tamponade and atiro-esophageal fistula.

A new cryoballoon ablation system became recently available (POLARx, Boston Scientific) with the additional feature of being able to maintain constant pressure and size during inflation and ablation. This system showed comparable safety and procedural efficacy to the Medtronic Arctic Front Advance Pro system (AFA-Pro, Medtronic) with acute isolation achieved in 99.8% of all pulmonary veins (POLARx: 99.5% vs. AFA-Pro: 100%, \( p = 1.00 \)) [65]. Further studies are still needed to confirm these findings and assess PVI durability.

3.2. Ultra-low temperature cryoablation

This is novel ablation technique that is based on ‘single shot’ ultralow temperature cryoablation catheter. The system (Adagio Medical) uses liquid nitrogen which can produce

| Table 1. (Summary of new AF mapping techniques). |
|-------------------------------------------------|
| **Catheter** | **Contact vs noncontact** | **Signal Analysis** | **Clinical outcomes** |
| FIRM | Basket Catheter | Contact | Phase Mapping | CONFIRM – 82.4% vs 44.9% freedom from AF[28] \ REAFFIRM – 69.3% Vs 67.5% freedom from AF/AT at 1 year[31] |
| AcQMap | Ultrasound data | Non-contact | Charge density | 73% single procedure freedom from AF at 12 months[40] |
| CartoFinder | Pentarray | Contact | Unipolar Signals | Repetitive atrial activation patterns mapped – 35% RA, 65% LA[36] |
| STAR | Mapping | Contact | Activation Mapping | 78.5% AF termination rate (PVI + STAR guided)[43] |
| Dominant Frequency | Array Catheter | Contact and Non-contact | High Frequency sites | Ongoing - Initial outcomes suggested utilising correlation between mean DF’s and OIs to improve specificity[48] |
| Dielectric sensing | Diagnostic or Ablation | Contact and Non-contact | Dielectric Sensing | high accuracy of 3D dielectric mapping system in confirming occlusion with cryoballoon[50] |
| ECGi | Multi-electrode Vest | Non-invasive | Phase Mapping | 77% AF freedom at 1 year[23] |
temperature as low as −196°C. The catheter uses an anatomical approach and has interchangeable stylets that allow to modify the delivery catheter to the chosen target, either linear, circular, oval, or focal. However, similar to other cryoablation systems, continuous caution must be observed to avoid collateral tissue damage. Safety measures, such as phrenic nerve stimulation, placement of a continuous warm balloon in the esophagus and deep sedation or general anesthesia remains an integral part of the procedure set-up.

The ‘Cryocure’ trials (CC1, NCT02355106 and CC2, NCT02839304) sought to evaluate ultra-low temperature cryoablation’s safety and efficacy as the first-in-human studies. These were single arm, prospective and multicentre. They collectively enrolled 30 patients (17 with atrial flutter and 13 with atrial fibrillation). This aimed to assess the safety as well as the acute success of Cavitricuspid isthmus (CTI) ablation using ultra low temperature cryoablation. Among the 30 patients enrolled, acute success (defined as the confirmation of complete bidirectional conduction block cross the cavo-tricuspid isthmus at the end of the procedure after a minimum of 30 min following the last CTI freeze) was achieved in all. There was one serious adverse event reported as being procedure-related and no unexpected procedural safety events were reported.

After 12 months of follow-up, 14 out of 17 atrial flutter (AFL) patients remained free from any AFL [66].

Furthermore, Results from the Cryocure-2 study (NCT02839304) presented at Heart rhythm society 2021 congress demonstrated 82% clinical efficacy rate among 79 patients undergoing first catheter ablation for either paroxysmal or persistent AF. There was also a 1.5% adverse event rate which consisted completely of phrenic nerve palsy.

The iCLAS™ for Persistent Atrial Fibrillation (NCT04061603) is a single-arm clinical trial looking to enroll 200 participants with symptomatic persistent AF having first time AF ablation in 20 different sites, aiming to assess safety and efficacy with follow-up at one, three, six and twelve months [67].

3.3. Endoscopic laser balloon, RF balloon and hot balloon based PVI

The endoscopy laser balloon is a compliant balloon with a variable diameter that is used to deliver laser energy at operator determined sites using real-time endoscopic visualization [68].

A 28-mm diameter spherical compliant Multielectrode Heliosstar RF Balloon Catheter ( Biosense Webster Inc, Irvine, CA) combining the ability to both simultaneously deliver and directionally tailor the dose of ablative energy delivered through the balloon circumference has been shown to achieve safe and effective PV isolation [69]. The RADIANCE study demonstrated that HELIOSTAR RF balloon provided rapid and safe PVI with 86% of PAF patients free from atrial arrhythmias at 12 months and 75% drug-freedom from atrial arrhythmias [70].

The HeartLight clinical trial (NCT01456000) conducted a prospective 1:1 randomized multi-center comparison of PVI using visually guided laser balloon vs standard ablation. Among 342 patients, Laser balloon ablation was noninferior in terms of primary efficacy defined as freedom from atrial arrhythmias at 12 months off AAD compared to radiofrequency ablation (RFA) (61.1% vs. 61.7%; p = 0.003 for non-inferiority). The incidence of primary adverse events was also comparable between the two groups (11.8% vs. 14.5%; p = 0.002 for noninferiority) [71].

A recent observational multi center LIGHT-AF study (NCT04544397) also demonstrated promising procedural safety and efficacy outcomes for AF ablation using second generation laser balloons [72]. Chun et al also demonstrated comparable safety and efficacy between Laser and cryoballoons [64].

Another type of non-cryo balloons is the hot balloon. The SATAKE Hot Balloon ablation system (Toray Industries, Inc., Tokyo, Japan) utilizes thermal energy conducted by the balloon to ablate the targeted tissues. This is relatively different from RFA, where energy is locally delivered to induce tissue necrosis. It uses a 13-F balloon with a RF generator that controls the temperature of the balloon [73]. This did not show statistically significant difference compared to cryoballoon ablation systems when it comes to medium-term outcomes [74].

3.4. Combined contact-mapping plus ablation

The novel multielectrode Globe array is formed of 16 flat ribs with 122 gold-plated electrodes. Each electrode can map, ablate or pace. It also has the advantage of multielectrode contact voltage mapping, which is updated continuously, including during ablation, offering new options in real-time substrate identification. A first clinical study (Global AF) showed its feasibility for single-shot PVI, the Global AF study (Global multielectrode contact-mapping plus ablation with a single catheter in patients with atrial fibrillation) included sixty patients with symptomatic AF undergoing PVI, the globe array catheter was advanced into the antrum of each PV and used for initial PVI and data from the 122 electrodes was then translated into different maps. FLOW and Contact maps were used to determine the amount of tissue contact and hence the optimum electrodes for ablation, a voltage map reflecting the electromgram amplitude for every electrode and a wave map which demonstrated wave front propagation, both maps were continuously updated allowing real-time PVI. Voltage, contact and flow maps were then used to determine the optimum sites for circumferential PVI. At the beginning of this clinical trial, the system was adjusted to ablate at a maximum of 16 electrodes simultaneously. However, this was increased to 24 electrodes in 34 patients to achieve ‘single shot ablation.’ Acute PVI was achieved in (99.1%) of targeted PVs in all sixty patients and in all (100%) targeted PVs in the subgroup treated with ‘single shot ablation’ [75].

3.5. Pulsed field ablation/electroporation

Pulsed field ablation (PFA) is a novel, unique and tissue selective ablation approach that uses non-thermal modalities for ablation [76] delivered in very short duration of high energy pulses providing the advantage of causing less risk of injury to
Figure 5. Durability of PVI using PFA with different wave forms (invasive remapping data).

1. The number of patients presented for the remapping procedures (bars). 2. The percentage of PVs that remained durably electrically isolated (solid line). 3. The percentage of patients with all PVs durably electrically isolated (dashed line). (From Reddy VY, Neuzil P, Koruth JS, Petru J, Funoirako M, Cochet H, Sediva L, Chovancova M, Dukkipati SR, Jais P. Pulsed Field Ablation for Pulmonary Vein Isolation in Atrial Fibrillation. J Am Coll Cardiol. 23 July 2019;74(3):315–326. doi: 10.1016/j.jacc.2019.04.021; Epub 11 May 2019. PMID: 31085321. With permission.)

the adjacent myocardial tissue and phrenic nerve [77,78]. It causes cell death by destabilizing cell membranes by creating irreversible nanoscale pores. Since the myocardium has a lower injury threshold than the phrenic nerve and esophagus, PFA can uniquely ablate atrial myocardium thanks to its novel nonthermal ablation mechanism.

A multispline PFA catheter has recently been used to treat patients with paroxysmal AF with PVI in the IMPULSE (Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation) and the PEFCAT (Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation) clinical trials. These first-in-human trials enrolled patients with symptomatic PAF resistant to AADs (total of 81) undergoing PFA, monophasic waveforms were used in 15 patients and biphasic in 66 patients. Repeat mapping was done at 75 days for PEFCAT and 90 days for IMPULSE, clinical follow-up was done at 7,30 and 3, 6 and 12 months after the procedure. Recurrence was assessed by a (1) trans telephonic monitor at the time of the remapping study to send transmissions weekly and with symptoms; and (2) 24-h Holter monitors at 6 and 12 months. The primary safety endpoints included a composite of major events occurring within 7 and 30 days postprocedure, this occurred in one patients in the form of pericardial tamponade that was successfully drained. Primary efficacy endpoints were in the form of the percentage of pulmonary veins electrically isolated at the end of the procedure by PFA alone (achieved in 100% of patients).

52 patients presented for invasive remapping and successive wave-front refinement improved the durability of PV isolation at 3 months from 18% to 100% of patients [76,79–83].

The PFA system consists of a custom generator that delivers a pulsed electrical waveform over multiple channels (Farastar, Farapulse Inc., Menlo Park, California), a 13-F steerable sheath (Faradrive), and 2 PFA catheters. PersAFOne is a first-in-humans study that evaluated PFA using multispline catheter for PVI and Left atrial posterior wall ablation in patients with persistent AF and achieved durable, safe, and efficient PVI [84]. However, larger prospective studies are pending, including the PULSED AF trial (Pulsed field ablation to irreversibly electroporate tissue and treat AF 'NCT04198701').

The ADVENT trial is also a prospective premarket trial to assess the safety and efficacy of the Farapulse PFA system, where patients will be randomized in a 1:1 fashion to either receive Farapulse PFA or conventional ablation by RF energy or cryoballoon, primary outcome measures will include freedom from AF at 12 months after a single procedure “NCT04612244”.

Other PFA technologies are being developed by a number of established and new Electrophysiological device companies. An example is the Lattice tip ablation catheter. This is a novel ablation catheter with a 9 mm
A nitinol tip that is able to deliver focal RFA or PFA lesions, each in 2–5 s. It was recently used in a first-in-human trial for either a combined RF/PF approach or a complete PFA approach, achieving successful lesions with no device related complications [85].

Current data suggest that the effectiveness of PFA lesions is dependent on the specific waveform and energy delivered where preclinical work is required for the titration and detailed clinical studies needed to assess efficacy. In addition, the acute abolition of electrical signals during the procedure does not
appear to be translated into permanent block where the formation of effective and durable chronic lesions would require longer-term assessment. Nonetheless, this is an exciting new area which could represent a game-changer in catheter ablation for AF.

3.6. Temperature-controlled high-power, short-duration ablation catheters

For radiofrequency ablation of AF, operators have used decreasing power down to 20 watts (W) to avoid causing damage to surrounding structures. At the expense of perceived safety, this means longer duration of power delivery with the risk of catheter instability and subsequently suboptimal lesion delivery [25].

An alternative strategy is high-power short-duration (HPDS) RF ablation which was first reported in 2006 with improved procedural efficacy [86]. Higher power, usually of 45–50 W, for shorter duration of 2–10 seconds per lesion for the posterior wall and 5–15 seconds elsewhere has been shown to be efficacious and safe [87].

PV reconnection in patients undergoing a redo procedure was also found to be lower among the HPDS group (n = 18, using 45–50 W for 8–15 s) compared to moderate power moderate duration (n = 23, using 20–40 W, 20–30 s; 16.6% vs. 52.2%; p = 0.03) [88].

A recent systematic review and meta-analysis comparing High power short duration (HPDS) radiofrequency ablation (RFA) versus conventional RFA in patients with AF, suggested that higher power short duration ablation was associated with shorter procedure duration and reduced fluoroscopy. HPDS-RFA and conventional RFA showed similar safety outcomes and subgroup analysis even showed better outcomes represented in higher freedom from arrhythmias in patients with paroxysmal AF with the use ≥ 50 W and Contact force (CF) sensing catheters [89].

The DiamondTemp (Epix, Medtronic, Minneapolis, MN) ablation system includes three thermocouples at the tip of the catheter and a low irrigation rate of 8 mL/s for more accurate catheter-tissue interface temperature sensing. DiamondTemp catheter allows a maximum power of 50 W with a target temperature of 50°C in the posterior wall and 60°C at the anterior [90]. The DIAMOND-AF trial was designed to assess the safety and efficacy of the system in patients with paroxysmal AF and proved non-inferiority compared to a force-sensing catheter [91].

The QDOT Micro Catheter (Biosense Webster, Irvine, California) has three thermocouples at the tip of the catheter and three proximal thermocouples positioned 3 mm from the tip that provide real-time temperature monitoring. It allows a power delivery up to 100 W with an improved irrigation system that allows many different possibilities for high power, short duration delivery [92,93] but typically with either 50 W (Q-mode) or 90 W (Q-mode plus) energies [94,95]. The improved temperature sensing allows safe reduction of irrigation flow and resistive heating rather than conductive heating with high irrigation flow which achieves temperature controlled ablation with reduced risk of collateral damage (Figure 5).

The QDOT-FAST study is a prospective, multicentre study that evaluated the safety and acute performance of a very high-power, short-duration (vHPSD) ablation mode (i.e. Q-mode plus: 90 W, 4s) to treat AF. It was a first-in-human study of the QDOT microcatheter with follow up done at 7 days, 1 month, and 3 months after the procedure. Short-term procedural success, defined as PVI confirmed after adenosine or isoproterenol was achieved in all patients who underwent ablation with the QDOT microcatheter, PVI was achieved in almost 80% of the patients using the vHPSD mode only, and in 26.9% of the patients, PV reconnection was demonstrated after adenosine or isoproterenol, requiring additional lesions. The study also demonstrated the safety and efficacy of vHPSD ablation with the advantage of a significantly lower procedural and fluoroscopy time [96]. This was also recently reproduced in the Fast and furious AF study with remarkably shorter procedural time [97]. Additional benefit of this technology would be a more specific lesion delivery aimed at improving contiguity of sequential lesions and adequate depth while avoiding collateral damage. This, however, has not yet translated into long-term outcomes and PVI durability following vHPSD ablation is yet to be investigated in further trials, particularly with of the recently published Nakagawa et al study, suggesting a smaller lesion associated with vHPSD in canine thigh muscle preparation [98] (Figure 6).

4. Conclusion

Recent promising advancements have been made in AF mapping including localization of tentative AF drivers which are responsible for AF initiation and maintenance. Continued development in ablation tools are evident through the use of very high power (short duration) or ultra-low cryo-ablation energies with distinctive catheter design. More importantly, the realization of electroporation for left atrial ablations may represent an important milestone in establishing an efficient and safe AF ablation practice, paving a bright future from both operators’ and patients’ perspectives. A summary of the mapping and ablation techniques discussed in this article is provided in Tables 1 and 2, respectively.

5. Expert opinion

The two pillars of catheter treatment for atrial fibrillation remain as follows: (1) identify the trigger and the associated anatomical/functional substrates by means of the different mapping techniques with the aim of (2) creating durable, tissue-specific and safe ablation lesions.

Several new and promising mapping techniques have been demonstrated in this article, all aiming to help gain insight into the unfolding mystery of this atrial electrophysiologic phenomenon.

When it comes to the ‘what to ablate?’ question, the stepwise ablation approach (Bordeaux) which initially showed promising results in single-centered studies failed to borne out in the STAR AF II trial. PVI with additional linear ablations were not shown to be superior to PVI. On the other hand, success rate was only about 50% in the PVI-only arm suggesting that PVI per se is not enough for persistent atrial fibrillation.

Our current strategy is a combination of the stepwise ablation approach guided by the CARTOFINDER to localize
additional targets for substrate modification following PVI. It is our opinion that atrial fibrillation by principle should be driven by the fastest driver. Our engineering colleagues have helped with gaining insights into the kinetics of this chaotic activity by analyzing the frequency and phase characteristics in fibrillation. This has helped in identifying the areas of high dominant frequencies which are potentially driving and maintaining AF.

As for the second pillar of AF ablation, cryoablation when combined with dielectric mapping system demonstrated great potential due to the latter aiding in balloon occlusion of the pulmonary veins without the need of fluoroscopy. Ultra-low temperature cryoablation achieved by using liquid nitrogen as a cryogen has the potential of increasing the efficacy of single-shot cryoablation devices. The new iCLAS™ catheter also has the capability of delivering focal cryoablation with any diagnostic shape making it a flexible tool for cryoablation.

Another breakthrough was the ‘very high-power short-duration’ RF ablation (RFA), using 90 W for 4s, delivering lesions in much shorter time compared to the conventional point by point ablations with radiofrequency energy of <50 W. This ablation set-up is now the status quo at our center and has showed promising initial results in reducing procedure time, fluoroscopy time and the intraprocedural sedation/analgesic requirement. Another potential game changer in ablation technology has also appeared in the form of pulsed field ablation (PFA) which could be viewed as an ultrashort DC shock causing electroporation with resultant tissue-specific ablation. We believe this could have the potential of gradually replacing Radiofrequency energy in the future. There are still some answered questions in terms of its safety and efficacy on the long term. However, initial results have paved the way for larger prospective randomized trials comparing PFA to RFA and cryoablation.

The nascent Artificial intelligence algorithms and Machine learning are also expected to have a greater role in the foreseeable future. We have been working on some in-house algorithms within our research group to use EGMs obtained using noncontact mapping together with supervised learning algorithms to predict catheter ablation responses in patients with persistent AF. This is mainly measured by AF cycle length (AFCL) changes and AF termination. This can potentially allow targeting areas with the relevant frequency characteristics to improve persistent AF ablation outcomes. More work is still ongoing to further validate this.

In summary, complete and sustained isolation of the PV is crucial for a good outcome in AF ablation, especially for paroxysmal AF. However, the situation with nonparoxysmal AF is complex, requiring additional mapping and ablation strategies to target both functional and anatomical substrates.

All the new tools discussed in this article have helped in improving AF outcomes in an evolving procedural landscape of AF ablations. Yet, prospective studies are needed in the ongoing work to confirm the safety and efficacy of these new tools. The future of AF ablation, we believe, lies in identifying valid AF drivers as targets for effective ablation ultimately leading to long-term freedom from AF.

Declaration of Interest

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References

Papers of special note have been highlighted as either of interest (†) or of considerable interest (++) to readers.

1. Hindricks G, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS). Eur Heart J. 2021;42(5):373–498.
2. Kirchhof P, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893–2962.
3. Marrouche NF, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018;378(5):417-427.
4. Kuck KH, et al. Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: the randomized AMICA trial. Circ Arrhythm Electrophysiol. 2019;12(12):e007731.
5. Packer DL, et al. Ablation versus drug therapy for atrial fibrillation in heart failure. Circulation. 2021;143(14):1377–1390.
6. January CT, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. Circulation. 2019;140(2):e125–e151.
7. Haissaguerre M, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659–666.
8. Calkins H, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012;14(4):528–606.
9. Schotten U, et al. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev. 2011;91(1):265–325.
10. Ho SY, Cabrera JA, Sanchez-Quintana D. Left atrial anatomy revisited. Circ Arrhythm Electrophysiol. 2012;5(1):220–228.
11. Verma A, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 372(19 / (SJM)):812-822. 2015.

† (Huge impact on evaluating different approaches for AF ablation and fuelling the need for further research).
12. Ammar-Busch S, et al. Correlation between atrial fibrillation driver locations and complex fractionated atrial electrograms in patients with persistent atrial fibrillation. Pacing Clin Electrophysiol. 2018;41 (10):1279–1285.

13. Tanaka K, et al. Spatial distribution of fibrosis governs fibrillation wave dynamics in the posterior left atrium during heart failure. Circ Res. 2007;101(8):839–847.

14. Jadidi AS, et al. Inverse relationship between fractionated electrograms and atrial fibrosis in persistent & atrial fibrillation. J Am Coll Cardiol. 2013;62(9):802–812.

15. Bolrich M, et al. 3D mapping for PVI- geometry, image integration and incorporation of contact force into work flow. J Arrhythm. 2018;10(6):1795.

16. Masuda M, et al. Left atrial voltage mapping with a direction-independent grid catheter: comparison with a conventional circular mapping catheter. J Cardiovasc Electrophysiol. 2019;30 (12):2834–2840.

17. Ptaszek LM, et al. Rapid acquisition of high-resolution electroanatomical maps using a novel multielecetrode mapping system. J Interv Card Electrophysiol. 2013;36(3):233–242.

18. Sohns C, et al. The first clinical experience using a novel high-resolution electroanatomical mapping system for left atrial ablation procedures. Clin Res Cardiol. 2016;105(12):992–1002.

19. Zaman J, Baykaner T, Narayan SM. Mapping and ablation of rotational and focal drivers in atrial fibrillation. Card Electrophysiol Clin. 2019;11(4):583–595.

* (A useful guide discussing role of drivers in atrial fibrillation)

20. Berenfeld O, Jafiee J. Mechanisms of atrial fibrillation: rotors, ionic determinants, and excitation frequency. Cardiol Clin. 2014;32 (4):495–506.

21. Mohanty S, et al. Impact of rotor ablation in nonparoxysmal atrial fibrillation patients: results from the randomized OAAS trial. J Am Coll Cardiol. 2016;68(3):274–282.

22. Knecht S, et al. Multicentre evaluation of non-invasive biatrial mapping for persistent atrial fibrillation ablation: the AFACART study. EP Europace. 2017;19(8):1302–1309.

23. Haissaguerre M, et al. Noninvasive panoramic mapping of human atrial fibrillation mechanisms: a feasibility report. J Cardiovasc Electrophysiol. 2013;24(6):711–717.

24. Atienza F, et al. Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. Heart Rhythm. 2009;6(1):33–40.

25. Terricabras M, Piccini JP, Verma A. Ablation of persistent atrial fibrillation: challenges and solutions. J Cardiovasc Electrophysiol. 2020;31(7):1809–1821.

26. Umaphthy K, et al. Phase mapping of cardiac fibrillation. Circ Arrhythm Electrophysiol. 2010;3(1):105–114.

27. Narayan SM, et al. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial. J Am Coll Cardiol. 2012;60(7):628–636.

28. Mohanty S, et al. Impact of rotor ablation in non-paroxysmal AF patients: findings from the per-protocol population of the OAAS trial at long-term follow-up. Am Heart J. 2018;205:145–148.

29. Brachmann J, et al. Prospective randomized comparison of rotor ablation vs. conventional ablation for treatment of persistent atrial fibrillation—the REAFFIR trial. Heart Rhythm. 2019;16(6):963–965.

30. Cheniti G, et al. Noninvasive mapping and electrocardiographic imaging in atrial and ventricular arrhythmias (cardiolnights). Card Electrophysiol Clin. 2019;11(3):459–471.

31. Rodrigo M, et al. Noninvasive assessment of complexity of atrial fibrillation: correlation with contact mapping and impact of ablation. Circ Arrhythm Electrophysiol. 2020;13(3):e007700.

32. Bolrich M, Sommer P. Cardiac mapping systems: rhythmia, topeka, ensite precision, and CARTO. Card Electrophysiol Clin. 2019;11 (3):449–458.

33. Alhusseini M, et al. Two independent mapping techniques identify rotational activity patterns at sites of local termination during persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2017;28(6):615–622.

34. Honarbakhsh S, et al. A novel mapping system for panoramic mapping of the left atrium: application to detect and characterize localized sources maintaining atrial fibrillation. JACC Clin Electrophysiol. 2018;4(1):124–134.

35. Hemam ME, et al. Epiphenomenal re-entry and spurious focal activation detection by atrial fibrillation mapping algorithms. JACC: Clinical Electrophysiology. 2021;7(7):923–932.

36. Verma A, et al. Characterization and significance of localized sources identified by a novel automated algorithm during mapping of human persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2018;29(11):1480–1488.

37. Conti S, et al. Novel multipolar mapping system identifying coexistence of multiple conduction patterns in persistent AF: a case report. Pacing Clin Electrophysiol. 2018;41(2):210–213.

38. Targeting non-PV sources in persistent atrial fibrillation identified by combined ultrasound imaging and dipole density mapping: the UNCOVER-AF trial. J Cardiovasc Electrophysiol. 2019;30(9):1736–1737.

39. Honarbakhsh S, et al. Development, in vitro validation and human application of a novel method to identify arrhythmia mechanisms: the stochastic trajectory analysis of ranked signals mapping method. J Cardiovasc Electrophysiol. 2019;30(5):691–701.

40. Honarbakhsh S, et al. Ablation in persistent atrial fibrillation using stochastic trajectory analysis of ranked signals (star) mapping method. JACC Clin Electrophysiol. 2019;5(7):817–829.

41. Honarbakhsh S, et al. Ablation guided by STAR-mapping in addition to pulmonary vein isolation is superior to pulmonary vein isolation alone or in combination with CFAE/linear ablation for persistent AF. J Cardiovasc Electrophysiol. 2020.

42. Ng J, et al. Electrogram morphology recurrence patterns during atrial fibrillation. Heart Rhythm. 11(11):2027–2034. 2014.

* (valuable insights into understanding the electrical behaviour behind atrial fibrillation.)*

43. Haiman JL, et al. Distinctive patterns of dominant frequency trajectory behavior in drug-refractory persistent atrial fibrillation: preliminary characterization of spatiotemporal instability. J Cardiovasc Electrophysiol. 25(4):371–379. 2014.

* (a novel platform for DF analysis and DF-guided ablation.)*

44. Chu G, et al. Targeting cyclical highest dominant frequency in the ablation of persistent atrial fibrillation. Eurocase. 2016;17:v1–v2.

45. Li X, et al. An interactive platform to guide catheter ablation in human persistent atrial fibrillation using dominant frequency, organization and phase mapping. Comput Methods Programs Biomed. 2017;141:83–92.

* (Correlating patterns of high dominant frequency with AF drivers)*

46. Li X, et al. Automatic extraction of recurrent patterns of high dominant frequency mapping during human persistent atrial fibrillation. Front Physiol. 2021;12:649486.

47. Maurer T, et al. High-resolution imaging of LA anatomy using a novel wide-band dielectric mapping system: first clinical experience. JACC Clin Electrophysiol. 2019;5(11):1344–1354.

48. Cauti FM, et al. Occlusion tool software for pulmonary vein occlusion verification in atrial fibrillation cryoballoon ablation to avoid the use of contrast injection. HeartRhythm Case Rep. 2020;6(8):516–519.

49. Nicholls M. KODEX-EPD mapping for AF ablation: cardiologists in the UK are trialling a new system they believe could be a game-changer in the treatment of atrial fibrillation (AF). Eur Heart J. 2019;40(36):3003–3005.

50. Arbelo E, et al. Benefit of left atrial roof linear ablation in paroxysmal atrial fibrillation: a prospective, randomized study. J Am Heart Assoc. 2014;3(5):e000877.

51. Ouyang F, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation. 2010;122(23):2368–2377.

52. Tilt RR, et al. Ten-year clinical outcome after circumferential pulmonary vein isolation utilizing the Hamburg approach in patients with symptomatic drug-refractory paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol. 2018;11(2):e005250.

53. Brooks S, et al. Insights into ablation of persistent atrial fibrillation: lessons from 6-year clinical outcomes. J Cardiovasc Electrophysiol. 2018;29(2):257–263.
54. Wasmier K, et al. Pulmonary vein reconnection and arrhythmia progression after antral linear catheter ablation of paroxysmal and persistent atrial fibrillation. Clin Res Cardiol. 2016;105(9):738–743.

55. Kanamori N, et al. Optimal lesion size index to prevent conduction gap during pulmonary vein isolation. J Cardiovasc Electrophysiol. 2018;29(12):1616–1623.

56. Das M, et al. Ablation index, a novel marker of ablation lesion quality: prediction of pulmonary vein reconnection at repeat electrophysiology study and regional differences in target values. Europace. 2017;19(5):775–783.

57. Santoro F, et al. Left atrial anterior line ablation using ablation index and inter-lesion distance measurement. Clin Res Cardiol. 2019;108(9):1009–1016.

58. Münkler P, et al. Ablation index for catheter ablation of atrial fibrillation - clinical applicability and comparison with force-time integral. Circ J. 2018;82(11):2722–2727.

59. Osei K, et al. Local impedance-guided radiofrequency ablation with standard and high power: results of a preclinical investigation. J Cardiovasc Electrophysiol. 2021;32(8):2060–2068.

60. Kuck K-H, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med. 2016;374(23):2225–2245.

61. Rottner L, et al. Is less more? Impact of different ablation protocols on periprocedural complications in second-generation cryoballoon based pulmonary vein isolation. EP Europace. 2017;20(9):1459–1467.

62. Chun KR, et al. Individualized cryoballoon energy pulmonary vein isolation guided by real-time pulmonary vein recordings, the randomized ICE-T trial. Heart Rhythm. 2017;14(4):495–500.

63. Chen S, et al. Impact of cryoballoon freeze duration on long-term durability of pulmonary vein isolation: ice re-map study. JACC Clin Electrophysiol. 2019;5(3):551–559.

64. Chun JKR, et al. Cryoballoon versus laserballoon. Circ Arrhythm Electrophysiol. 14(2):e009294. 2021.

• (Prospective randomised trial comparing Cryoballoon vs Laser balloon)

65. Yap SC, et al. Comparison of procedural efficacy and biophysical parameters between two competing cryoballoon technologies for pulmonary vein isolation: insights from an initial multicenter experience. J Cardiovasc Electrophysiol. 2021;32(3):580–587.

66. Klaver MN, et al. Ultralow temperature cryoablation using near-critical nitrogen for cavotricuspid isthmus-atriablation, first-in-human results. J Cardiovasc Electrophysiol. 2021;32(8):2025–2032.

67. De Potter TJR, Boersma LVA. Ultra-low temperature cryoablation: the coolest innovation EP has been waiting for? J Cardiovasc Electrophysiol. 2021;32(3):578–579.

68. Dukkipati SR, et al. Visual balloon-guided point-by-point ablation: reliable, reproducible, and persistent pulmonary vein isolation. Circ Arrhythm Electrophysiol. 2010;3(3):266–273.

69. Reddy VY, et al. Pulmonary vein isolation with a novel multielectrode radiofrequency balloon catheter that allows directionally tailored energy delivery: short-term outcomes from a multicenter first-in-human study (RADIANCE). Circ Arrhythm Electrophysiol. 2019;12(12):e007541.

70. Dhillon GS, et al. Use of a multi-electrode radiofrequency balloon catheter to achieve pulmonary vein isolation in patients with paroxysmal atrial fibrillation: 12-Month outcomes of the RADIANCE study. J Cardiovasc Electrophysiol. 2020;31(6):1259–1269.

71. 38th BSC annual congress. Acta cardiologica. 2019, 74.

72. Rovaris G, et al. Second-generation laser balloon ablation for the treatment of atrial fibrillation assessed by continuous rhythm monitoring: the LIGHT-AF study. EP Europace. 2021;23(9):1380–1390.

73. Sohara H, et al. HotBalloon ablation of the pulmonary veins for paroxysmal atr. multicenter randomized trial in Japan. J Am Coll Cardiol. 2016;68(25):2747–2757.

74. Nagashima K, et al. Hot balloon versus cryoballoon ablation for atrial fibrillation. Circ Arrhythm Electrophysiol. 2018;11(5):e005861.

75. Kottkamp H, et al. Global multielectrode contact-mapping plus ablation with a single catheter in patients with atrial fibrillation: global AF study. J Cardiovasc Electrophysiol. 2019;30(11):2248–2255.

76. Kourth J, et al. Preclinical evaluation of pulsed field ablation: electrophysiological and histological assessment of thoracic vein isolation. Circ Arrhythm Electrophysiol. 2019;12(12):e007781.

77. van Driel VJ, et al. Low vulnerability of the right phrenic nerve to electrophoration ablation. Heart Rhythm. 2015;12(8):1838–1844.

78. Stewart MT, et al. Intracardiac pulsed field ablation: proof of feasibility in a chronic porcine model. Heart Rhythm. 2019;16(5):754–764.

79. Koruth JS, et al. Pulsed field ablation versus radiofrequency ablation: esophageal injury in a novel porcine model. Circ Arrhythm Electrophysiol. 2020;13(3):e008303.

80. Koruth JS, et al. Endocardial ventricular pulsed field ablation: a proof-of-concept preclinical evaluation. EP Europace. 2020;22(3):434–439.

81. Reddy VY, et al. Ablation of atrial fibrillation with pulsed electric fields: an ultra-rapid, tissue-selective modality for cardiac ablation. JACC: Clinical Electrophysiology. 2018;4(8):987–995.

82. Reddy VY, et al. Pulsed field ablation for pulmonary vein isolation in atrial fibrillation. J Am Coll Cardiol. 2019;74(3):315–326.

83. Reddy VY, et al. Pulsed field ablation of paroxysmal atrial fibrillation: 1-year outcomes of IMPULSE, PEFCAT, and PEFCAT II. JACC Clin Electrophysiol. 2021;7(5):614–627.

• (Promising long-term outcomes of pulsed field ablation)

84. Reddy VY, et al. Pulsed field ablation in patients with persistent atrial fibrillation. J Am Coll Cardiol. 2020;76(9):1068–1080.

85. Reddy VY, Anter E, Rackauskas G, et al. Lattice-tip focal ablation catheter that toggles between radiofrequency and pulsed field energy to treat atrial fibrillation: a first-in-human trial. Circ Arrhythm Electrophysiol. 2020;13(6):e008718.

86. Nilsson B, et al. The effectiveness of a high output/short duration radiofrequency current application technique in segmental pulmonary vein isolation for atrial fibrillation. Europace. 2006;8(11):2025–2032.

87. Winkle RA, et al. Low complication rates using high power (45-50 W) for short duration for atrial fibrillation ablations. Heart Rhythm. 2019;16(2):165–169.

88. Yavin HD, et al. Impact of high-power short-duration radiofrequency ablation on long-term lesion durability for atrial fibrillation ablation. JACC Clin Electrophysiol. 2020;6(8):973–985.

89. Ravi V, et al. High-power short duration vs. conventional radiofrequency ablation of atrial fibrillation: a systematic review and meta-analysis. Europace. 2021;23(5):710–721.

90. Iwasawa J, et al. Temperature-controlled radiofrequency ablation for pulmonary vein isolation in patients with atrial fibrillation. J Am Coll Cardiol. 2017;70(5):542–553.

91. Kautzner J, et al. A novel temperature-controlled radiofrequency catheter ablation system used to treat patients with paroxysmal atrial fibrillation. JACC: Clinical Electrophysiology. 2021;7(3):352–363.

92. Lesher E, Zilberman I, Tschabrunn CM, et al. High-power and short-duration ablation for pulmonary vein isolation: biophysical characterization. JACC Clin Electrophysiol. 2018;4(4):467–479.

93. Lesher E, et al. High-resolution mapping of ventricular scar: evaluation of a novel integrated multielectrode mapping and ablation catheter. JACC Clin Electrophysiol. 2017;3(3):220–231.

94. Barkagan M, et al. High-power and short-duration ablation for pulmonary vein isolation: safety, efficacy, and long-term durability. J Cardiovasc Electrophysiol. 2018;29(9):1287–1296.

95. Rozen G, et al. Safety and efficacy of delivering high-power short-duration radiofrequency ablation lesions utilizing a novel temperature sensing technology. Europace. 2018;20(Ft_3):f444–f450.

96. Reddy VY, et al. Pulmonary vein isolation with very high power, short duration, temperature-controlled lesions: the QDOT-FAST trial. JACC Clin Electrophysiol. 5(7):778–786. 2019.

• (Introducing the game-changer ablation modality of very high power short duration ablation)

97. Richard Tiz R, et al. Very high-power short-duration temperature-controlled ablation versus conventional power-controlled ablation for pulmonary vein isolation: the fast and furious - AF study. Int J Cardiol Heart Vasc. 2021;35:100847.

98. Nakagawa H, et al. Comparison of in vivo tissue temperature profile and lesion geometry for radiofrequency ablation with high power–short duration and moderate power–moderate duration: effects of thermal latency and contact force on lesion formation. Circ Arrhythm Electrophysiol. 2021;14(7):e009899.