Pulsed-Field Ablation: The 'perfect' energy source?

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Take Home Messages

- Pulmonary vein isolation (PVI) is the cornerstone of AF ablation and the most common ablation procedure.
- Long-term success of single-procedure PVI with thermal energy sources (radiofrequency and cryoablation) remains suboptimal.
- Pulsed-field ablation is a novel nonthermal energy source which causes irreversible tissue injury with high sensitivity for cardiomyocyte with the potential to improve procedural efficacy and safety.
- Initial clinical experience showed promising results, but further studies are needed to establish safety, particularly the risk of asymptomatic cerebral embolism, and long-term efficacy.

Introduction

The main aim of ablation is to electrically isolate the arrhythmogenic area by creating durable full-thickness (transmural) damage to the target tissue whilst sparing adjacent structures. Traditionally, thermal injury sources have been used. However, as thermal ablation causes indiscriminate tissue injury, a trade-off exists between safety and efficacy — transmurality may only be achieved with higher energies and/or longer durations at the expense of an increased likelihood of inadvertent collateral injury. Pulsed-field ablation (PFA) promises to revolutionise the field of catheter ablation by delivering non-thermal ultrafast, irreversible tissue injury with high sensitivity for cardiomyocytes and, thus, improve both safety and efficacy with shorter procedural times.

The electrophysiology community has welcomed this new technology with many postulating that PFA is a 'game changer' and 'the future' of arrhythmia management. Similar excitement is shared by the industry with several companies developing proprietary PFA delivery systems and sponsoring research

studies. Preclinical data has been encouraging but does the initial clinical experience live up to this hype?

Overview of catheter ablation for atrial fibrillation

Percutaneous catheter ablation for atrial fibrillation (AF) is the most commonly performed ablation procedure and an important tool in the electrophysiologist's armamentarium, particularly for symptomatic patients and those with impaired left ventricular systolic function (Table 1).[1, 2]

Table1. Indications for catheter ablation for atrial fibrillation

ESC guidance (2020)	NICE guidance (2021)
Class I recommendation • Symptomatic AF patients with failure or intolerant to AAD (class I or III) • Tachycardia-induced cardiomyopathy **Class IIA recommendation** • Symptomatic PAF patients as first-line therapy • Heart failure with reduce injection fraction **Class IIb recommendation** • Persistent AF without major risk factors for AF recurrence	• Symptomatic AF patients with failure or intolerant to AAD • Hear failure caused by non-permanent AF

The seminal paper from Haïssaguerre and colleagues in 1998, demonstrated that pulmonary vein (PV) ectopy initiated and maintained AF and electrically isolating these targets terminated the arrhythmia.[3] Pulmonary vein isolation (PVI) techniques have since evolved and emerged as the cornerstone of catheter ablation.[1, 2] Although there have been significant technological advancements, with integration of more sophisticated mapping tools and ablation strategies, the pathophysiology of AF remains poorly understood and long-term freedom from AF following a single-procedure PVI is still suboptimal ; 60-70% in paroxysmal AF patients and approximately 50% in persistent AF.[4-7] The dominant mechanism of post-ablation AF recurrence is PV reconnection which occurs in up to 80% of patients; hence, establishing a durable PVI has long been a major focus of research.[8, 9] In a small proportion of patients, regions of abnormal electrical substrates (non-PV triggers) are responsible for post-ablation recurrence but it is unclear if additional ablation, particularly in persistent AF, is beneficial with studies reporting contrasting results.[10]

Although catheter ablation is a relatively safe procedure in experienced centres with a mortality rate of <0.1%, serious complications from inadvertent damage to adjacent structures still occur.[11, 12] Particularly worrisome are injuries to the oesophagus, which lies posteriorly to the left atrium and is

particularly vulnerable to thermal injury. Mucosal damage can progress to an atrial oesophageal fistula, a rare but life-threatening complication.[13]

Thermal ablation techniques

Conventionally, thermal energy sources have been used to induce cell death during ablation. Direct current ablation was initially employed in the 1970s but has since been abandoned due to an unfavourable safety profile, notably the high risk of barotrauma. The two most used modes of ablation are radiofrequency (heating) and cryoablation (freezing),. In paroxysmal AF patients, cryoablation and radiofrequency ablation have comparable procedural efficacy and safety.[5] Incremental gains have been reported with new generation catheters which incorporate contact-force feedback and ablation index, but PV reconnection still remains a hurdle.[9]

Alternative methods of ablation include laser, microwave, and high-focussed ultrasound which are mainly limited to clinical research and ultimately rely on thermal energy to be effective.[14, 15]

Pulsed-field ablation and preliminary data

Pulsed-field ablation creates tissue injury through a non-thermal energy source: electroporation. An intermittent high intensity electrical field is generated between two electrodes which disrupts the cell membrane by creating nanometer-sized pores that disturb intracellular homeostasis (Figure 1). At a tissue level, the effect is dependent upon the strength of the electrical fields. If a strong electrical field is applied, the nanopores do not reverse leading to increased membrane permeability which ultimately results in cell death (irreversible electrophoresis).

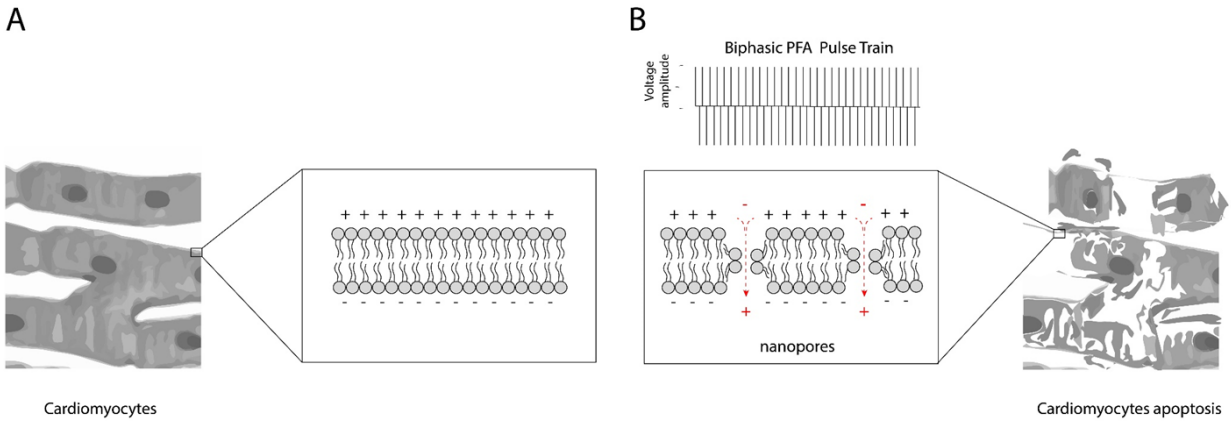

Figure 1: A) Pre-ablation cardiomyocytes with an intact phospholipid cell membrane B) Pulsed field ablation creates a transient electrical field that leads to reorientation of the heads of the phospholipid layers in discrete areas of the cell membrane whilst the tails continue to interact with the hydrophobic area thus creating nanopores. Increased membrane permeability can result in cell death.

Preclinical data has demonstrated several advantages of PFA over thermal energy sources. PFA is non-contact dependent — only requiring close proximity with target tissues — and a single PFA can be delivered be in a few seconds. In contrast, radiofrequency and cryoablation require good contact with the underlying cardiac tissue to create transmural lesions and achieve conduction block. Typically, at least a few seconds to minutes are required to deliver a satisfactory lesion and stability of intracardiac catheters is challenging. Loss of contact may result in incomplete lesions, reducing procedural success and promoting AF recurrence. Histological sections also demonstrate that ablated tissue following PFA is sharply demarcated and more continuous without coagulation necrosis.[16]

Perhaps most impressive is its tissue specificity for cardiomyocytes. The electroporation threshold appears to be lower in cardiomyocytes than in surrounding structures, and direct application of electrical currents that induce cardiac necrosis have little effect on coronary vessels, the oesophagus.[17, 18] and the phrenic nerve .[19, 20] Taken together, preclinical data certainly suggest that PFA may overcome limitations of thermal injury sources.

Clinical experience

Thus far the bulk of clinical research has utilised the Farawave (Farapulse; Menlo Park, CA) PFA platform. Other companies are actively investigating their proprietary PFA technology but published data is limited to acute procedural success (Table 2 and 3).

Table 2. Summary of published pulmonary vein isolation (PVI) studies						
Study	**Company/ Device**	**Patients**	**Acute procedural success (PVI)**	**Serious Adverse Events 30-days**	**Successful PVI (3 months)**	**Arrhythmia freedom (1-year)**
Reddy et al[21]	Farawave (Farapulse)	22 PAF	100% (15 endocardial)	—	NR	NR
IMPUSE[22, 23]	Farawave (Farapulse)	40 PAF	100%	1 cardiac perforation —	Combined IMPULSE, PETCAT I&II - Total: 64.5% - Biphasic: 84.1%	Combined IMPULSE, PETCAT I&II - Total: 78.5% - Biphasic: 84.5%
PETCAT[22, 23]	Farawave (Farapulse)	71 PAF	100%			
PETCAT II[23]	Farawave (Farapulse)	10 PAF	100%	1 pericardial effusion 1 TIA 1 Vascular haematoma		
INSPIRE[25]	Biosense Webster	35 PAF	100%	—	NR	NR
PULSED-AF[26]	PulseSelect (Medtronic)	38 (35 PAF,PersAF)	100%	—	NR	NR
PAF; Paroxysmal Atrial fibrillation. PersAF; Persistent atrial fibrillation. PVI; pulmonary vein isolation. NR; not reported.						

In 2018, the first in-human PVI study by Vivek and colleagues demonstrated the feasibility of single-shot monophasic Farawave PFA platform.[21] Fifteen out of twenty patients underwent ablation via an endocardial route with all PVs (52/52) isolated. No procedural complications were reported. Similar acute procedural success was reported the following year in a study that combined 81 patients enrolled in IMPULSE (NCT03700385) and PEFCAT (NCT03714178); one patient had a pericardial tamponade.[22] The PFA delivery protocol was refined during the course of this study which accounts for the discrepancy rate of PV reconnection at 3 months. Of the 52 patients that underwent remapping, only 18% of those in the monophasic pulse protocol had PV isolation compared to all patients in the optimised biphasic waveforms. Finally, 1-year combined outcome data involving 121 patients from 3 trials (IMPULSE, PEFCAT, PEFCAT II [NCT04170608]) was also encouraging. Overall arrythmia freedom was 78.5% for the whole cohort and this increased to 84.5% in those with optimised biphasic protocol (49 patients).[23]

It should be noted that secondary safety data presented in these 3 trials is sparse. For example, only 38 out 121 patients had post-ablation gastroscopy although no mucosal lesions were found. It would be important to confirm preclinical observations that PFA is more forgiving to adjacent structure. In addition, there have been previous reports of microbubbles during PFA in preclinical and clinical

studies raising concerns regarding potential asymptomatic cerebral embolism. More striking is the lack of post-ablation brain MRI data which was previously considered an important safety endpoint in their original feasibility study. Only 18 (14.9%) patients had post-ablation brain MRI and of these, 2 had positive diffused-weighted imaging suggestive of a new ischaemic event, with one patient presenting with clinical signs in keeping with a transient ischaemic attack.

Table 3. Pulsed-field ablation studies in clinicaltrial.gov

Studies	Company/ Device	Sponsor	Study design	Population (n)	Primary Outcome
NCT05114954	CardioPulse	CardioPulse	Single-centre, single-arm	158 PAF	- AF freedom (1-year)
NCT04524364	Biosense Webster	Biosense Webster	multicentre, single-arm	550 PAF	- Adverse events (7days) - Arrhythmia freedom (1 year)
NCT05113056	Acutus Medical	Acutus Medical	Single-centre, single-arm	60 PAF	- Acute PV isolation (20 minutes) - Adverse events (6 months)
FARA-Free (NCT04474054)	Farapulse	Farapulse	Single-centre, single-arm	50 PAF	- Adverse events (7days-12 months)
PULSED-AF NCT04198701	Medtronic	Medtronic	multi-center, non-randomized	418 (PAF &PerSAF)	- Adverse events (6 months) - Arrhythmia Freedom (12 months)
ADVENT (NCT04612244)	Farapulse	Farapulse	Multi-centre RCT (PFA vs Radiofrequency and cryoablation)	900 PAF	- Adverse events (7days-12 months) - Treatment success (12 months)
PULSE-EU (NCT05164107)	Kardium	Kardium	Single-centre, single-arm	40 AF	- Device or procedure related adverse events (3 months)
BEAT PAROX-AF NCT05159492	Farapulse	University of Bordeaux	Multi-centre RCT (PFA vs Radiofrequency and cryoablation)	292 PAF	- Single-procedure clinical success (12 months)

PAF; Paroxysmal Atrial fibrillation. PersAF; Persistent atrial fibrillation. RCT; randomised control trial.

Discussion

PFA may well be the 'perfect' energy source for ablation delivering safe and durable lesions. However, current evidence has important limitations and uncertainty remains. First, PFA platforms are proprietary and, unlike thermal energy sources, current efficacy and safety data cannot be generalised or used interchangeably due to difference in pulse width, shape, number of trains, fibre orientation and current voltage.[24] Second, acute procedural success is undoubtedly an important metric, but PV durability must be studied at 3-months to provide further information of PFA efficacy, particularly as it is correlated with long-term arrhythmia freedom. Third, further work on determining optimal PFA parameters is required, as there was a large discrepancy in PV reconnection between PFA protocols and only a small number of patients received the 'optimised' biphasic protocol. Finally, fewer than 200 patients have undergone PFA and although major safety events were low, higher quality safety data incorporating brain MRI and gastroscopies, are desirable before embarking on larger studies.

Undoubtedly, the litmus test for PFA will be an adequately powered randomized clinical trial (RCT) to determine long-term efficacy and safety PFA vs state-of-the-art radiofrequency and/or cryoablation − two RCTs are currently recruiting (Table 3) − but more preliminary work to refine current technology and address safety concerns is needed.

Conclusion

There is a palpable enthusiasm for PFA, with many editorials and reviews predicting that it will be the dominant ablation modality in the future. But enthusiasm should be tempered with caution and realism. Preclinical data is impressive, but clinical experience whilst encouraging is limited and long-term data is lacking. PFA technology must evolve and mature prior to widespread adoption. Many other devices have been proclaimed as being 'game changers' but have overpromised and undelivered.

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