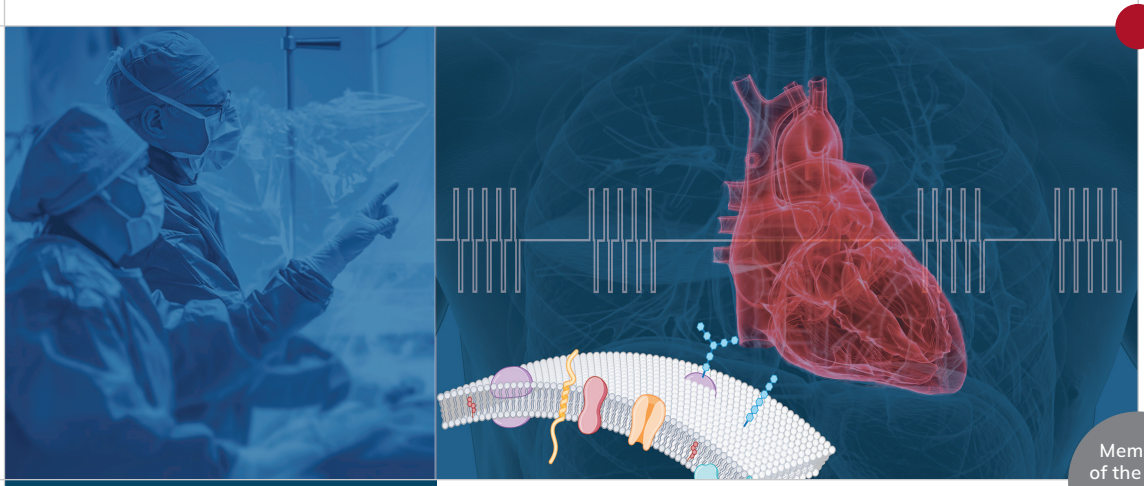
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Pulsed Field Ablation for Cardiac Arrhythmias: The Basis for Clinical Practice

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Pulsed Field Ablation for Cardiac Arrhythmias: The Basis for Clinical Practice

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Foreword: An educational reference for pulsed field ablation

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Within only a few years, pulsed field ablation (PFA) has evolved from an emerging concept to a therapeutic modality adopted worldwide and increasingly considered to be a central component of modern catheter ablation. Its rapid adoption has generated tremendous interest among clinicians, researchers, engineers, and industry who share a common goal: improving the safety, efficacy, and reproducibility of catheter ablation procedures.

As with many transformative technologies, however, clinical adoption has progressed faster than the consolidation of knowledge. While the number of scientific publications on PFA has dramatically increased, clinicians, researchers, engineers, and trainees seeking to understand PFA often face a fragmented body of literature scattered across multiple disciplines, and it is not possible to find a single educational resource to learn about all aspects of PFA technology.

The idea behind this Europace Supplement was born from the recognition of this challenge. Our objective was simple but ambitious: to bring together, in one place, the current scientific understanding of PFA and create the first complete comprehensive educational reference for the electrophysiology community.

The result is what we believe to be the first educational resource specifically designed to provide a complete overview of PFA mechanisms, technology, tissue interactions, procedural and clinical considerations, and emerging developments.

Our objective was to create a comprehensive educational resource that becomes a resource to which readers return repeatedly throughout their professional journey. For experienced operators, a deeper understanding of these mechanisms can support more informed clinical decision-making and facilitate critical evaluation of emerging technologies. For physicians beginning their journey with PFA, the supplement provides a structured introduction to the scientific principles behind the therapy. For fellows, researchers, and allied professionals, it offers a framework that connects engineering principles with clinical practice and creates a common language for the entire scientific and clinical communities. We hope that readers from all levels of experience will find relevant and practical knowledge within these pages.

The educational value of this supplement deserves particular emphasis. Understanding why PFA behaves differently from thermal ablation technologies requires breaking barriers, clarifying misconceptions and accessing new knowledge that extends beyond traditional electrophysiology training. The contents of the supplement follow a logical progression. The opening articles establish the foundations of PFA, ranging from cell membrane electroporation, system design and technological concepts to differential tissue effects, lesion formation, or interactions with surrounding tissues. Subsequent contributions examine in detail the mechanisms and procedural aspects that underpin both efficacy and safety. The final articles focus on clinical aspects aimed at optimizing the therapy, ranging from sedation and anaesthesia strategies and approaches to the treatment of atrial fibrillation, to current perspectives of PFA and Left atrial appendage closure, as well as the future evolution of PFA technologies and applications.

Readers will notice that the supplement does not attempt to provide definitive answers to every question. On the contrary, many chapters highlight areas where knowledge remains incomplete. The field continues to evolve rapidly, and several scientific, technical, and clinical questions remain open. We believe that acknowledging uncertainty is an important component of scientific education. By identifying current knowledge gaps, we hope this publication will not only educate but also stimulate future investigation.

The multidisciplinary nature of the contributing authors also deserves special attention. The development of PFA has been driven not only by electrophysiologists, but also by experts in electroporation science, biomedical engineering, and translational research. Bringing these perspectives together was essential to creating a complete and balanced educational resource. Many of the most important questions surrounding PFA can only be answered through collaboration between disciplines, and this supplement reflects that philosophy.

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We would like to express our sincere gratitude to all authors for their dedication, expertise, and commitment to this project. The development of a comprehensive educational resource of this scope requires substantial effort and collaboration. We are deeply appreciative of their contributions and their willingness to share their knowledge and unvaluable experience with the wider scientific community.

Looking forward, PFA is expected to continue its evolution through improvements in waveform design, catheter technologies, dosing strategies, treatment personalization, and novel clinical applications. At the same time, the need for high-quality education will only increase. Our aspiration is that this supplement becomes a reference resource that supports learning and discussion and serves as a catalyst for continued innovation, research and optimized clinical practice to ultimately improve patient care.

Finally, the Guest Editors thank Boston Scientific for supporting this initiative and their vision of creating an accessible, high-quality educational reference on PFA. The scientific content, interpretations, and conclusions presented in the supplement remain the responsibility of the authors and Guest Editors.

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Biophysical principles of pulsed field ablation

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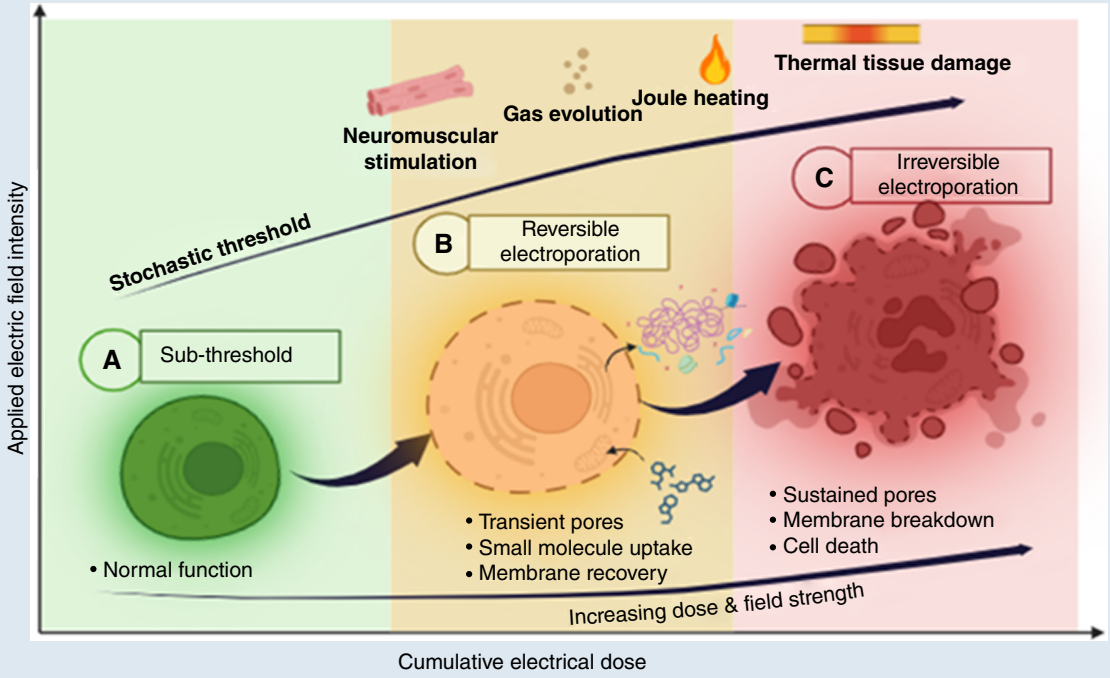
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Abstract

Pulsed field ablation (PFA) is emerging as a major advance in cardiac ablation because it induces irreversible electroporation rather than relying primarily on thermal injury. This article provides an overview of the core biophysical principles underlying PFA, focusing on concepts broadly relevant across systems and clinical applications. Externally applied pulsed electric fields interact with biological tissues and affect their transmembrane potential. When a critical threshold is exceeded, nanoscale aqueous pores form in the lipid bilayer, initiating electroporation. Depending on pulse amplitude, duration, number, repetition frequency, waveform, and tissue characteristics, membrane permeabilization may remain reversible or progress to irreversible injury and cell death. This article focuses on the fundamental biophysical principles of electroporation that underpin PFA. The article outlines how membrane charging, cell geometry, and tissue heterogeneity influence electric field distribution and biological response and explains why lesion formation depends on both field intensity and exposure conditions. It also summarizes the molecular basis of pore formation, the potential contribution of lipid peroxidation and membrane proteins, and the downstream processes linking sustained permeability to loss of homeostasis and delayed cell death. Finally, it places cardiac PFA in the broader context of electroporation-based therapies developed in oncology, drug delivery, and gene transfer, while highlighting the remaining need for cardiomyocyte-specific mechanistic evidence to further optimize safety, precision, and durability.

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Graphical Abstract



Keywords Pulsed field ablation • Electroporation • Irreversible electroporation • Cardiac ablation • Biophysics • Electric field • Lesion formation • Tissue selectivity

Introduction

Pulsed field ablation (PFA) has emerged as a transformative energy modality for treating cardiac arrhythmias, introducing a mechanism of action fundamentally different from thermal ablation technologies.[1–6] Rather than relying on tissue heating or cooling, PFA applies high-intensity, short-duration pulsed electric fields (PEFs) to induce irreversible electroporation (IRE) in myocardial cells. Recent randomized and real-world data have established PFA as a clinically relevant modality beyond mechanistic promise. The ADVENT randomized trial demonstrated non-inferior effectiveness with a favourable safety profile compared with thermal ablation in paroxysmal atrial fibrillation.[7] Findings supported by large real-world safety analyses report low rates of oesophageal, phrenic nerve, and cerebrovascular injury.[8,9] Emerging head-to-head comparisons with cryoballoon ablation further suggest that clinical outcomes depend on delivered waveform and dose, reinforcing the need for standardized, evidence-based PFA energy definitions.[10]

The non-thermal basis has important implications for lesion formation, preferential tissue effects, procedural safety, and clinical workflow. A clear understanding of the underlying biophysical principles is therefore essential for interpreting preclinical data, optimizing system design, and translating this technology into safe, effective, and reproducible clinical practice.

This chapter summarizes the mechanistic foundation of electroporation by describing how externally applied PEFs interact with biological tissues, how these interactions lead to electroporation at the cellular level, and how waveform characteristics influence biological outcomes. The concepts introduced here provide the scientific framework needed to understand the PFA engineering choices, tissue effects, and clinical observations discussed in subsequent chapters of this Supplement.

Scope of this article

This article focuses on the fundamental biophysical principles of electroporation that underpin PFA. Its scope is to present the core biophysical concepts that govern electroporation-based medical applications, with a focus on principles that are universally applicable across PFA systems and clinical indications. Emphasis is placed on electric field–tissue interactions, membrane electroporation mechanisms, and the role of PEF waveform parameters in determining biological response. The discussion draws from the wider electroporation literature developed across biomedical engineering, oncology, and cell biology.

This foundational knowledge serves as the basis for catheter and generator design, lesion characterization, tissue preferential effects, procedural strategies, and clinical outcomes.

Interaction of electric fields with biological tissues

Biological tissues are electrically heterogeneous structures composed of cells, extracellular matrix, and conductive fluids. When an external electric field is applied, charges redistribute within and around cells, leading to the induction of transmembrane potential (TMP) across the lipid bilayer.[11,12] The magnitude and spatial distribution of this induced TMP depend on the applied field strength, pulse parameters, tissue conductivity, cell size and orientation, and the local electric field distribution.

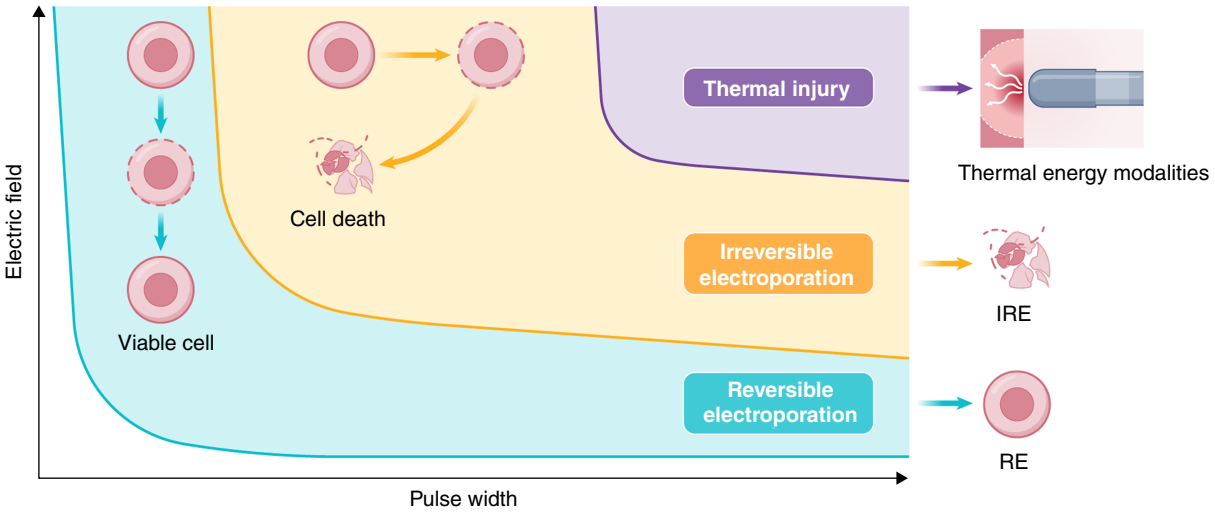


Figure 1 Relationship between electric field strength and pulse width showing transitions from reversible electroporation (RE) to irreversible electroporation (IRE) and, at higher energy delivery, thermal injury.

At lower electric field strengths, the induced TMP remains below the threshold required to disrupt membrane integrity, and cellular effects are transient and reversible. When the appropriate electric field strength and pulse durations are applied, nanoscale aqueous defects form within the lipid bilayer, a phenomenon known as electroporation.[13–15] When the extent of membrane disruption exceeds the cell's ability to recover its functions, IRE occurs, leading to loss of homeostasis and subsequent cell death.[16–18]

This electric field–driven mechanism is central to PFA and distinguishes it from thermal ablation modalities, which require a higher electric field and longer exposure time to occur (*Figure 1*). Because energy deposition is not primarily mediated by resistive heating, tissue effects depend more directly on electric field distribution than on temperature gradients. Understanding how electric fields propagate through complex cardiac anatomy and how cells respond to these fields is therefore essential for predicting lesion formation, safety margins, and tissue response.

Induced transmembrane potential

In PFA, microsecond-range electric fields drive ionic movement across cell membranes, creating TMP that triggers electroporation, whereas much higher-frequency fields act via different mechanisms not used in current cardiac PFA.[19–22]

Charges arising from ionic displacement and, at higher frequencies, dipolar orientation accumulate at the cell membrane, leading to an asymmetric charge distribution across the lipid bilayer, with positive charge on the extracellular side and negative charge on the intracellular side.[22,23] This charge separation generates an additional voltage across the membrane, superimposed on the physiological resting potential, referred to as the induced TMP. When the externally applied electric signal (i.e. voltage or electric field) is of sufficient amplitude, the induced TMP can destabilize the lipid bilayer, resulting in the formation of transient aqueous defects (electropores) and initiation of *electroporation*.[21,22] The interaction between externally applied PEFs and biological membranes can be described as a two-step process: electroporation followed by electropermeabilization.[13,22,24] In brief, electroporation occurs when the induced TMP exceeds a threshold (i.e. electroporation threshold E_{th}), triggering a rapid lipid membrane reorganization and the formation of hydrophilic pores during the electric pulse application (see the section 'Initiation of aqueous pores in lipid bilayers at high transmembrane potentials' for more details). *Electropermeabilization* then describes the state of increased membrane conductivity and permeability that may persist beyond the electric pulse duration. Depending on the waveform pulse parameters, this state can be transient or permanent.[13,22,25] The overall phenomenon, comprising electroporation (increase of cell permeability during PEF delivery) and electropermeabilization (increase of cell permeability after PEF delivery), is often referred to as *electropulsation*.[26]

Electroporation thresholds vary among tissues and cell types.[13,22,27,28] For μsPEF, larger cells tend to accumulate higher induced TMP for a given external field, making them easier to electroporate (see the section 'Principles of membrane charging, dependence on cell size, geometry, and extracellular electric field distribution'). Nevertheless, recent evidence highlights the role of cytoskeletal structure, membrane proteins, lipid bilayer composition, and the cell-to-nucleus size ratio influencing this threshold, complicating predictions based on size alone.[13,22,29,30]

Independently of the specific electroporation threshold, the development of the induced TMP is limited by how fast the cell membrane can charge, a property that depends on cell and tissue characteristics. This membrane charging time determines how cells respond to different pulse durations and waveforms and is therefore a critical parameter in PFA.[31,32] Electroporation depends not only on electric field strength but also on how the field is distributed in space and time within the target tissue. Tissue architecture, cell shape, and cell–cell organization strongly influence the locally induced TMP, making its distribution heterogeneous across the tissue. As a result, validated numerical modelling is often required to predict where electroporation occurs in structurally complex tissues.[33,34]

Principles of membrane charging, dependence on cell size, geometry, and extracellular electric field distribution

From a simplified physical perspective, a cell can be modelled as a spherical dielectric shell, representing the capacitive cell membrane, surrounded by conductive intracellular and extracellular media and exposed to an externally applied electric field.[12,35] Under this approximation, the membrane behaves as a capacitor, with charge accumulating on its surfaces and the induced TMP increasing over time towards a value determined by cell geometry and tissue conductivity. The induced TMP is not uniform along the membrane but varies spatially, reaching its maximum at the cell poles aligned with the direction of the applied electric field. This spatial distribution has been demonstrated experimentally using voltage-sensitive fluorescent probes.[36] An established expression for a non-permeabilized spherical cell is:

$$\Delta V_m(\theta, t) = \frac{3}{2} R E_0 \cos\theta (1 - e^{-t/\tau charge})$$

Where ΔV_m is the induced TMP, R is the cell radius, E_0 the applied electric field, θ the polar angle, and τ_{charge} the membrane charging time constant. The corresponding passive steady-state TMP is $\Delta V_{m,ss}(\theta) = \frac{3}{2} R E_0 \cos\theta$. At the cell pole considered in *Figure 2* ($\theta = 0$), $\Delta V_{m,ss}^{pole} = \frac{3}{2} R E_0$. The membrane charging time constant is defined as:

$$\tau_{charge} = R C_m \left(\frac{1}{2G_{ext}} + \frac{1}{G_{cyt}} \right) \quad (1)$$

where C_m is the membrane capacitance per unit length, and G_{ext} and G_{cyt} the extracellular and cytoplasmic conductances, respectively.

Thus, larger cells exhibit longer τ_{charge} and higher steady-state induced TMP, and they require longer electric pulses to reach maximal TMP.[32–34]

When electroporation occurs, membrane conductance increases due to the formation of aqueous pores in the lipid bilayer, which allows enhanced ionic transport across the membrane, which shortens the charging time and alters TMP spatial distribution:

$$\tau_{charge} = R C_m \frac{(G_{cyt} + G_{ext})}{2 G_{cyt} G_{ext} + R G_m \frac{(G_{cyt} + 2G_{ext})}{d}} \quad (2)$$

where G_m is the membrane conductance and d the membrane thickness.[32] Physiological membrane charging times are typically in the microsecond range, indicating that PEF of a few microseconds can readily induce TMP values exceeding the critical electroporation threshold (commonly < 1 V, though broader ranges up to ≈1 V are reported depending on conditions).[37,38] Experimental studies confirm these predictions, showing that membrane permeabilization depends on electric field strength and pulse duration, as well as on cell geometry and orientation relative to the applied field.[39]

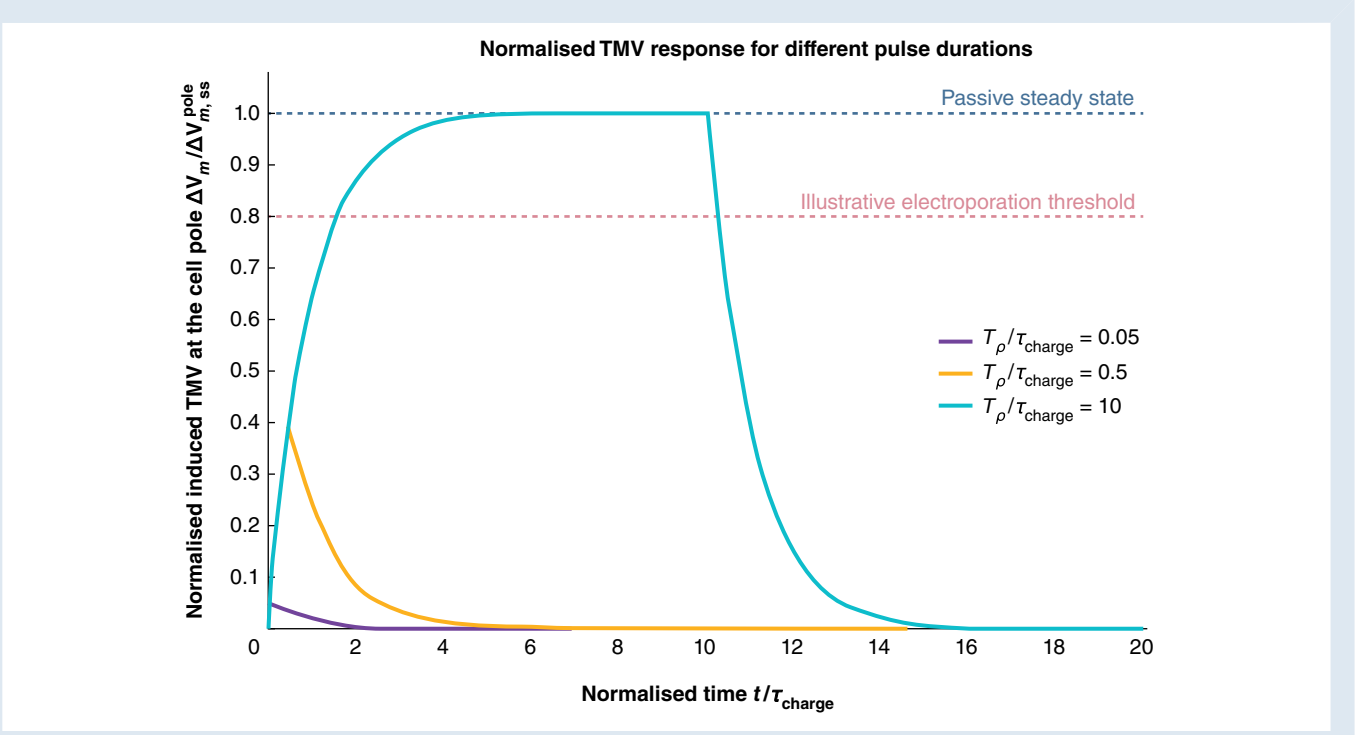


Figure 2 Normalized temporal evolution of the induced transmembrane potential (TMP), ΔV_m, at the pole of an intact spherical cell ($\theta = 0$) during rectangular electric pulses of different durations. Here, θ is the polar angle relative to the direction of the applied electric field, t is time, T_p is the pulse duration, and τ_{charge} is the characteristic membrane charging time constant. Time is normalized to τ_{charge}, and the induced TMP is normalized to its passive steady-state value at the cell pole, ($\Delta V_{(m,ss)}^{pole} = 3RE_0/2$). The curves illustrate incomplete membrane charging when ($T_P \leq \tau_{charge}$) and quasi-steady-state charging when ($T_p \gg \tau_{charge}$). The dashed blue line indicates the normalized passive steady-state TMP, whereas the dashed red line denotes an illustrative normalized electroporation threshold and should not be interpreted as a universal or cell-specific threshold.

For non-spherical geometries, such as the elongated morphology of cardiomyocytes, the description given by Eq. (1) becomes substantially more complex. In such cases, the cell can be approximated as an ellipsoid, and the corresponding analytical formulation of the TMP has been derived and discussed in detail elsewhere.[40–42] Although the spherical approximation neglects cell elongation and other geometrical features, it remains a valuable and extremely simple tool for obtaining first-order estimates of the TMP. Indeed, deviations between spherical and ellipsoidal models for representative cellular aspect ratios over a frequency range extending up to a few MHz remain below one order of magnitude[43] depending on cell aspect ratio. Therefore, while more sophisticated geometrical descriptions are required for accurate quantitative predictions, the spherical model can still provide reasonable estimates of TMP under many practical conditions. However, a rigorous assessment of the TMP requires mandatory numerical modelling, typically based on finite-element methods, to account for realistic cell morphologies and cell–cell aggregation, and to accurately predict the resulting distributions of TMP and membrane poration, as demonstrated in the studies by De Angelis et al. and Golberg et al.[33,34]

In these cellular models, the dielectric permittivity and electrical conductivity of the various cell compartments are typically derived from literature data available for different cell types.[35,44–48] However, the anisotropy of cardiac tissue, which arises from the elongated morphology and preferential alignment of cardiomyocytes, should be accounted for when performing dosimetric assessments at higher levels of biological organization, such as tissue and organ models. This anisotropy strongly affects the distribution of the induced electric field and therefore plays a key role in determining optimal electrode configurations as well as the size and geometry of the resulting PFA lesions.

Influence of pulse duration and tissue heterogeneity on the magnitude and spatial distribution of induced voltage

PEF duration controls the extent of charge redistribution across dielectric interfaces, particularly the plasma membrane.[36,39]

For electric pulse durations longer than the membrane charging time, induced TMP approaches a quasi-steady-state value governed by geometry and conductivity contrasts. When applied electric pulses are comparable to or shorter than the membrane charging time, membrane charging is incomplete, peak induced TMP is reduced, and displacement currents dominate (*Figure 2*).[49–51] In this regime, dielectric properties of cell/tissues become critical, and electric fields may also penetrate the cell cytoplasm.[35]

Tissue heterogeneity further complicates voltage distribution through Maxwell–Wagner polarization. This phenomenon arises from the accumulation of charges at interfaces between regions with different electrical conductivity and permittivity. This interfacial polarization introduces a frequency-dependent redistribution of the electric field, thereby affecting local TMP and current density.[42] Interfaces between regions of different conductivity and permittivity (e.g. vessels, fibrous septa, and fat/muscle boundaries) can locally amplify or attenuate the local electric field, generating ‘hot spots’ or ‘sinks’. Low-conductivity and permittivity regions tend to concentrate electric fields (such as the pericardium), whereas highly conductive regions shunt current, decreasing the induced electric field (such as blood). These effects are three-dimensional and tissue orientation-dependent, often requiring numerical solutions of Maxwell’s equations again to get the temporal and spatial distribution of the induced electric field and voltage.[33,34,39]

Electropulsation as the core phenomenon behind PFA: physico-chemical basis of pore formation

To safely and effectively use PFA, it is essential to understand how electric fields interact with cardiac tissue at the cellular level. The physical basis of electroporation is rooted in molecular-scale membrane processes, while the distinction between reversible and irreversible outcomes emerges progressively at higher organizational levels (*Figure 3*). Molecular events define the probability and stability of pore formation, but cellular recovery, tissue architecture, and electric field distribution determine the macroscopic and clinical effects observed in PFA. This multilevel interpretation is consistent with recent clinical–mechanistic analyses of PFA, which emphasize how

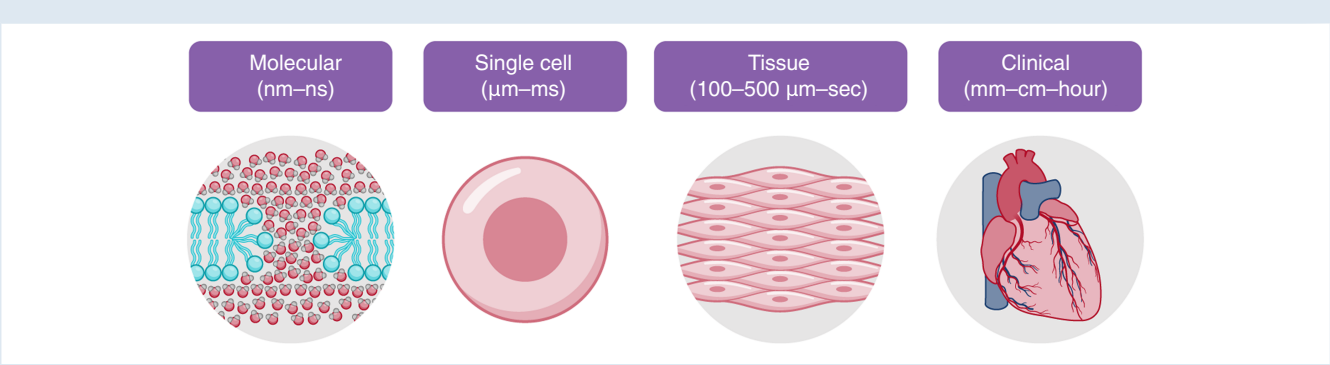


Figure 3 Multiscale framework of electroporation in pulsed field ablation. Schematic representation of the hierarchical organization of electroporation phenomena across spatial scales. At the molecular level, electric fields stabilize transient aqueous pores in lipid bilayers in a stochastic manner. At higher levels of organization, cellular recovery mechanisms, tissue architecture, and electric field distribution modulate the transition from reversible to irreversible electroporation. Clinical lesion formation in pulsed field ablation emerges from the integration of these multiscale processes rather than from a single deterministic membrane threshold.

electroporation thresholds, tissue-specific properties, and cumulative pulse delivery jointly determine lesion formation and safety profiles at the organ level.[52]

Initiation of aqueous pores in lipid bilayers at high transmembrane potentials

Intense electric fields induce high TMPs that destabilize the lipid bilayer, forming aqueous pores.[17,22,53,54] Classical continuum theories describe this as an electric-field–dependent lowering of the free-energy barrier, explaining threshold behaviour and macroscopic permeability changes.[20,51,55,56] However, direct electrophysiological measurements on planar lipid bilayers have challenged the quadratic field-dependence predicted by this classical model, showing instead that the activation barrier for pore formation decreases with the absolute value of the electric field rather than its square, a result more consistent with a field-driven reorganization of the lipid–water interface than with the standard electromechanical picture.[57] Molecular dynamics (MD) simulations provide nanoscale insight, showing that water dipoles first align at the lipid–water interface, forming 'aqueous fingers' that penetrate the hydrophobic core and guide lipid headgroup reorientation to stabilize the pore (*Figure 4*).[14,58–61] These events occur without membrane proteins, indicating electroporation is an intrinsic lipid property.[61,62] Although MD studies are limited in timescale and complexity, their findings align with continuum models and experimental evidence within a multiscale framework.[22,63]

Lipid peroxidation and its impact on cell membrane

The molecular composition of the lipid bilayer and chemical modifications, such as lipid peroxidation, can significantly alter membrane structure, hydration, and mechanical properties, creating a state more susceptible to electroporation without directly forming pores.[25,64,65] This view has, however, been challenged by molecular dynamics simulations showing that sufficiently high degrees of lipid oxidation can nucleate aqueous pores directly, even in the absence of an applied electric field.[66] Conversely, quantitative free-energy calculations indicate that the increase in ionic permeability and conductance conferred by peroxidized lipids alone, although substantial (up to several orders of magnitude), is insufficient to account for the full extent of membrane permeabilization measured experimentally in electropermeabilized cells,[67] suggesting that lipid oxidation likely acts synergistically with, rather than as a substitute for, field-driven pore formation. Oxidative reactions introduce polar groups into the hydrophobic core, disrupt lipid packing, increase polarity, and partially hydrate the membrane, reducing mechanical stability and lowering the energetic barrier for pore formation[65,68] (*Figure 5A*). PEFs can indirectly enhance these effects by increasing intracellular reactive oxygen species, promoting lipid peroxidation over hours[69,70] (*Figure 5B*). These delayed oxidative changes are mechanistically distinct from the immediate, field-driven pore formation but can influence membrane properties over longer timescales.[64,71]

Potential involvement of membrane proteins

While the lipid bilayer is the primary substrate for electropore formation, membrane proteins can locally modulate or bias electroporation.[22,61,62] Experimental studies and molecular dynamics simulations show that electric fields induce structural changes in proteins and reorganize protein-associated water, creating pathways that influence pore nucleation.[26,72–74] Cellular membranes, with their dense transmembrane proteins *Figure 5A*, introduce local dielectric and structural heterogeneities that affect electroporation dynamics without being required for pore formation.[22,75] MD simulations consistently highlight the role of water polarization as a unifying mechanism (*Figure 6*): above threshold electric fields, water dipoles align and form localized aqueous perturbations near proteins, often preceding lipid bilayer poration.[61,74,76] In cardiac cells, abundant ion channels and transporters may therefore contribute to spatial heterogeneity in electroporation susceptibility.[22]

Electric field strength and exposure time drive variability in response

Electroporation is a probabilistic process rather than a deterministic event. The formation and stabilization of nanoscale aqueous pores depend on lipid rearrangement, lipid oxidation, and protein–membrane interactions, with pore likelihood, size, and lifetime increasing nonlinearly with electric field intensity and exposure time.[22] MD simulations show substantial variability in the timing, location, and size of pores, even under identical TMPs, reflecting the stochastic stabilization of thermally fluctuating water and lipid molecules.[14,71,77]

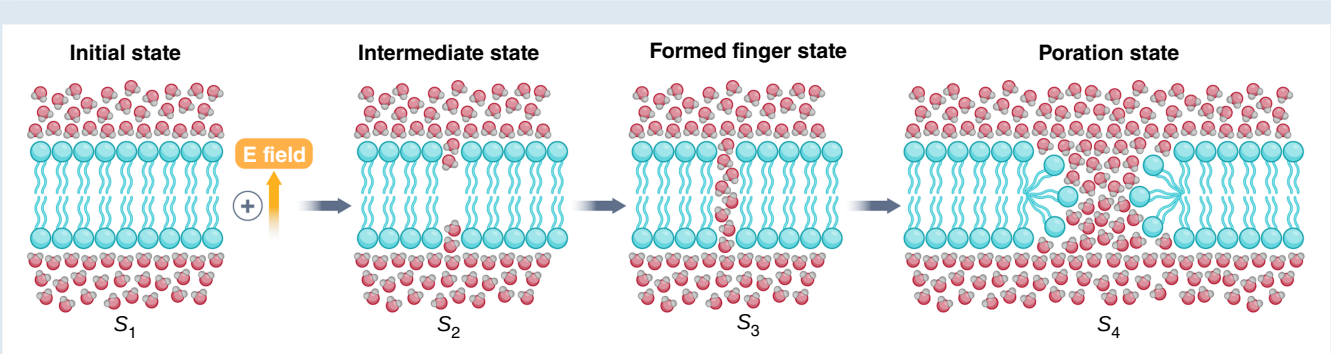


Figure 4 Sequence of molecular events leading from aqueous defect initiation to pore formation in lipid bilayers under high TMPs. The schematic illustrates the progression from an intact membrane (S1), through intermediate states characterized by field-driven water penetration and aqueous finger formation (S2 and S3), to the formation of a continuous hydrophilic pore across the membrane (S4). Adapted from Marracino et al.[21].

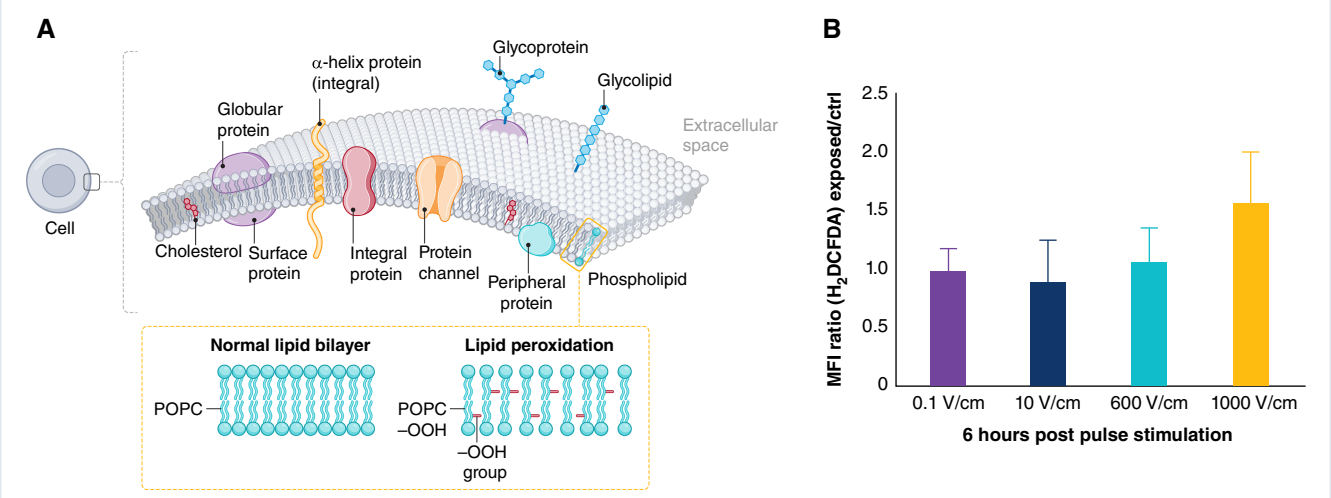


Figure 5 Modulatory role of lipid peroxidation in membrane susceptibility to electroporation. (*A*) Schematic representation of membrane lipid peroxidation. Oxidative modification of unsaturated phospholipid acyl chains introduces polar hydroperoxide groups (–OOH), locally disrupting bilayer packing, increasing membrane polarity, and facilitating water penetration into the lipid core. These changes alter membrane material properties without directly inducing pore formation (Páez-Pérez et al.[27]). (*B*) Experimental evidence of increased intracellular oxidative stress following pulsed electric field exposure, shown as the mean fluorescence intensity (MFI) ratio of the ROS-sensitive probe H_2DCFDA measured 6 h after stimulation at increasing electric field strengths adapted from.[70]

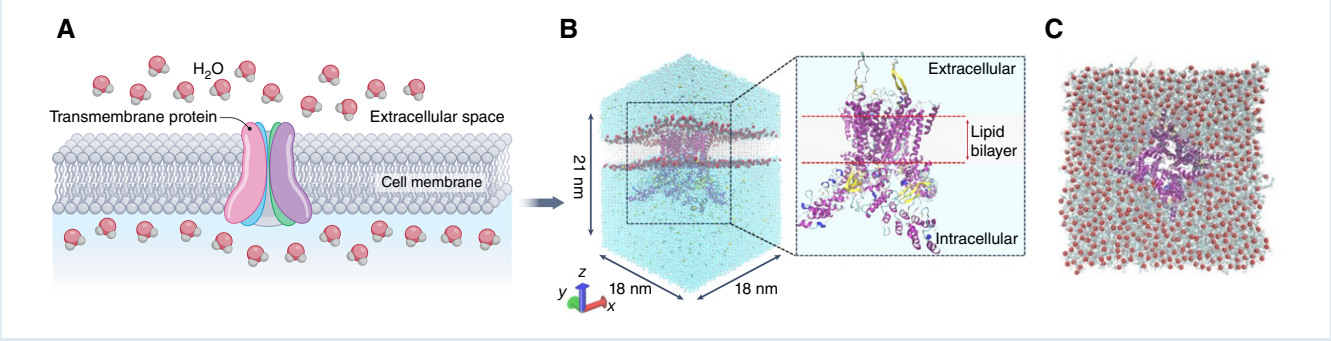


Figure 6 Conceptual and molecular dynamics representation of protein-associated modulation of electroporation. (*A*) Conceptual schematic linking a simplified representation of a transmembrane protein embedded in a lipid bilayer with its atomistic molecular dynamics model. (*B*) Atomistic view showing the corresponding simulation box used to investigate protein–membrane assemblies under electric field exposure with a magnified side view of the transmembrane protein spanning the lipid bilayer. (*C*) Top-down (xy-plane) view of the same protein–membrane assembly in its pre-pore, intact state, showing no aqueous pore formation, provided as a reference baseline for comparison with the field-induced pore formation sequence illustrated in *Figure 4*.

Higher electric field strength lowers the energetic barrier for pore formation, increasing the probability of larger and longer-lived pores, while longer exposures cumulatively raise the chance that transient pores evolve into metastable or irreversible pathways.[51,78] At the tissue level, this behaviour gives rise to an apparent permeabilization threshold emerging from the collective response of many cells, rather than from a sharply defined molecular transition.[62,79]

In PFA, this probabilistic framework explains why the extent of reversible electroporation vs. IRE depends on both pulse amplitude and duration across the targeted tissue volume, forming the basis for dose–response relationships and lesion formation discussed in the section 'Lipid peroxidation and its impact on cell membrane'.

Reversible electroporation

Reversible electroporation occurs when the electric field transiently increases membrane permeability, but the cell's repair mechanisms restore membrane integrity and homeostasis afterwards. Under these conditions, the membrane reseals within minutes to hours, and the cell can recover its normal functions, making this regime useful for molecular

delivery and gene transfection applications.[80] Survival after reversible electroporation depends on pulse parameters such as electric field strength, pulse duration, waveform, and number of pulses, as well as intrinsic cell characteristics including size, shape, and cytoplasmic conductivity.[81–83] Cells that experience only limited permeabilization tend to maintain viability if electric stress does not overwhelm their repair capacity.

What means 'reversible electroporation'

Historically, before 'electroporation,' the delivery of short and intense PEFs to microorganisms and vegetal products was known as 'dielectric breakdown,' illustrating by this term the capability of the electric pulses to destroy almost any tissue and cell. When E. Neumann published in 1982[15] the seminal article in which he coined the term 'electroporation', the demonstration was made that, after the exposure of cells to DNA and to short and intense electric pulses, some of the cells could survive and incorporate external molecules such as the DNA previously added in the electropulsing medium.[80] later found electrical parameters allowing for the reversible permeabilization of all the *in vitro* treated cells with minimal cell loss (cell death). The same group found that reversible electropermeabilization was an efficient physical method for the vectorization of drugs and nucleic acids.[84,85]

Reversible electroporation is defined operationally by post-pulse recovery and survival under given conditions. By itself, it does not 'kill' the cells, and the only 'visible' effect is a transient (and limited) swelling of the treated cells. To detect the reversible permeabilization of the membrane, a non-permeant probe (a molecule that does not cross the intact plasma membrane and that is not transported actively across it) must be added outside the cells before the delivery of the electric pulses. Depending on its physico-chemical characteristics, and on the strength of the signal generated by the probe when it reaches the cell inside, some probes can also be added just after the delivery of the electric pulses since the permeabilized state lasts for up to a few minutes (depending on the electric pulse parameters).

Characteristics of the reversible regime

Conditions allowing cell survival despite transient loss of membrane integrity

The two main conditions to respect for achieving reversible electroporation of the membranes are an appropriate working medium and an appropriate set of electrical parameters.

Indeed, the external medium must be isoosmotic with the cell's internal medium. Otherwise, after the electric pulse's delivery, the movement of ions or solutes across the membrane, and the subsequent movement of water, will cause the swelling or shrinking of the cells, which, if excessive, will necrotize the cells. *In vitro*, this condition must absolutely be respected, while *in vivo*, this is not an issue as the body fluids (blood, serum, etc.) are all equilibrated in terms of ion composition. It must be noted that, although ion concentrations are important, the critical consideration in this context is osmolarity (the concentration of solutes), rather than conductivity (which depends on the concentration of ions). *In vitro*, it is possible to play with osmolarity and conductivity independently, and both parameters must be under control.

Four PEF waveform parameters are important: the pulse amplitude, the duration of each pulse, the number of pulses, as well as the frequency of repetition of the pulses. All the parameters must be operated within well-defined ranges of values, which also depend on the characteristics of the target cells (size, shape, orientation with respect to the electric field direction, etc.).

Temporary nature of membrane permeabilization

During electroporation, cells undergo chemical changes over different time scales. Some occur during pulse delivery and in the minutes immediately afterwards, directly affecting the membrane, whereas others are associated with increased membrane permeability and membrane repair, processes that may continue for minutes to hours. Studies by Lluis M. Mir's group using mass spectroscopy, Coherent Anti-Stokes Raman Spectroscopy, and Terahertz spectroscopy showed that reversible electroporation causes primary lipid oxidation, increased membrane water content lasting minutes, and leakage of small molecules.[25,28,86] Principal component analysis or latent variable analysis of the Raman spectra revealed that reversible electroporation restores membrane properties, while IRE produces lasting changes, indicating it involves qualitatively different structural defects rather than simply an accumulation of reversible pores.[26,86]

Irreversible outcomes despite membrane resealing

Cells may still undergo death even when the plasma membrane reseals after electroporation. This can happen when poration triggers downstream pathways such as calcium overload, mitochondrial dysfunction, reactive oxygen species generation, or disruption of critical cellular processes.[87] Electroporation-induced loss of intracellular molecules, impaired homeostasis, or secondary biochemical damage contribute to lethality, indicating that irreversible outcomes are not solely due to failure of membrane resealing but can arise from effects initiated during reversible poration that overwhelm cellular survival mechanisms.

Irreversible electroporation

IRE denotes a regime of PEF exposure in which electrically induced injury exceeds the cellular capacity for recovery, resulting in loss of viability.[22] IRE is commonly characterized by persistent membrane defects and failure of membrane resealing following pulse delivery. However, restoration of membrane integrity does not necessarily imply long-term cell survival, as cells may still undergo delayed death through secondary processes including calcium overload, mitochondrial dysfunction, metabolic exhaustion, oxidative stress, and disruption of ionic homeostasis. Cellular fate following electroporation therefore exists along a continuum and depends not only on membrane recovery but also on the ability of the cell to re-establish intracellular homeostasis after exposure. In IRE, sustained permeability, progressive metabolic stress, and failure of these recovery mechanisms ultimately drive irreversible injury and cell death (*Figure 7*).

While both cancer therapy and cardiac PFA utilize electroporation-based tissue selectivity, they do so through different mechanisms. In cancer treatments, some studies suggest differences in the susceptibility of malignant and non-malignant cells under certain electroporation conditions: the electric field parameters are set to destroy all cellular components (malignant and healthy) within a targeted volume while sparing the non-cellular collagen scaffolds of blood vessels, nerves, and ducts.[18,91–95] Conversely, tissue selectivity in cardiac PFA relies on cellular susceptibility thresholds. Cardiomyocytes exhibit different electroporation susceptibility thresholds than adjacent structures.[90] This allows clinicians to target myocardial tissue while minimizing the risk of collateral damage.

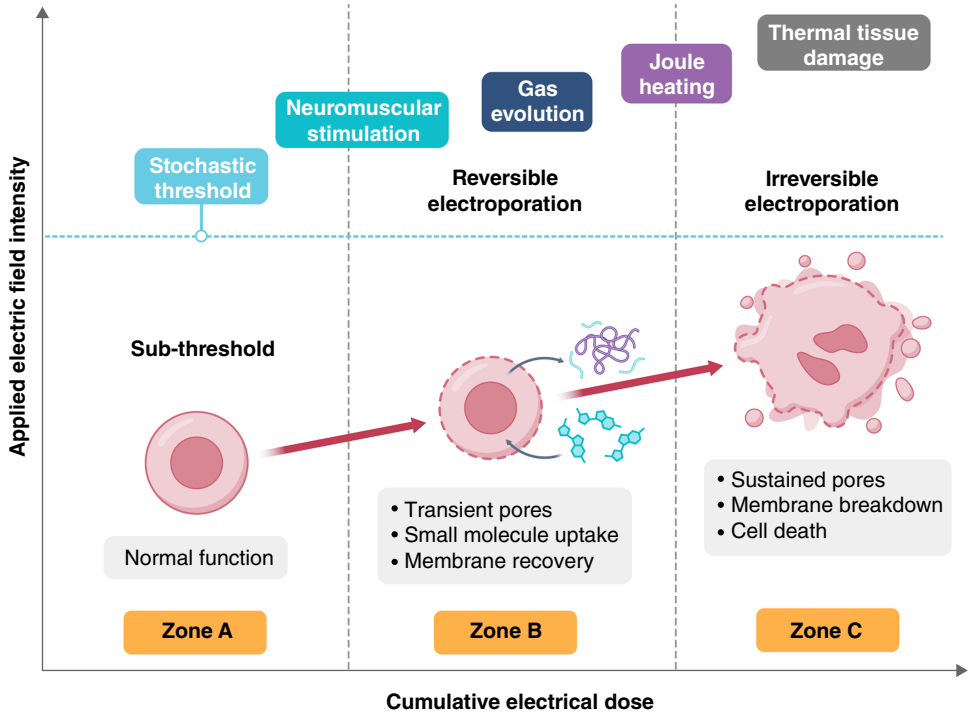


Figure 7 Transition from reversible to irreversible electroporation as a function of applied electric field intensity and cumulative electrical dose. Cellular responses progress from sub-threshold conditions (Zone A), through reversible electroporation with transient membrane permeabilization and recovery (Zone B), to irreversible electroporation associated with loss of cellular recovery capacity and progression towards cell death (Zone C). The boundary between reversible and irreversible effects is stochastic, reflecting biological variability. Higher doses may induce side effects such as Joule heating, gas evolution, and neuromuscular stimulation.[88–90] Protocols in PFA are intentionally designed to exceed cellular recovery capacity to induce controlled, non-thermal tissue ablation. This energy modality enables spatially confined lesion formation while preserving extracellular matrix architecture and minimizing collateral damage to adjacent structures.[90]

Transition from reversible to irreversible states

The shift from reversible to IRE is progressive, reflecting the declining ability of cells to repair electrically induced membrane damage rather than a sharply defined boundary. In reversible electroporation, PEFs induce transient membrane permeabilization that allows molecular transport while preserving the cells' capacity to reseal, maintain ionic gradients, and survive. As cumulative exposure increases, recovery efficiency steadily declines.[22]

Higher electric field amplitudes, longer pulse durations, more pulses, or prolonged exposure convert transient permeabilization into persistent defects. This transition causes sustained ionic flux, osmotic imbalance, and collapse of electrochemical gradients.[96] Waveform characteristics, including monophasic, biphasic, or high-frequency bipolar pulses, modulate this trajectory by affecting membrane charging and cumulative stress, but irreversible outcomes consistently occur when repair capacity is exceeded.[97]

Biological and tissue factors such as cell size, membrane composition, resting potential, and tissue heterogeneity further shape the transition between reversible electroporation and IRE. This variability produces spatially heterogeneous responses resulting in irreversible injury in high-dose regions and reversible effects nearby.[98] This spatial gradient is highly relevant to the clinical efficacy of PFA. Peripheral zones subjected to sublethal, reversible electroporation are transiently stunned immediately post-procedure, showing an acute loss of excitability and mimicking a successful ablation. However, because these cells recover their membrane integrity and electrical conduction over hours to days, this peripheral zone can fail to achieve permanent block, creating an incomplete lesion that acts as a proarrhythmic substrate.[99] PFA technologies must therefore be optimized to maximize the irreversible ablation volume while minimizing this surrounding zone of reversible, sub-lethally affected tissue.

Thresholds beyond which membrane repair fails due to excessive electric stress

IRE occurs when membrane repair mechanisms fail after PEF exposure, marking the shift from transient permeabilization to persistent defects and loss of homeostasis. Cells may still die even if membranes reseal if permeability overwhelms recovery capacity. (Arena et al., 2011) This repair failure involves excessive pore density, pore coalescence, irreversible lipid rearrangement, cytoskeletal decoupling, disrupted membrane–protein interactions, impaired endocytic repair, and local membrane phase changes. Tissue-level modelling and experimental mapping reveal irreversible injury in regions exceeding the threshold and sub-lethal electroporation effects in adjacent peripheral tissues.[91,93,100]

The threshold for cell death is governed by the combined, non-linear interaction of different parameters including electric field strength, pulse duration, number of pulses, repetition frequency, and waveform types.[81] Rather than depending on a single parameter the threshold is determined by the cumulative electrical dose and total energy delivered.[101] Recent studies demonstrate that this threshold is highly dependent on tissue-specific susceptibilities and external environment properties. Myocardium is particularly sensitive to electroporation damage compared to adjacent tissues,[102] showing a graded response to voltage and pulse number changes.[103] Furthermore, constant power PEFs have been shown to predict electroporation area and treatment outcomes in a conductivity-dependent manner, overcoming patient-to-patient variability.[104] Precise control of pulse conditions is essential to achieve predictable and safe clinical outcomes.[105–107]

Cellular responses following irreversible electroporation

IRE initiates a cascade of cellular responses rather than constituting an instantaneous destructive event (*Figure 8*). Cellular outcomes depend on the overall severity of the electrical insult, which is determined collectively by pulse amplitude, duration, waveform, pulse number, repetition frequency, and tissue-specific factors and on the cumulative electrical dose delivered, rather than on any individual parameter.[108] During IRE, cells first experience primary physical consequences of sustained membrane permeability, which subsequently propagate into secondary biological processes that evolve over timescales ranging from minutes to hours. Tissue-specific factors, including extracellular matrix composition, cell density, and perfusion, modulate the kinetics of ionic redistribution, metabolic stress, and lesion maturation.[109]

Primary loss of homeostasis from sustained permeability and osmotic imbalance

Sustained membrane permeabilization immediately disrupts ionic gradients and water homeostasis. Uncontrolled fluxes of sodium, potassium, calcium, and water across the plasma membrane result in osmotic swelling, blebbing, and mechanical stress on cellular structures. The resting TMP collapses rapidly, impairing the function of energy-dependent ion pumps such as Na^+/K^+-ATPase and Ca^{2+} transporters that are required to

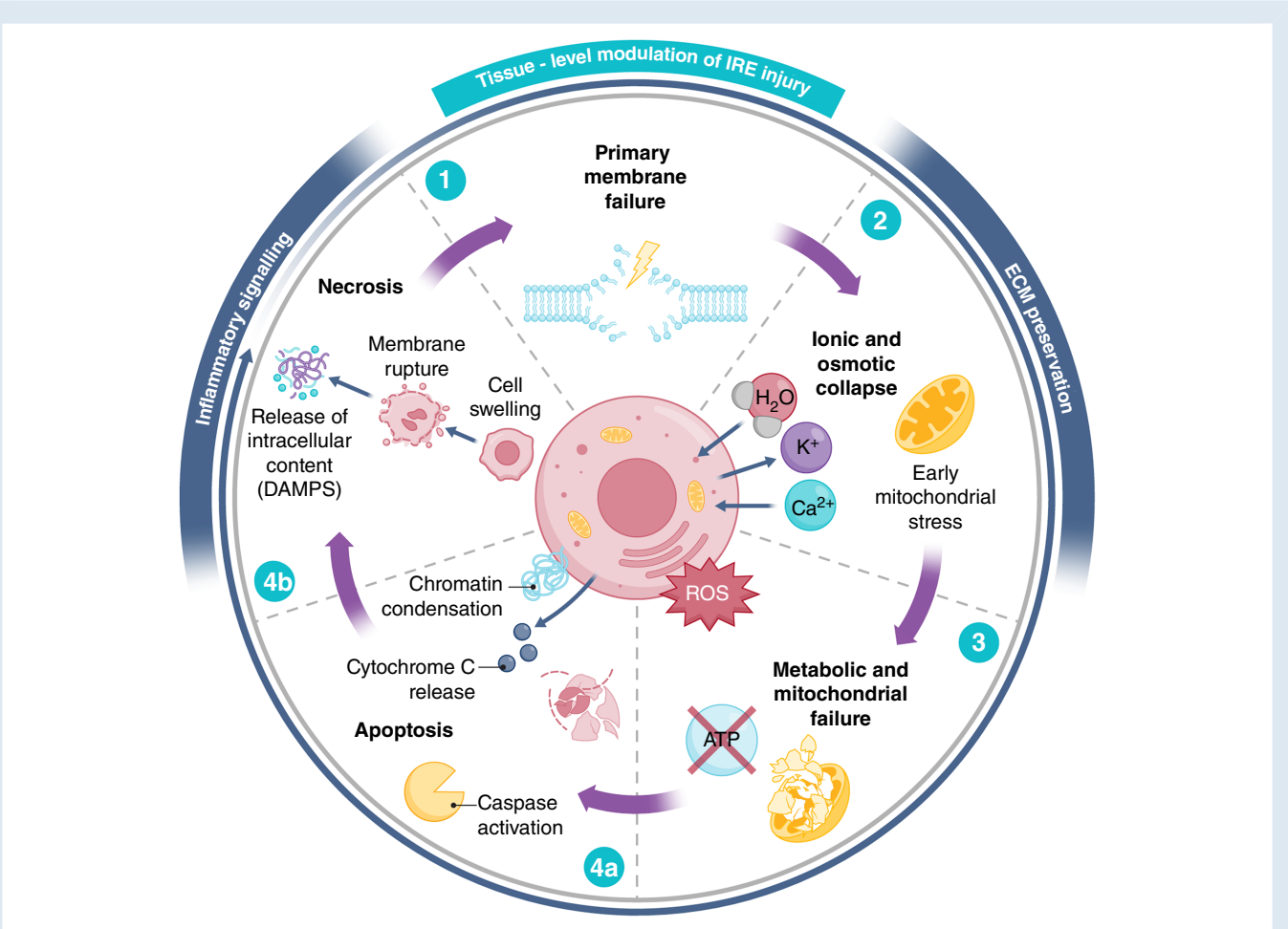


Figure 8 Cellular responses after irreversible electroporation. Following application of a pulsed electric field, a cell undergoes sustained membrane permeabilization, initiating a cyclic injury cascade. This includes (1) primary membrane failure, (2) ionic and osmotic collapse driven by ion flux and water influx, (3) metabolic and mitochondrial dysfunction with ATP depletion and oxidative stress, and (4) energy-dependent cell death, progressing to apoptosis or necrosis depending on injury severity. Tissue-level factors modulate the extent and evolution of injury during PFA.

maintain electrochemical gradients. These early events, occurring within seconds to minutes following pulse delivery, represent the initiating phase of irreversible cellular injury and establish the conditions for subsequent metabolic and structural failure.[22,98]

Secondary downstream processes including metabolic depletion and delayed cell death

Following the initial loss of homeostatic control, cells experience progressive metabolic depletion as ion pumps attempt to restore disrupted gradients in the presence of persistent membrane permeability.[13,22,110] Sustained ATP consumption, intracellular calcium accumulation, and mitochondrial dysfunction amplify cellular stress and compromise energy production.[111–113] Depending on the magnitude and duration of metabolic collapse, cells may engage regulated cell death pathways, including apoptosis, necroptosis, or pyroptosis, or alternatively, when the energy depletion is severe, cells progress towards necrotic outcomes characterized by membrane rupture and release of intracellular contents.[114–116]

Delayed cellular responses develop over hours to days and contribute to lesion maturation at the tissue level.[92,93,117] Persistent metabolic stress can promote secondary processes such as reactive oxygen species generation, inflammatory signalling, and immune cell recruitment, thereby shaping the local tissue environment.[118–120] As a result, IRE-induced lesions frequently exhibit a combination of apoptotic, necrotic and regulated lytic features, reflecting the interplay between immediate electroporation-induced injury and downstream biological responses.[16,115,119] Spatially, these effects mirror gradients in cumulative electrical dose, with irreversible injury localized to the lesion core and sub-lethal, potentially reversible effects observed at the periphery[18,91,93]; As discussed already, delayed recovery within these peripheral, reversibly electroporated regions may contribute to incomplete lesion maturation and an increased risk of arrhythmia recurrence.

Safety considerations and side effects of IRE-based tissue ablation

Even though IRE-based ablation therapies are designed to ablate tissue nonthermally, improper waveform settings, suboptimal catheter geometry, or uneven electric field distribution can lead to unintended side effects.[109,121,122] These include localized temperature rises (thermal hotspots) resulting from Joule heating under high cumulative energy doses, and electrochemical reactions at the electrode–solution interface that generate microbubbles.[123,124] In addition, high-voltage pulses can cause neuromuscular stimulation and severe muscle contractions if the electric field extends into areas of reversible electroporation where peripheral motor nerves are polarized.

To mitigate these side effects, contemporary cardiac PFA utilizes biphasic and high-frequency (H-FIRE) pulse trains instead of long monophasic pulses. Biphasic waveforms alternate polarization rapidly, preventing sustained nerve excitation and significantly reducing muscle contraction and pain.[125] Rapid charge cancellation and optimized pulse-repetition frequencies minimize gas evolution and bubble formation while maintaining therapeutic myocardial ablation volumes.[123,124] Careful optimization of pulse parameters, catheter design, and procedural workflow remains essential to keep these off-target effects to minimal volumes.[123,124] Detailed strategies for mitigation in PFA applications are discussed in other sections of this supplement.

Historical applications outside the heart

This section summarizes established non-cardiac applications of electroporation, including electrochemotherapy, IRE for tumour ablation in the liver, pancreas, and prostate, and gene-delivery approaches in skeletal muscle. These applications represent important steps in the broader evolution of electroporation-based therapies and form the scientific and clinical foundation for cardiac PFA. Fundamental discoveries in reversible electroporation, electrochemotherapy, gene electrotransfer, and later IRE established the biological principles and clinical feasibility of using PEFs to modulate or destroy living tissues in a controlled manner. Decades of experience across these fields have also provided valuable insights into electroporation mechanisms, dose–response relationships, dosimetry, safety, tissue-selective effects, and strategies to minimize off-target effects.

Paving the way to clinical applications of the delivery of short and intense electric pulses to PFA

Preclinical precedents

As described in the section ‘Reversible electroporation’ of this article, the group led by Mir systematically optimized electric pulse parameters *in vitro* to achieve transient cell membrane permeabilization with minimal cell loss.[80] They further demonstrated that reversible permeabilization increased the cytotoxicity of the anticancer drug bleomycin by several orders of magnitude.[85]

Based on the low intrinsic toxicity of the electric pulses themselves, these findings were translated *in vivo* by administering bleomycin intravenously and applying locally optimized electric pulses to tumours in mouse models. In 1991, this approach led to the first successful treatments of mice bearing superficial tumours using the combination of bleomycin and reversible electroporation, with complete tumour regression achieved after a single treatment in the initial experiments. Importantly, these studies also demonstrated the high safety of the procedure, which the authors termed electrochemotherapy (ECT).[126,127]

Electrochemotherapy of tumours in other organs such as liver, pancreas, and prostate

In parallel, the first attempts to treat tumours in the liver and pancreas were performed on human patients, under laparotomy or transcutaneously, using long needles.[128,129]

ECT has become the treatment of vertebral metastases that compress the spinal cord, a serious oncological situation quickly leading to paraplegia and inflicting intractable pain on the patient. The expertise at Gustave Roussy involves more than 300 patients today. An initial evaluation of the first 40 patients treated at Gustave Roussy showed, at 1 month, 46% complete regressions and 23% partial responses, knowing that the effect of the ECT session is still progressing in the following two months or more.[130] An improvement in the quality of life was observed, because the pain, at an average level of 7 on a visual scale of 10 before treatment, was reduced to an average level of 1 in a few days, and in any case less than a month after treatment.

Treatment of vascular anomalies

A new application of the same concepts and protocols emerged recently: the treatment of vascular anomalies by bleomycin and reversible electropermeabilization as the method to vectorize

the drug.[131] BEST (Bleomycin ElectroScleroTherapy) is quite efficient in the case of the slow-flow vascular malformations (whether venous, arterial, or lymphatic) and BEET (Bleomycin ElectroEmboTherapy) in the case of the fast-flow arteriovenous malformations. The procedures are disseminating quite rapidly in clinics since they are efficient and safe.

History of IRE-based ablation for tumour treatment

IRE was first developed in oncology after studies showed that electric fields exceeding membrane recovery thresholds cause permanent cell death without thermal coagulation.[16,18] Preclinical work demonstrated sharply demarcated lesions governed by electric-field distribution with preservation of extracellular matrix, vessels, and ducts.[92,93] These findings established key principles directly relevant to cardiac PFA: tissue response depends on electric-field thresholds rather than temperature, structural scaffolds are preserved, and lesion size is predictable from delivered dose.[91,100] The same characteristics underpin the myocardial preferentiality and safety profile observed in contemporary PFA procedures.

Lessons relevant to PFA

Understanding tissue-specific electroporation thresholds and safety profiles from non-cardiac experience

The extensive clinical experience accumulated with ECT and, more recently, with BEST, BEET, and gene electrotransfer has generated a large body of data on the delivery of short, high-intensity PEF to human tissues across multiple clinical settings. These studies first established the overall safety of electroporation-based procedures, while also defining the boundaries of that safety, particularly in tissues adjacent to the treatment zone.[132]

In parallel, numerical modelling frameworks originally developed for electrochemotherapy to predict electric field distribution as a function of tissue properties, electrode configuration, and treated volume proved directly transferable to IRE and, subsequently, to cardiac PFA. In particular, the critical role of tissue conductivity heterogeneity in shaping electric field distribution was already being characterized when PFA began to emerge. Adapting this body of knowledge to the cardiac environment nevertheless required additional experimental validation and clinical refinement specific to myocardial anatomy and procedural constraints.[52]

Evidence on healing dynamics, inflammation, and long-term tissue remodelling in extracardiac organs

Clinical experience with electrochemotherapy revealed that the effects of PEFs extend beyond transient membrane permeabilization. Local vascular effects and immune responses were identified as important contributors to treatment outcomes. Although immune activation has been observed after both reversible electroporation and IRE, the nature and magnitude of these responses differ, reflecting distinct patterns of cellular injury and cell death.[133]

For cardiac PFA, these observations are relevant because they highlight that electroporation can initiate secondary biological processes that influence tissue response beyond the immediate electrical injury. At the same time, prior oncologic applications provided limited information on healing dynamics and structural remodelling of normal tissues, since ECT is highly selective for tumour cells and spares surrounding healthy tissue at clinically used drug doses. As a result, the translation of electroporation to myocardial ablation required dedicated investigation of myocardial injury, inflammation, and healing, which were not addressed in earlier non-cardiac applications.[132]

Summary and future directions

PFA represents a paradigm shift in cardiac ablation by exploiting IRE rather than thermal injury to destroy myocardial tissue. Its clinical promise builds on decades of biophysical, molecular, and translational research, combined with system-level innovations tailored to cardiac anatomy and electrophysiology. At the cellular level, short, high-intensity pulses induce TMP, forming nanoscale pores in the lipid bilayer. Membranes may reseal (reversible electroporation) or fail to recover, causing IRE and cell death. The transition is progressive and dose-dependent, explaining the spatial heterogeneity of lesions, with irreversible injury at the core and reversible effects at the periphery.

Tissue architecture and electrical heterogeneity shape the electric field distribution, as differences in conductivity, permittivity, cell orientation, and extracellular composition create regions of enhanced susceptibility or protection. These effects are pronounced in the heart, where fibrosis, scar, infarcted tissue, and blood-filled cavities complicate lesion prediction, making modelling and experimental validation essential. Cardiac PFA builds on lessons from other electroporation-based therapies, including ECT, tumour IRE, and gene transfer, which established safety and dose–response relationships but offered limited insight into normal tissue remodelling.

Looking forward, several open questions remain central to the evolution of PFA. These include optimization of ablation in non-homogeneous myocardium, the role of preheating or combined RF–PFA strategies, refinement of electroporation thresholds in diseased tissue, and continued innovation in waveform design and catheter technology. In parallel, important knowledge gaps persist at the basic science level, particularly regarding cardiomyocyte-specific mechanisms of membrane repair, delayed cell death, and the transition from reversible to irreversible injury. Addressing these challenges will be critical to fully realizing the potential of PFA as a precise, durable, and safe modality for cardiac ablation.

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Data availability

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PULSED FIELD ABLATION FOR CARDIAC ARRHYTHMIAS SUPPLEMENT

Pulsed field ablation: from concepts to technology

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Aims Pulsed field ablation (PFA) has emerged as a transformative approach for treating cardiac arrhythmias by exploiting irreversible electroporation to preferentially injure myocardium while limiting collateral damage. Translating this biophysical principle into safe and effective clinical systems requires careful integration of waveform design, catheter engineering, computational and experimental modelling, safety testing, and procedural workflow.

Objective This review summarizes the fundamental physical and engineering principles that govern cardiac PFA and examines how these principles influence efficacy, safety, lesion formation, and clinical usability.

Biophysical and technical considerations Electroporation is governed primarily by the local electric field and waveform-dependent lethal thresholds rather than generator voltage alone. Key waveform variables include monophasic vs. biphasic pulses, microsecond vs. nanosecond pulse widths, duty cycle, and total application duration. Catheter design further determines electric field distribution, lesion geometry, current density, and applicability across anatomic targets, with important distinctions between bipolar and monopolar configurations.

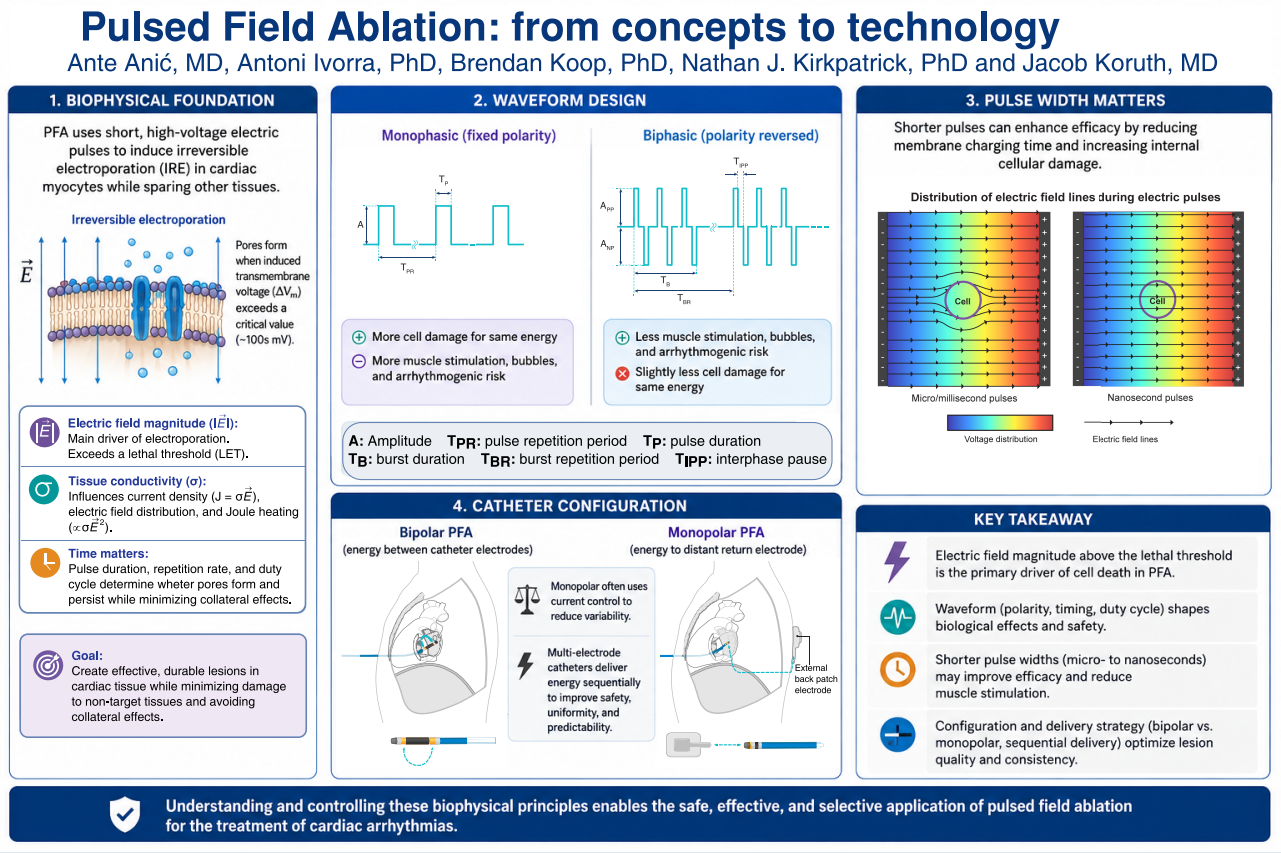
Modelling and safety Experimental and computational approaches used to investigate PFA include finite element simulations, cell culture systems, vegetal substrates, and *in vivo* animal models, each with distinct strengths and limitations. High-voltage pulse delivery can also produce unintended effects, including Joule heating, electrochemical reactions, bubble formation, arcing, and interactions with implanted electronic devices. These phenomena highlight the importance of optimized waveform design, electrode configuration, and safety monitoring.

Clinical usability Clinical adoption depends not only on biological efficacy and safety but also on workflow efficiency, catheter versatility, procedure duration, mapping integration, anaesthesia requirements, and adaptability to differing clinical practices and geographic settings.

Conclusions The performance of a PFA system reflects the interaction of biophysics, waveform characteristics, catheter design, modelling, safety controls, and procedural usability. Understanding these interconnected principles is essential for developing PFA technologies that are effective, safe, predictable, and practical for contemporary electrophysiology laboratories.

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Graphical Abstract



Keywords Pulsed field ablation • Irreversible electroporation • Cardiac arrhythmias • Electric field • Waveform design • Catheter design • Computational modeling

Introduction

Pulsed field ablation (PFA) to treat cardiac arrhythmias is a revolution in the ability to preferentially ablate myocardial cells, with several advantages over thermal ablation technologies. However, it is a large leap from the concept of PFA to the actual implementation of technologies that allow this revolution to proceed. The aim of this article is to describe how the biophysical principles of PFA can be harnessed in safe, effective, and usable technical implementations.

Main physical variables in pulsed field ablation

The cytotoxic effect of PFA is driven by irreversible electroporation (IRE), and the two terms are often regarded as synonymous.[1] Much of the current understanding of PFA for treating cardiac arrhythmias originates from earlier use of IRE to treat solid tumours.[2] Therefore, the biophysical foundations of PFA are those of electroporation.

Electroporation refers to the increase in cell membrane permeability to ions and molecules in response to a sufficiently strong electric field.[3] This phenomenon is commonly approximated as a threshold process: it occurs when the change in transmembrane voltage (ΔV_m) induced by the applied electric field ($\vec{E}$) exceeds a critical value on the order of hundreds of millivolts.

The induced transmembrane voltage is directly proportional to the magnitude ($|\vec{E}|$) of the applied electric field, commonly expressed in units of V/cm. For spherical or ellipsoidal cells in suspension, simple analytical expressions can be derived to relate the applied field to the induced transmembrane voltage.[4] Although simulations have been performed using idealized tissue structures,[5,6] accurately predicting induced transmembrane voltages in real tissues remains infeasible due to insufficient knowledge of their detailed architecture. Nevertheless, because the proportionality between the induced transmembrane voltage and the electric field is preserved, it can be assumed that electroporation occurs when the local electric field magnitude exceeds a critical threshold.

While the main physical variable that drives electroporation in PFA is the local electric field magnitude, the parameter that is usually reported or can sometimes be modified by the operator in PFA generators is the output voltage. It is important to understand that output voltage and electric field magnitude are not equivalent. The application of voltage by a PFA generator creates an electric field distribution between the electrodes. However, the magnitude of this electric field depends not just on the voltage delivered but also on the geometry of the catheter.

Electroporation is not a static phenomenon but a dynamic process, and the temporal characteristics of the applied field also play a crucial role in PFA. According to molecular dynamics simulations,[7,8] pores form in the cell membrane within nanoseconds after the critical transmembrane voltage is reached. However, this critical voltage is not attained immediately and requires several fractions of a microsecond, primarily depending on cell size. The lipid bilayer acts as an insulating barrier between two conductive media (the intracellular and extracellular ionic solutions) and therefore behaves like a capacitor. Mobile ions in the surrounding medium must accumulate across the membrane to establish the transmembrane voltage. Consequently, when high-frequency alternating fields are applied, the membrane may repeatedly charge and discharge without reaching the critical voltage necessary for electroporation.[9] *Table 1* provides definitions for basic principles associated with PFA.

Models to study electroporation

This section describes the experimental models commonly used to study electroporation, ranging from *in silico* to *in vivo* models at different complexity levels. As the mechanisms of PFA are fundamentally different from other thermal ablation technologies, the models used to study this phenomenon are also conceptually different.

Computational models

Basic concepts

As explained above, the main physical parameter governing PFA is the electric field. Therefore, accurate calculations of the electric field distribution for a specific geometry are fundamental to the study of a PFA system. Most electroporation computer models at the tissue scale operate under the assumption that, for a specific tissue and a given waveform, there exists a critical electric field magnitude that must be exceeded to achieve the intended electroporation effect. Importantly, this critical field magnitude—such as the lethal threshold for cardiomyocytes in cardiac PFA—is not only tissue-specific but also waveform-specific. Consequently, it is not straightforward to scale these thresholds across different waveforms. Unlike thermal damage, where a metric can be computed and used to extrapolate thresholds, no analogous dosimetric metric exists for electroporation. This means that thresholds must be determined experimentally for each distinct waveform. However, it is worth noting that US Food and Drug Administration researchers have recently published comprehensive *in vitro* data characterizing a wide range of PFA waveforms, which can serve as a reference for approximating how thresholds vary with waveform features such as pulse duration and number.[15]

While analytical expressions can be derived to compute electric field distributions for idealized electrode geometries in homogeneous tissues, these models rarely reflect clinical reality. In practice, electrode configurations are often complex, and biological tissues exhibit highly irregular geometries and heterogeneous electrical properties. Consequently, numerical techniques—and in particular the finite element method—are used to accurately map the electric field distribution and predict which regions will reach the necessary thresholds for successful electroporation.[16]

Zooming out in both time and spatial scale, a variety of models based on different mechanistic or phenomenological assumptions have been proposed to describe membrane permeabilization to ions and molecules over time scales on the order of seconds to minutes.[17] However, none of these models have been able to consistently reproduce the full range of experimental observations.

Computational modelling of lesion formation in pulsed field ablation

The validity of computational modelling of electroporation treatments based on the assumption of a critical electric field threshold has been demonstrated repeatedly across a range of scenarios. This approach has been validated *in vitro*[18] in relatively homogeneous tissues such as plant tissues[19] and liver (*in vivo*[20] and clinically,[21]), as well as in some heterogeneous scenarios that involve tailored treatment planning.[22,23] Crucially, the accuracy of this modelling approach has improved with the incorporation of tissue conductivity dependence on both the electric field—where conductivity increases due to electroporation—and temperature, which rises because of Joule heating.[24] Hence, it is unsurprising that published cardiac PFA studies performing computer modelling for lesion formation adopt this framework.[10–14,25–30]

It should be noted that careful histological observations, particularly of lesions created with monopolar catheters, have shown that the conventional modelling framework cannot accurately predict the shape of actual cardiac PFA lesions.[31,32] Ventricular myocardial lesions are substantially deeper than predicted by the models. Even after accounting for conductivity anisotropy, lesions are still not accurately represented, and in some cases, anisotropy predicts shallower lesions. Lesion dimensions can be reasonably approximated if two distinct thresholds are used for orthogonal fibre orientations.[33] Nevertheless, the underlying cause of this behaviour, which had not been reported previously in the electroporation community, remains unclear. One hypothesis is that the effect arises from anisotropic tissue damage, with cardiomyocytes oriented transverse to the electric field being more susceptible due to a larger exposed membrane area. A computational multiscale model has been developed that appears to support this hypothesis and suggests that this mechanism may partially explain the observed lesion morphology.[34]

In vitro models

In vitro models have been essential for studying the electroporation phenomenon. Since electroporation is a universal phenomenon possible in any lipid bilayer, highly idealized *in vitro* models—specifically planar artificial membranes (black lipid membranes) and giant unilamellar vesicles—have been utilized to elucidate the physical and biochemical fundamentals of electropermeabilization.[35,36]

Cell cultures have provided further insights into the biological consequences of electroporation and how these effects are modulated by diverse physiological variables. Notable efforts have involved the use of adult cardiomyocytes isolated from living tissue,[37,38] rat ventricular cardiomyocytes,[33,34] immortalized cell lines,[39] and human induced pluripotent stem cell-derived cardiomyocytes.[40] Cell culture studies have highlighted the importance of repeated pulses for effective permeabilization[41] and have provided insight into the mechanisms of cell death following pulse exposure.[42] These models have also demonstrated the critical role of extracellular calcium in determining cell death.[43–46]

It is worth highlighting the study by Maizels and colleagues, in which electrical activity in two-dimensional cultures of cardiomyocytes was subjected to different PFA protocols using voltage-sensitive fluorescent probes.[47] Remarkably, this study demonstrated that PFA can terminate arrhythmias with high spatial precision by creating sustained bidirectional conduction

Table 1 Basic physical parameters relevant in PFA

Parameter	Common symbols	Description	Implications
Induced transmembrane voltage	ΔV_m	Change in transmembrane voltage caused by the presence of an electric field, expressed in volts (V)	Electroporation occurs when ΔV_m exceeds a critical value, on the order of hundreds of millivolts.
Electric field	$\vec{E}$	At each point in space, a vector quantity (i.e. it has magnitude and direction) that represents the electric force that a charge of 1 coulomb would experience if placed there	The electric field arises from the presence of neighbouring charges, each of which would exert a force on the test charge according to Coulomb's law. Under equilibrium conditions, positive and negative charges in biological tissues are balanced and evenly distributed, resulting in a null macroscopic electric field. When a voltage is applied across electrodes or a current is driven through the tissue, this balance is disrupted, and an electric field is induced.
Electric field magnitude	$\lvert\vec{E}\rvert$ or, simply, E	Magnitude of the electric field vector, expressed in V/m in SI units, but is often reported in V/cm	In electroporation treatments, the electric field magnitude is not constant but takes the form of a time-varying waveform. For a specific tissue and a given waveform, there exists a critical electric field magnitude that must be exceeded to achieve the intended electroporation effect (e.g. molecular uptake or tissue ablation). The critical field threshold decreases as the total energy of the waveform increases. However, it is important to note that this dependence cannot be described with a linear relationship.
Lethal electric field threshold	LET	Magnitude of the electric field vector required to ablate a specific tissue for a given waveform.	Very few published *in vivo* studies report lethal electric field thresholds in the heart while also fully disclosing the applied waveform: 360 V/cm (pig, 48 monophasic pulses of 100 µs),[10] 640 V/cm (rat; 10 monophasic pulses of 100 µs) and ~1200 V/cm (rat, 10 bursts of 10 biphasic pulses of 5 µs+5 µs).[11] Commercial PFA systems likely employ waveforms that produce cardiac lethal electric field thresholds in the range of 300–700 V/cm.[12]
Tissue conductivity	σ	Quantifies how easily electric charges can move through a material under an applied electric field, expressed in siemens per metre (S/m)	It is determined by both the concentration of free charge carriers and their mobility within the medium. In soft living tissues, it typically ranges from ~0.02 S/m (fat) to 1.5 S/m (plasma). Electroporation can cause a substantial increase in tissue conductivity. Tissue conductivity also increases with temperature (~2%/°C).[13,14] In anisotropic materials, conductivity is not a single value but depends on the direction of current flow. This is observed in skeletal muscle where the longitudinal conductivity (σ_L)—aligned with the fibre orientation—is significantly higher than the transverse conductivity (σ_T).

Continued

Table 1 *Continued*

Parameter	Common symbols	Description	Implications
Applied voltage	v	Applied voltage across electrodes, expressed in volts (V)	The amplitude of the waveforms applied in electroporation treatments, including cardiac PFA, typically ranges from several hundred volts to a few kilovolts.
Delivered current	i	Resulting current through tissues when a voltage is applied across electrodes, expressed in amperes (A)	The relationship between voltage and current is defined by Ohm's law: $v = iR$ where R is the resistance of the conductor, expressed in ohms (Ω). The resistance depends on the conductivity of the material but also on its geometry (i.e. the electrodes geometry and their distance). Current amplitude in electroporation treatments typically ranges from several amperes to a few tens of amperes.
Current density	$\vec{J}$	Vector quantity that represents both the magnitude and direction of electric current flow per unit area	According to Ohm's law, $\vec{J} = \sigma\vec{E}$
Current density magnitude	$\lvert\vec{J}\rvert$ or, simply, J	Magnitude of the current density vector, expressed in A/m^2	$\lvert\vec{J}\rvert = \sigma\lvert\vec{E}\rvert$
Joule heating	Q_J	Heat produced due to the flow of electric current in a conductive material, typically expressed as power density, that is, as watts per unit volume (W/m^3)	It is proportional to the square of the electric field magnitude ($Q_J = \sigma\lvert\vec{E}\rvert^2$). This implies that in regions where the electric field is highly concentrated—such as near the sharp edges of electrodes—thermal energy dissipation may increase dramatically. As a reference for its impact: a single pulse of 100 µs with an amplitude of 1000 V/cm will produce a sudden temperature increase of about 0.35°C in saline. The accumulative temperature increase of multiple exposures can be counteracted by heat dissipation mechanisms such as blood flow. However, it must be noted that while the temperature increase is instantaneous, heat dissipation may take several seconds or even minutes to return the tissue to baseline temperature. Exposure to 50°C for several seconds causes damage to all soft tissues.

block lines. However, it also revealed that the acute presence of functional conduction block does not necessarily translate into long-term lesion persistence, a well-recognized issue in clinical cardiac PFA.[28]

A limitation of conventional cell cultures is their inability to replicate the dense cell packaging found in living tissues. Consequently, these models fail to simulate the significant increase in bulk conductivity that occurs during electroporation—an effect that alters electric field distribution and subsequent lesion formation. This constraint, combined with a lack of three-dimensionality, renders standard cell cultures unsuitable for evaluating catheters. Cell spheroids address these limitations, yet they cannot reach large sizes without developing an ischaemic or necrotic core.[48]

Vegetal models

Excised animal tissues can only be used for electroporation studies for a few hours after removal[49] due to the rapid deterioration of their cell membrane integrity. In contrast, plant tissues exhibit greater structural resilience after excision, primarily due to the presence of rigid cell walls and a reduced reliance on immediate energy-dependent processes for maintaining cellular integrity. As a result, vegetal tissues, specifically potato tubers, are frequently utilized in electroporation studies. A distinct advantage of this model is that irreversibly electroporated regions naturally darken over several hours,[25] which eliminates the need for staining, although staining can still be employed for faster and more precise visualization of the lesions.[50,51]

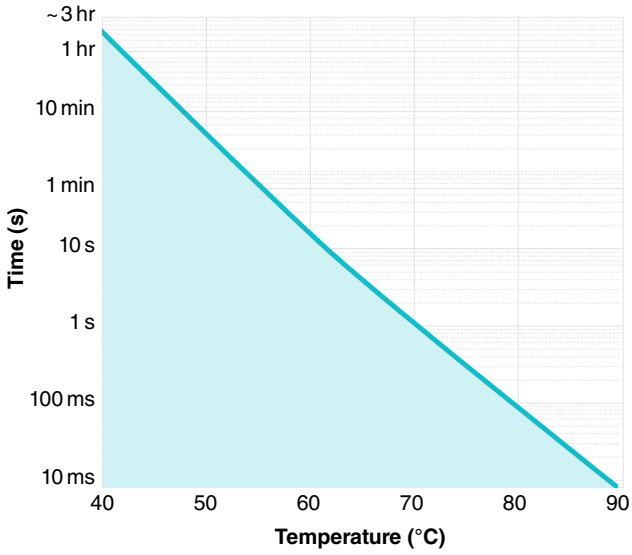


Figure 1 Time duration required to cause thermal damage at various temperatures. An Arrhenius-type model was fit to experimentally derived data using parameters for cardiac tissue previously published. Data taken from Niemiera, B., Ranjan, R., Piccini, J.P. et al. Microbubble and thermal profile of an eight-spline pulsed field ablation system in a preclinical model. J Interv Card Electrophysiol (2025). https://doi.org/10.1007/s10840-025-02145-1.

While potato tubers are often assumed to be homogeneous, they possess inherent structural variations, and their conductivity properties and lethal critical thresholds substantially differ from those of the myocardium. Nevertheless, despite these physiological discrepancies, they constitute an attractive intermediate model for minimizing the necessity of *in vivo* assays. In this regard, their use aligns with the Replacement principle of the 3Rs (Replacement, Reduction, and Refinement) ethical framework for animal research.[52]

In vivo models

In vivo models constitute the most realistic framework for studying the acute and chronic effects of electroporation in human tissues.[27,30] Preclinical porcine models are considered the gold standard due to their anatomical and electrophysiological similarities to the human heart.[53] However, ovine models have also been used in preclinical studies due to their ability to withstand relatively long surgical procedures.[54]

Lesions are often assessed using imaging methods such as late gadolinium enhancement MRI. However, the most accurate assessment remains histopathology, which allows for a detailed cellular analysis of the ablation zone. In addition, triphenyl tetrazolium chloride (TTC) staining is frequently used because it provides a fast, macroscopic evaluation of tissue viability. By reacting with enzymes in healthy mitochondria, TTC stains viable tissue red while leaving lesions pale, allowing acute lesion volume to be clearly demarcated shortly after the procedure. Remarkably, TTC staining exhibits a hyperstained red zone around the lesion, which has been attributed to reversible electroporation.[55] The timing between PFA treatment and lesion analysis influences results. Waiting at least 4 h after PFA allows reversible electroporation to recover and irreversible areas to undergo cell death. Delays of 2–7 days after the procedure may more accurately reflect chronic lesion size.[38]

Physical effects of high electric fields

Joule heating

While PFA has a non-thermal mechanism of action, introduction of high voltage across a resistive load such as myocardial tissue will inevitably result in some thermal impact. This effect, called Joule heating, is proportional to the conductivity of the tissue and scales with the square of the electric field. Unlike traditional radio frequency (RF) catheters, PFA involves energy delivery via pulse trains with pulse widths on the order of milliseconds to microseconds. This reduction in energy delivery time produces transient thermal spikes. Furthermore, the peak temperatures are found at the edges of the electrode surfaces, where current densities are the highest.[2] Excessive Joule heating as a by-product of non-optimized PFA workflows can result in coagulative necrosis of tissue,[56] and microbubble formation.[57]

A time-temperature history governs the generation of thermal injury. Arrhenius thermal damage models can be used to show the effects of cumulative thermal injury on tissue[58] and the blood.[59] Coagulative necrosis can occur when temperatures above 55°C are sustained for over 70 s[60] timescales common for RF ablations (*Figure 1*). With the localized and pulsatile nature of Joule heating with PFA, peak temperatures are sustained for less time, allowing for the potential for higher maximum temperatures while still maintaining a less impactful time-temperature history. However, PFA waveform considerations are paramount to ensure that inter-pulse intervals are sufficient to allow for thermal dissipation between pulses[61] while resulting in greater and more stable membrane permeabilization.[41,62]

Electrochemical reactions

Electric charge carriers in conventional electrical circuits are electrons, whereas in biological tissues, the charge is carried

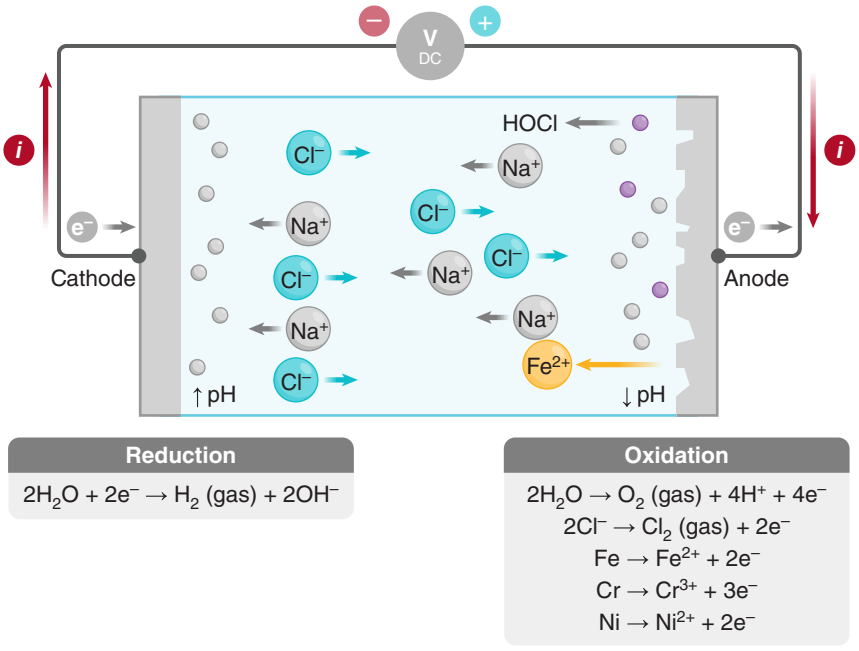


Figure 2 Electrochemical reactions due to a voltage between stainless steel electrodes in saline.

by ions (both anions and cations). Therefore, any system that connects electronic conductors to biological media must include interfaces where this change in charge carriers occurs. These interfaces are found at the electrodes.

Electrodes can enable the flow of electricity through two distinct mechanisms: capacitive (non-faradic) and electrochemical (faradic). In the capacitive mode, the interface between the conductive electrode and the ionic medium (i.e. the electrolyte) behaves as a capacitor. A layer of water molecules acts as a dielectric, physically separating the electrons in the metal from the ions in the electrolyte. Here, charges do not cross the interface; only accumulation and deaccumulation of charge occur. Consequently, only transient or time-varying currents can be sustained via this capacitive pathway.

Continuous currents, on the other hand, can flow if the electrochemical pathway is engaged. Here, electron exchange reactions (i.e. reduction and oxidation reactions) occur between the chemical species in the ionic medium and those of the electrode. For most metals used in catheters, such as gold, platinum, titanium, and stainless steel, these reactions do not occur spontaneously. Electrons require a small amount of energy, typically achieved by applying hundreds of millivolts to overcome the energy barrier and initiate the reactions. However, in electroporation treatments, where hundreds to thousands of volts are applied, electrochemical reactions at the electrodes become substantial. These reactions can generate pH gradients, release gaseous microbubbles, and liberate metallic ions, all of which pose a risk of localized tissue toxicity or, as discussed below, embolic events. *Figure 2* illustrates the electrochemical reactions expected at a pair of stainless steel electrodes in saline. While the electrolysis of water is almost always the dominant process, secondary reactions—such as the evolution of chlorine gas and the anodic dissolution of metal ions—frequently occur simultaneously.

Nevertheless, it must be noted that when high-frequency biphasic waveforms are applied, the capacitive pathway becomes highly favoured. Due to the high rate of change in voltage, the displacement current across the dielectric interface dominates, effectively bypassing the slower faradaic processes. Furthermore, electrochemical products generated during a phase are often partially or fully reversed during the subsequent phase of opposite polarity. This rapid alternation prevents the accumulation of long-lived chemical species and gaseous precursors at the electrode surface, thereby significantly mitigating the adverse impacts of electrochemical reactions.

Bubbles

When high current is forced through electrodes in an aqueous electrolyte—such as blood plasma or intra- and extracellular media—gas bubbles may form via three pathways: the previously discussed electrochemical reactions, the formation of steam bubbles due to Joule heating, and the release of dissolved gases (e.g. nitrogen) resulting from the inverse relationship between temperature and solubility. This topic has recently been addressed experimentally by Mahnič-Kalamiza and colleagues.[57] In their *in vitro* saline study, they found that bubbles arising from electrochemical reactions are more prevalent under monophasic pulsing waveforms, whereas high-frequency biphasic pulsing primarily produces bubbles through boiling of the medium. Degassing due to reduced gas solubility at elevated temperatures appears to contribute only marginally. They further observed that boiling-induced bubbles collapse rapidly, while those formed via electrochemical reactions or degassing exhibit longer lifetimes.

Since early clinical PFA studies, microbubbles have been occasionally observed on intracardiac echocardiography immediately after energy delivery.[63] These microbubbles have raised concerns due to their association with gaseous microemboli, which may contribute to silent cerebral lesions and stroke. The extent to which these events are directly attributable to the delivered current remains uncertain. Procedural factors such as catheter exchanges and other pathways for air entry into the

bloodstream are also likely to play a significant role.[64] In this regard, however, it is worth noting that a recent study using transcranial Doppler to monitor microembolization detected a higher rate of microembolic signals during PFA than during high-power short-duration radiofrequency ablation, with the ablation phase identified as the most embolic stage of the procedure.[65]

Nevertheless, the occurrence of embolic events cannot be attributed solely to gaseous microemboli. Given that most PFA systems employ high-frequency biphasic waveforms, which appear to generate bubbles primarily through boiling that collapse rapidly, it is plausible that at least a proportion of these microemboli instead arise from thrombus formation by blood coagulation due to excessive local heating.

Prevention or minimization of microbubble formation represents an opportunity for optimization of PFA systems. Catheter design can be refined to minimize gas entrapment, avoid sharp electrode edges, and reduce regions of high current density, thereby limiting thermal hotspots and arcing.[66] In parallel, waveform and energy delivery can be carefully tailored to achieve effective tissue ablation while minimizing bubble generation. Further optimization of duty cycles and delivered energy, together with the introduction of pauses between bursts or the increase of irrigation rates, may allow sufficient time for gas and heat dissipation and thereby reduce bubble formation.[65,67]

Arcing during pulsed field ablation

Arcing can occur when a gas is exposed to an electric field of sufficient strength to cause gas ionization (plasma) and dielectric breakdown. A similar phenomenon can happen during PFA if the transmission of pulsed electric fields causes bubble formation.[68,69] Presence of gas is a necessary element of arcing, though a true arc is a continuous discharge of plasma, whereas 'sparking' is a better term for the PFA phenomenon. Since 'arcing' is almost universally used to refer to sparking during PFA, the term 'arcing' is used here.

Arcing was a major factor in complications from direct current (DC) ablation, such as barotrauma to cardiac tissue, when investigated in the 1980s using extracardiac defibrillators connected to diagnostic catheters.[70,71] Since the pulse width used in DC ablation is milliseconds in duration, the level of gas formation and arcing that could occur was beyond what is typical in modern PFA systems. Modern PFA systems utilize microsecond or nanosecond pulse widths, which can limit the size of bubble formation and the consequences of arcing. Still, arcing continues to be relevant for modern PFA, as high current density (affected by electrode size and spacing) and energy-dense waveforms can result in arcs. The presence of metallic parts, namely left atrial appendage occlusion (LAAO) devices, in close proximity to the ablation catheter can produce a distortion of the electric field leading to a localize current density amplification. A bench test showed a similar risk of local arcing for three commercial PFA systems only when the distance between the catheter and the device was $\leq$1 mm. Good practices should avoid direct contact between PFA catheter and LAAO devices.[72] However, PFA generators today include complex circuitry to detect high current discharge and stop ablations if necessary or the ability to turn off electrodes that are too close together.[73]

Pulsed electric field interactions with other implanted electrical devices

Patients undergoing pulsed field ablation for the treatment of cardiac arrhythmias often have chronically implanted electronic devices for the treatment of cardiac or other conditions.[74,75] Since PFA involves transmission of high-strength electric fields inside the body, such fields could interact with implanted electronic devices by interfering with their function or causing damage. Physical proximity is generally the biggest factor in adverse interactions of implantable devices and high-strength pulsed electric fields, as the field strength drops rapidly with distance from PFA catheter electrodes (proportional to $1/r$ or $1/r^2$, depending on catheter and electrode geometry). The importance of proximity makes interactions with cardiac implantable electronic devices (CIEDs) of particular interest.

The most common CIEDs that can interact with PFA electric fields include pacemakers (with transvenous leads and leadless), implantable cardiac defibrillators, and cardiac resynchronization therapy defibrillators. Though PFA was initially thought to be benign in regard to interactions with such CIEDs,[76,77] issues have been discovered as the number of patients treated with PFA has increased.[78] Adverse interactions of PFA and CIEDs fall into the following categories:[76]

- CIED oversensing of PFA signals
- Damage to a CIED due to PFA therapy
- Temporary or permanent damage to tissue surrounding a CIED
- Induction of an arrhythmia
- Ineffective PFA therapy or arcing
- Dislodgment of leads or device

Due to the recognized risk, a Heart Rhythm Society/European Heart Rhythm Society scientific statement now lists CIED interactions as a PFA safety issue, noting that risks can be platform-specific due to differences in catheter design, waveform, and ablation vector.[79]

Pulsed field ablation waveform design

Since the specific characteristics of a PFA waveform can significantly impact the safety, efficacy, and usability of PFA systems,[80] it is the purpose of this section to discuss the practical effects of some of the most impactful waveform characteristics. *Table 2* summarizes the key parameters that define these waveforms.

Monophasic vs. biphasic pulses

High voltage pulses are applied between opposing polarity electrodes during PFA to create a high-strength electric field in cardiac tissue. Such pulses can be applied in a monophasic (maintains the same polarity throughout the pulse) or biphasic (polarity is reversed during the pulse) morphology (*Figure 3*).

Monophasic pulses have been shown to be more effective at creating cell damage than biphasic pulses for the same total energy,[13,81] but they can also cause more undesired collateral effects.[68,82] Biphasic pulses cause less musculoskeletal stimulation,[80,83] less electrolytic bubble formation,[68] and less risk of arrhythmogenicity due to cardiac stimulation,[84] which is why most PFA systems utilize biphasic pulses.[79,85]

Microsecond vs. nanosecond pulse widths

The duration of each pulse in a PFA waveform can cause cell damage via differing biophysical mechanisms. Pulse widths in the microseconds are hypothesized to induce a transmembrane voltage across the cell membrane, permeabilizing the cell via induction of pore formation and ion channel damage.[86] Nanosecond pulse widths may cause more internal damage to

Table 2 Main features of PFA waveforms

Feature	Definition	Remarks
Amplitude	Maximum magnitude of waveform variation from its baseline.	Amplitude may refer to the peak magnitude of voltage, current, or electric field, depending on the context.
Pulse	Short-duration variation in the waveform, typically characterized by a rapid change from baseline to amplitude, followed by a return to the baseline.	Pulses are most commonly monophasic or biphasic square pulses, although sinusoidal oscillations or exponential decays have also been used in electroporation.
Phase configuration	It describes whether the magnitude of the waveform stays on one side of the baseline or alternates between positive and negative values.	Two possible configurations: Monophasic: The magnitude deviates from the baseline in only one direction. The pulses are either entirely positive or entirely negative. Biphasic: The magnitude alternates between two opposite polarities. A single pulse consists of both a positive and a negative phase.
Biphasic pulse	A biphasic pulse is a type of pulse consisting of two consecutive phases with opposite polarities. The waveform first deviates from the baseline in one direction (positive or negative), then reverses to an equal or different magnitude in the opposite direction before returning to baseline.	Biphasic pulses are often used to balance charge delivery and minimize electrochemical issues.
Interphase pause	Brief interval between the two phases of a biphasic pulse, during which the magnitude returns to baseline before the second phase begins.	
Burst (or train, or packet)	A burst is a sequence of pulses delivered in rapid succession as a single group, separated from other groups by longer intervals.	
Repetition rate (or frequency)	The repetition rate is the frequency at which pulses or bursts are delivered, typically expressed in hertz (Hz).	f
Repetition period	Inverse of the repetition rate (or frequency). It is the time interval between the start of one pulse (or burst) and the start of the next pulse (or burst).	$T = \frac{1}{f}$
Duty cycle	The duty cycle is the fraction of time a waveform is active relative to the total time, usually expressed as a percentage.	The duty cycle is generally proportional to the delivered energy. Low duty cycle waveforms are used in PFA because they enable the delivery of high electric field magnitudes while minimizing thermal side effects.

the cell, bypassing the capacitive effects of the cellular membrane[85,87] (*Figure 4*).

The selection of whether to use microsecond- or nanosecond-scale pulse widths depends on design goals for the PFA system across catheter, generator, patient anaesthesia, ablation dosing, and other factors. Of note, microsecond pulse widths can be produced with more straightforward generator hardware, as they require lower voltage for effective lesions (1–3 kV generally[84]). Nanosecond pulse widths require a higher voltage (8–12 kV generally) and thus require specialized generator designs,[88] but may have advantages in ablation dosing and speed. Though many details of PFA waveforms remain trade secrets of PFA system manufacturers, the general scale of 'microsecond' or 'nanosecond' pulse widths is typically published.[84] Many current microsecond-scale PFA systems use pulse widths in the low-microsecond range (roughly 1–10 ms),[89] while nanosecond-scale PFA waveforms are more difficult to categorize. Nanosecond PFA waveforms could utilize pulse widths from single-digit nanoseconds up to hundreds of nanoseconds depending on manufacturer definition.

Time duration and duty cycle of pulsed field ablation waveforms

Balancing competing goals in PFA waveform design also extends to total duration of each application and the distribution of pulses across the waveform. Pulsed field ablation applications can be shorter than those of thermal ablation modalities, with one commercially available PFA system utilizing 2.5 s per application as an example.[85] Certainly, shorter ablation durations can allow faster procedures, though the number of ablations must be taken into account as well. The total duration of a PFA application is governed by the generator design (charging speed, voltage drop, etc.), the catheter design (number of electrodes, pulse vectors, catheter stability, heating near electrodes, etc.), and the biological environment (ability to capture tissue,

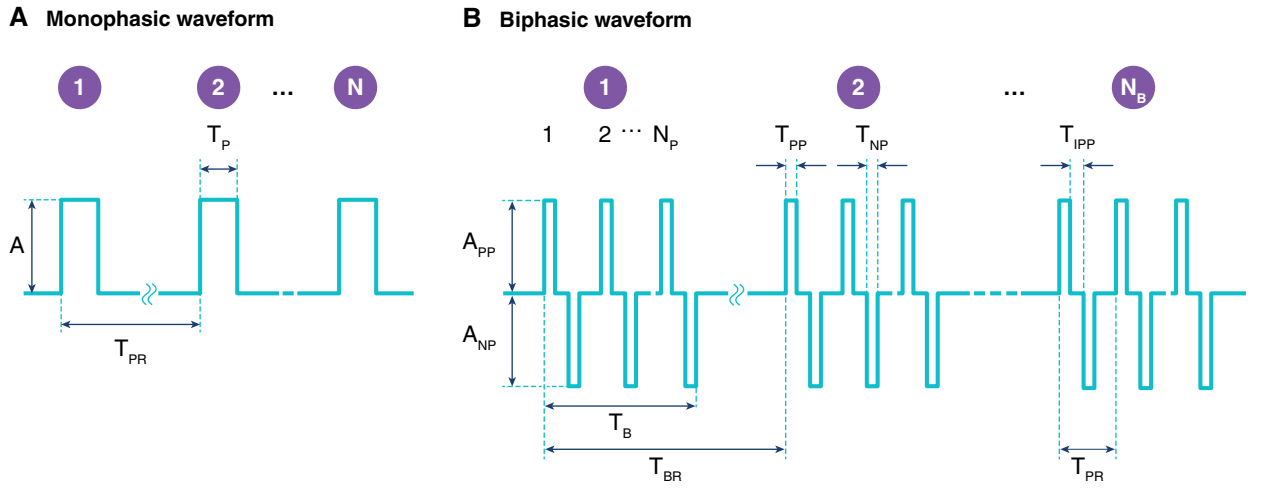


Figure 3 Main features of PFA waveforms composed of square pulses. *A*) Monophasic waveform: A = amplitude, T_P = pulse duration, T_{PR} = period of pulse repetition (i.e. 1/repetition rate), N = number of pulses. *B*) Biphasic waveform: A_{PP} = amplitude of the positive phase (of the biphasic pulses), A_{NP} = amplitude of the negative phase, T_{PP} = duration of the positive phase, T_{NP} = duration of the negative phase, T_{IPP} = duration of the interphase pause, T_{PR} = period of pulse repetition (i.e. 1/repetition rate), T_B = duration of the bursts (=trains = packets), T_{BR} = period of burst repetition, N_P = number of biphasic pulses in a burst, N_B = number of bursts.

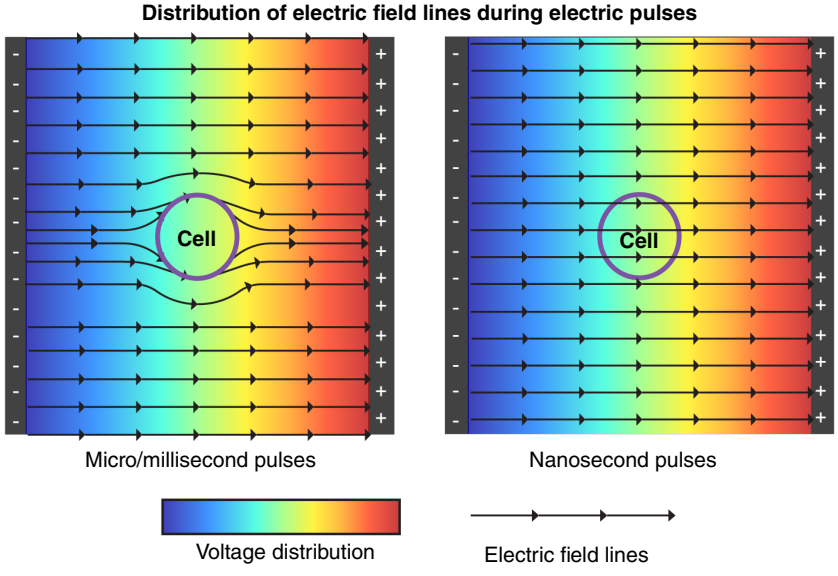


Figure 4 Differences in electric field flow around cells for microsecond and nanosecond pulses. Nanosecond pulses may bypass the capacitive effects of the cell membrane and cause more internal damage to the cell.

proximity to sensitive structure, etc.). Pulsed field ablation waveforms are often delivered in bursts or trains of pulses that are repeated throughout the waveform, as opposed to a continuous pulse output. Pulse delivery in bursts can allow synchronization to the ventricular refractory period to reduce risk of arrhythmia induction,[90] though most PFA in the atria is done in an unsynchronized fashion.[84]

Pulsed field ablation catheter design considerations

An electric field is induced in living tissue when a voltage is applied across two electrodes. In the idealized case of a rectangular tissue volume sandwiched between two parallel plates, the electric field magnitude is simply the applied voltage divided by the

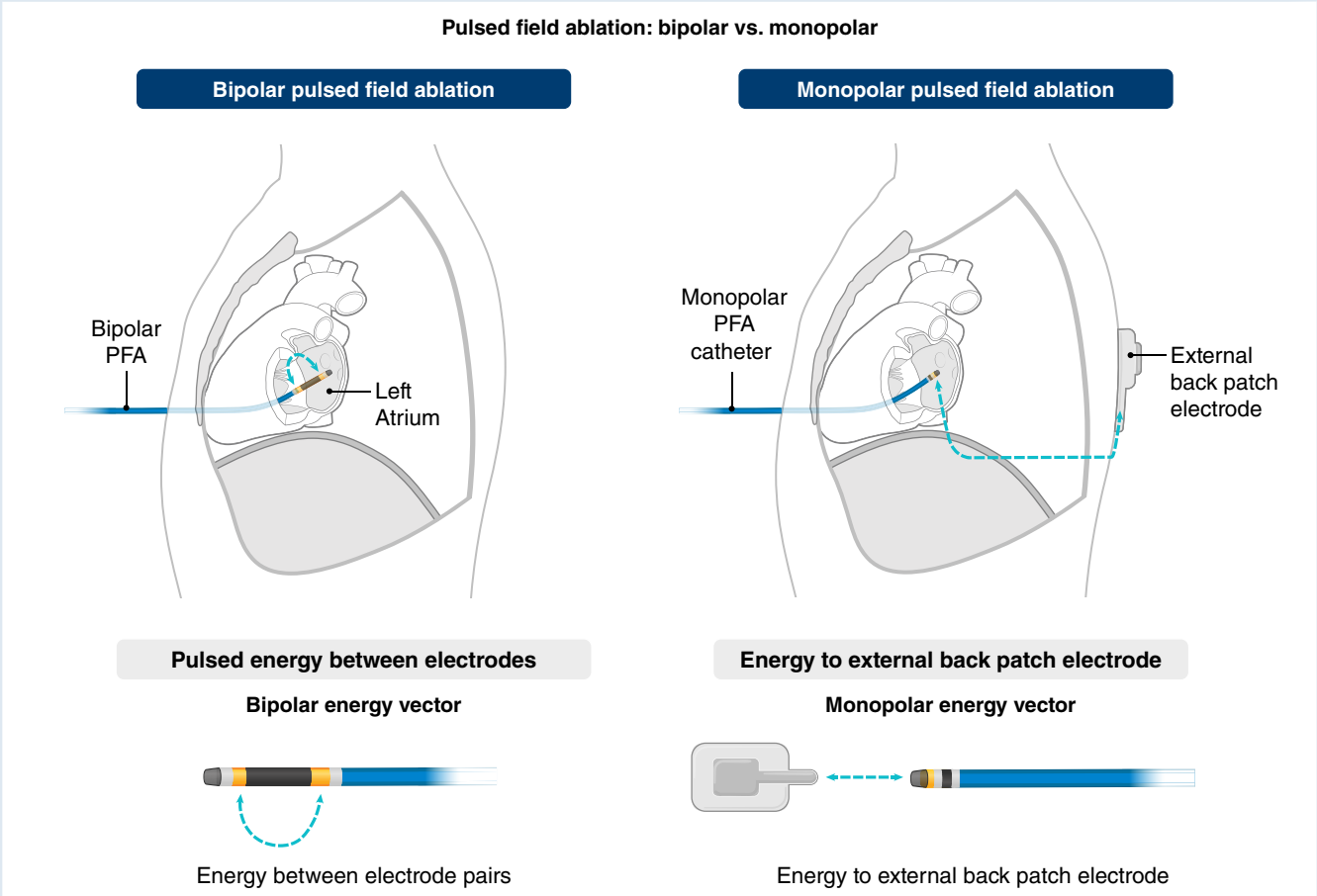


Figure 5 Differences in bipolar and monopolar energy vectors in pulsed field ablation. Bipolar ablations utilize electrode(s) on the catheter itself. Monopolar ablations send energy between electrode(s) on the catheter to the adhesive grounding pad, typically found on the back of the patient.

electrode spacing. However, for other geometries—such as the catheters used in cardiac PFA—this relationship does not hold, and the electric field distribution must be determined via numerical methods (i.e. computer simulations). The electrode configurations are designed to maximize field magnitude and uniformity within the target region while minimizing localized hotspots. These high-intensity regions typically occur near electrode boundaries due to the edge effect. Additionally, material considerations such as electrode composition and surface roughness factor into the safety and efficacy of PFA application. Biocompatibility, electrochemical stability, corrosion resistance, and other factors typically lead to the use of platinum-iridium or gold instead of other materials like stainless steel for the electrode surface.[91] In catheters with variable configurations or sizes instead of a fixed shape, the electric field dynamics must be investigated across the possible configurations.

Two main types of PFA catheter configurations can be distinguished: bipolar and monopolar configurations (*Figure 5*). In the bipolar configuration, electrical energy is delivered between two closely spaced electrodes on the same catheter, resulting in a well-defined and confined electric field. In contrast, in the monopolar configuration, catheters deliver energy from electrodes at the catheter to a distant return electrode, typically a dispersive patch placed on the patient's skin. A few PFA systems allow catheter configuration in either bipolar or monopolar mode but most commonly operate in a fixed configuration.

Because the return path in monopolar configurations is not well defined, it is often advantageous to control the delivered current rather than the voltage. Doing so helps reduce variability in the electric field strength near the catheter electrode, making it less sensitive to differing tissue and patch interface impedances in the return path.

In multi-electrode PFA catheters, whether operating in monopolar or bipolar configurations, energy is typically delivered sequentially to subsets of electrodes rather than simultaneously across the entire array. This approach reduces peak power demand and may enhance the uniformity and predictability of lesion formation by mitigating the effects of local tissue heterogeneities.[92] Furthermore, the inclusion of additional electrodes within a bipole increases the effective surface area, thereby reducing the current density and associated risks.

Clinical usability

Pulsed field ablation has always held the promise of increased patient safety as one of its primary appeals among clinicians. However, the possibility of simpler, faster, and more predictable ablation procedures also held appeal. Thermal ablation

modalities, especially radiofrequency ablation, frequently required procedure durations of 1–2 h or longer, with poor predictability.[93] The advent of PFA brought with it shorter procedure times and more predictability,[94] important factors for optimizing caseload and managing lab staff. Beyond these positive procedural aspects of PFA, patient management has also become more straightforward. Patients complain less of chest pain and discomfort after a typical AF ablation with PFA, and the burden of patient follow-up is less for hospital staff.[95] These are all positive factors that allow increasing the number of ablations completed per day and lessening the burden on lab staff.

Though the overall gains in procedure duration and lab management are important, there are usability aspects specific to each PFA system that must be considered, beginning with the most common ablation procedure, pulmonary vein isolation (PVI) for the treatment of AF. Usability here refers to the degree to which the full system—catheter, waveform, ablation workflow, and lab integration—facilitates intuitive, efficient, and reproduceable PFA procedures across diverse operators, anatomies, and clinical environments. The ideal for PVI has always been so-called 'single-shot isolation,' where each vein is permanently isolated from the rest of the left atrium by a single energy application. Though this could be accomplished with a cryoballoon, each ablation lasted minutes in duration.[90] Perhaps an amended ideal of *rapid* single-shot isolation is required, and this has proven elusive, even for PFA. The most widely used PFA system across the globe, incorporating the pentaspline PFA catheter, prescribes a minimum of eight ablation applications per pulmonary vein for durable isolation. This ablation workflow includes catheter rotations and shape changes between ablations. Though such a workflow cannot be termed single-shot isolation, a widespread adoption of this technology serves as proof of the advantages of the ability to change catheter shape. Ablations can be form-fit to complex and varying patient anatomy, and the posterior wall ablation is increasingly being reported with 'single-shot' designs. On the other end of the spectrum are the spherical array or balloon-based PFA catheters, which can be used for true single-shot isolation for each pulmonary vein. However, this catheter form typically requires ablations of 40 s in duration[96] and may not be as easily manoeuvrable and usable for other ablation targets as multispline catheters. Thus, trade-offs continue to be part of selecting a PFA system, at least until future generations are developed that can eliminate these trade-offs.

As PFA system designs continue to mature, continuously improving in safety and efficacy, it is possible that usability may be the defining difference between them. For instance, it is possible that the most usable systems of the future will be the ones able to accomplish the most tasks without catheter exchanges. One system and one catheter that can do complex electroanatomical mapping, single-shot PVI, posterior wall ablation, focal ablation, and lines of block in both atria would be a powerful tool. Ventricular mapping and ablation will also only grow in importance. And we must never forget that each geography around the world has different requirements, including in anaesthesia and procedural workflows. The most usable PFA systems may also be the ones that accommodate the most workflows and patient management options around the globe.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Specific effects of Pulsed Field Ablation on the cardiac tissue, the nervous system and the conduction system in experimental and clinical studies

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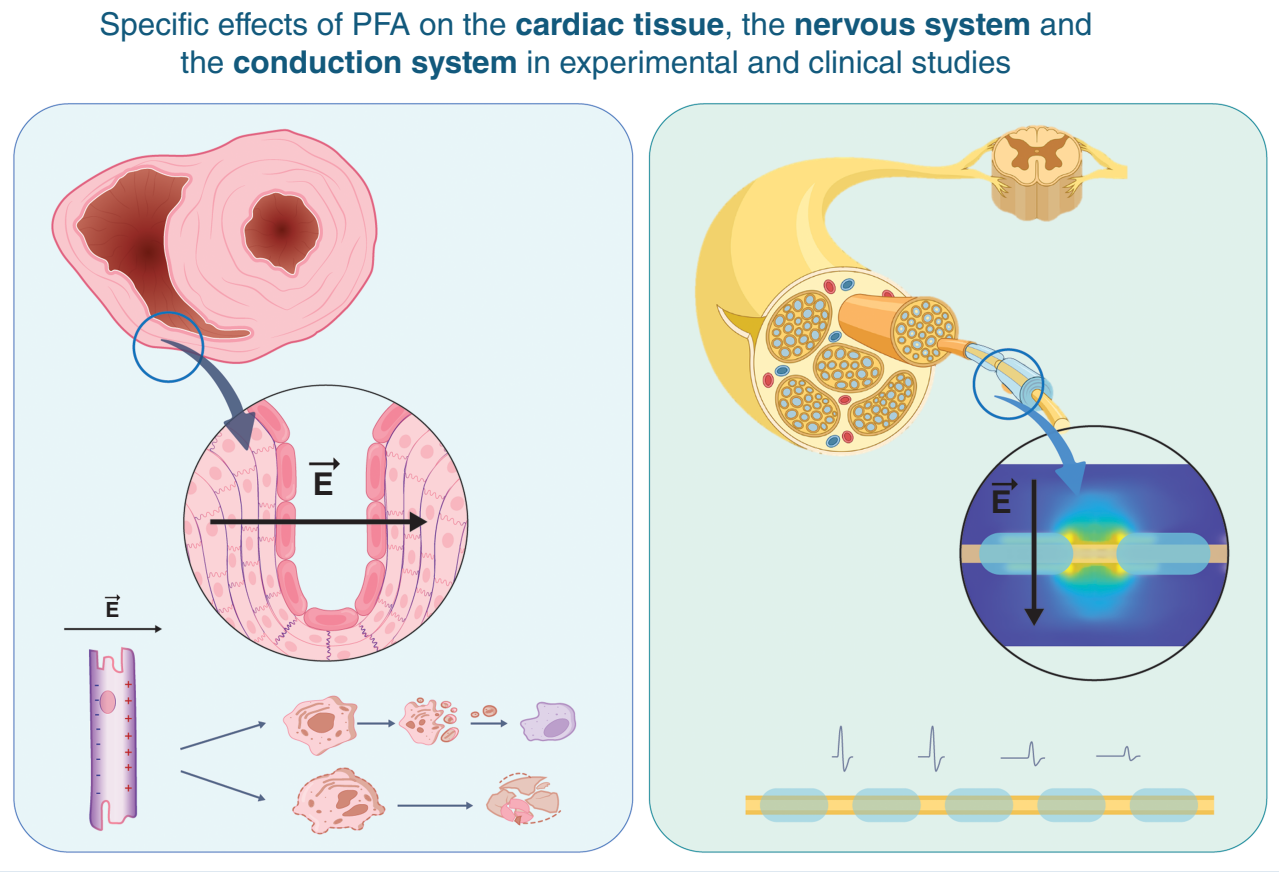
Aims Pulsed field ablation (PFA) has emerged as a novel ablation modality for the treatment of cardiac arrhythmias and has rapidly reshaped contemporary electrophysiology practice. This article provides a comprehensive analysis on the mechanisms underlying the specific effects of PFA on myocardial, neural tissue structures, and the cardiac conduction system, integrating biophysical principles with preclinical and clinical evidence relevant to contemporary electrophysiology practice.

Methods and results This document provides an exhaustive mechanistic explanation for the preferential effects of PFA on myocardium and the limits of the 'tissue-selectivity' concept. The complex interplay between cellular and tissue-level biophysics, biological responses, and tissue regenerative capacity that determines differential susceptibility to electroporation across tissues is analysed. Distinct patterns of lesion formation and maturation following PFA are also reviewed, highlighting the temporal and histopathological differences compared with radiofrequency ablation. Additionally, lesion formation in heterogeneous substrates is analysed, including fibrotic and adipose-rich myocardium, where local electric field distribution critically influences lesion durability.

Conclusion The article further examines the interaction between pulsed electric fields and neural tissue, with emphasis on the phrenic nerve and intrinsic cardiac autonomic nervous system. While nerve stimulation and transient reversible conduction disturbances produced by reversible electroporation can occur during ablation, permanent neural injury appears extremely rare in current clinical experience. Finally, this manuscript examines current understanding regarding the specific effects of PFA on the cardiac conduction system, which according to the limited available evidence appear strongly dependent on electric field dose and anatomical proximity.

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Graphical Abstract



Keywords Pulsed field ablation • Preferential myocardial ablation • Tissue selectivity • Lesion formation • Heterogeneous substrate • Phrenic nerve • Vagal responses • Conduction system

Introduction

The term pulsed field ablation (PFA) was first used in a clinical publication in 2019 to refer to the specific use of irreversible electroporation (IRE) for the ablation of myocardial tissue in the treatment of cardiac arrhythmias.[1] Electroporation is a general phenomenon that describes the increase in cell membrane permeability leading to reversible or irreversible effects depending on the electric dosing. It is a broad biophysical phenomenon that can be observed in every cell type and even in artificial lipid bilayers. In this article, we will focus on the theoretical arguments and experimental evidence that can explain the specific responses of cardiac and nerve tissues to electroporation both from a biophysical and a biological perspective and its implications for clinical practice.

It is important to emphasize that the purpose of this review is to summarize common observations and underlying mechanisms associated with PFA. Nevertheless, caution should be exercised when generalizing these concepts across different PFA technologies, as important differences may exist between platforms.[2] Variations in waveform design, energy delivery, and electrode configuration may influence both the extent and nature of tissue responses. For instance, although PFA is widely considered a non-thermal ablation modality because electroporation is the predominant mechanism of cell injury, temperature increases will always exist due to Joule heating. Consequently, thermal contributions to tissue injury may vary between platforms, potentially leading to differences in the biological response when thermal exposure is not adequately controlled or minimized.

The first part of the article will focus on the specific properties of cardiac tissue that contribute to its high sensitivity to electroporation. The second part of this article will focus on the effects of electroporation on nerves with a specific focus on neural structures that are relevant for cardiac ablation procedures.

Part I: PFA effects on cardiac tissue

Preferential myocardial ablation

Revisiting the selectivity concept

When the first modern PFA systems were introduced for treating cardiac arrhythmias, PFA was described as a tissue-selective ablation modality.[1,3] This term was used to describe the potential of PFA to spare collateral structures as the oesophagus or the phrenic nerve during pulmonary vein isolation (PVI) procedures and is one of the main advantages of this ablation modality.

While the 'selectivity' concept is still widely used by part of the EP community, a more scientifically accurate description

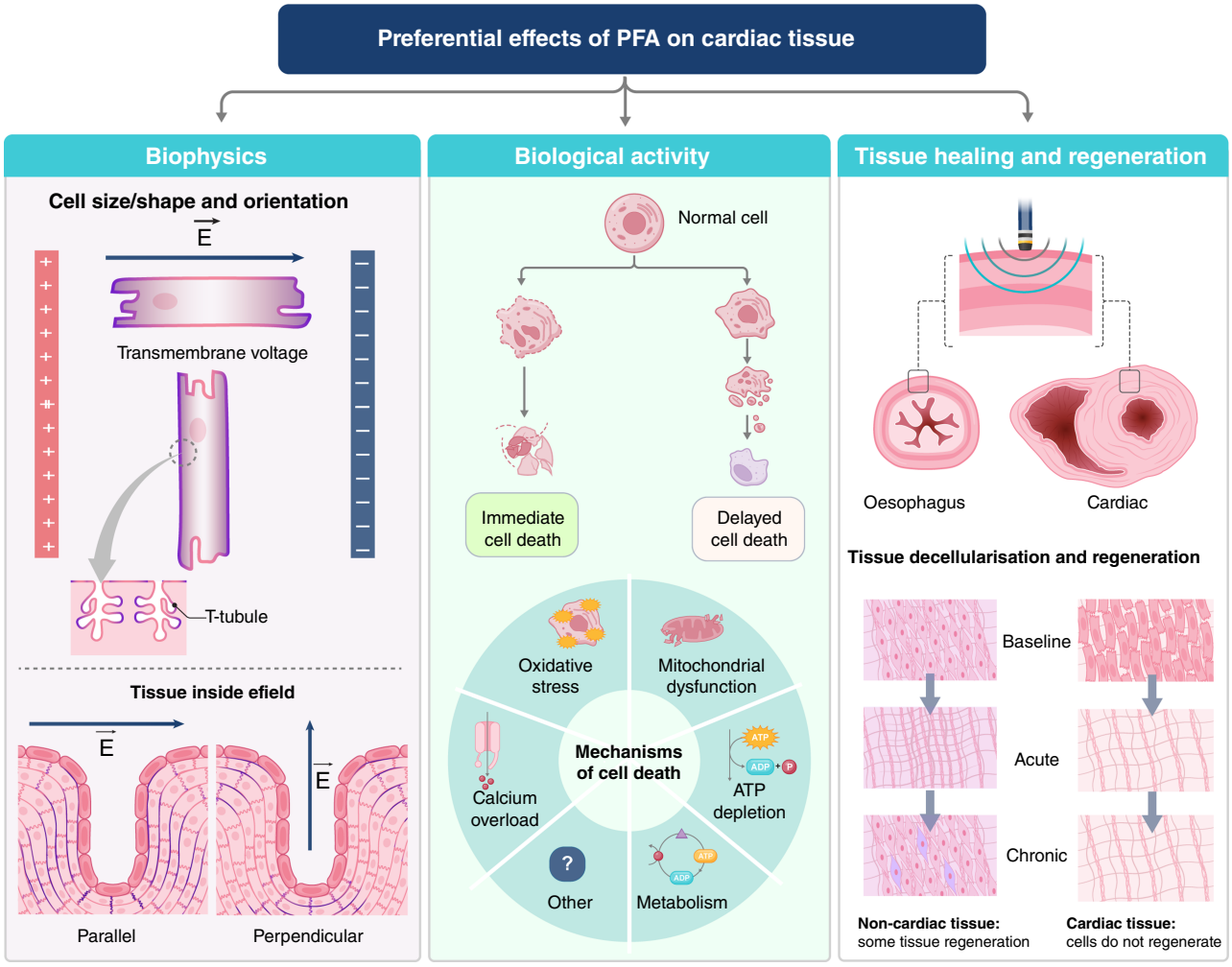


Figure 1 Summary of preferential effects of PFA on cardiac tissue. (*A*) Schematic representation of the transmembrane voltage induced under an electric field in different directions at the cell and tissue levels. (*B*) Summary of main biological mechanisms involved in cardiomyocyte cell death after PFA. (*C*) Example of differential response of cardiac tissue and oesophageal tissue in the event of acute damage by PFA; as extracellular matrix is preserved, oesophageal cells have the ability to regenerate and tissue heals, cardiac tissue does not have the ability to regenerate.

of PFA is that it is a *preferential* myocardial ablation modality.[4,5] While this change of wording seems subtle, it proves how the growing scientific evidence about PFA is helping evolve our understanding about this ablation modality. Additionally, this shift in terminology may also have important implications in refining the perception of clinical users about PFA safety limits and optimization of their clinical practice. The initial selectivity concept could lead to the misconception that PFA only affects cardiomyocytes, without any associated risks to other tissue types. Nowadays, the scientific community widely accepts that while PFA displays a wider safety margin than thermal ablation modalities, side effects are still possible in clinical practice.

Both the selectivity concept and the updated preferential ablation concept were born from scientific evidence and experimental observations. Tissue-specific effects were initially reported in many studies using IRE for tumour ablation.[6–8] Subsequently, similar findings were observed in the cardiac arrhythmia ablation space. Detailed chronic histological studies in preclinical models systematically observed preferential fibrotic replacement of cardiomyocytes with preservation of other intramyocardial or surrounding structures such as nerves or vasculature.[5,9–12]

Following this, we will review the main concepts related to the preferential ablation properties of PFA and will discuss the current limits and knowledge gaps about this phenomenon.

Experimental evidence for preferential ablation

Experimental evidence accumulated not only in cardiac ablation applications but also in the field of tumour ablation with IRE, has repeatedly demonstrated, both *in vitro* and *in vivo*, specific effects and differential cell death susceptibility of different cells or tissues.[5,13,14] While specific *in vivo* comparative studies for cardiac tissue are still scarce, some works have shown that myocardial tissue was more susceptible to IRE than vascular, neural, hepatic, and skeletal muscle tissues[5] and have provided experimental evidence for higher susceptibility of cardiac tissues compared to other tissues except for the skeletal muscle.[15] However, the waveform parameters used in these studies

significantly differ from the short biphasic pulses generally used in PFA commercial applications.

From a simplified perspective, the preferential effects of PFA on cardiomyocytes have been attributed to a significantly lower electric field electroporation threshold than other tissues, rendering cardiac cells more susceptible to the electric field exposure than other cell types. An important consideration is to understand that the electric field threshold value depends on the PFA-specific waveform and other parameters such as the duration of field exposure, its distribution over time or the repetitive dosing strategy.[15–17] This concept has important implications when trying to compare different tissue types or even different PFA systems because threshold is system-specific and there is not a unique value that can be generalized.

Some initial studies tried to provide proof of a lower cardiomyocyte threshold extracting data from very different studies with very different waveforms and experimental conditions, limiting the value of these initial comparisons.[1] More recently, *in vitro* studies were able to demonstrate a lower electric field threshold for cardiomyocytes compared to smooth muscle cells and neurons under identical experimental conditions.[5,13,14]

In the following section, we will focus on the characteristics of cardiomyocytes and tissue that affect their susceptibility to IRE.

Biophysical properties of cardiomyocytes

It has been extensively experimentally and theoretically studied that the necessary condition for initiating electroporation is reaching a critical transmembrane voltage.[18] From a purely biophysical perspective, the stationary transmembrane voltage induced by an external field varies in magnitude and direction across the cell membrane, depending on the orientation of the membrane elements relative to the field. The maximum induced voltage across the whole membrane of a cell is proportional to cell size, and for non-spherical cells, the eccentricity can either amplify or reduce the maximum induced transmembrane voltage, depending on the cell's orientation.[19,20] Thus, the electroporation threshold (pore formation probability) has been shown to correlate to some extent to biophysical magnitudes such as cell radius, geometry, orientation, and cytoplasm/nucleus ration.[21–23]

Biophysics predicts that, for electroporation using pulses in the microsecond-duration range, larger cells will be more susceptible than small cells. Cardiomyocytes are large, elongated cells, often exceeding 100 µm in length. In this way, the geometry of individual cardiomyocytes makes them particularly sensitive to electroporation (see *Figure 1*). However, it is important to consider that the characteristics of the PFA waveform, specifically, pulse duration, will strongly affect the impact of biophysical parameters (size and orientation). For example, experimental *in vitro* evidence demonstrated that dependence on orientation is much less relevant when using biphasic, short microsecond-duration waveforms compared to longer pulses.[24]

Cardiomyocytes also possess an extensive transverse-tubule system—an invaginated continuation of the sarcolemma that greatly expands membrane surface area and tightly coupled membrane integrity to calcium handling machinery. Severe electroporation therefore may disrupt not only the outer membrane but also a complex internal membrane network, facilitating increased cell death.[3]

Cellular biophysics cannot fully explain PFA effects in actual cardiac tissue because the electric field distribution in tissue is strongly affected by its architecture, including cell-to-cell coupling, the presence of electrically insulating structures, distribution of cell types with different electrical properties, and tissue anisotropy.[25]

Biophysical properties of cardiac tissue

Cardiac tissue is highly cellular and electrically conductive, with relatively little insulating extracellular matrix in non-fibrotic atrial myocardium. This favours penetration of electric fields rather than dissipation through collagen-rich stroma. In contrast, other tissues have a more complex architecture that can greatly impact electric field distribution. Peripheral nerves are bundled within multilayered connective tissue sheaths and frequently insulated by myelin, while vessels and hollow organs contain layered smooth muscle and elastic components that may impact effective electric field distribution and thus their susceptibility to electroporation.[26–29]

Additionally, cardiomyocytes form a functional syncytium via abundant gap junction coupling at intercalated discs, enabling low-resistance current flow between neighbouring cells. As a result, the classical single-cell intuition that induced transmembrane voltage scales primarily with cell size and orientation as discussed above, is only partially applicable to intact heart tissue, where tissue geometry, conductivity anisotropy, and intercellular coupling shape the field gradients that drive electroporation. Myocardial tissue architecture exhibits pronounced electrical and structural anisotropy arising from the aligned arrangement of elongated cardiomyocytes into fibre bundles and laminar sheets (see *Figure 1*). At the macroscopic scale, this produces a conductivity tensor with substantially higher conductivity along the local fibre axis than transverse to it.[30–32] During PFA, the imposed quasi-static electric field, therefore, redistributes through the myocardium in a fibre-orientation–dependent manner with the electric field expected to distribute preferentially along the fibres leading to non-symmetrical lesions.[33] However, recent computational models have demonstrated that lesion shape observed with focal PFA catheters would fit to the electric field distribution at a macroscopic level alone but to more complex predictions based on relative cell membrane damage at a microscopic level.[30]

The high content of cardiomyocytes promotes preferential ablation. The fact that cardiac tissue forms a syncytium does not necessarily increase or decrease PFA efficacy, but it profoundly affects the field distribution in cardiac tissue and means that PFA efficacy is ultimately an emergent property of the coupled anisotropic tissue network: local electroporation probability reflects not only cardiomyocyte membrane biophysics but also the structure-dependent redistribution of the electric field within the syncytium.

Besides the biophysical properties that help to explain how electric fields damage cell membranes, the ultimate fate of electroporated cells and tissues also depends on their biology, specifically on their ability to repair membranes, maintain homeostasis and replace damaged cells.[34]

Biological properties of cardiomyocytes

Cell biology must be considered as an important element in the complex interplay between electroporation and resulting cell death. In vitro studies have provided some general biological mechanisms for cell death induced by electroporation that could explain why cardiac tissue could undergo preferential ablation with PFA (see *Figure 1*).[34] Among them, one of the most relevant is the differential ability for cell membrane repair after electroporation. This was observed between normal and cancer cells in a process mediated by calcium-dependent mechanisms.[35–37] It was also shown in human-induced pluripotent stem cells, where regulated cell death played an important role following PFA.[38] However, other factors such as cytoskeleton integrity could also be important.[39] Calcium homeostasis could also play a crucial role in cell death after electroporation, leading to

mitochondrial dysfunction and ATP depletion.[40] Differences in mitochondrial properties, internal calcium reserves, etc., between different cell types could also contribute to the preferential cell death observed in cardiomyocytes.

In fact, electroporation-related disruption associated with Ca^{2+} influx and mitochondrial dysfunction has been described as a key pathway leading from severe membrane injury to cell death in excitable cells, including cardiomyocytes.[34,38,41,42] As cardiomyocytes maintain a 10 000-fold electrochemical gradient of calcium across their plasma membrane, which is one of the highest in the body, augmentation of cardiomyocytes by calcium is a plausible explanation for high sensitivity of cardiomyocytes to PFA damage. In this context, Maizels and colleagues successfully demonstrated in human-induced pluripotent stem cells how PFA damage to cardiomyocytes can be enhanced through electroporation Ca^{2+}-sensitization.[38]

Many other biological mechanisms could potentially explain differences observed between cardiac tissue and other tissue types. For example, it has been shown that PFA can alter the metabolic activity of cardiomyocytes by affecting electron transport in the mitochondria[41] and that the effect is sensitive to PFA voltage and energy dose.[42] Comparative studies between different tissue types are needed to clarify the role of such effects in preferential cardiac ablation.

Additionally, most of the current knowledge comes from basic *in vitro* studies. However, some of the biological components that may explain PFA cell death mechanisms such as effects on microcirculation and vasculature, regenerative capabilities, inflammatory and immune responses, etc., are tightly linked to *in vivo* conditions and cannot be replicated *in vitro* increasing the complexity of mechanistic studies.

Tissue regeneration

Besides biophysics and cell biology, the third reason for the observed preferential effects of PFA on cardiac tissue is that cardiac tissue does not regenerate after electroporation injury as many other tissues do. While radiofrequency ablation (RFA) destroys not just cells but also the extracellular matrix, independent of tissue type, which induces non-specific tissue damage, IRE preserves the extracellular matrix and other tissue components such as the microcirculatory system.[6,8] In this way, IRE decellularizes the target tissue while keeping the patency of extracellular structures.[43] The most important consequence of this phenomenon is that it can be applied to nearby critical structures such as vessels, nerves, and others as demonstrated in cancer applications.[8]

Decellularized scaffolds left after IRE can potentially be repopulated with cells, and they are widely studied for applications in regenerative medicine.[44,45] Previous studies have shown how the preservation of the extracellular matrix after IRE enables cell regeneration and tissue healing in the liver,[46] blood vessels,[27,47,48] nerves,[49] oesophagus,[50–53] etc. Depending on the electric field application conditions and tissue under study, some works reported full regeneration of the full tissue or partial regeneration of some tissue layers.[47]

Adult mammalian cardiomyocytes are widely regarded as terminally differentiated with minimal regenerative capacity, and cell loss is typically not replaced by new contractile myocardium. Reviews of myocardial biology note that adult cardiomyocytes exhibit extremely low rates of cell turnover and respond to injury primarily by scar formation rather than regeneration.[8] It is not surprising, then, that cardiac tissue has not been found to spontaneously regenerate after IRE.

For other types of tissues, the ability to regenerate after PFA has been convincingly demonstrated. Nerves can achieve complete functional recovery within weeks.[49] Treated liver tissue was replaced by normal hepatocytes with minimal scarring within 3 weeks.[54] For skeletal muscle, PFA can create massive myofibre necrosis that is followed by efficient muscle regeneration.[55] Collectively, these examples demonstrate that the very limited regeneration of myocardium is part of the reason for PFA acting preferentially on cardiac tissue (see *Figure 1*).

Relevant to cardiac applications, several preclinical works have shown how oesophageal tissue can heal and regenerate after PFA.[50,51,53] Although the process of tissue regeneration after IRE is still poorly characterized, some preclinical studies have shown how the tissue microenvironment, including nerves, lymph vessels, and blood vessels, is preserved providing a necessary functional framework for cell regeneration. Production and migration of progenitor cells have been reported in histological examinations[52] likely facilitated by differential cell death pathways activated like pyroptosis or necroptosis. Finally, although some studies have reported reduced inflammation in cardiac tissue after PFA compared to RFA,[56,57] it is well known that IRE can produce a local innate immune system activation. The specific characteristics of this non-thermal immune response, including the release of damage-associated molecular patterns could also play an important role in facilitating tissue regeneration.

PFA in different cardiac substrates

Despite its potential, several gaps in knowledge regarding PFA in different substrates remain. Evidence about the chronic durability of PFA lesions has been extensively developed for pulmonary veins (PVs) but is still scarce in thick, extra-PV substrates. Remapping studies have shown very high rates of reconnection when using PFA tools designed for PVI in targets like the mitral isthmus (5.5% durability), left atrial appendage (4.6%), and the coronary sinus (1.3%).[57]

Heterogeneity of myocardial tissue

As previously explained, local electroporation depends on the redistribution of the electric field at a tissue level, which is intrinsically linked to the complex, non-uniform nature of the cardiac substrate. Cardiac myocardium is not a simple syncytium but a 3-dimensional entanglement of compact muscular bundles, adipose tissue, vascular networks and collagen-rich areas. This heterogeneity varies from patient to patient and from region to region and is present both in ventricles and atria alike. In the posterior mitral isthmus region, for example, compact myocardium consistently ranges from 2 to 4 mm in thickness, but it is frequently interspersed with non-conductive epicardial fat that can reach depths approaching 1 cm. In diseased myocardium, structural complexity is further increased by the presence of fibrosis but also potential fat or calcifications.

This structural heterogeneity creates significant challenges for energy delivery. While traditional thermal modalities are impeded by the thermal and electrical insulating properties of fat and fibrotic tissue and the convective cooling of vessels, PFA effects depend mostly on the passive electrical properties of these different components. Electric field distribution for non-homogenous tissues will depend on the electrical conductivity transitions between adjacent tissues. Transitions in conductivities between myocardium, fat or connective or fibrotic tissue will create local modifications of the electric field intensity amplifying or reducing the electric field locally (see *Figure 2*).

Ablation in healthy vs. diseased myocardial tissue

The effects of PFA across varying myocardial substrates have been examined in computational simulations, preclinical models

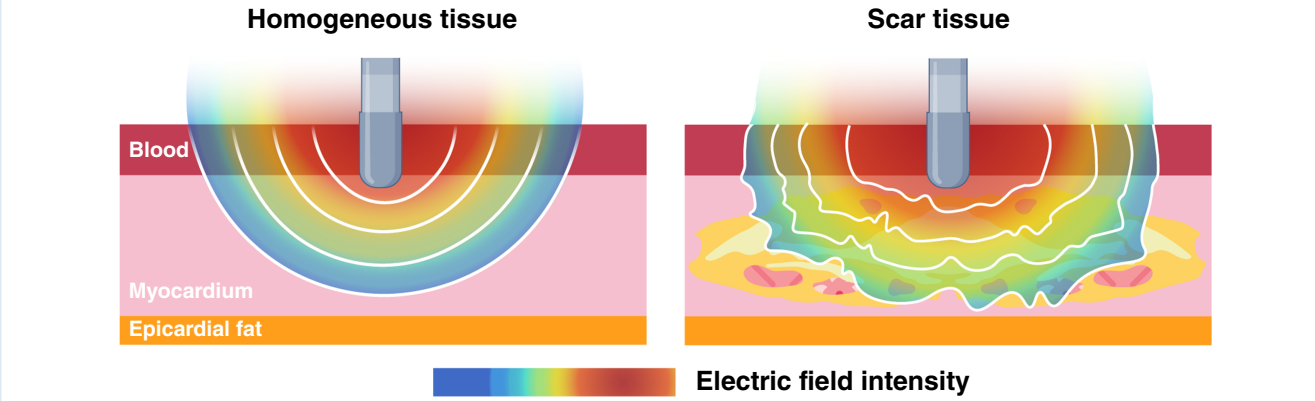


Figure 2 Schematic comparison of electric field distribution in homogenous vs. scar cardiac tissue. Computational models predict electric field penetration even with a dense scar tissue. Presence of fibrosis and fat can produce localized distortions of electric field distribution. Partially adapted from ref.[58].

(mostly swine),[59–61] and clinical studies. Computational modelling suggests that while fibrotic tissue has a negligible impact on electric field distribution (and hence on lesion formation), the presence of intramyocardial fat within the scar significantly alters lesion morphology (see *Figure 2*).[58]

Preclinical studies in porcine models of chronic myocardial infarction confirm that PFA successfully penetrates both ischaemic and iatrogenic RFA scars. In these models, lesion depth remained consistent between infarcted border zones (5.9 ± 1.0 mm) and healthy remote myocardium (5.7 ± 1.3 mm; P = 0.53). Furthermore, the lethal electric field threshold required for irreversible injury appears similar in both healthy and infarcted porcine hearts.[62] 'Redo' models further indicate that PFA is highly effective when ablating over chronic RFA scars, producing lesions that are significantly deeper and more uniform than repeat RFA applications (7.1 ± 1.3 mm vs. 3.9 ± 1.6 mm; P < 0.01).[63]

Early clinical experience shows the important potential of focal PFA for scar-related ventricular tachycardia ablation. Case reports and clinical series show high success rates in achieving transmural tissue homogenization that is often unattainable with conventional thermal energy.[64–66] These results have been achieved in a variety of settings, underlying substrates and as bailout therapy after failed RFA, confirming the value of PFA in this setting.

Ablation around fat and vascular structures

As explained before, the biophysical interactions between PFA and different tissues are governed by differences in electrical conductivity. Adipose tissue has a conductivity 10- to 20-fold lower than healthy myocardium producing a local alteration of the electric field.[67] Although it could seem counterintuitive, computational modelling shows that fat serves as an 'attractor' for the electric field, around which field strength tends to peak. This creates localized 'hot points' of high electric field strength in the lateral areas of fat deposits, while 'cold points' appear at the entry and exit points of the electrical current.[58] It is important to highlight that the effects of PFA depend on the electric field intensity, which is directly proportional to the current density and inversely proportional to the conductivity. This explains how electric field can be higher in areas of low conductivity.

Other structures in the tissue such as blood vessels can also significantly modify the electric field distribution. Due to the higher conductivity of the blood inside the vessels, there will be a local modification of the electric field around the vessel with areas of low and high electric field, which may contribute to inhomogeneous ablation of target myocytes residing in the immediate vicinity of these sinks. This was modelled and experimentally confirmed in liver tissue.[68,69] On the contrary, the vascular wall has relatively lower conductivity, which may create electric field peaks in the transition areas between tissue and blood.[68]

Comparison with RFA

Radiofrequency ablation lesions are often limited by the insulating effects of intramyocardial collagen and fat. In preclinical comparisons within heterogeneous scar, PFA produced lesions that were deeper and more transmural than those of RFA (6.4 vs. 5.4 mm; P = 0.024), effectively eliminating viable myocytes separated from the catheter by adipose and fibrotic barriers.[61] Furthermore, PFA is not subject to the 'heat-sink' effect of local blood flow or poor thermal conductive properties of scar tissue, which significantly blunts the intramyocardial temperature rise during RFA in infarcted tissue. Recent preclinical studies have explored the potential of colocalized sequential combinations of RFA and PFA as a strategy to increase lesion depth in healthy ventricular myocardium with mixed results.[70,71] Although potential mechanisms are still not demonstrated and available evidence is still scarce, future research should explore if scar tissue could be an interesting target for colocalized energy combinations.

Lesion formation mechanisms

Pulsed field ablation has introduced a novel paradigm for myocyte injury during catheter ablation. Unlike conventional thermal ablation modalities, PFA employs high-intensity electric fields and is characterized by distinct mechanisms of cell death, unique histopathological features, and a different temporal course of lesion maturation. A comprehensive understanding of the *in vivo* processes underlying lesion formation after PFA, as compared with conventional thermal ablation, is essential to optimize both the safety and efficacy of this technology in clinical practice. In this section, we review the acute, subacute,

and chronic phases of the lesion formation following PFA and compare these findings with those observed after RFA.

Acute observations

The mechanisms of cell death induced by PFA are thought to include necrosis and apoptosis, among several other potential pathways.[34] However, the temporal evolution of these processes and their relative contribution to contemporary PFA waveforms used in cardiac ablation remain incompletely characterized. Compared with RFA, PFA is believed to preferentially induce non-thermal apoptosis-like delayed cell death, which renders PFA lesions difficult to identify immediately after energy delivery as no changes are observed macroscopically. Over the subsequent 2–4 h, PFA lesions gradually become discernible if a metabolic activity staining as triphenyltetrazolium chloride is used (*Figures 3A* and *4A*). This temporal evolution is also relevant for lesion assessment using intracardiac echocardiography (ICE). Unlike RFA, maximum echogenic changes cannot be visualized on ICE immediately after application and become progressively more apparent few minutes after PFA with a peak at up to 60 min (*Figure 3B*).[70] It has been suggested that at least 24 h are required for acute PFA lesions to fully mature, and an animal study has demonstrated that apoptosis becomes apparent by 6 h and peaks at 24 h post-ablation.[71] Consistent with these findings, clinical studies have reported that myocardial injury biomarkers reach their maximum levels within 3 h while NT-proBNP levels peaked at 24 h following PFA procedures.[77,78]

Histologic reports describing tissue changes within the first 1–2 h after PFA are limited. An important aspect to consider is that observed histological changes may differ between areas very close to the application catheter, where the electric field is maximum, and areas at a certain distance from it.[79] Available studies have noted that the most distinctive observation of PFA lesions is the almost immediate development of contraction bands and interstitial oedema accompanied by nuclear condensation, cardiomyocyte swelling, and inflammatory cell infiltration with some areas of myocardial necrosis and haemorrhage.[80,81] Electron microscopy studies have likewise demonstrated some distinct features of PFA lesions compared to RFA with basement membrane disruption, interstitial oedema, and bleeding notably reduced in comparison to the corresponding RFA. Other features such as nuclei deformation with condensed chromatin and changes in mitochondria (swollen with focal deposits and in clustered arrangements) were still apparent.[82,83] Compared with RFA, PFA lesions are associated with milder oedema, reduced intravascular erythrocyte accumulation, and less erythrocyte extravasation (*Table 1*). Notably,

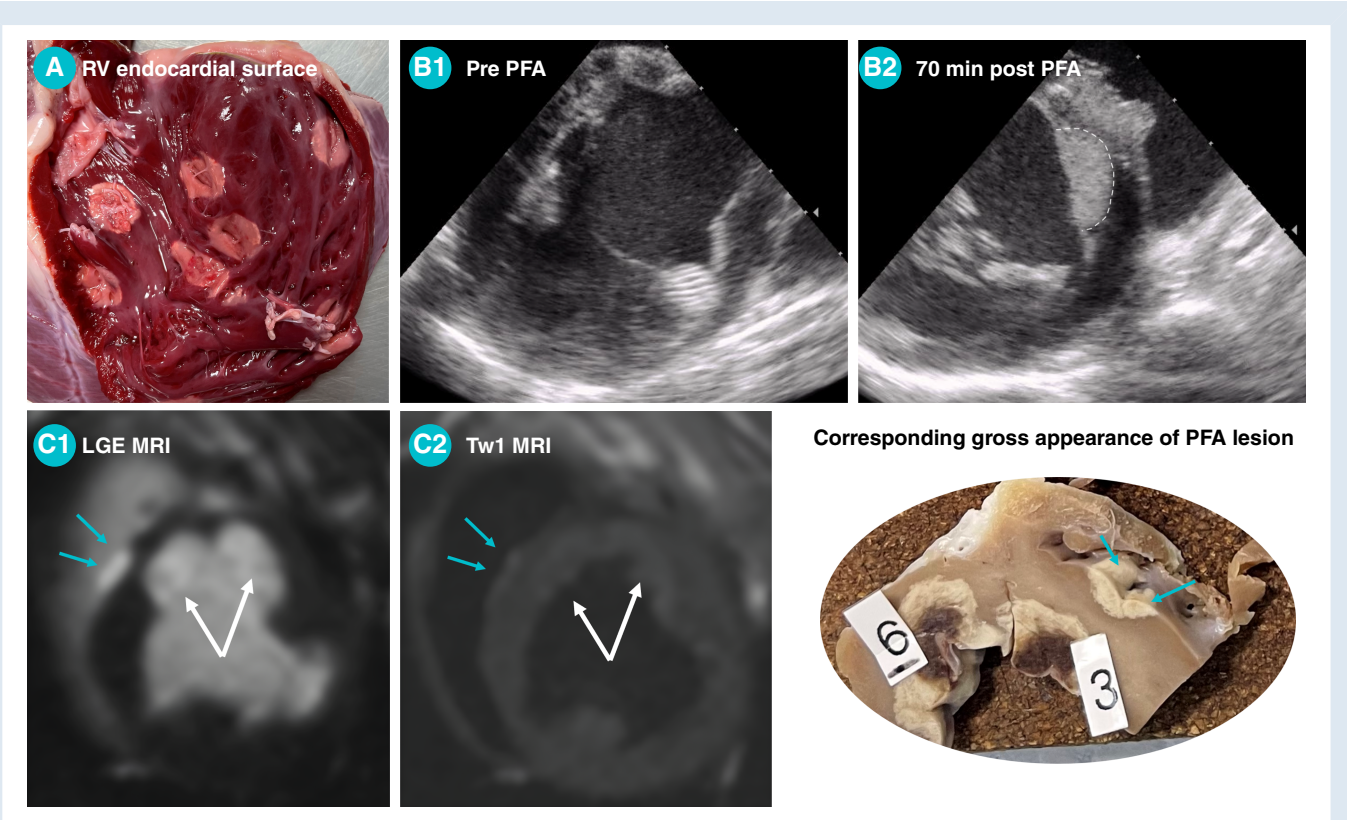


Figure 3 PFA lesions; histology, intracardiac echocardiography, and MRI. (*A*) Gross findings of PFA lesions on the right ventricular surface 24 h after PFA, stained with triphenyltetrazolium chloride. Uniform lesion formation is observed even in tissue with relatively developed trabeculae, with clearly demarcated borders. In addition, intralesional haemorrhage is minimal. Modified from ref.[59]. (*B*) ICE images obtained before PFA lesion formation and 70 min after PFA show a hyperechoic lesion becoming visible at 70 min. PFA lesions are difficult to visualize immediately after ablation on ICE. Modified from ref.[59]. (*C*) MRI images acquired 24–48 h after PFA demonstrate no obvious findings of microvascular obstruction in PFA lesions, with homogeneous late gadolinium enhancement and minimal enhancement on T1-weighted images. Black arrows indicate right ventricular lesions, and white arrows indicate left ventricular PFA lesions.

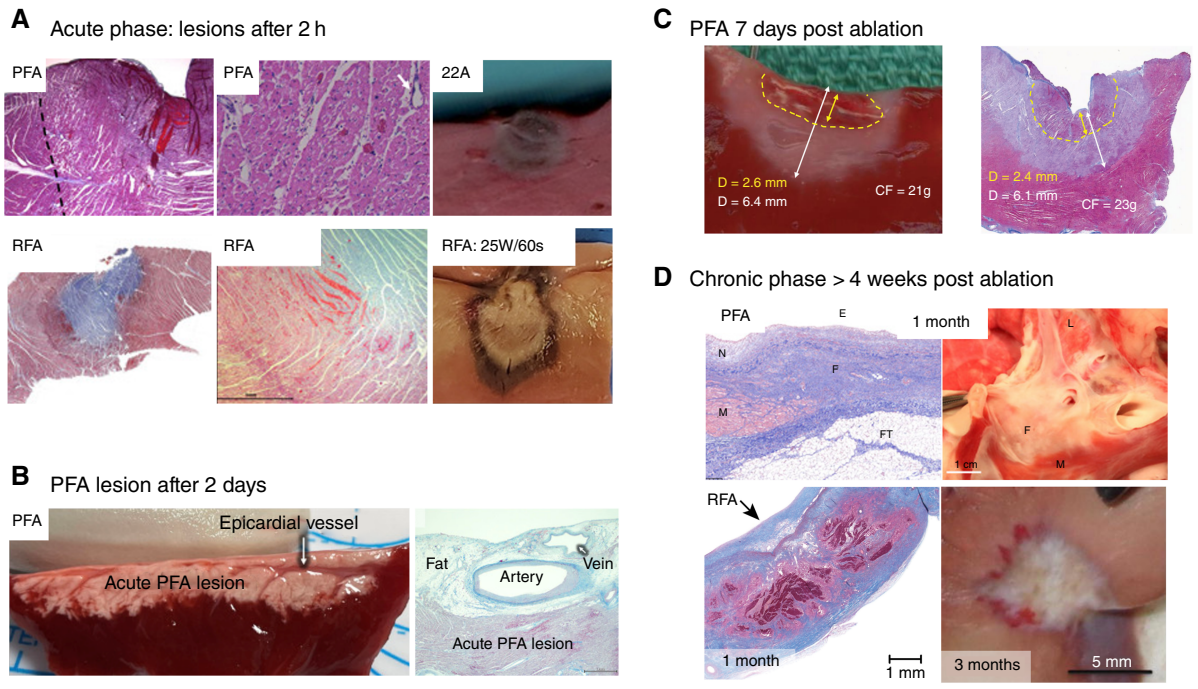


Figure 4 Different stages of lesion formation after PFA and RFA. (*A*) Acute phase: Histologic (left and middle) and macroscopic images (right) of PFA (monopolar, biphasic, top row) and RFA (bottom row) delivered via a 3.5 mm focal ablation catheter. Note the subtle macroscopic features of the acute PFA lesion as compared with the clearly demarcated coagulative RFA lesion. Histopathology shows well-demarcated non-coagulative acute myocardial damage in the ablated area (right of dashed line) with intact vessels (arrow). In contrast, histopathology of RFA lesions shows coagulation necrosis (blue) surrounded by haemorrhagic contraction band necrosis (dark purple). Modified from ref.[75]. (*B*) PFA lesion 2 days after epicardial delivery using a 9 mm lattice-tip catheter showing a homogeneous, sharply demarcated lesion with preservation of intralesional fat and blood vessels. Modified from ref.[59]. (*C*) Gross pathology (left) and histopathology (Masson's trichrome staining) of a PFA lesion created with an investigational 2.3 mm tip focal ablation catheter using an output of 2.0 kV. The lesion is composed of two areas. The central, shallower area (yellow dotted line) shows evidence of coagulative necrosis, indicating a minor thermal effect in the lesion's centre using this investigational catheter and ablation settings. The remaining, larger area of the lesion (white arrow) exhibits homogeneous fibrosis consistent with pulsed field ablation injury. ×20 magnification. Modified from ref.[89]. (*D*) Chronic phase >4 weeks post-ablation. The top row shows a PFA lesion at the opened RSPV macroscopically (right) and in histopathology (left) at 4 weeks post-ablation using a nine-electrode circular ablation catheter (bipolar PFA, 1.5 kV). Both images illustrate homogeneous replacement fibrosis. Histopathology confirms transmural fibrosis without residual necrosis or inflammation. In comparison, RFA lesions show islands of persistent cardiomyocyte necrosis in the lesion centre 4 weeks post-ablation (left). The black arrow indicates endocardial hyperplasia. The right image shows a fully mature RFA lesion 3 months post-ablation at gross necropsy. The lesion appears more inhomogeneous with a pale/brown lesion core with dense fibrosis, surrounded by a purple partially haemorrhagic rim. E, endothelium; F, fibrotic lesion; FT, fat tissue; L, lung; M, myocardium (untreated); N, neointima; RPSV, right superior pulmonary vein. Modified from refs [76,161,162].

even at the ultrastructural level, PFA lesions exhibit an abrupt transition in the degree of myocyte damage, reflecting the sharp demarcation characteristic of PFA-induced injury.[82] The state of increased cell membrane permeability after IRE can span from minutes to hours until cell death is observed.[84] Indeed, myocyte membrane structure and organelle structure progressively deteriorate by at least 4 h post-ablation in the electron microscopic study.[82]

Subacute observations

Radiofrequency ablation primarily induces coagulative necrosis as the dominant mechanism of cell death, which is followed by a marked inflammatory response characterized by macrophage infiltration and subsequent fibroblast proliferation. In contrast, PFA can also promote delayed cell death pathways such as apoptosis. Histological findings at 24–48 h after PFA application demonstrate reduced haemorrhage as compared to RFA, suggesting less extensive vascular damage[85] (*Figures 3A* and *4B*). Lesion borders were well-demarcated, with immunohistochemical analysis at 48 h showing an abrupt loss of troponin I expression at the lesion margins, along with blurring of cell membrane staining.[59]

Inflammatory response also evolves with time, with inflammatory cells such as lymphocytes, macrophages, and multinucleated giant cells observed in 7-day samples and reduced over time.[86] Seven days after PFA using an investigational 2.3 mm focal ablation catheter with moderate contact force, lesions displayed a large area of homogeneous collagenous replacement fibrosis with a shallow central zone identified as potential thermal injury (*Figure 4C*).[73] In an animal study

Table 1 Comparative summary of main histological findings between PFA and RFA at 1 and 4 h after ablation

	1 h PFA	1 h RFA	4 h PFA	4 h RFA
Cardiomyocyte disruption	++	+	+++	++
Mitochondria misalignment, swelling and focal deposits	+	+	++	++
Membrane disruption	+	+	+	+++
Oedema	+	++	++	++++
Intravascular erythrocyte accumulation	–	+	–	+++
Extravasation of erythrocyte	–	+	–	+++

(+) and (–) symbols indicate presence or absence of specific findings.
PFA, pulsed field ablation; RFA, radiofrequency ablation.

comparing tissue inflammation between RFA and PFA at 2–4 weeks after ablation, inflammation within PFA lesions has been demonstrated to be substantially milder as compared to RFA. Parameters including necrosis, inflammation, oedema, haemorrhage, and thrombus formation were more frequent and severe in RFA lesions.[87] In contrast, PFA lesions evolve into homogeneous fibrotic tissue without residual viable myocardium, while non-myocardial structures such as blood vessels and nerves are preserved (*Figure 4B*).[87] Mineralization is also a common observation at subchronic timepoints, suggesting an inflammatory response to calcium-rich cell debris.[85,86]

On cardiac magnetic resonance imaging, PFA also displays distinct features suggesting different tissue damage and healing processes. RFA lesions typically exhibit high signal intensity on T1-weighted images due to iron oxidation induced by thermal injury (oxidation of ferrous (Fe^{2+}) to ferric (Fe^{3+}) iron within haemoglobin and myoglobin occurs at temperatures of 55–65°C, whereas this finding is less pronounced in PFA lesions (*Figure 3C*). With gadolinium-enhanced imaging, RFA lesions often demonstrate microvascular obstruction because vessels are occupied by erythrocytes, whereas PFA lesions more frequently show homogeneous late gadolinium enhancement (*Figure 3C*).[62,88]

Chronic observations

Histologically, mature lesions represent sharply demarcated, homogenous areas of replacement fibrosis with preserved tissue architecture and spared non-myocardial structures such as nerves and blood vessels. Preclinical studies have demonstrated that PFA lesions are mostly mature by 3 weeks post-ablation, only showing a further increase in collagen density at later time points.[80] In contrast, RFA produces more extensive central tissue damage, where coagulation necrosis and non-selective protein denaturation disrupt tissue architecture and vasculature. Consequently, RFA lesions often mature into less homogeneous scars with chronic inflammation and persistent necrosis present even at 1 month post-ablation (*Figure 4D*).[89] Compared with thermal ablation, a limited inflammatory response is observed that typically resolves within 30 days after PFA in preclinical models.[86]

Tissue contraction during scar formation after RFA is a well-recognized cause of PV stenosis when ablation is performed within the PVs. In contrast, due to its non-thermal mechanism, preservation of extracellular matrix and distinct inflammatory response, PFA has not been associated with PV stenosis, even when applied deep within the PVs in preclinical studies.[90] PFA has been reported to induce less PV fibroblast proliferation compared with thermal energy-based ablation.[91,92] These favourable safety findings have been confirmed in large clinical registries.[93] In light of these data, direct ablation of arrhythmogenic myocardial sleeves within the PVs has recently been reintroduced in novel PFA protocols to improve PVI durability.[94] However, the safety of PFA for PV stenosis in patients with a prior history of thermal ablation, particularly in those who have already developed PV stenosis as a consequence of previous thermal energy delivery, requires further investigation.[95] Furthermore, the reversible 'stunning effect' after PFA raised questions about potential lesion regression during maturation. However, clinical data from invasive remapping studies demonstrate that lesion size, as assessed by low-voltage areas in 3D electroanatomical mapping, does not significantly decrease until 3 months after PFA using a pentaspline catheter.[96]

Post-ablation inflammation and remodelling processes are integral to injury healing and lesion maturation but may trigger early arrhythmia recurrences that do not necessarily predict long-term outcomes. Traditionally, arrhythmia recurrences during the so-called 'blanking period' have not prompted long-term treatment decisions such as repeat ablation. This blanking period was historically defined as the first 3 months following ablation, although recent guidelines recommend shortening it to 8 weeks.[97] This new definition has also been challenged, as arrhythmia recurrences occurring more than 1 month after thermal ablation strongly predict poor long-term success.[98] The advent of PFA, with its reduced inflammatory response and rapid lesion formation, provides further rationale for a more nuanced definition of the blanking period, as the timing and significance of early recurrences may differ following PFA.[98]

Part II: PFA effects on nerves

Effects of PFA on nerves

During PFA treatments, nerve structures surrounding the target ablation area can potentially be exposed to relatively high electric field intensities due to their relative anatomical position with respect to cardiac tissue.

Biophysics of PFA effects on nerves

The two most important effects that PFA can exert on nerves are either electrical stimulation or electroporation (reversible or irreversible). The mechanism in both cases is that an externally applied electric field induces a transmembrane potential distribution along the axons; wherever the local transmembrane potential exceeds the stimulation threshold for a sufficient time, the axon is stimulated; wherever it exceeds the electroporation threshold, electroporation occurs (see *Figure 5*).[99,100] The most important difference between these two phenomena is the minimum electric field necessary to induce one or other effect (the electric field threshold) being the threshold for stimulation considerably lower than the threshold required for electroporation.

Nerves contain multiple fibre bundles, which are in turn composed of individual nerve fibres. Each nerve fibre contains an axon, i.e. a long, slender cellular extension of a neuron optimized for electric signal conduction. For faster signal transduction, many axons are enveloped in myelin sheaths, except at isolated nodes of Ranvier, and this anatomy affects their response to the high-amplitude fields that are applied during PFA. Like cardiomyocytes, or other excitable cells, axons are excited when their membrane is depolarized to the point at which the

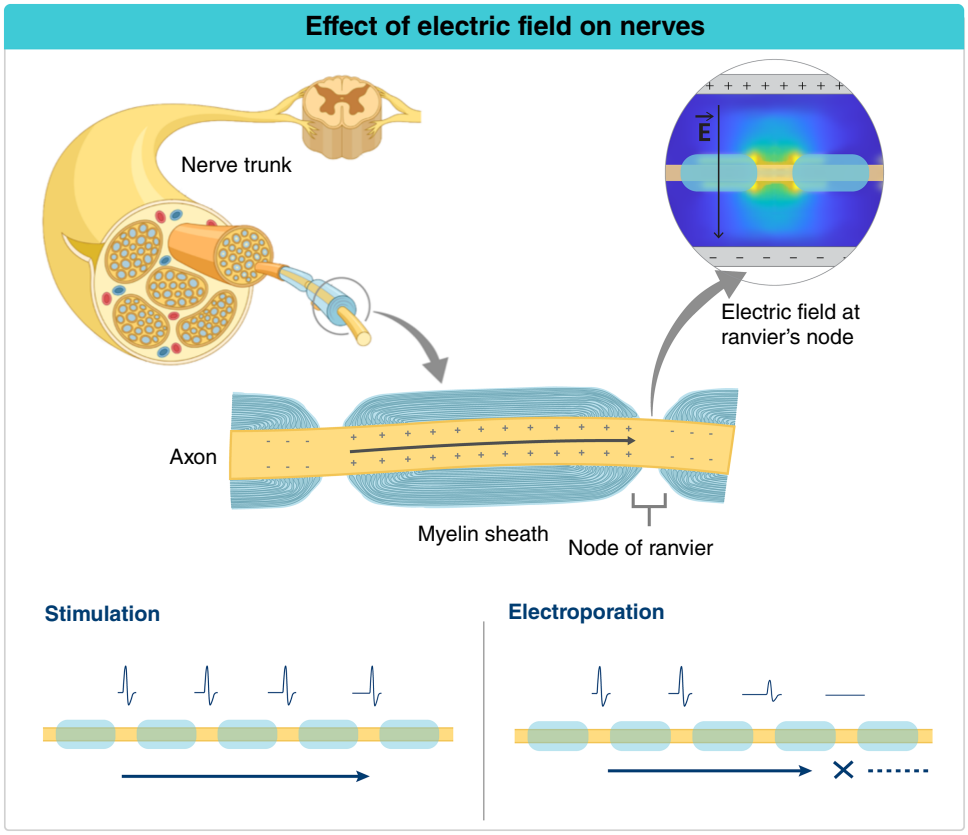


Figure 5 Schematic representation of the interaction of an electric field with a myelinated axon. Electric field concentrates in the unmyelinated areas leading to depolarization and stimulus propagation or local cell membrane electroporation leading to a possible transient conduction block.

voltage-gated channels open. Since multiple axons run in parallel to the same destination, there can be a graded effect depending on the distance from the high electric field source ranging from electrical stimulation producing recruitment of axons to electroporation potentially producing partial nerve block. Another important factor to consider for long nerve fibres is electric field direction with respect to the fibre. The transmembrane voltage induced by an electric field in the direction of the fibre is much higher than the transmembrane voltage induced by a transverse electric field. However, the membrane charging time is also significantly longer for longitudinal orientations.[101] For long-duration electric field pulses, longitudinal orientation is more effective to excite long fibres but when pulse duration is below a certain value (< 100 ns) the transverse orientation can be more effective at generating action potentials with a lower electric field intensity.

Stimulation

When considering off-target neuromuscular side effects of PFA, inadvertent stimulation of myelinated nerve fibres is of particular concern because myelinated axons exhibit lower extracellular stimulation thresholds and are preferentially excited by high spatial gradients of applied electric fields.[102,103] Activation of these fibres mediates acute, readily apparent effects, such as sharp pain and skeletal muscle contraction, through recruitment of fast sensory and motor axons.[104,105] In contrast, unmyelinated autonomic fibres generally exhibit higher activation thresholds and slower conduction velocities, and their activation typically produces delayed or less immediately perceptible physiological effects.[102,106]

Myelin has a high electrical resistance and low capacitance, which markedly attenuate transmembrane polarization along internodal regions; as a result, myelinated axons are largely insulated from externally applied electric fields except at the nodes of Ranvier, where myelin is absent.[102,107] At the nodes of Ranvier, geometric concentration of transverse current leads to enhanced induced transmembrane voltage, while voltage-gated sodium channels are clustered at densities orders of magnitude higher than in internodal membranes.[104,108] Consequently, extracellular electrical stimulation of myelinated axons is generally initiated at nodes of Ranvier.[103,104]

Experimental studies have demonstrated that peripheral nerves can be stimulated using a wide range of pulse durations and waveforms. Classical nerve stimulation has most commonly employed millisecond- to hundreds-of-microsecond-duration pulses.[104] However, repeated stimulation can also be achieved with short microsecond pulses[102] and even pulses as short as 12 ns, without any apparent damage.[109]

Electroporation

Like any other lipidic bilayer, the cell membrane of nerves can also undergo electroporation if the local electric field is high enough to exceed the electroporation threshold. Theoretically,

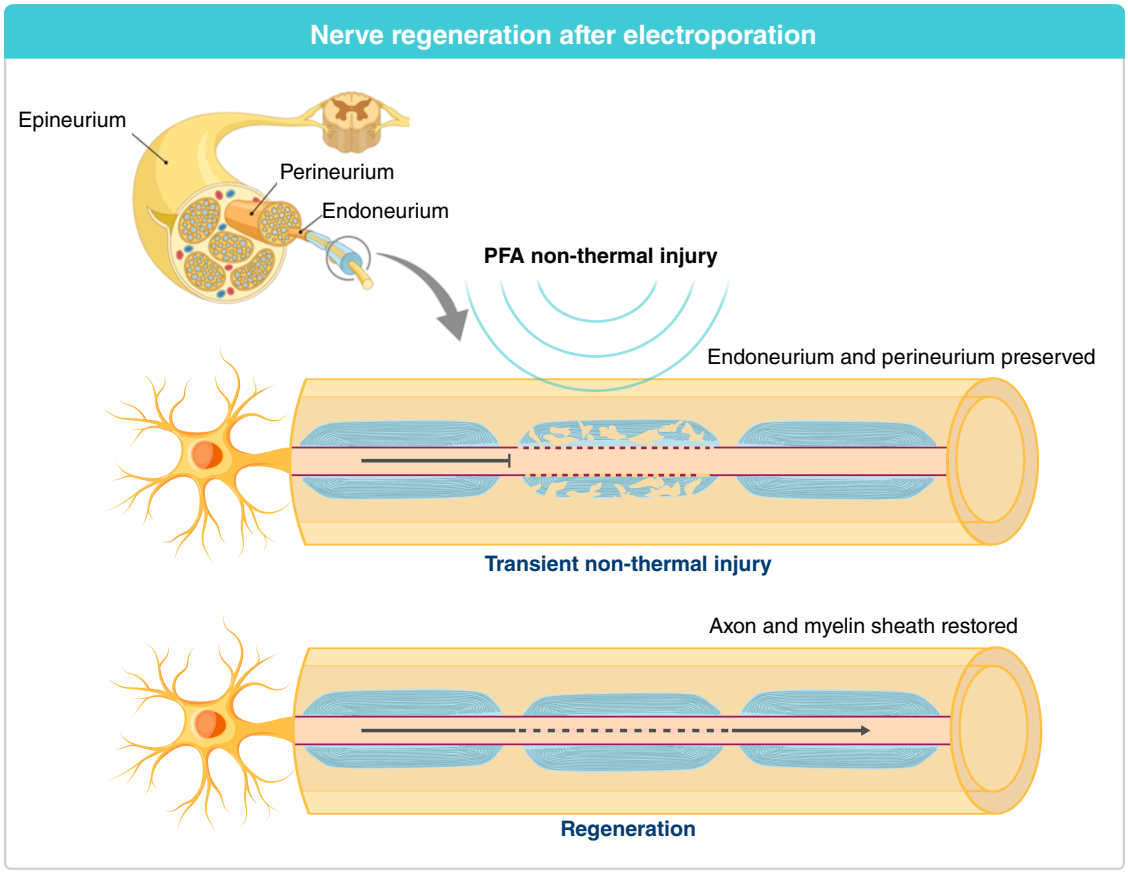


Figure 6 Possible nerve regeneration mechanisms after electroporation. Axons and myelin sheath can be transiently disrupted after exposure to very strong electric fields. However, nerve structures such as the endoneurium and perineurium are not thermally damage in PFA enabling subsequent nerve regeneration mechanisms and nerve function restoration.

different effects could be expected in different areas of nerves based on local membrane curvature, size, and electrical field distribution. In this sense, the soma (cell body) of neurons should display a higher vulnerability than the axons. However, there is no solid experimental evidence demonstrating this. In myelinated axons, the myelin sheath markedly attenuates transmembrane polarization along internodal regions, externally applied electric fields also preferentially polarize nodal membranes, rendering nodes of Ranvier the most susceptible sites for electrically induced membrane perturbation, including electroporation, in myelinated axons.[102,103,110] This nodal vulnerability reflects both the absence of myelin and the concentration of electric stress at discrete, highly excitable membrane regions (see *Figure 5*).[103] Consequently, electroporation of axons is expected to be a localized phenomenon occurring preferentially at the nodes of Ranvier more than a generalized effect across the entire membrane of the axon.

The state of increased permeabilization of the cell membrane due to electroporation can produce nerve conduction abnormalities, transient nerve dysfunction has been reported including nerve conduction velocity reduction without complete nerve block, with spontaneous recovery observed in clinical case reports.[111–113] Reversible electroporation typically resolves within minutes to hours as membrane integrity is restored,[23] and more extensive yet non-degenerative membrane disruption involving multiple nodal or paranodal regions may recover over days to weeks.[49]

Permanent structural nerve injury is generally associated with more extensive or sustained membrane damage, which may extend beyond isolated nodal membranes to involve multiple adjacent nodes and/or disrupt paranodal axo-glial junctions and myelin integrity.[114] Such disruption can compromise ionic homeostasis and axonal transport, ultimately leading to axonal degeneration, including Wallerian degeneration in severe cases with subsequent regeneration.[49,115,116] Experimental observations have described preservation of endoneurium and epineural extracellular matrix architecture and proliferation of Schwann cells suggesting the potential for axonal regeneration at later stages as observed in different studies (see *Figure 6*).[49,115] These observations are radically different to what is observed in thermal ablation modalities, where nerve extracellular nerve structures can also be damaged.

Effects of PFA on the phrenic nerve

Among the different nerve structures that may be affected by PFA, the phrenic nerve is particularly relevant, especially in AF ablation because of its anatomical proximity to the right PVs and the superior vena cava. In the context of thermal ablation technologies, the term phrenic nerve injury (PNI) has traditionally been used to describe any alteration in phrenic nerve

function, whether transient or permanent. With the emergence of non-thermal PFA, it may be appropriate for the scientific community to reconsider the continued use of the term injury. This terminology implies structural damage to the nerve, which may not accurately reflect the mechanisms associated with PFA. Consequently, alternative terminology—such as phrenic nerve dysfunction—may better characterize functional alterations observed with this technology.

Transient effects

The most common effect observed on the phrenic nerve during PFA procedures is electrical stimulation. Electric field intensities above the simulation threshold can reach the phrenic nerve particularly in the right PVs where the distance between the catheter and the phrenic nerve is lower. Local nerve stimulation can lead to abrupt diaphragmatic contractions during each PFA application without further clinical implications. However, studies have also reported a very low incidence of other transient phrenic nerve conduction disturbances.

Observations with traditional thermal ablation have reported transient effects on the phrenic nerve, displaying temporary conduction block with either immediate intraprocedural or delayed recovery within days to weeks. The transient nature of these effects for the specific case of cryoablation has been mainly attributed to local axonal conduction block without structural axonal disruption due to direct cooling of the phrenic nerve due to thermal spread.[117] Other suggested mechanisms include transient reduced blood supply to the nerve due to microvascular constriction or injury.[118] Also, local inflammation and tissue oedema may compress or irritate the phrenic nerve producing delayed effects.[119]

In the case of PFA, transient effects on the phrenic nerve leading to temporary conduction block have also been reported. Due to the completely different nature of PFA energy, the behaviour and mechanisms behind the observed transient effects are also different. First, according to clinical observations, the dynamics of recovery seem to be much faster than for thermal injury. Detailed compound motor action potential characterization revealed a rapid recovery phase 1–2 min after PFA applications with complete (53%) or partial (47%) signal recovery without X-ray changes in either case.[120] Preclinical data also showed similar recovery dynamics in swine in a dose–response manner.[121]

The most plausible mechanism explaining the rapid transient effects observed after PFA is reversible electroporation. Electroporation will create a state of high membrane permeability of axons producing a transient electrical conduction block. Reversible electroporation generally resolves within seconds to minutes, although in some experimental observations it may persist for several hours,[23,122,123] which appears to be consistent with the observed time course of phrenic nerve functional recovery. Once cell membrane reseals, local conduction capability is restored without any other relevant structural changes to the nerve. Although not experimentally proven, other alternative mechanisms such as oedema or transient inflammation cannot be ruled out as contributing factors to some more durable, still transient, observations which may not be possible to explain by reversible electroporation.

Chronic effects

Traditional thermal ablation technologies have demonstrated that permanent PNI is an important complication to consider when evaluating new ablation technologies with persistent damage, leading to hemidiaphragmatic paralysis, occurring in about up to 0.3–1.5% of cases depending on the technology used.[124,125]

In the context of PFA, the incidence of permanent phrenic nerve paralysis appears to be extremely low based on current clinical trials and large registries with only isolated case reports described. Preclinical work already suggested this low vulnerability of the phrenic nerve to PFA acutely with no chronic damage observed.[121,126,127] However, more recent preclinical literature with the ballon-in-basket PFA catheter reported some instances of minimal axonal degeneration with multifocal myelin sheath and axonal swelling at 34 ± 4 days even without noticeable functional impact.[128]

Clinical data have also shown the remarkable safety profile of PFA. In the MANIFEST-PF registry including 1568 patients ablated with the pentaspline catheter, only one case of persistent PNI was reported (0.06%).[129] Similarly, the large MANIFEST-17 K study involving more than 17 000 patients reported no cases of permanent PNI and only 0.06% transient phrenic nerve dysfunction.[130] A recent case report described persistent right phrenic nerve palsy after PVI, presenting with dyspnoea and elevation of the right hemidiaphragm detected shortly after the procedure and persisting 8 weeks post-procedure without subsequent follow-up information.[131] Another report highlighted a similar complication with a circular PFA catheter attributed to an ablation delivered in close proximity to the pericardiac phrenic bundle.[132] These cases suggest that although the phrenic nerve may be significantly less susceptible to PFA effects, permanent phrenic nerve dysfunction may occur even at extremely low rates.

Practical clinical considerations

The potential effects of pulsed electric fields on the phrenic nerve largely depend on the cumulative electric field dose to which the nerve is exposed. Basically, this will be defined by the electric field strength, the total number of applications that may overlap in a certain region, and importantly, by the intrinsic waveform characteristics of each particular PFA system. Thus, comparing the safety profile of different PFA systems on the phrenic nerve based on simple variables as the output voltage or distance is not possible and robust clinical data should be the standard to compare.

From a clinical practice perspective, it seems extremely challenging to generalize best practices for phrenic nerve safety. Some current PFA systems do not include any specific phrenic nerve safety recommendations, while others recommend reducing output voltage or catheter repositioning to mitigate potential risks. Overall, it seems reasonable to think that as the observed effects follow dose–response behavior, being mindful of catheter position and being vigilant of acute responses could be adopted as general phrenic nerve safety best practices.

Specific effects of PFA on the cardiac ganglionated plexi

Introduction

In this section, the effects of PFA on the autonomic nervous system will be analysed. Across studies, a consistent phenotype emerges: vagal reactions are common during PVI, whereas durable autonomic denervation surrogates—resting heart rate (HR) increase and heart rate variability (HRV) suppression—are smaller than with thermal energy;[133–137]

A key challenge in the available literature is that ‘autonomic effects’ are frequently treated as a single construct. Here, three related but non-equivalent outputs are separated:

(1) Acute vagal reactions during energy delivery [bradycardia, asystole, atrioventricular (AV) block], which can reflect stimulation/reflex activation or transient stunning;[134]

(2) Durable intrinsic cardiac autonomic nervous system (ICANS) injury/denervation, typically inferred indirectly via resting HR/HRV and/or denervation-associated biomarkers;[135] and
(3) Targeted ganglionated plexus (GP) modulation/ablation efficacy, best supported by physiological endpoints [e.g. abolition of high-frequency stimulation (HFS) responses, changes in effective refractory period [ERP] or inducibility] and histology when available.[135,138,139]

It is important to highlight that PFA is not a uniform intervention, as factors such as waveform, catheter design, pulse number, and tissue contact can significantly influence its biological effects. Comparative statements between PFA and thermal energy should be obtained, when possible, in randomized data (e.g. ADVENT autonomic subanalysis) or direct PFA-vs.-thermal biomarker comparisons.[135,139]

Acute vagal responses during PFA application

In contemporary clinical practice, acute vagal reactions during PFA are frequent, sometimes dramatic, and generally manageable. Acutely, vagal reactions typically occur immediately during or shortly after energy delivery and are usually self-limited. Several constraints limit interpretation of the vagal responses produced by PFA across studies: non-uniform definitions of 'vagal response,' heterogeneity in anaesthesia, analgesia, and anticholinergic use, and reliance on surrogate autonomic markers rather than direct neural histology in humans.

For example, one of the biggest multicentre prospective studies using the pentaspline catheter predefined clinically relevant vagal responses as sinus bradycardia <40 bpm, asystole >6 s, AV block, or the need for temporary backup pacing. This registry reported intraprocedural vagal reactions in 27.1% of cases overall. Importantly, in the absence of anticholinergic prophylaxis, reactions occurred in 62.5% of patients, while prophylactic administration markedly reduced event rates: glycopyrrolate (0.2 mg IV) lowered reactions to 7.5%, while atropine (1 mg IV) reduced reactions to 11.3%. Glycopyrrolate was associated with fewer drug-overdose-related adverse events, whereas atropine was more frequently linked to adverse effects, including drug-induced AF.[134]

Mechanistic interpretation. Current evidence favours acute parasympathetic ganglion activation or stimulation, possibly followed by transient post-stimulation refractoriness, rather than permanent vagal denervation as the primary mechanism underlying these reactions. Similar to other nerve structures such as the phrenic nerve, electrical stimulation during PFA deliveries can occur on the surrounding vagal system without associated tissue damage. Supporting this interpretation, biomarker studies comparing PFA with cryoballoon ablation demonstrated substantially lower S100 protein release with PFA indicating less neural damage.[139] In addition, a pilot clinical study (n = 18) reported no persistent changes in autonomic tone or nerve injury biomarkers ~30 days after PFA-based PVI, consistent with limited durable autonomic injury in at least some patient cohorts.[140]

Some case reports have illustrated that prolonged pauses may occur after PFA despite anticholinergic treatment. One report described more than 48 s of atrial asystole following an RSPV application, with subsequent spontaneous recovery. The authors attributed this to transient vagal stimulation near right-sided vagal pathways and emphasized the need to better delineate sinoatrial and AV nodal vulnerability during PFA.[141] Reversible electroporation could also explain some of these prolonged observations.

Clinical implications. *Table 2* summarizes the main findings from clinical studies reporting vagal reactions. The available evidence supports (i) routine readiness for temporary backup pacing and consideration of anticholinergic prophylaxis, favouring glycopyrrolate when appropriate; (ii) procedural strategies that prioritize RSPV isolation to reduce pause burden because vagal events' frequency depends strongly on lesion sequencing and PV location, consistent with anatomically clustered parasympathetic inputs[133]; and (iii) heightened caution in patients with baseline nodal disease or in those susceptible to atropine-related proarrhythmia.

Durable effects of PFA on ganglionated plexi and the intrinsic cardiac autonomic nervous system

The ICANS is organized around epicardial fat pads containing ganglionated plexi (GP), which integrate parasympathetic and sympathetic signalling and can facilitate AF initiation and maintenance. In thermal ablation (radiofrequency or cryoballoon), GP modulation or denervation may have an ancillary effect of PVI that may contribute to symptomatic improvement and possibly rhythm outcomes,[135] while other studies failed to show any improvement.[143]

Evidence. *Table 3* provides a summary of the main studies addressing the effects of PFA in the ICANS. The most direct human evidence that routine PVI with PFA causes limited durable GP ablation comes from a mixed retrospective–prospective study that physiologically mapped GP sites using HFS and then retested them after PFA-PVI. Resting HR increased at 3 months after radiofrequency and cryoballoon ablation but was essentially unchanged after PFA, implying less sustained autonomic denervation with PFA.[137,138] In the same work a detailed substudy suggested that most GPs remained functional even when they were likely within or adjacent to the ablation footprint.[138]

Additionally, another study that compared the effects on nerves of PFA vs. cryoballon, demonstrated that neural damage biomarker S100 increased in both groups but was substantially lower with PFA. Importantly, vagal responses during PFA were not linked to higher S100 release, supporting the concept that acute pauses are not simply a marker of 'more denervation'.[139]

Finally, the ADVENT autonomic subanalysis provided a higher-level evidence (randomized dataset) that durable autonomic denervation was attenuated with PFA compared with thermal ablation: HR increase and HRV suppression were greater in the radiofrequency/cryoballoon arms than in the PFA arm at 6 and 12 months. Taken together, these data support the conclusion that PFA translates into less chronic autonomic perturbation, despite frequent acute vagal reactions.[135]

Mechanisms. There are several potential mechanisms explaining reduced effects of PFA on GP. The two main constraints are geometry (distance) and tissue threshold. GPs are epicardial and often embedded in fat. Endocardial PVI lesions (even when 'wide antral') may not generate sufficient electric field strength at GP depth to exceed neural electroporation thresholds, even if adjacent myocardium is ablated at lower thresholds. This was observed in early preclinical work, which noted that endocardial PFA had limited impact on epicardial GPs owing to distance, whereas epicardial delivery might be effective.[146] Also, a potential mechanism is neural regeneration after electroporation injury suggesting that even when neural elements are affected, durable denervation may not be guaranteed.[148]

GP-related effects time course can be framed as follows:

- Early post-procedure (hours–days): transient modulation or stunning may occur (e.g. sequence effects reducing subsequent vagal

Table 2 Summary of the main findings from clinical studies reporting vagal reactions.

Study	Study type/ model	Sample size	PFA system and parameters reported	Endpoints	Main findings
Giampaolo Vetta *et al.* 2025[136]	Clinical (multicentre prospective)	240 patients	Pentaspline PFA catheter; prophylactic glycopyrrolate vs. atropine vs. none	Incidence of clinically relevant vagal reactions; drug adverse events	Vagal reactions in 27.1% overall; without prophylaxis: 62.5% (asystole 33.8%, pacing 23.8%); prophylaxis reduced reactions to 7.5–11.3%; atropine associated with more drug-related adverse events and drug-induced AF
Alvise Del Monte *et al.* 2024[135]	Clinical (prospective cohort)	80 patients	Pentaspline PFA catheter. PFA-PVI with extracardiac vagal stimulation testing; left superior pulmonary vein (LSPV)-first vs. right superior pulmonary vein (RSPV)-first sequencing	Vagal response incidence; pacing requirement; acute HR change	Vagal responses in 78% with LSPV-first vs. 13% with RSPV-first; pacing 35% vs. 8%; no residual HR or extracardiac vagal stimulation (ECVS) change at procedure end
Christopher Kowalewski *et al.* 2024[146]	Clinical (mechanistic; preprint)	24 patients	Pentaspline PFA catheter. transjugular vagal stimulation (TJVS) before/after each PV; PV order randomized	TJVS-induced sinus pause and AV block duration; pause frequency by PV order	RSPV isolation produced the largest reduction in TJVS-induced pauses and AV block; LSPV applications associated with more pauses; findings support a parasympathetic mechanism involving right-sided GP regions
Anna-Sophie Eberl *et al.* 2023[143]	Clinical (case report)	1 patient	Pentaspline PFA (RSPV application); atropine administered	Rhythm effects during PFA	Prolonged but reversible atrial asystole (>48 s) during PFA; favoured transient vagal stimulation near right vagal pathways

PFA, pulsed field ablation.

response burden), but durable 'denervation endpoints' are usually not met in endocardial PVI practice.[133]
- Delayed (months): compared with thermal ablation, autonomic profile changes (HR increase, HRV reduction) are smaller after PFA, implying less durable autonomic remodelling/denervation in typical PVI workflows.[135]

Feasibility in a clinical setting. Given the above mechanistic explanation, targeted GP ablation with PFA in a clinical setting becomes more plausible in two scenarios:

- Endocardial PFA with dedicated GP-focused dosing and strategy. Preclinical data provide early signals that endocardial PFA can partly blunt vagal reflexes and modify nodal electrophysiology, but results are variable and appear to depend on the extent and number of application sites. In a porcine model, investigators defined a positive vagal response as >15% HR drop and delivered bipolar PFA at GP sites; vagal responses improved in 3/7 (trend) and AV nodal ERP improved, but complete elimination was not achieved.[144] Increasing the number of sites and lesions correlated with greater reduction in HR drop; the authors concluded that at least 3 sites and 10 lesions across both atria were needed for an 'adequate' vagal response decrease.[145]
- Epicardial PFA directly applied to GP sites. This setting provides the most convincing mechanistic evidence. In an open-chest pig model targeting five epicardial GP sites, epicardial bipolar PFA increased atrial ERP, reduced AF inducibility (100% → 33%) and AF duration, and demonstrated decreased S100 protein intensity within GP cytoplasm/membrane (interpreted as acute GP damage) while sparing surrounding arteries and sympathetic network.[146] That pattern, functional autonomic modification without obvious atrial myocardial electrogram loss, suggests that epicardial PFA could be used for 'cardioneuroablation'.

The NEURAL AF study (single-arm prospective during CABG) showed feasibility and acute physiologic effect of PFA in GPs: 24 patients underwent epicardial GP ablation with pulsed-field energy, yielding ~20% atrial ERP prolongation and a rise in mean HR, without significant HRV change at 1 month.[147]

However, several constraints are particularly relevant for assessing the long-term effects of PFA on the GP:

- Endpoint ambiguity: abolition of an HFS response, resting HR increase, and biomarker release are related but non-equivalent endpoints; they can diverge.[138]
- Access and anatomy confounding: endocardial vs. epicardial delivery fundamentally changes electric field distribution; open-chest pig models may overestimate feasibility relative to percutaneous human epicardial access constraints.[146]
- Dose heterogeneity: 'PFA' is not a single dose; waveforms, electrode geometry, pulse counts, and field strength vary across systems, limiting generalization.[144,145]

To conclude, PFA-PVI should not be expected to confer the same 'bonus denervation' often attributed to thermal ablation. If a clinical hypothesis relies on GP ablation (e.g. vagal AF or vasovagal syncope-oriented cardioneural ablation), current

Table 3 Summary of the main studies addressing the effects of PFA in the intrinsic cardiac autonomic nervous system.

Study	Study type/Model	Sample size	PFA system and parameters reported	Endpoints	Main findings
Daniel R. Musikantow *et al.* 2023[140]	Clinical (retrospective + prospective physiological mapping)	Retrospective: 120 (40 per energy); Prospective PFA: 20	Pentaspline PFA; HFS-defined GP mapping pre/post;	HR change at 3 months; HFS vagal response persistence; GP site involvement	HR rose after radiofrequency (RF) and cryo but not PFA; post-PFA HFS reproduced vagal effects at 76% of tested GP sites, supporting minimal durable GP ablation with PFA-PVI
Shota Tohoku *et al.* 2023[141]	Clinical comparison (PFA vs. cryoballoon)	97 (PFA 54; cryo 43)	Pentaspline PFA Serum S100 measurements pre/post; cerebral MRI to address CNS confounding	Denervation-relevant biomarker (ΔS100); relation to vagal response	S100 rose in both but markedly lower with PFA; vagal responses during PFA not associated with S100 release; supports less nervous tissue destruction with PFA vs. cryo
Naoto Otsuka *et al.* 2024[147,149]	Preclinical-experimental (swine; endocardial PFA for GP)	7 animals	Non-commercial bipolar PFA at GP sites; 1500 V/400 ms or 1250 V/300 ms; 50 pulses; anatomy + fractionated potentials used to localize sites	HR-drop response to vagal stimulation; AV nodal ERP	Partial vagal response improvement (subset); stronger effects with more sites/lesions; suggested threshold of ≥3 sites and ∼10 lesions across both atria for adequate reduction
Julie Norup Hertel *et al.* 2025[144]	Preclinical-experimental (open-chest pig; epicardial GP targeting)	PFA 6; sham 2	Non-commercial saline-irrigated bipolar epicardial PFA guided by HFS response	aERP, AF inducibility/duration, histology (S100-protein in GP)	Increased aERP, reduced AF inducibility/duration; decreased GP S100-protein intensity (acute GP damage) with sparing of adjacent arteries/sympathetic network and no local electrogram amplitude loss
NEURAL AF trial, 2025[150]	Clinical (during CABG; epicardial GP ablation)	24 patients	Non-commercial Epicardial PFA system. GP ablation during surgery;	Change in AERP; HR/HRV; safety	Feasible and safe; ∼20% AERP prolongation; HR increased; no

Continued

Table 3 *Continued*

Study	Study type/Model	Sample size	PFA system and parameters reported	Endpoints	Main findings
					significant HRV changes at 1 month; needs randomized validation
ADVENT autonomic subanalysis, 2024[137]	Clinical (randomized trial subanalysis)	379 patients	Pentaspline PFA vs. thermal (RF or cryo); HR from ECG; HRV from 72 h Holter at 6/12 months	Change in HR and HRV at 6/12 months	Thermal ablation produced larger HR increases and greater HRV reduction than PFA; RF and cryo similar within the thermal arm

GP, ganglionated plexi, HFS, high-frequency stimulation; HR, heart rate; HRV, heart rate variability; PFA, pulsed field ablation.

evidence suggests that standard endocardial PFA-PVI is unlikely to be sufficient, and that dedicated strategies, potentially epicardial, are required and remain investigational.[138] Conversely, attenuated durable denervation may be beneficial by reducing unwanted long-term vagal impairment syndromes, but this remains an inference requiring prospective testing.[135]

Part III: PFA effects on the conduction system

Effect of PFA on the conduction system

The effects of PFA on the conduction system, and specifically on the atrioventricular node (AVN) and AV conduction properties are nowadays still a topic of active research as many mechanisms remain unclear. When considering conduction system effects of PFA, it is essential to separate phenomena that may appear similar on surface ECG but have distinct mechanisms and implications:

- Vagally mediated nodal block (functional, common during PVI, usually preventable and caused by transient reversible electroporation) or stunning of conduction system structures (often reversible and dose-dependent).[149]
- A rare and yet to be proved potential mechanism related to ischaemia-mediated conduction disturbance from proximity-related coronary spasm during non-PV PFA (rare, but potentially severe).[130,136]
- Irreversible electroporation leading to permanent ablation of conduction system structures.

Transient observations

Most reports using PFA near different structures of the conduction system demonstrate the possibility of triggering transient conduction disturbances. Effects observed can greatly vary from study to study. For example, a recent clinical study proposed that PFA delivery close to the AVN for the treatment of atrioventricular nodal re-entrant tachycardia (AVNRT) was safe,[150] while other studies showed AV conduction delay and transient AV block.[151–153]

Other case reports include prolonged atrial asystole during PFA-PVI after an RSPV application, with sinus node recovery only after >48 s; despite atropine, recurrence occurred.[141] Additionally, transient sinoatrial node dysfunction was observed shortly after PFA-PVI, resolving within 6 h; direct stimulation during ablation and reversible electroporation stunning were discussed as plausible mechanisms.[154] His–Purkinje conduction disturbances during cavotricuspid isthmus PFA led to right bundle branch block plus left posterior fascicular hemiblock plus PR prolongation, resolving within 12 h.[155]

The available evidence suggests that while PFA in standard PVI workflows is often delivered at a distance from compact AV nodal tissue, conduction tissue can be affected when fields reach nodal/His–Purkinje regions (or when autonomic reflexes predominate).[155]

Preclinical models have directly interrogated conduction tissue vulnerability to PFA. A preclinical canine study showed His bundle voltage-dependent responses. When applying pulsed electric fields at the site of maximal His potential all animals developed transient third-degree AV block, with recovery time increasing in a voltage-dependent fashion (40 s at 600 V up to 438 s at 1800 V).[149] AH intervals prolonged, HV did not significantly change, and Masson staining showed no apparent structural damage to His bundle cells. This pattern is most consistent with reversible conduction block due to transient functional impairment (reversible electroporation, oedema, or injury to adjacent myocardium supporting conduction continuity), rather than necrosis of specialized conduction fibres.[149] Another chronic canine model performed ablation using bipolar nanosecond electroporation across the basal interventricular septum, transient infrahisian AV block could be induced in all animals with gradual recovery; right bundle branch block could occur transiently, and more extensive dosing could yield longer-lasting conduction block (including persistent right bundle branch block morphology).[156] Finally, another study demonstrated that pulsed electric fields can acutely modulate Purkinje potentials with relative resistance of the His bundle in certain experiments (e.g. disappearance of smaller Purkinje potentials with preserved His signals), suggesting regional differences in susceptibility and/or local field distribution at catheter positions.[157,158]

Intentional permanent ablation

It is important to highlight that although PFA may display myocardial tissue preferential ablation, studies have demonstrated that the conduction system is not always spared. PFA has also been demonstrated as a feasible option for AV node ablation. Some studies have demonstrated that conduction tissue can be ablated by PFA under specific catheter positioning and dosing.[151,159,160] In a preclinical model, authors demonstrated that that monopolar focal PFA delivery directly at the AV junction resulted in sustained AV block. In contrast, PFA delivery indirectly at the AV junction from within the non-coronary cusp resulted only in transient AV conduction delay, highlighting the importance of distance to the AV node. The same study also demonstrated PFA ability to permanently ablate AV node with focal PFA.[151]

Mechanisms

- *Field distribution:* PFA effects on the conduction system are largely dependent on electric field dosing, which may be controlled by distance to the ablation catheter and applications repetition and overlap. Additionally, the intrinsic fibrotic structure of the conduction system with a dense network of fibrosis surrounding the specialized conduction cells may create some insulating effects creating heterogeneous field distributions leading to reversible block of specialized cells.[149]
- *Reversible electroporation and oedema:* Preclinical models suggest that these two mechanisms could also partially explain the effects observed. For example, the voltage-dependent recovery relationship observed in preclinical models targeting His fibres supports graded reversible impairment rather than a binary effect supporting reversible electroporation mechanisms.[149] Additionally, biophysics of electroporation predict that cells with a smaller diameter, as the AVN cells, may be less susceptible to similar electric field exposure, leading to reversible electroporation rather than irreversible injury. Oedema observed in the PFA could also partially explain transient effects beyond the reversible electroporation recovery time frame.
- *Other mechanisms* can cause conduction deterioration: although not yet completely understood, some authors have speculated with the hypothesis that coronary spasm could cause transient ischaemia and trigger AV block or ventricular arrhythmias during PFA at locations such as the cavotricuspid isthmus (CTI), where coronary anatomy is relevant.[130]

Clinical implications

Practical considerations regarding conduction system effects to consider when using PFA include:

For PFA-PVI workflows: Anticipate nodal pauses (backup pacing/anticholinergic strategy), interpret many AV blocks as functional vagal phenomena, and monitor higher-risk patients more closely.[134]

For non-PV applications (CTI, septal targets): Recognize that PFA can affect conduction tissue and can be associated with coronary spasm-related ischaemia; consider cautious dosing, catheter positioning, and, until better evidence exists, energy-source selection based on substrate location and operator experience.[130,136,149]

Future research should focus on controlled human studies to quantify safety margins and define the feasibility of reversible 'electroporation mapping' protocols around His/AV node regions.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Controlling pulsed field ablation efficacy during ablation procedures

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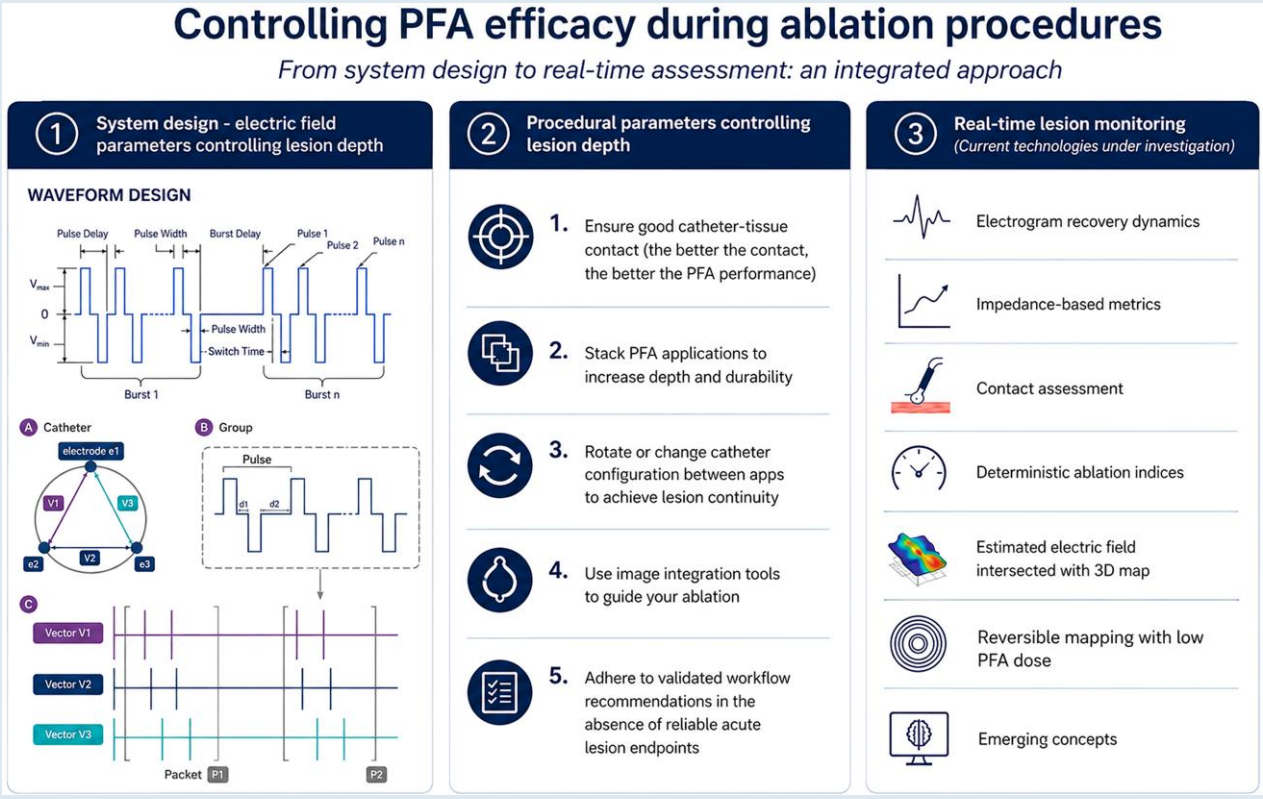
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Abstract

Pulsed field ablation (PFA) has rapidly emerged as a promising ablation modality for the treatment of cardiac arrhythmias because of its myocardial tissue preferential ablation and favourable safety profile. However, procedural control of lesion formation and reliable assessment of lesion durability remain important challenges. This review summarizes the main determinants of PFA efficacy and current approaches for intraprocedural lesion assessment. Experimental and clinical studies indicate that PFA lesion formation results from the interaction between delivered electrical energy, catheter design, tissue coupling, and application strategy. Lesion size and geometry are primarily determined by electric field distribution and cumulative electroporation exposure, while excessive energy delivery may induce unwanted thermal or electrochemical effects. Procedural efficacy also depends on stable catheter positioning, adequate tissue proximity, and sufficient lesion overlap. Unlike thermal ablation technologies, conventional procedural markers such as electrogram attenuation, impedance changes, and pacing threshold variation correlate poorly with durable irreversible electroporation. Multiparametric lesion estimation models integrating electrical, mechanical, and positional data have shown encouraging preclinical results, although clinical validation remains limited. Emerging strategies combining electroanatomical mapping, imaging, and automated electrogram analysis may improve real-time evaluation of lesion continuity and durability. Current PFA workflows rely mainly on standardized energy delivery protocols, optimized catheter positioning, and lesion overlap rather than real-time titration of energy. Although robust intraprocedural markers of irreversible electroporation are still lacking, ongoing advances in catheter technology, imaging, and lesion assessment tools are expected to improve procedural reproducibility and long-term lesion durability. Further studies are needed to establish validated endpoints for durable PFA lesion formation.

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Graphical abstract



Keywords Pulsed field ablation • Irreversible electroporation • Reversible electroporation • Atrial fibrillation • Lesion durability • Electrogram analysis • Catheter ablation • Intracardiac echocardiography • Electroanatomical mapping • Ablation indexes • Contact assessment

Introduction

The goal of pulsed field ablation (PFA) is to preferentially eliminate or electrically isolate aberrant cardiomyocytes through irreversible electroporation while avoiding thermal injury to adjacent critical structures. Therefore, the primary targets for treatment design are safety and efficacy. Secondary targets include efficiency, as faster and easier treatments can improve the accessibility and throughput of clinicians. Since the clinical outcomes (i.e. lesion area) and by-products (i.e. Joule heating, haemolysis, bubbles, pain, and muscle stimulation) are both functions of the catheter and recipe,[1] no ubiquitous protocol has been established to date. The catheter shape, tissue type and health, contact, and waveform all influence the electric field distribution within the tissue, but the thresholds for inducing electroporation and lethal cell death are only dependent on the waveform and the tissue.[2] Different tissues can have distinct irreversible electroporation thresholds that depend on cellular size and orientation, local conductivity, and sensitivity to homeostatic disruption. Therefore, catheter and recipe design are symbiotic, with each unique catheter potentially possessing different ideal waveforms and delivery vectors for its use cases. Unlike thermal ablation, where tissue injury develops immediately around the electrode and several procedural surrogates (e.g. impedance drop, electrogram attenuation, temperature, and contact force) can help estimate lesion formation, PFA produces a more complex and dynamic biological response. Exposure to pulsed electric fields generates a central zone of irreversible electroporation surrounded by a peripheral region of reversible electroporation, in which cardiomyocytes may transiently lose excitability and conduction but ultimately recover membrane integrity and function. Consequently, acute conduction block or electrogram attenuation (or disappearance) does not necessarily indicate permanent tissue injury, as transient electrical silence may simply reflect reversible membrane permeabilization rather than irreversible cell death. The extent of this reversible penumbra depends on the local electric field distribution, waveform characteristics, catheter configuration, and tissue properties, while its recovery kinetics are influenced by the severity of electroporation. Furthermore, unlike thermal coagulation necrosis, irreversible electroporation initiates a cascade of biological processes (including disruption of membrane homeostasis, ionic imbalance, metabolic failure, and regulated cell death pathways) that continue to evolve after energy delivery. As a result, acute procedural endpoints may not accurately reflect chronic lesion durability, and clinicians currently lack a validated intraprocedural marker capable of distinguishing reversible from irreversible electroporation or reliably predicting long-term lesion permanence. This limitation shifts procedural optimization towards understanding the biophysical determinants of lesion formation and identifying procedural parameters that maximize the likelihood of durable irreversible injury.

This complexity raises a central procedural question: in the absence of direct methods for measuring lesion formation, what parameters can the operator meaningfully control during a PFA procedure to influence efficacy, and how can procedural decisions be guided to ensure that the intended biological effect is achieved?

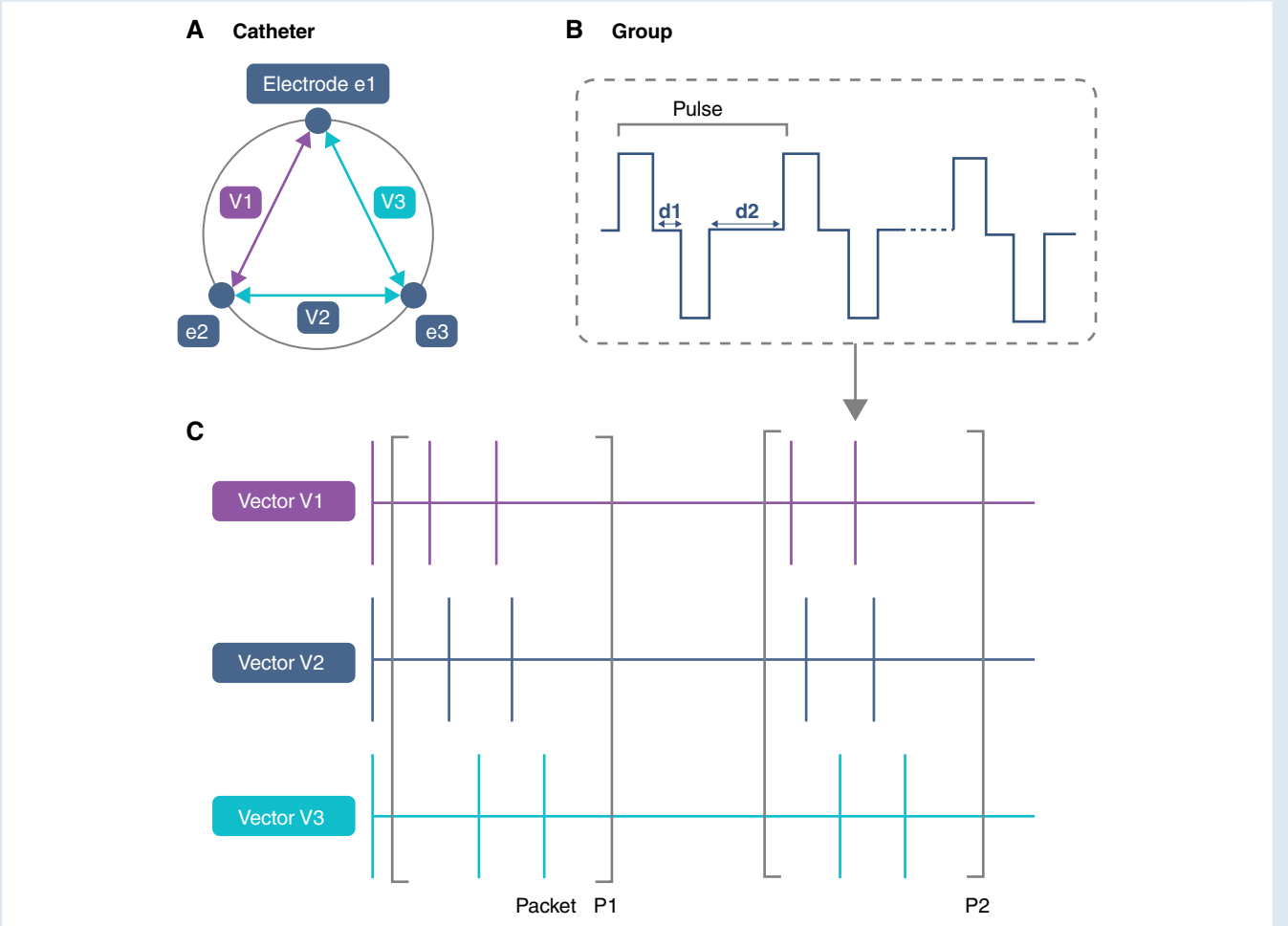


Figure 1 *A*) Defined vectors delivered between catheter electrodes. *B*) A singular group with biphasic pulses separated by interphase (d1) and interpulse (d2) delays. *C*) A single packet, P, is typically delivered per heartbeat and is assembled by vectors that deliver groups in specified orders. The series of predefined packets, P, constitutes an application.

This article explores the mechanisms, limitations, and practical levers available to clinicians for controlling PFA efficacy in real time.

Electric field parameters controlling ablation efficacy

Factors increasing lesion depth

While specific parameter values for commercial PFA systems are not disclosed, the waveforms are typically comprised of the same components, with different nomenclatures.[2–4] One application of PFA treatment consists of a train of packets, each containing a series of biphasic square pulses (*Figure 1*). The biphasic square pulses are separated by interphase and interpulse delays and repeated for several cycles. For multielectrode probes, only one electrode pair is typically active at a time; therefore, this pulse series is repeated for a defined sequence of electrode pairings (the vector) to form the packet. From early PFA implementation, packet delivery was typically synchronized with the R-wave of the paced heart rate (~500 ms).[5,6] Although asynchronous delivery is now commonly utilized, the rate of packet delivery has been conserved.[7] The train of delivered packets constitutes the application, with different anatomical locations sometimes receiving different application counts, typically due to differences in tissue thickness. For example, the pentaspline catheter delivers eight applications per pulmonary vein, whereas only two applications are delivered at each location along the left atrial (LA) posterior wall.[8]

Among waveform variables, lesion depth is primarily governed by peak electric field magnitude and cumulative time above the critical transmembrane potential, with pulse width and pulse number acting as coupled modulators. Timing parameters (interphase, interpulse, and interpacket delays) exert secondary effects unless they alter total application duration. Pulse width has a positive logarithmic correlation with lesion size,[9–12] and values ranging from 350 ns to 100 µs have been shown to generate cardiac lesions in preclinical models.[13,14] The use of short pulses around or below the cell membrane charging time (0.5–2 µs) reduces the influence of cell membrane capacitance on current flow, providing more uniform and predictable lesions and mitigating neuromuscular excitation.[15–17] However, with shorter pulse widths, the portion of the membrane that exceeds the critical transmembrane potential is

exposed for a shorter time.[18,19] Pore formation and subsequent mass transport then decrease, leading to smaller areas of irreversible electroporation.[9–11] Thus, longer pulse widths remain more electroporatively efficient per pulse, whereas shorter pulses trade efficiency for predictability and safety. To increase lesion sizes at short pulse widths, higher local electric fields must be generated by increasing the waveform magnitude to increase the rate of electroporation within the shorter time frame.[20] The number of pulses can also be increased to extend the total duration during which the membrane is above the critical transmembrane potential. However, increasing the waveform magnitude and the number of pulses both result in additional Joule heating and electrolytic effects.[21–23] Joule heating is not affected by parameters equally, scaling quadratically with waveform magnitude and linearly with duration and pulse number.

As a result, increasing pulse number is generally a more thermally efficient strategy for lesion enlargement than increasing amplitude, provided neuromuscular and electrolytic limits are respected. Increasing the separation between packets may also allow for thermal diffusion to reduce maximal temperatures during treatments at the expense of application time. Applying the same number of pulses over a longer period has also been shown to extend the pore lifetime, improving total transmembrane mass transport and moderately increasing lesion size.[24,25] The distinction between packet separation and pulse separation has not been fully elucidated, but it appears that the lesion will be affected if either separation extends the overall application time.[26] Clinically, this distinction is relevant because packet timing and numbers are often constrained by requirements for rapid delivery times, whereas interpulse timing is a waveform design variable. Experimental data demonstrate that cardiac lesions are not affected by interphase and interpulse delays when the application length is maintained.[9] Computational models of neuromuscular excitation suggest that shorter interphase delays and longer interpulse delays theoretically decrease neuromuscular excitation,[27] but experimental results showed mixed results, with shorter interphase delays only marginally decreasing neuromuscular excitation and pain during PFA delivery.[28,29]

Cumulative dose and saturation effects

While increasing the number of pulses through waveform adjustments or additional applications generally increases lesion size, electroporation effects saturate.[11,30,31] In PFA, dose is not a single controllable variable but instead reflects the cumulative exposure of tissue to supra-electroporative field, where higher electric fields increase the rate of mass transport and, subsequently, decrease the time for disruption of homeostasis. The formation of pores creates alternative ion pathways, significantly increasing cardiac tissue conductivity.[10,16] When subsequent pulsed electric fields are applied, the current preferentially enters the now lower-impedance tissue, thereby extending the reach of the cumulative electrical field and region of mass transport.[32] However, as electroporation progresses, conductivity-mediated field redistribution equilibrates, and additional pulses no longer expose new tissue volumes to supra-electroporative fields. The timescale and pulse number for this saturation are not yet clear in cardiac tissue, but at this point, further increases in pulse number primarily reinforce already electroporated regions rather than expanding the zone. Although this conceptual framework is supported by experimental and computational studies, the mechanisms governing saturation of lesion expansion remain incompletely characterized in human and diseased myocardium, requiring further clinical validation.

In parallel, cellular permeability is not uniform across the entire electroporated region, as cells at the periphery experience reduced transmembrane mass transport compared with those at higher electric fields closer to the electrodes. Also, regions initially reversibly electroporated can, upon repeated PFA pulses, experience pore enlargement, increased pore number, or prolonged pore stability. Consequently, areas that would have recovered after a single application may undergo irreversible electroporation after repeated exposure, even at the same applied field intensity and independently of local conductivity changes induced by the first application. In this way, cumulative membrane destabilization converts previously reversible regions into permanent lesions.

Catheter design parameters controlling lesion characteristics

Procedural parameters controlling ablation efficacy

Catheter position, proximity, contact, and force

Effect of proximity and contact

Contact force has historically been used to verify apposition and to predict lesion depth with thermal modalities,[33,34] but it has played a more limited role in PFA. In radiofrequency ablation (RFA), increasing force directly augments resistive heating and conductive heat transfer, yielding a strong correlation with lesion size and depth. In contrast, PFA lesion formation depends on whether the local electric field exceeds a critical electroporation threshold, making electrical parameters the dominant drivers of tissue effects. However, adequate contact is still required to ensure stable electrode–tissue apposition, and insufficient force can cause catheter movement that shifts the effective field within the tissue, increasing the likelihood that portions of the target tissue are exposed to electric fields below the threshold for irreversible electroporation, resulting in incomplete lesion formation. Small increases in electrode–tissue spacing on the order of millimetres will also reduce the local field strength, as the entire field distribution shifts away from the tissue and into the blood pool.[35,36] Consequently, shunting current into the blood rather than into tissue increases the potential for bubble formation and haemolysis, so a minimum contact-force threshold is necessary to consistently generate the field within the targeted areas[30,37,38] for both reliable lesion efficacy and safety.

Impedance-based contact and proximity indicators have emerged as a practical surrogate for assessing electrode–tissue apposition:[39–41] because cardiac tissue is more resistive than blood, the PFA catheter can deliver low-voltage bipolar electrical signals between its electrodes to determine the impedance at the treatment electrodes. The sensitivity of measurements is proportional to the current density within the sample relative to the current leaving the catheter, so measurements are often superficial to the electrode surface where the current density is highest. Further, contact impedance is often limited to bipolar configurations, as the noise from current passing through extra-cardiac regions would outweigh the contact signal at the electrode surface in monopolar configurations. However, the contact measurement electrode pairs do not necessarily need to match the treatment pairs, thereby allowing monopolar ablation with bipolar sensing. Although absolute impedance values are influenced by factors such as anatomical location, tissue disease state

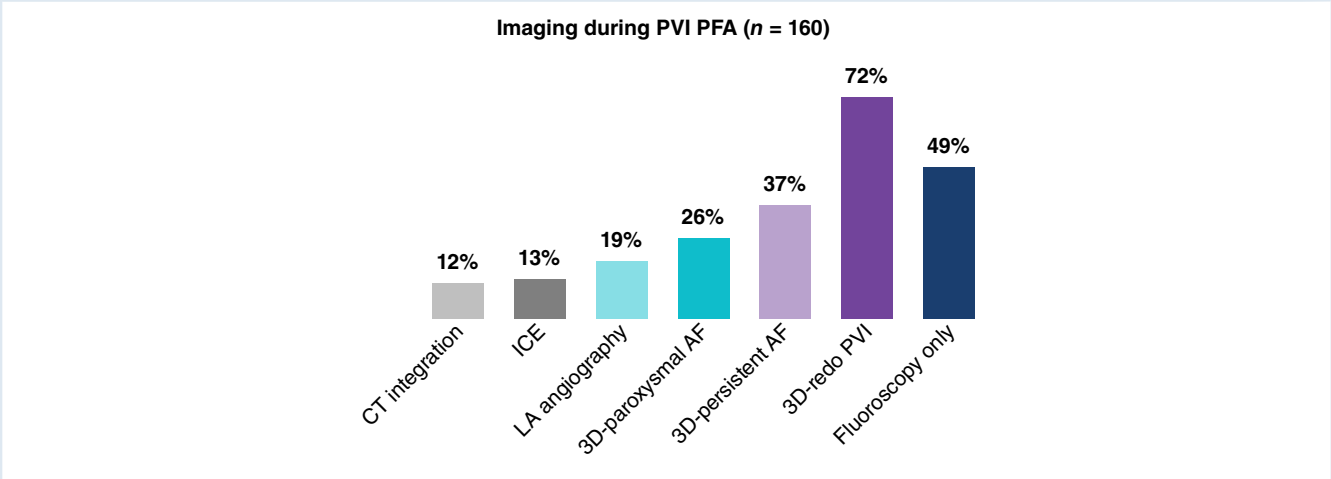


Figure 2 2025 EHRA survey detailing intraprocedural workflows with respect to imaging. During the procedure, half of the 160 respondents relied solely on fluoroscopy, while the remainder variably used 3D electroanatomical mapping systems, intracardiac echocardiography, and atrial angiography. Adapted from Bergonti *et al.*[1] 3D, three-dimensional; CT, computed tomography; ICE, intracardiac echocardiography; LA, left atrium; PFA, pulsed field ablation; PVI, pulmonary vein isolation.

(i.e. fibrosis and oedema), and haematocrit, limiting their standalone utility, sampling impedance relative to blood pool measurements provides a more reliable indicator of proximity.[39,42,43] These impedance-based metrics can be integrated into indices of tissue proximity to guide ablation delivery, improving lesion continuity while avoiding excessive engagement or energy deposition into blood. Yamashita *et al.* indicated an impedance change of >10% predicted adequate pentaspline (Farapulse) catheter contact, which subsequently reduced pulmonary vein gaps in a contact index-guided prospective cohort.[39] The authors also proposed that very large impedance increases may indicate deep catheter seating within structures such as the pulmonary veins, where slight withdrawal can optimize positioning and reduce unintended tissue injury.

Is force predictive of lesion depth?

While the importance of catheter apposition has been repeatedly demonstrated, the influence of additional contact force on lesion depth is less clear. Most studies report significant increases in lesion depth with increasing contact force,[31,44–47] while others show a minimal but positive influence.[37,48,49] The versatile nature of PFA has enabled a wide range of catheter designs, from small focal tips to large baskets and paddles. Certain design parameters, particularly electrode size and positioning relative to the tissue surface, may influence how a catheter responds to contact force. Mattison *et al.* reported an increase of 0.01 mm in lesion depth per gram of applied force using a 4.1 mm diameter focal catheter.[28] One mechanism by which force can influence lesion depth differently across catheter designs is mechanical tissue compression. Higher force may allow deeper tissue layers to experience lethal electric fields, not by increasing field strength but by shifting tissue closer to a fixed electric field distribution. For small tip focal catheters, force is not required to establish contact between the tip electrode and tissue surface (i.e. contact can be reached at 0 g force), while for multielectrode catheters like baskets, ensuring uniform contact with all electrodes placed on multiple sides may require an additional force to deform the tissue surface and reduce the electrode-to-target distance.

While force has primarily been studied with small focal-tip catheters, its role in larger-footprint catheters is less straightforward. In these systems, the applied force is distributed over a larger surface area, meaning that local pressure, rather than total force, governs tissue deformation and electrode contact. Consequently, measured force may be a poor surrogate for effective contact unless sufficiently high levels are applied to ensure consistent electrode–tissue engagement across the entire array. With force-sensing focal-tip catheters, the force sensor and the ablating electrode are co-located, meaning that the measured force closely reflects the actual contact between the electrode and the tissue. In this context, increases in contact force provide a relatively accurate indication of electrode–tissue interaction and positioning.

At the same time, excessive force may introduce treatment variability by distorting tissue or catheter geometry into non-physiological or unvalidated configurations. These proposed mechanisms are primarily derived from preclinical observations and engineering principles; their relative contribution across different clinical catheter platforms remains to be established. Overall, the role of contact force in PFA is best understood as a tool to guide catheter positioning, maintain apposition, and, in some cases, enhance tissue engagement through compression. Although its impact is evident in focal catheter studies, it appears less pronounced than in RFA. Therefore, the integration of contact force into catheter design and lesion prediction models should be balanced against other influential parameters, such as voltage and number of applications. Additionally, excessive force (particularly with small or sharp electrodes) may increase the risk of perforation, highlighting the need to define catheter-specific safe and effective force ranges.

The role of imaging integration

For atrial fibrillation ablation, the use of intraprocedural imaging depends on multiple factors, including the specific PFA system employed, the availability of imaging modalities, the experience of the operator and the team, and associated costs.

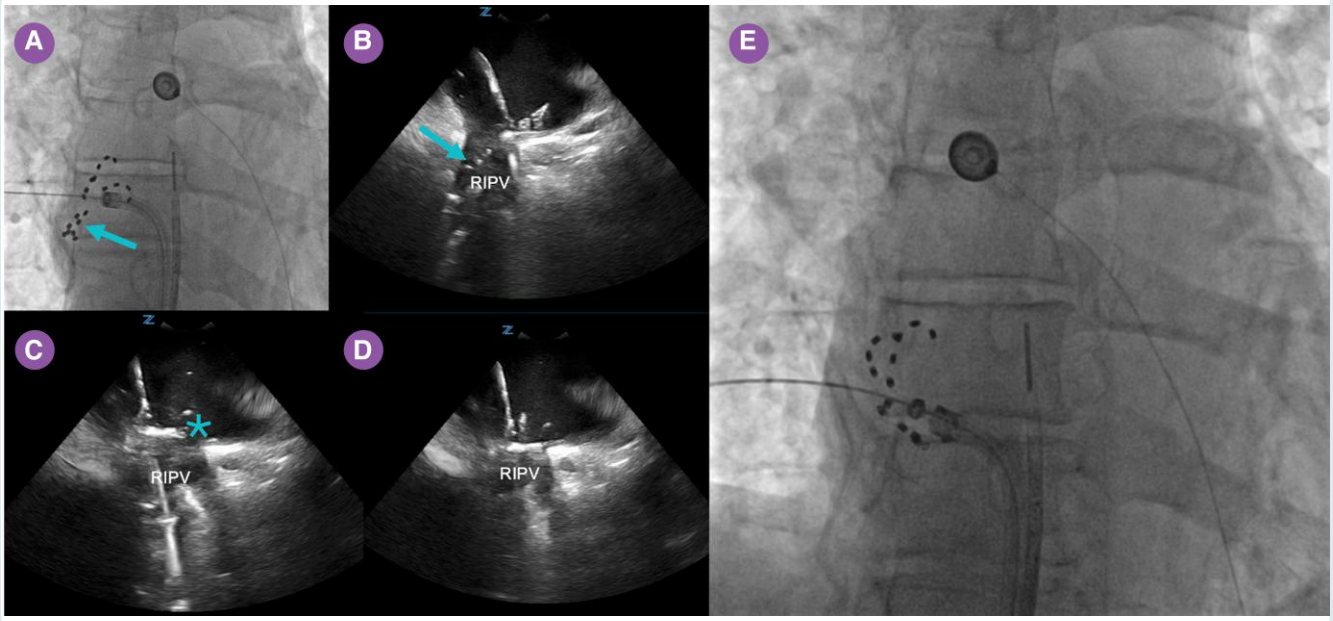


Figure 3 Assessment of catheter-tissue contact using ICE. *A* and *B*) Two petals of the pentaspline catheter (arrow) are in the RIPV as demonstrated by fluoroscopy and ICE imaging. *C*) After gentle clockwise rotation, the petals are rotated outside the RIPV, but there is suboptimal contact (asterisk). *D* and *E*) After advancement of the pentaspline catheter and the sheath electrode–tissue contact is optimized as demonstrated by ICE imaging (*D*) and the backflip sign of the petals on fluoroscopy (*E*). Images are courtesy of Dr Khan Mahmoodi (Erasmus MC). ICE, intracardiac echocardiography; RIPV, right inferior pulmonary vein

Over-the-wire PFA catheters [e.g. pentaspline catheter (Farawave), circular multielectrode catheter (PulseSelect), and balloon-in-basket catheter (Volt)] are typically used in conjunction with a fluoroscopy-based workflow, while other PFA catheters [e.g. variable loop circular catheter (Varipulse) and lattice-tip catheter (Sphere9)] necessitate integrated 3-dimensional electroanatomic mapping (3D-EAM) systems for catheter positioning and navigation. Among these, the pentaspline ablation catheter is the most widely used, and most evidence regarding the incremental value of intraprocedural advanced imaging pertains to this catheter.

Fluoroscopy

Fluoroscopy, with or without pulmonary vein (PV) angiography, has remained the primary modality for guiding single-shot PFA in many centres, particularly when costs, infrastructure, or training pose limitations on the use of advanced imaging technologies (*Figure 2*).[8,50] Main reasons for not using 3D-EAM systems are additional costs, procedural time, and perceived lack of added value.[50] Coaxiality and contact of the PFA catheter to the PVs are important for achieving optimal ablation lesions. For the pentaspline catheter, a practical guide was recently published providing tips for a primarily fluoroscopy-based workflow.[8] Using fluoroscopy, electrode–tissue contact can be assessed by the slight squeeze of the splines in the basket pose or by the slight backflip sign in the flower pose. Fluoroscopy can also be used to guide the pentaspline catheter to targets beyond PVs, including the LA roof, posterior wall, cavotricuspid isthmus, and superior vena cava.[8,51] However, there are concerns regarding the durability of ablation lesions when the pentaspline catheter is used for mitral isthmus ablation, coronary sinus, and LA appendage isolation.[52] Despite the widespread use of fluoroscopy, there are significant inherent limitations to fluoroscopy-based ablation. Specifically, fluoroscopy offers no tissue detail, does not provide direct visualization of myocardial contact, and exposes both the patient and operator to radiation hazards.

Intracardiac echocardiography

Intracardiac echocardiography (ICE) addresses one of the major limitations of fluoroscopy-based ablation: the inability to reliably visualize catheter-tissue contact. By providing high-resolution, real-time imaging of intracardiac anatomy, catheters, and sheaths, ICE ensures better catheter-tissue contact (*Figure 3*), as demonstrated for the pentaspline catheter, ultimately reducing arrhythmia recurrence and reconnection rates.[53,54] Intracardiac echocardiography offers other benefits, such as guiding transseptal access, handling anatomical variations of the pulmonary veins, monitoring catheter stability during pulse delivery, and detecting complications like pericardial effusion or thrombus formation.[8] However, despite these advantages, ICE does not seem to improve other procedural metrics such as procedure time, fluoroscopy time, and number of PFA applications.[53,54] Due to costs and reimbursement limitations, ICE remains less widely used in Europe compared with the USA.[50]

3D Mapping

By providing detailed 3D anatomical visualization, precise catheter location tracking, and the ability to perform 3D activation and voltage mapping, 3D-EAM systems help minimize the reliance on fluoroscopy and ICE during ablation. Impedance-based, open-platform 3D-EAM systems (e.g.

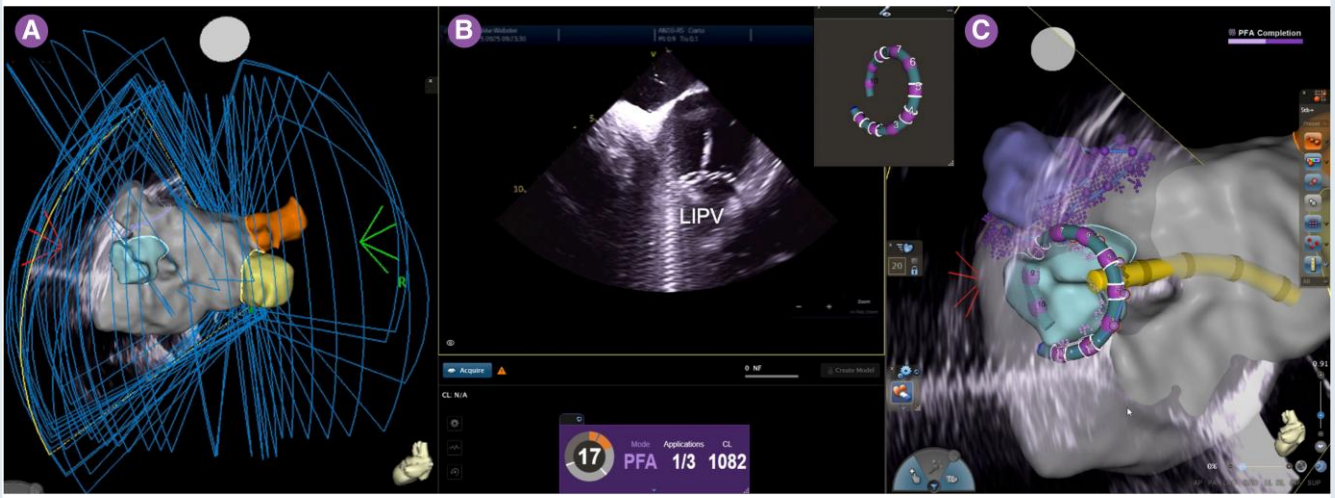


Figure 4 3D anatomical mapping using the CARTOSOUND FAM MAP Module. *A*) Using the SOUNDSTAR ICE catheter, several frames are acquired from each left atrial structure, including the left atrial appendage and pulmonary veins, both from the right atrium and right ventricular outflow tract. Using a deep learning algorithm, an anatomical FAM shell is reconstructed from the acquired frames. *B* and *C*) This reconstructed shell can be used to navigate the variable loop catheter towards the antral side of each pulmonary vein. There is a good correlation of the position of the PFA catheter on ICE imaging (*B*) and the FAM shell (*C*). Images are courtesy of Dr Yuri Blaauw (UMCG). ICE, intracardiac echocardiography; PFA, pulsed field ablation

EnSite X or EnSite Precision) allow for real-time visualization of the pentaspline or circular multielectrode catheter, aiding in the precise navigation and guidance of atrial fibrillation ablation.[55–57] To maximize the accuracy of these systems, optimizing visualization parameters is crucial to ensure the most accurate anatomical geometry.[58]

Unlike thermal-based lesion assessments, where operators can rely on changes in electrograms, impedance, and temperature, PFA lesion assessment is more challenging. For successful creation of contiguous overlapping lesions, it is essential to precisely track pulse delivery. 3D-EAM systems provide this vital information, allowing for the accurate visualization of PFA lesion location and extent. Several fully integrated mapping platforms (e.g. navigational pentaspline catheter in the OPAL HDx mapping system, lattice-tip catheter in Affera Prism-1, variable loop circular catheter in CARTO3, and balloon-in-basket catheter in ENSITE) enable precise tracking of lesion areas. For example, when the navigational pentaspline catheter is used in conjunction with the FARAVIEW software of the OPAL HDx system, the system can automatically display the electric field relative to the anatomical shell, with automated tags that have demonstrated good correlation with chronic post-ablation low-voltage areas.[7]

Recently, the acquisition of the 3D anatomical shell can also be done by ICE imaging. For example, artificial intelligence-assisted ICE mapping, such as the CARTOSOUND FAM Module, can reconstruct detailed 3D LA anatomy from two-dimensional ICE clips, typically obtained from the right atrium and right ventricular outflow tract (*Figure 4*), enabling even zero-fluoroscopy procedures.[59] When combined with the variable loop circular catheter platform, this approach has been shown to significantly reduce mapping time, LA dwelling time, and fluoroscopy time compared with conventional 3D mapping.[60] Despite these advancements, formal evaluation of the long-term efficacy and cost-effectiveness of integrating ICE with 3D-EAM systems is still needed.

Dosing and workflow optimization considerations

Pulsed field ablation produces myocardial injury through electroporation, creating a central irreversible electroporation zone surrounded by a reversible electroporation border. Reversible electroporation can transiently suppress excitability and conduction yet recover, whereas irreversible electroporation leads to delayed cell death and durable lesion formation. From a dosing perspective, this means that acute electrogram suppression is necessary but not sufficient. The practical goal is to reliably convert enough of the intended target volume from reversible into irreversible electroporation while maintaining spatial continuity around the PV antra.

Stacking applications: why additional pulses can deepen lesions

A key dosing lever in PFA is stacking lesions by repeating pulse packages and stacking applications in the same catheter position. Preclinical data support that lesion dimensions depend on application number. In a ventricular model, lesion formation correlated with application number and contact force and was approximately linear for low numbers of applications but plateaued with higher numbers/contact force.[44] A separate investigation using a monopolar ablation vector showed a similar relationship.[30] In yet another, authors show a clear dose-response relationship for both monopolar and bipolar ablation vectors and that monopolar waveforms may reach deeper into the tissue.[61]

From biophysics to workflow: overlap for homogeneity, stacking for depth

Workflow optimization must solve two problems simultaneously: homogeneity (avoid gaps) and adequate depth. Morphometry work with the pentaspline catheter provides a practical rationale for rotation: depending on catheter pose, single applications can produce linear lesions with gaps, while repeating applications

and using different orientations increase circumferential continuity and lesion width.[62] This translates clinically into delivering applications with rotations between applications and ensuring overlap across splines. In addition, extra applications in the carina region ensure confluent periosteal lesions.

Clinical protocol extensions follow the same logic. The 'olive strategy' adds two applications in a smaller olive-shaped configuration, increasing dosing from 8 to 10 applications per PV. In 400 consecutive patients treated with this strategy, redo remapping showed PV reconnection in 13.6% (3 of 22 patients) compared with 45% (36 of 80 patients) after a conventional strategy ($P = 0.007$)[63] At the other end of the spectrum, simplified protocols with fewer total applications have been reported in select cohorts, but small redo cohorts limit firm conclusions.[64] As additional PFA applications typically prolong procedures by only a few minutes, workflow optimization should focus on lesion continuity and durability rather than marginal time savings, with the understanding that optimal protocols are platform-specific and evolve with experience.[65,66]

As additional single-shot platforms and emerging true single-shot concepts mature, platform-specific dosing and optimized workflows will remain central because in PFA, durable outcomes are shaped as much by where and how energy is delivered (coverage, overlap, and tissue coupling) as by how many applications are applied.

Limitations on titration capability

In PFA, effective dosing is largely achieved through repetition of applications rather than continuous adjustment of waveform parameters. This reflects both the threshold-based nature of electroporation and system-level safety constraints. Incremental changes in application number or parameter modifications therefore do not translate into proportional or predictable changes in lesion depth or width.

From a biophysical perspective, deeper electroporation can be achieved by increasing electric field strength through higher voltages or longer effective pulse trains. However, both approaches increase thermal loading at the electrode–tissue interface, promoting microbubble formation, electrochemical reactions, and arcing. Minimizing gas formation favours biphasic trains of short microsecond pulses, substantial interpulse delays (low duty cycle), and electrode designs that avoid high local current densities.[1,23] As a result, maximum usable voltage amplitude, pulse width, and duty cycle are constrained by safety considerations. Achieving deeper lesions therefore depends more on catheter and waveform designs that can safely sustain higher field strengths than on indefinitely stacking applications at the same site.

These constraints shift titration from the operator to the system designer. Voltage amplitude, pulse width, pulse number, and interpulse delay must be optimized for a specific catheter geometry and electrode configuration to control current density and heating. Once validated, these parameters are largely fixed, leaving the operator with limited adjustable variables. This contrasts with RFA, where power, temperature targets, duration, and irrigation can be modified and interpreted using established lesion indices.[1]

Consequently, practical titration in PFA is reduced to a discrete set of procedural controls: application count, catheter pose and orientation, overlap and rotation strategy, and electrode-to-tissue coupling. For this reason, titration by increasing delivered 'energy' is not a meaningful clinical concept in PFA. Durable lesion formation instead relies on protocolized application repetition and optimized catheter positioning and coverage.

Lack of real-time lesion feedback

A further limitation is the absence of a widely accepted real-time lesion quality marker for PFA comparable to radiofrequency surrogates such as impedance drop, electrogram attenuation, or interval prolongation. Acute effects may reflect reversible electroporation and transient conduction suppression, meaning that acute block does not necessarily indicate durable lesion formation.

Preclinical data underscore this limitation. In a swine study targeting specific lesion depths using a PFA index derived from contact force and pulse count, intracardiac electrogram attenuation, impedance decrease, and electrode temperature showed little or no correlation with lesion size, whereas an index incorporating contact force and pulse count predicted lesion depth with high accuracy.[67] Ultimately, effective PFA lesion formation likely depends on catheter-to-tissue coupling, where higher contact force, in the case of a focal PFA catheter, might help improve stability and reduce intermittent contact loss during cardiac motion in the beating heart, even if the influence of force in stationary models remains debated. Notably, contact force remains the most reliable surrogate of lesion formation in RFA, outperforming electrogram attenuation, impedance changes, and other commonly used real-time markers.[68,69]

Practical implication

In summary, PFA titration is limited because lesions are delivered as short waveforms, platform parameters are fixed by design to balance efficacy with safety constraints such as heating and gas formation, and real-time feedback markers that reliably track lesion size are still evolving. As a result, contemporary PFA workflows favour standardized protocols and discrete procedural adjustments rather than continuous titration of energy delivery.

Real- time monitoring of ablation success in pulsed field ablation

Multiparametric estimators

Current knowledge and limitations

Ablation indexes have been developed to standardize lesion delivery and improve procedural reproducibility in catheter ablation workflows. In RFA, composite metrics such as the ablation index (AI) have demonstrated utility in estimating lesion depth and have been incorporated into standardized protocols (e.g. CLOSE protocol[70]) to guide lesion delivery and interlesion distance. These approaches have contributed to workflow harmonization across centres and operators.

In the context of PFA, several indexes have been proposed[30,31,44] to estimate lesion characteristics based on procedural input parameters, including contact force, applied voltage, and the number of pulse trains or applications. Preclinical studies have reported correlations between such indexes and lesion depth or geometry.[71] However, these indexes remain inherently limited by factors that influence the actual electric field distribution and tissue response, which are not fully captured by procedural input parameters alone.

Multiple determinants affect lesion formation in PFA, including catheter orientation, tissue–electrode coupling, tissue composition, and myocardial anisotropy.[30,72] Tissue properties such as fibrosis, ischaemia, and adipose infiltration alter electrical

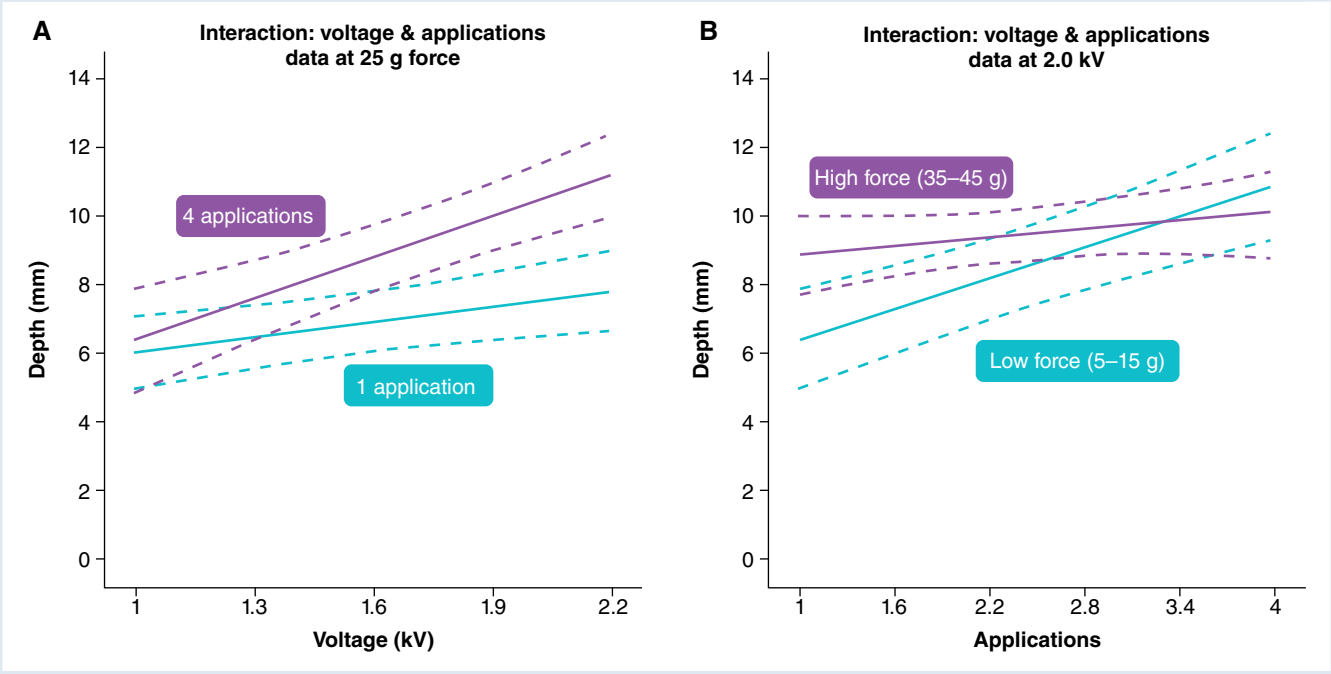


Figure 5 Two-way interactions between voltage, number of applications, and contact force and their effect on lesion depth. Among voltage, number of applications, and CF, two separate interactions were identified as having an effect on lesion depth. *A*) Examines the interaction between voltage and the number of applications at a fixed CF of 25 g, while *B*) evaluates the interaction between CF and the number of applications at a fixed voltage of 2.0 kV. *A*) At low voltages, the number of applications has little effect on lesion depth. However, at higher voltages, lesion depth increases with more applications. The lines indicate the predicted lesion depth for four applications and one application across varying voltage levels. *B*) With only one application, contact force strongly influences lesion depth, with higher force (35–45 g) producing deeper lesions than lower force (5–15 g). However, when four applications are applied, the effect of contact force on lesion depth is reduced. Adapted from Younis *et al*. Factors influencing lesion titration in a monopolar PFA point catheter: a preclinical study, Circ Arrhythm Electrophysiol. 2026;19:e014157. CF, contact force; PFA, pulsed field ablation

conductivity and susceptibility to electroporation, thereby influencing lesion size and transmurality. Consequently, the current delivered to the myocardium may differ substantially from that predicted by nominal system settings.

Future perspectives

The concepts discussed in this section represent emerging approaches intended to improve procedural guidance. Unless otherwise stated, these strategies remain investigational and have not yet been validated for routine clinical decision-making. Recent work has explored composite PFA indexes incorporating voltage amplitude, contact force, catheter orientation, and the number of applications to estimate lesion geometry (depth and width).[30] This study has reported correlations between such composite index and lesion depth in experimental models.

Additionally, interdependencies among procedural parameters have been identified. For example, the incremental effect of repeated applications on lesion depth appears to depend on the applied voltage, with limited additional depth observed at lower voltage levels. Low-voltage PFA produces smaller reversible and irreversible zones due to the lower electric field gradient, whereas high-voltage PFA generates larger zones of both types. When a second application is delivered, part of the reversible zone can be converted into irreversible injury. Because high voltage creates larger reversible zones, this conversion results in a proportionally greater increase in irreversible damage. Similarly, the relative importance of contact force may decrease with increasing number of applications, suggesting that limited contact force can be partially compensated by repeated pulse delivery. Conversely, contact force may play a more significant role at lower voltage levels.

These interdependencies indicate that single-parameter or purely additive models may not accurately predict lesion depth and that multivariable interactions should be considered when developing predictive indexes. Furthermore, PFA systems differ substantially in electrode geometry, field distribution, and delivery modality, necessitating system-specific validation of any proposed PFA index. For example, the influence of contact force may vary according to catheter form factor (focal, multielectrode, or large-area electrodes) and delivery configuration (monopolar vs. bipolar).[37] Most published PFA indexes to date have been derived from monopolar systems, and their applicability to bipolar systems remains uncertain. In bipolar configurations, factors such as catheter orientation may exert a greater influence on lesion formation due to differences in electric field confinement and current pathways (*Figure 5*).

Multiparametric estimators are calculated values primarily derived from ablation inputs and do not directly measure tissue response. In RFA, local impedance serves as a surrogate of tissue coupling and characteristics and has been shown to independently predict lesion efficacy and durability.[73]

Ivorra *et al*. described the dynamics of tissue impedance changes following PFA in rat liver, suggesting that impedance variations may differentiate reversible from irreversible

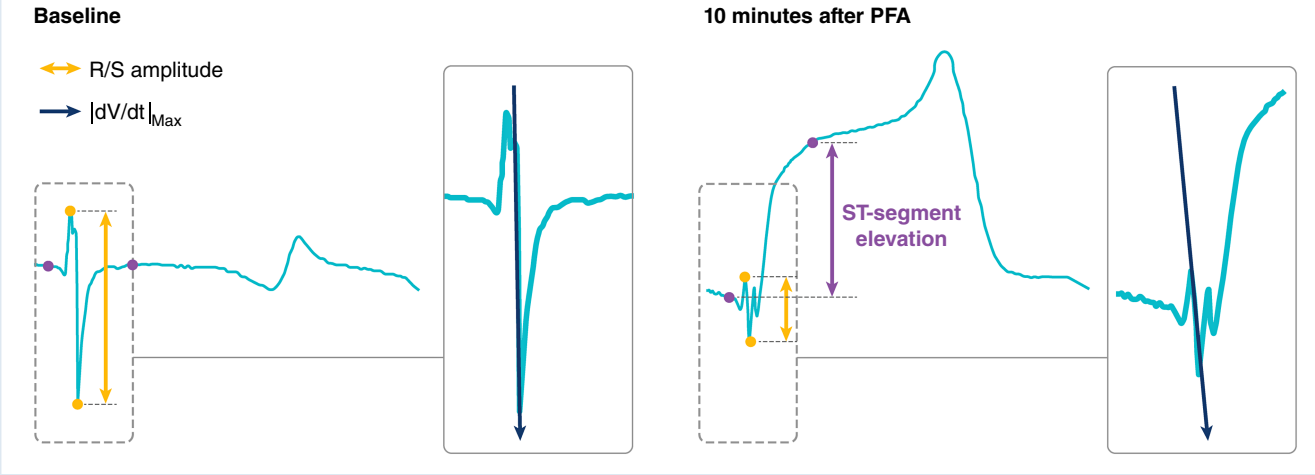


Figure 6 Main acute electrogram morphology changes observed immediately after PFA delivery. Adapted from Amorós-Figueras G, *et al.* Dynamics of High-Density Unipolar Epicardial Electrograms During PFA. Circ Arrhythm Electrophysiol. 2023 Sep;16(9): e011914. PFA, pulsed field ablation

electroporation. However, the complex temporal evolution of impedance after PFA and the need for measurements at multiple time points limit its feasibility in routine clinical practice.[74]

Similarly, several studies have evaluated the temporal evolution of unipolar electrograms and demonstrated their potential to distinguish reversibly from irreversibly electroporated tissue.[75,76] Nevertheless, this approach also requires repeated measurements at different time points and dedicated software algorithms to ensure consistent analysis of amplitude and slope changes.

Finally, while quantitative indexes may support lesion assessment and procedural standardization, they should be integrated with clear manufacturer-provided workflow recommendations, including interlesion distance guidance, to ensure lesion contiguity and procedural consistency. Standardized workflows remain critical to achieving durable lesion sets, irrespective of the ablation modality.

Electrogram-based feedback

Decades of experience with RFA have allowed a better understanding of the acute behaviour of intracardiac electrograms. Local electrogram amplitude reduction is a well-recognized electrophysiological marker of effective thermal lesion formation, as well as impedance drop and pacing threshold increase. However, attenuation—or even complete abolition—of local electrograms and pacing threshold increase immediately after PFA does not necessarily correlate with durable myocardial lesion formation. Additionally, the details of impedance change before, during and after PFA are incompletely understood.

Tissue injury induced by electroporation is mediated by increased cell membrane permeability resulting from the formation of nanoscale pores within the lipid bilayer in response to the application of a high-intensity electric field. The size, density, and persistence of these pores are determined by the magnitude of the applied electric field, which may reach a critical threshold of irreversibility, beyond which durable cellular injury and cell death occur.[77] When this threshold is not exceeded, cells ultimately recover, and the effects of electroporation may remain transient and fully reversible. Reversible electroporation should not be confused with exposure to electric fields below the electroporation threshold. Rather, it occurs when the applied electric field exceeds the threshold required to induce membrane permeabilization but remains below that required to produce irreversible cell injury. At lower field strengths, below the electroporation threshold, membrane permeabilization does not occur, and tissue remains electrically and structurally unaffected. The cellular repair mechanisms resulting in either membrane sealing or late cell death in humans are complex and incompletely understood.

At the cellular level, reversible electroporation is acutely associated with a pronounced but transient dysregulation of Ca^{2+} homeostasis, which gradually returns to baseline over minutes. Consistent with these acute cellular mechanisms, myocardial excitation–contraction coupling may be markedly impaired or temporarily abolished for several minutes.[78] Early preclinical studies evaluating intracavitary electrogram behaviour after PFA have shown a significant acute reduction in local electrogram amplitude, followed by progressive recovery over time in regions exposed to reversible electroporation.[79]

The ability to distinguish acutely between transient impairment of cardiomyocyte function and irreversible electroporation-induced injury is therefore critical for accurately assessing lesion efficacy during ablation procedures. To this end, several experimental studies have analysed the acute temporal evolution and morphological characteristics of intracardiac electrograms following PFA in swine models, correlating these findings with lesion development over time.

Acute electrogram changes and their limitations

The main acute changes in electrogram morphology observed in both ventricular and atrial tissue following PFA are shown in *Figure 6*: (i) a significant reduction in bipolar and unipolar peak-to-peak amplitude (R/S-wave), (ii) marked ST-segment elevation on unipolar electrograms, and (iii) a pronounced decrease in |(dV/dt)|max.[31,75,80]

- Onset and magnitude of electrogram changes: All electrogram changes occur more rapidly after PFA than after RFA.[75,81] The most pronounced morphological changes following PFA are observed within the first 2 min[31,75] However, the magnitude of acute electrogram changes observed in both the atrium and the

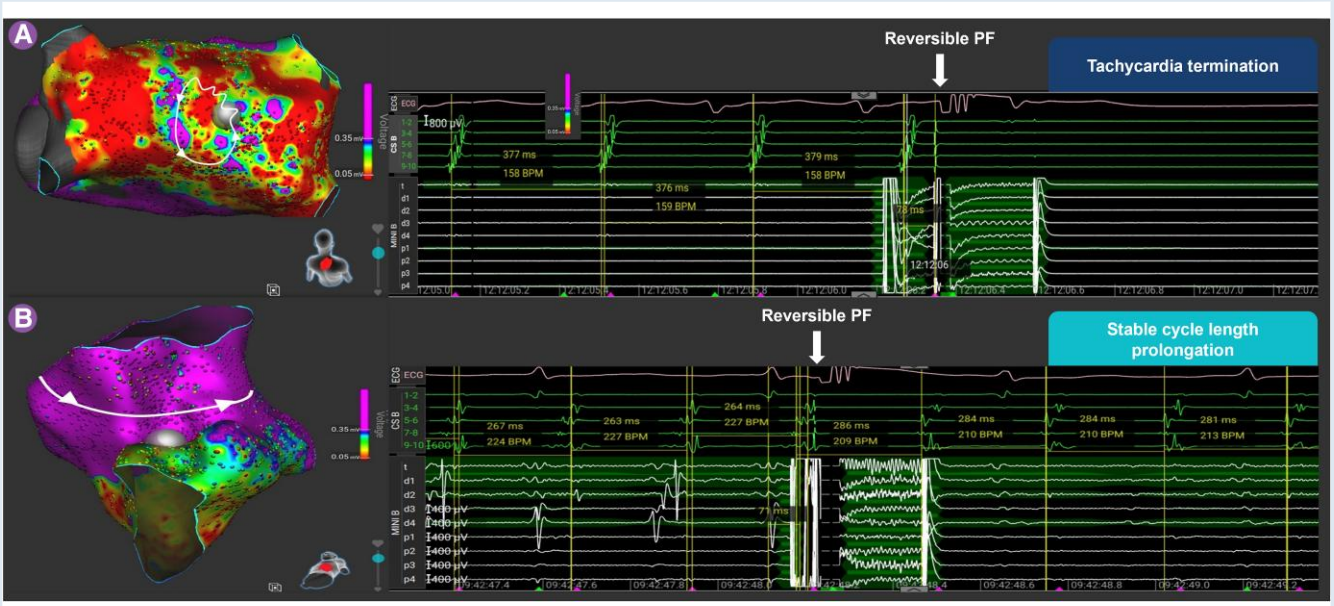


Figure 7 Illustrative examples of specific electrophysiological responses to reversible PF delivered at the critical isthmus. *A*) Non-propagated reversible PF delivered at the left atrial posterior wall leading to tachycardia termination. *B*) Non-propagated reversible PF delivered at cavotricuspid isthmus leading to stable tachycardia cycle length prolongation. PF, pulsed-field

ventricle does not reliably predict lesion durability or transmurality.[75,82]

- Electrogram recovery dynamics: Following PFA, electrogram parameters exhibit dynamic short- and long-term recovery over time. In the ventricle, the ST segment progressively returns towards baseline within the first 30 min of observation, whereas unipolar peak-to-peak amplitude and |(dV/dt)|max gradually increase but remain significantly below baseline acutely. Following RFA, the initial recovery phase is also slower: although ST-segment elevation gradually decreases, electrogram amplitude and |(dV/dt)|max remain largely stable throughout the observation period.[75]

The magnitude and temporal evolution of electrogram changes after PFA are primarily determined by PFA parameters—particularly the applied voltage—and by the resulting electric field strength, which decreases with increasing distance from the catheter.[80] Although PFA affects a relatively wide area of tissue surrounding the catheter, electrogram changes in the periphery—corresponding to regions of reversible injury or penumbra—are less sustained and recover more rapidly than those in the central lesion core. By comparison, electrogram alterations after RFA are largely confined to the central ablation zone, with minimal or negligible changes in the surrounding tissue.

In the atrium, PFA transmural lesions show minimal changes in bipolar signals during the first 10 min, whereas non-transmural lesions exhibit rapid recovery, reaching a plateau at ~3.5 min. Similarly, ST-segment recovery on unipolar recordings occurs earlier and more steeply in non-transmural lesions. In contrast, lesions created by RFA do not display a significant recovery phase, regardless of transmurality.[82]

- Predictability of lesion size and durability: Several preclinical studies have correlated electrogram changes—both in magnitude and recovery dynamics—with histological findings to explore whether acute cut-off values could help to identify non-durable lesions after PFA. These thresholds have typically been established within the first 5 min in the atrium and 30 min in the ventricle.[75,82] However, although differences between irreversibly and reversibly electroporated tissue are evident, accurate delineation of lesion borders remains challenging because electrogram behaviour in the transitional zone is intermediate.[75]

Subacute lesion durability and limits of acute electrogram assessment

Beyond the acute effects of electroporation, the subacute evolution of ablation injury remains poorly characterized and incompletely understood. The cellular repair mechanisms and their temporal course that may lead to partial lesion recovery, pulmonary vein reconnection, and ablation failure occur with both RFA and PFA, yet are only weakly reflected by acutely observed electrogram changes.

In humans, clinical evidence suggests that delayed lesion recovery occurs with all currently available PF devices, as dose-finding studies required waveform optimization to reduce high pulmonary vein reconnection rates at obligate remapping, and even with optimized parameters, the MANIFEST redo study demonstrated durable pulmonary vein isolation in only 45% of patients. Consistent with these clinical observations, the correlation between acute electrogram changes and subacute lesion durability or morphology is limited. In ventricular tissue, only modest associations have been reported between unipolar amplitude reduction or ST-segment elevation and lesion depth or volume, while in atrial tissue, correlations with lesion transmurality are similarly weak and confined to specific frequency components of bipolar and unipolar electrograms in preclinical models.[31,80,82]

Despite being difficult to investigate even in animal studies, further research is needed to better characterize subacute cellular repair and lesion recovery, and to improve the ability of acute electrogram changes to predict subacute lesion durability.

Table 1 Current and emerging approaches for intraprocedural assessment of lesion durability in pulsed field ablation

Technology/marker	Signal/principle	Intended purpose	Development stage/evidence	Implementation/limitations
Electrogram recovery dynamics	Time-dependent evolution of bipolar/unipolar electrograms after PFA	Differentiate reversible from irreversible electroporation	Preclinical + emerging clinical evidence[75,76,82]	Requires prolonged intracardiac recordings at fixed sites (minutes-scale monitoring); limited feasibility for real-time workflow integration; complex signal interpretation
Impedance-based metrics	Electrical impedance variation during and after PFA delivery	Infer tissue injury and changes in conductivity	Preclinical[74,89]	Highly system-dependent; lack of standardized thresholds; limited specificity for lesion durability
Contact force	Mechanical coupling of catheter tip with tissue	Improve consistency of energy delivery and lesion reproducibility	Preclinical/ clinical[37,44,71,90]	Depends highly on catheter form factor. Correlation with lesion depth only demonstrated for small tip focal-monopolar catheters.
Composite deterministic ablation indices	Multivariable models incorporating CF, voltage, pulse number, and related parameters	Estimate lesion geometry (depth and volume)	Preclinical[30]	Limited generalizability across PFA systems; no validated clinical endpoint correlation
AI-based electrogram analysis	Morphology and temporal evolution of unipolar intracardiac electrograms	Detect residual conduction or incomplete lesion formation	Early development	Lack of validated association with chronic lesion durability; requires standardized datasets and prospective validation
Intracardiac echocardiography (ICE)—tissue characterization	Echogenicity changes ('tissue brightening'), interface visualization	Indirect assessment of acute tissue reaction after PFA	Clinical observational	No standardized criteria for lesion definition; interpretation is operator- and system-dependent; not a direct lesion quantification tool
Optical mapping	Optical/ birefringence-based detection of myocardial microstructural changes	Detection of electroporation-induced structural alterations	Preclinical/early translational[91]	Limited clinical availability; requires dedicated hardware; not validated for prediction of chronic lesion durability. Requires prolonged procedure time to analyze lesions
Catheter shadow projection in 3D electroanatomical map	Spatial tagging of catheter position and energy delivery	Ensure lesion coverage and continuity	Clinical	Purely anatomical/positional tracking; no direct information on tissue injury
Estimated electric field intersection in 3D electroanatomical map	Field-integrated tagging based on catheter position and estimated electric field exposure	Estimate lesion extent and predict chronic lesion size	Preclinical + clinical validation studies[7]	Promising correlation with chronic lesion size; system-specific implementation, anatomy-dependent; requires external validation across platforms

Summary of current technologies and procedural markers used or under investigation to assess lesion formation and predict chronic lesion durability during PFA. Technologies are categorized according to their underlying signal or measurement principle, intended clinical application, current level of evidence, and major implementation limitations. Importantly, no currently available approach has been universally validated to reliably predict chronic lesion durability during the acute procedure across different PFA platforms.

Abbreviations: AI, artificial intelligence; CF, contact force; ICE, intracardiac echocardiography; PFA, pulsed field ablation.

Evidence level: *Preclinical* indicates evidence derived primarily from experimental or animal studies. *Clinical observational* indicates evaluation in human studies without prospective validation of chronic lesion durability. *Clinical* refers to technologies currently used in routine clinical practice, although not necessarily validated as predictors of durable lesion formation. *Early development* denotes investigational technologies that remain under active development or early clinical evaluation.

Reversible pulsed-field mapping: translating transient electrogram changes into definitive lesion strategy

Transient changes in electrograms and cardiomyocyte conduction induced by reversible PFA may be advantageous for delineating complex arrhythmia circuits and identifying the optimal ablation target before creating definitive lesions. In this context, both preclinical and clinical experience have demonstrated the feasibility and high reproducibility of non-triggered pulsed-field (PF) mapping as a novel mapping tool for the evaluation of atrial flutter re-entrant circuits.[79,83] It should be noted, however, that the cellular behaviour in the reversible penumbra around irreversible electroporation may significantly differ from very short-duration reversible electroporation used for mapping.

Application of a single reversible PF pulse to a given circuit can elicit four distinct electrophysiological responses: (i) tachycardia termination, (ii) stable prolongation of the tachycardia cycle length (TCL) with preservation of the activation pattern, (iii) irregular TCL variations, and (iv) no observable change. Notably, only the first two responses are observed when the pulse is delivered at a critical site, within the circuit, with a reported specificity of 100%. These effects are attributed to reversible electroporation transiently disrupting cardiomyocyte excitation–contraction coupling, either by suppressing conduction and terminating the tachycardia or by slowing conduction, resulting in TCL prolongation.[83] Representative examples are shown in *Figure 7*.

At present, however, this strategy demonstrates only moderate sensitivity. Accordingly, reversible PF mapping should currently be viewed as an investigational mapping concept rather than an established procedural strategy, pending validation in larger clinical studies. This limitation is largely related to the lack of dose-titration capabilities in current clinical systems and to the influence of critical isthmus properties on the electrophysiological response to reversible PF delivery.

Emerging concepts and future directions

Emerging technologies in PFA increasingly aim not only to improve lesion depth but also to provide reliable intraprocedural assessment of treatment efficacy, addressing one of the major limitations of non-thermal ablation.[84,85]

Some catheters are combining both PFA and thermal energy to try to increase performance. The short-duration ultra-low-temperature catheter from Adagio Medical coats the catheter with ice and pre-freezes targeted myocardial tissue, focusing pulsed electric field to the frozen areas and reducing aberrant electric currents elsewhere. Clinically, this approach is intended to help minimize skeletal muscle contraction, phrenic nerve capture, and microbubbles (Adagio Medical). Similarly, sequential radiofrequency and PFA delivery has been investigated to create deeper lesions,[86] although results remain inconsistent and sometimes contradictory,[87,88] with several observations suggesting no clear advantage compared with optimized PFA alone. In contrast, repeated PFA applications ('PF + PF') appear capable of enlarging lesions through cumulative membrane destabilization and prolonged pore persistence, achieving deeper effects without introducing additional thermal injury.

Parallel developments focus on acute lesion assessment by implementing automated or AI-guided tools to analyse the electrical activity of the tissue after PFA. Tools such as the PFAanalyzer tool (CathVision) can interpret remaining unipolar electrograms and detect residual conduction through advanced signal characterization. Some other developments are focused on tissue mechanical and biophysical properties rather than electrical using optical mapping techniques. Polarization-sensitive imaging based on myocardial birefringence enables detection of microstructural alterations in cardiac fibres induced by electroporation (AblaView®, MedLumics), reflecting cytoskeletal disruption rather than conduction changes alone. Although these approaches are promising, there is currently insufficient clinical evidence to demonstrate that AI-assisted lesion assessment improves procedural outcomes or long-term durability.

Pulsed field ablation is likely to evolve towards a broader ecosystem of technologies, with new form factors, from focal to large-focal platforms, designed to address diverse indications across different cardiac chambers. The next major step for the field will probably be the adaptation of current technologies to ventricular applications, where achieving deep, durable lesions must be balanced with preservation of the conduction system, myocardial function, and coronary arteries. In parallel, the market will likely move towards the development of smarter procedural tools, such as lesion indexes, smart tags, or other feedback solutions, to enable real-time assessment of lesion performance and durability during the acute procedure (*Table 1*).

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Safety considerations and clinical monitoring during pulsed field ablation

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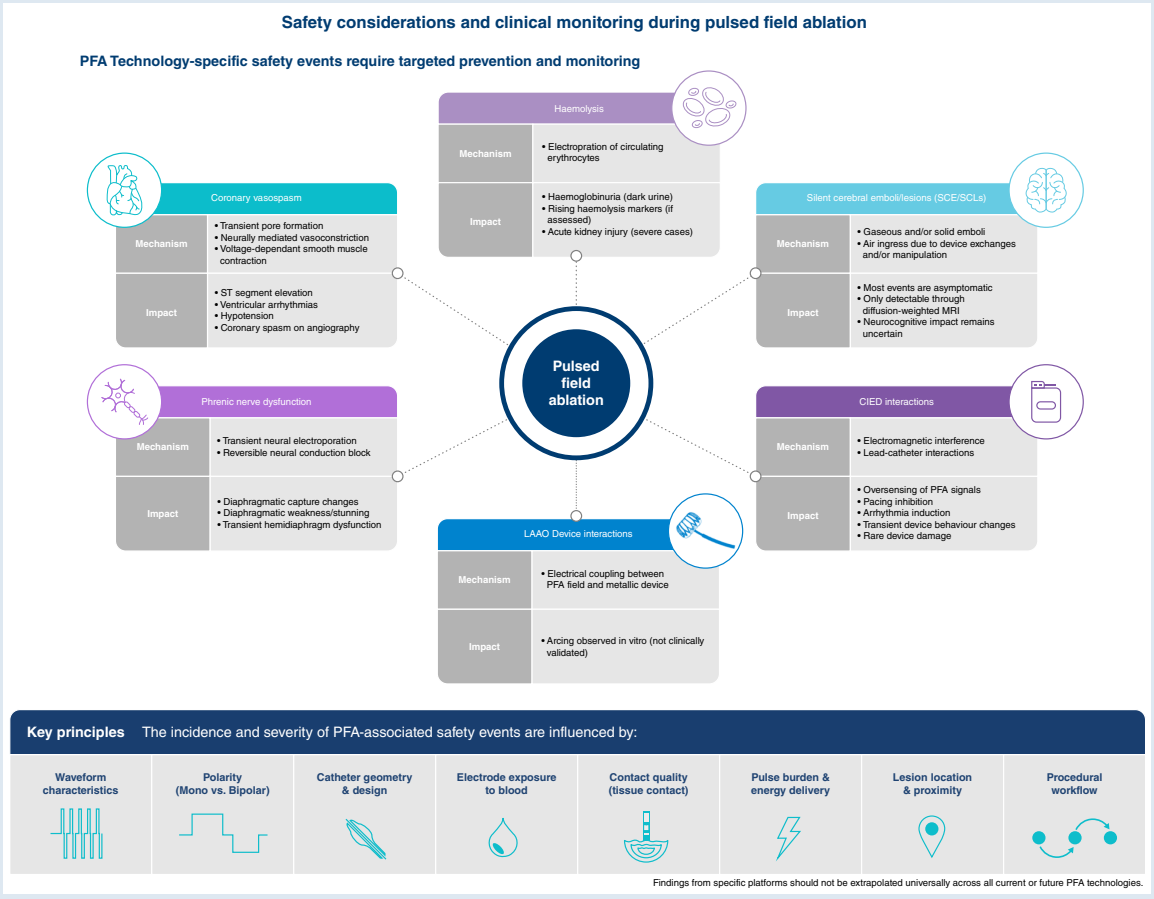
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Abstract

Pulsed field ablation (PFA) has emerged as a transformative technology in cardiac electrophysiology, offering a potentially superior safety profile compared with thermal ablation due to its non-thermal mechanism of irreversible electroporation. Clinical experience confirms a substantial reduction in traditional complications such as pulmonary vein stenosis, atrio-oesophageal fistula, and permanent phrenic nerve injury, though PFA introduces a distinct spectrum of physiologic effects requiring consideration. Coronary vasospasm is the most characteristic phenomenon, ranging from transient, subclinical constriction to rare ischaemic or arrhythmic events; mitigation relies on coronary anatomical awareness, optimized lesion placement, and prophylactic vasodilators. Haemolysis, caused by red blood cell electroporation, varies with catheter design and pulse burden and is typically mild, though high exposure and inadequate hydration may rarely lead to acute kidney injury. Silent cerebral lesions could result from procedural and/or energy-related factors, including gas formation, air ingress, catheter manipulation, and anticoagulation management, with uncertain long-term clinical impact but opportunities for technique-driven reduction. Interactions between PFA and cardiac implantable electronic devices are system- and context-dependent, with monopolar configurations and catheter-lead proximity influencing the risk of transient interference and rare permanent damage.

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Graphical Abstract



Overview of safety considerations during pulsed field ablation. Diagram illustrating major PFA-specific safety events, including coronary vasospasm, haemolysis, silent cerebral emboli/lesions, CIED interactions, LAAO device interactions, and phrenic nerve dysfunction, together with their mechanisms, clinical consequences, and key factors influencing event risk and severity.

Keywords Coronary spasm • Embolic effects • Microbubbles • Haemolysis • CIED interactions • Pulsed field ablation • Coronary injury • Phrenic nerve stunning • Irreversible Electroporation • Atrial fibrillation ablation • Safety profile • Coronary vasospasm • Coronary artery spasm • Acute kidney injury • Silent cerebral lesions • Microembolism • Thromboembolic events • Electromagnetic interference • Catheter design • Procedural complications • Risk mitigation • Electrophysiology

Introduction

One of the main advantages of pulsed field ablation is its potentially superior safety profile compared to thermal technologies.[1] The fundamentally different mechanisms of action of PFA, based on the non-thermal phenomenon of electroporation (IRE), have substantially reduced the risk of serious adverse events typically associated with thermal ablation technologies, such as pulmonary vein (PV) stenosis, atrio-oesophageal fistula (AEF), and permanent phrenic nerve injury (PNI).[2,3] Accumulated clinical evidence from large real-world patient populations has virtually confirmed the near complete elimination of some of these adverse events with occurrence rates approaching zero.[4,5] However, PFA has also revealed several relevant novel adverse effects that deserve special attention.

The main distinctive characteristic of PFA is the use of high-intensity electric fields, several orders of magnitude higher in intensity and shorter in duration than the field applied in radiofrequency (RF) ablation, to induce IRE in the target cardiac tissue. These high-intensity electric fields may give rise to a specific set of adverse effects.

Perhaps the most prominent technology-specific effect associated with PFA relates to its effects on coronary arteries, particularly acute effects leading to coronary artery spasm. Other observed coronary events, such as delayed spasm, remain incompletely understood, and their link to PFA energy has yet to be clearly established. The second safety event warranting attention is haemolysis associated with the application of high-intensity electric fields within the blood pool and the rarely observed ensuing acute kidney injury (AKI). Lastly, thromboembolic events, although not unique to PFA procedures, deserve special consideration, as the underlying mechanisms in PFA may differ from those observed with RF ablation.

Although the incidence rates of some of these events are very low and the clinical relevance of others remains apparently limited, it is important to stay vigilant and understand the

mechanism underlying their occurrence. This article summarizes the current scientific evidence regarding the principal mechanisms underlying the main PFA technology-specific effects, as well as potential mitigation and patient management strategies. Additionally, a direct comparison with thermal technologies is discussed to provide a clearer understanding of the main differences between technologies.

Coronary effects

Pathophysiology of acute coronary spasm

Pulsed field ablation–induced vasospasm is a long-recognized vascular phenomenon extensively characterized in multiple non-coronary tissues.[6] Foundational work in skeletal muscle, the microvasculature, neural pathways, and epithelial barriers consistently describes a reproducible electroporation-related vasomotor response involving immediate neurally mediated smooth-muscle contraction, transient endothelial pore formation, delayed microvascular constriction, vascular lock, increased vessel permeability, and red blood cell (RBC) stacking.[7–9] This experimental framework constitutes the primary foundation for understanding vascular responses to PFA.

By contrast, our coronary-specific understanding remains considerably more limited. Early descriptions of PFA-induced coronary vasospasm were predominantly angiographic, characterizing the response as acute, transient, and voltage-dependent.[10–17] Mechanistically, these observations appeared to parallel findings from non-coronary tissues; however, the interpretation was largely extrapolative, inferred from electroporation biology rather than directly demonstrated in the coronary circulation. From a physiological standpoint, beyond neurally mediated vasoconstriction and direct smooth-muscle contraction, the vascular endothelium likely plays a central role. High-intensity electric fields may induce transient endothelial poration, thereby altering local paracrine signalling. A shift towards a pro-vasoconstrictive milieu, marked by reduced nitric-oxide bioavailability or increased endothelin-1 release, could further amplify acute vascular hyperreactivity.[18] Additionally, electroporation-related injury to circulating blood elements has been proposed as a complementary mechanism: local haemolysis may scavenge nitric oxide, impairing endothelial-dependent vasodilation, and release potent vasoconstrictive mediators.[19]

Recently, an integrated angiographic and histological characterization of the acute coronary response was provided.[20] The study demonstrated that acute coronary vasospasm is peak-voltage dependent rather than energy-dose dependent, shows a brief delay to maximal constriction (~5 min), and is associated with endothelial disruption and luminal protrusions. Furthermore, computational simulations suggest a clear relationship of distance from the electrode generating the electric field to the coronary artery, consistent with other preclinical observations.[21] Together, these findings confirm that the coronary vasculature undergoes electroporation-linked processes analogous to those described in other tissues, while providing coronary-specific structural correlates and thresholds.

Delayed coronary vasospasm has been reported in isolated cases,[22,23] occasionally with significant haemodynamic compromise.[24] However, the mechanisms remain unknown. Autonomic imbalance,[25] endothelial dysfunction, and haemolysis-related nitric-oxide depletion have been proposed, but no causal pathway has been demonstrated, and current evidence is insufficient to move beyond speculation.

Overall, PFA-induced coronary vasospasm should be understood as a specific manifestation of a broader and well-documented vascular reaction to electroporation, with coronary-specific evidence only now beginning to emerge—substantially strengthened by recent findings.

Acute coronary artery spasm: clinical evidence

The first clinical report of a coronary artery spasm associated with PFA was published in 2021 during ablation at the mitral isthmus,[26] challenging the concept of strict myocardial tissue selectivity of PFA. Since then, with an increasing number of PFA procedures and more extensive lesion delivery, additional instances of coronary vasospasms have been observed, underscoring their potential clinical relevance.

Current clinical evidence indicates that PFA-associated coronary artery spasm occurs in two distinct patterns. First, *proximity-related spasm* may occur when ablation is performed within the atrioventricular groove, most commonly at the cavotricuspid or mitral isthmus, where the electrical field lies in close spatial relationship to the right or circumflex coronary artery.[4,10,26,27] Proximity-related coronary vasospasm has also been reported in 31% of patients during focal ventricular PFA using a solid-tip catheter.[28]

Second, *diffuse or generalized coronary spasm* may occur following ablation at sites remote from coronary arteries.[22,27,29] Both entities may present either immediately, during energy delivery, or after a temporal delay. Delayed spasm has been reported with a median onset of 16–20 min after the last PFA application (interquartile range, 4–238 min and 4–315 minutes[24]), indicating that clinically relevant events may occur beyond the procedure completion.[24]

The electric field during PFA appears particularly prone to inducing vasospasm, which has been observed in 100% of cases when ablation is performed in direct proximity to a coronary artery, such as during CTI ablation.[10] Importantly, most of these events remain subclinical, without accompanying electrocardiographic changes.[10,17] Clinically manifest coronary spasm most commonly presents with ST-segment elevation and, less frequently, may progress to malignant ventricular arrhythmias, haemodynamic compromise, or cardiac arrest.[10,24,30] ST-segment elevations are most commonly observed in the inferior leads, identified in 77% of reported cases.[30]

Consequently, the true incidence of coronary spasm is likely underestimated, as most reports derive from isolated case reports and subclinical spasms are not detected in clinical routine. In the MANIFEST-17K and MANIFEST-US surveys, including 17 642 and 41 968 patients undergoing PFA for atrial fibrillation, the reported incidence of coronary artery spasm was 0.14% and 0.10%, respectively.[4,27] In MANIFEST-US, proximity-related events accounted for 0.07%, whereas remote or diffuse spasms occurred in 0.024% (10 of 41 968 procedures), confirming proximity-related spasm as the more common presentation.[27] Consistent with prior observations, most vasospasms occurred during the procedure, were characterized by ST-segment elevation on the ECG, and lasted between 2 and 30 min.[27] While these large registries provide important real-world insights into coronary safety, an important caveat is that the findings primarily reflect the PFA technologies and workflows represented in these studies and likely do not apply uniformly across different PFA platforms.

To date, at least 17 cases of delayed coronary artery spasm have been reported in the literature.[22,24,27,29,31–33] The overall incidence of rare, life-threatening adverse events, including delayed myocardial ischaemia, malignant arrhythmias, and sudden

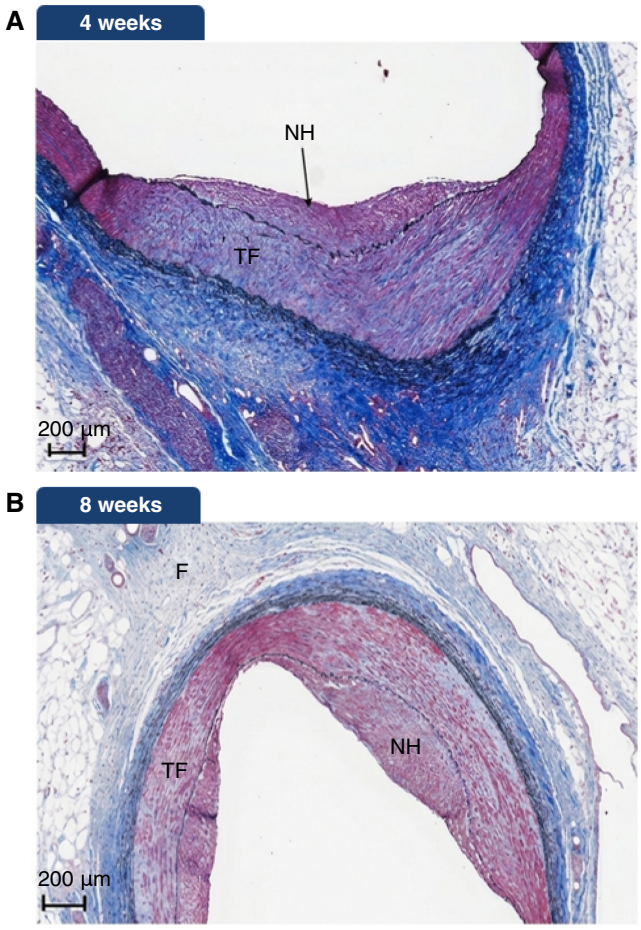


Figure 1 Haematoxylin and eosin stained histologic sections of the left anterior descending coronary artery 4 (*A*) and 8 weeks (*B*) after pulsed field ablation applied epicardially over the left anterior descending coronary artery using a linear catheter demonstrated mild neointimal hyperplasia (NH) and tunica media fibrosis (TF). F, adipose tissue fibrosis. Adapted from Higuchi *et al.*[12] with permission.

cardiac death, has been reported as 0.16% (11 of 6721 PFA procedures).[24]

Subacute and chronic structural changes of the coronary arteries

Application of high voltage electric fields with PFA near coronary arteries typically leads to spasm.[11,12,26] The induced vasoconstriction resolves spontaneously over 25–30 min and was initially thought to be a transient event.[12] However, chronic studies in animal models, although not identifying angiographically visible stenoses, have demonstrated histological injury at 4–8 weeks, characterized by neointimal hyperplasia and tunica media fibrosis (*Figure 1*).[11,12] Whether these changes would manifest in human coronary arteries was initially unclear. Malyshev *et al.* performed coronary angiography a median of 11 months after ablation in 30 patients who had developed coronary artery spasm during PFA, and none had visible angiographic narrowing at the site of prior spasm.[34] However, Tam and colleagues performed optical coherence tomography (OCT) acutely and at 3 months after PFA of the right atrial CTI using the pentaspline catheter in 19 patients.[16] The authors found a mean coronary artery luminal narrowing at 3 months of 10.1%. At 19 months follow-up, it was noted that while there was reduction of coronary luminal area initially, there was no lesion progression.[35] Importantly, although OCT demonstrated mild luminal reduction, no progression of stenosis or associated clinical ischaemic events have been reported to date, suggesting that the clinical significance of these structural findings remains uncertain. Pre-treatment with high dose intracoronary or intravenous nitroglycerin has been shown to mitigate the degree of acute spasm[10,17,36]; however, it is unclear whether this has any effect on the histologic changes which are likely due to direct injury from PFA.

Radiofrequency energy has been used for >30 years for CTI ablation with only rare cases of coronary artery injury.[37] In preclinical studies comparing the effect of PFA to RF energy, the same histologic changes (predominantly neointimal hyperplasia) were also noted with RFA,[38] with one study finding a greater degree of injury with RFA.[39] Therefore, a mild degree of coronary artery injury is likely not unique to PFA. The neointimal hyperplasia after PFA was also found to occur regardless of energy vector, i.e. whether bipolar or unipolar PFA was applied.[38] Whether alternate PFA waveforms (nanosecond, shorter pulse duration) would reduce the effects on coronary artery injury remains to be investigated. Historically, it was recommended with RF ablation that energy not be applied within 5 mm of a coronary artery. However, for PFA, it is not possible to provide a

universal safety distance, as the extent of coronary exposure is likely influenced by waveform characteristics, catheter design, electrode configuration, lesion set, energy delivery parameters, and patient-specific factors. Accordingly, reported distance thresholds should be interpreted as platform-specific observations. For example, in a preclinical study using an 8F linear bipolar PFA catheter, coronary artery effects were observed when energy was delivered within 6.5 mm of the vessel wall.[21] However, when it cannot be avoided, pre-treatment with high dose (2–3 mg) IV nitroglycerin (NTG) should be utilized. While preclinical data suggest that the effect may be peak energy-dependent rather than cumulative,[40] operators should still aim to avoid unnecessary PFA applications and limit exposure to the minimum required for procedural efficacy. In at least one case, application of PFA to a right coronary artery led to acute plaque rupture and myocardial infarction.[24] Therefore, knowledge of a patient's coronary anatomy and whether lesions exist in collateral vessels are also important to minimize complications. A critical unresolved question is whether these histological changes are clinically silent epiphenomena or modifiers of long-term coronary risk, particularly in patients with pre-existing coronary artery disease or endothelial dysfunction.

Clinical implications, management, and monitoring

The occurrence of coronary vasospasm during ablation procedures carries important clinical implications, requiring targeted management and vigilant patient monitoring. Management strategies should be tailored according to the specific coronary safety phenotype, as preventive measures for proximity-related spasm may not be applicable to diffuse vasospasm or subacute coronary remodelling. First, when ablating within the atrioventricular groove, such as during CTI or mitral isthmus ablation, preventive strategies to reduce proximity-related coronary vasospasm should be considered. These include careful selection of the energy source. In situations where ablation must be performed in close proximity to a major epicardial coronary artery, thermal ablation (e.g. using RF or dual-energy catheters) may be considered until more robust platform-specific safety data become available. Alternatively, if PFA is used, prophylactic nitroglycerin may be administered via intravenous, intra-atrial, or intracoronary routes prior to energy delivery to reduce the risk of coronary vasospasm.[41]

Accumulating evidence suggests that coronary spasm can be effectively prevented by prophylactic NTG administration. For example, in the prospective multicentre ADVANTAGE Phase II study, a standardized nitroglycerin protocol was recommended to prevent coronary spasm during CTI ablation with a focal PFA catheter, consisting of a 3-mg intravenous bolus administered 1 min before the first PFA application, followed by additional 2-mg doses every 2 min until completion of the lesion set.[42] Concomitant administration of intravenous vasopressors, such as phenylephrine, was used to prevent hypotension. Using this approach, CTI ablation with a focal short-linear PFA catheter was performed in 141 patients, with successful implementation of the prophylactic nitroglycerin protocol in 99.3% of cases and no observed ST-segment changes or ventricular fibrillation. The mean nitroglycerin dose was 4 ± 2 mg per patient, and more than half of patients received only the initial 3-mg bolus.

Despite these encouraging data, coronary spasm may still occur despite nitrate administration,[30] underscoring the importance of appropriate dosing, timing, and awareness of nitroglycerin's short half-life, which often necessitates repeated additional doses every few minutes.[17] In contrast to proximity-related events, diffuse or remote coronary spasms remain unpredictable, and patient-specific risk factors are not yet clearly defined.[24] Certain clinical characteristics, including pre-existing coronary artery disease, prior Prinzmetal's angina, heart failure, or specific ethnic backgrounds, may have an increased susceptibility, but this requires further mechanistic investigation.[24,27,30] Furthermore, the presence of these isolated reports could potentially be an indicator of autonomic or endothelial mechanisms that contribute to longer-term coronary vulnerability following PFA. Future work is needed to understand the long-term vascular consequences of PFA and how that compares to the RF standard of care.

Clinical features of coronary artery spasm

Clinically, coronary spasm may manifest along a broad severity spectrum, ranging from transient ST-segment elevation to profound haemodynamic compromise or cardiogenic shock, particularly in delayed or diffuse presentations.[17] Patients with a history of spasm should not have nitrates or calcium channel blockers held prior to the ablation procedure. Electrophysiology teams should be prepared for rapid escalation of care during the ablation procedure, including emergent coronary angiography for intracoronary nitrate administration, percutaneous coronary intervention in the setting of plaque rupture, or, in rare cases, temporary mechanical circulatory support. Although most reported events occurred during post-procedural recovery, delayed spasm up to 6 h and sudden cardiac death within the first month after PFA have been described. At present, no evidence-based recommendations exist regarding the optimal duration of post-procedural monitoring or the role of routine oral nitrate therapy after PFA. Although these events remain uncommon, recent reports of delayed coronary vasospasm, myocardial ischaemia, and sudden cardiac death highlight important gaps in our understanding of the coronary effects of PFA and support continued vigilance, particularly as the technology is increasingly applied to complex non-PVI lesion sets (*Figure 2*).

Haemolysis

Mechanisms

Haemolysis during PFA results from IRE of circulating RBCs exposed to intense electric fields. The electric pulses transiently disrupt cell membranes, inducing osmotic imbalance, cellular swelling, and membrane rupture, with subsequent release of free haemoglobin (fHb) and cytosolic enzymes such as lactate dehydrogenase (LDH) (*Figure 3*). Unlike thermal or mechanical haemolysis, this injury is likely non-thermal and field-dependent, occurring without tissue heating or shear stress.[50] From a biophysical standpoint, the small dimensions of RBCs would be expected to result in a higher electroporation threshold than that of larger cells such as cardiomyocytes. This arises from the size dependence of the induced transmembrane potential, which scales with cell radius.[43] However, in the near vicinity of any PFA catheter, the electric field intensity is high enough to induce electroporation of RBCs.

For a given PFA platform, the extent of RBC injury increases with pulse amplitude, number of applications, and total electrode exposure time. Both clinical and experimental data demonstrate a clear dose-dependent relationship.[44,45] For example, for the pentaspline catheter, significant haemolysis has been typically observed beyond 50–70 applications with higher risk for AKI when exceeding 100 applications. However, because of the marked differences across PFA systems (*Figure 4*), it is not possible to provide a general maximum number of applications to

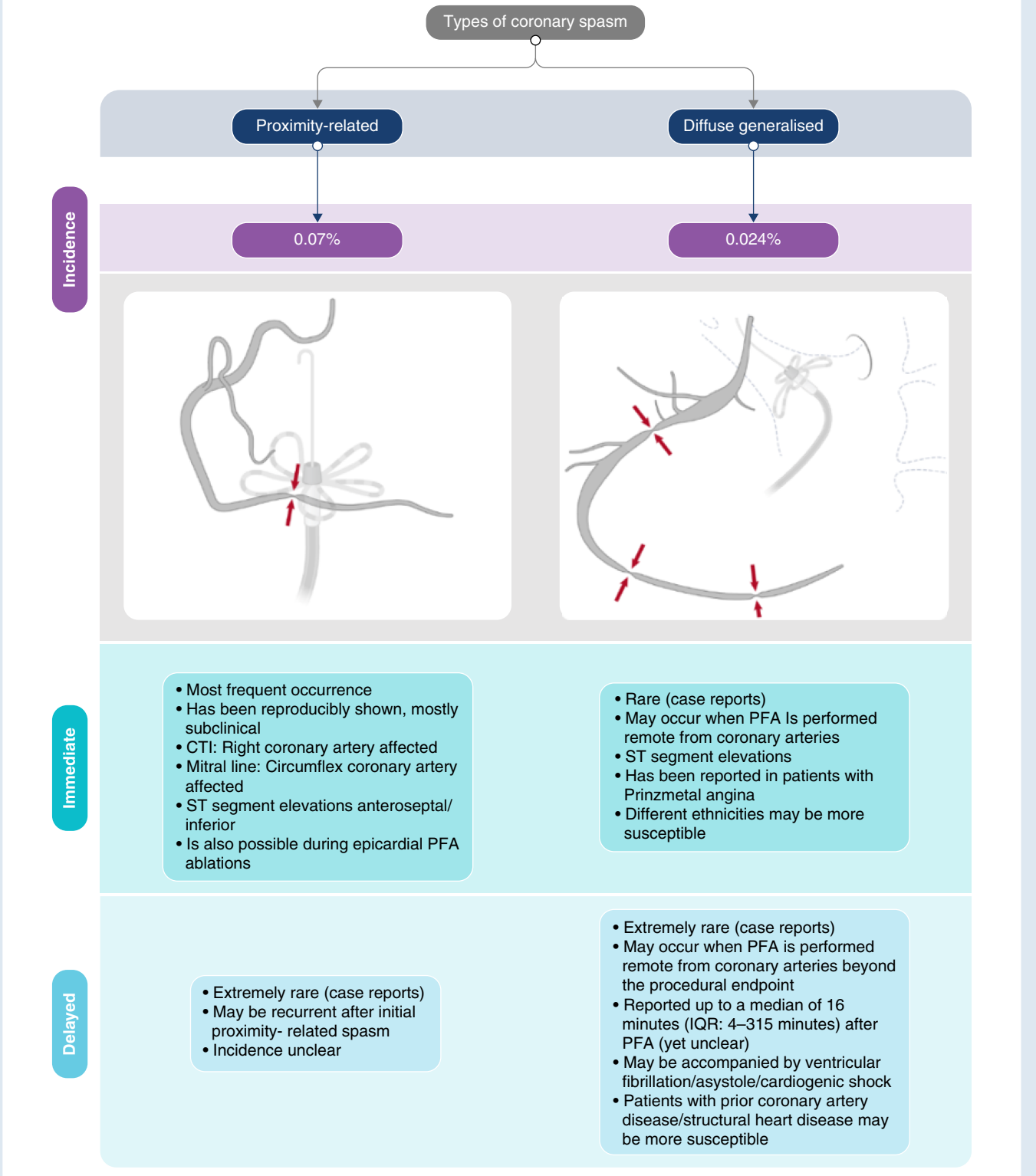


Figure 2 Types, incidence, timing, and clinical spectrum of PFA-associated coronary vasospasm. Proximity-related spasm (≈0.07%) occurs near the ablation site and is the most common pattern, whereas diffuse/generalized spasm (≈0.024%) affects multiple coronary segments remotely. Events may present immediately (more frequent) or in a delayed fashion (rare), with potential ST-segment elevation and severe arrhythmic or haemodynamic complications.

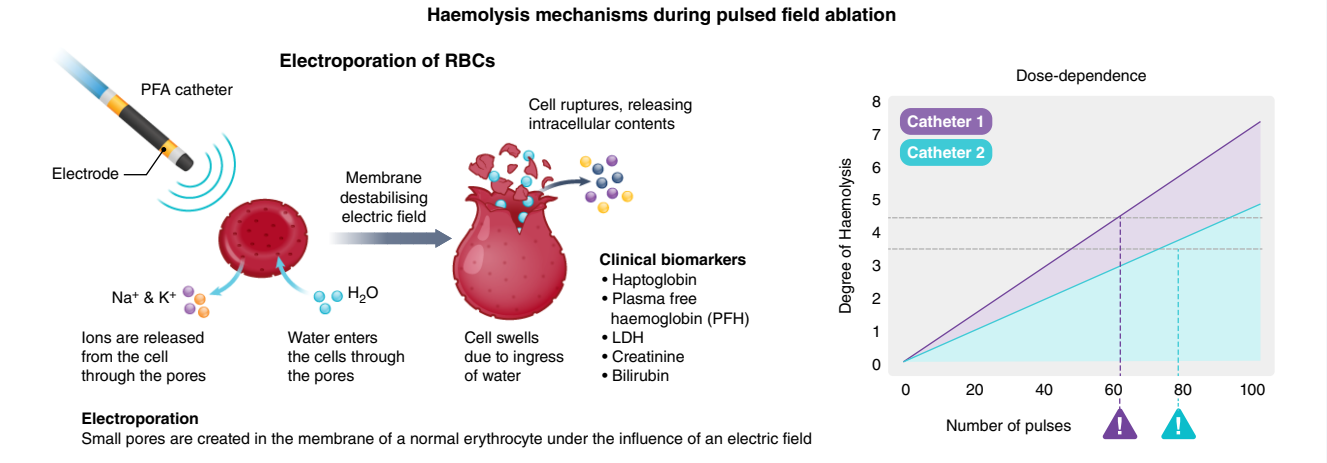


Figure 3 Mechanisms of haemolysis during pulsed field ablation. High-voltage electric pulses cause electroporation of red blood cell membranes, leading to osmotic imbalance, swelling, and rupture with release of free haemoglobin (fHb) and lactate dehydrogenase (LDH). The severity of haemolysis increases proportionally with the number of PFA applications and voltage amplitude.

limit the risk of significant haemolysis or AKI. These thresholds are likely to vary substantially across platforms.[44,45] Additionally, catheter geometry also modulates haemolytic intensity: multi-spline 'single-shot' systems generate greater elevations in haemolysis biomarkers compared with focal or balloon-in-basket devices, where the electrodes are relatively insulated from the blood pool.[48] Recent prospective comparative data demonstrated significant differences in laboratory-defined severe intravascular haemolysis across commercially available PFA technologies, occurring in 37.0% of patients treated with pentaspline catheter, 26.1% with circular-array catheter, and 14.7% with a lattice tip catheter, confirming catheter design as an important determinant of haemolytic burden despite the absence of clinically significant renal impairment.[49] Finally, poor electrode-tissue contact has also been associated with a greater degree of haemolysis.[48,50]

Thus, PFA-related haemolysis represents a predictable electroporation effect inherent to the technology, whose extent depends on the interplay between energy dose, catheter–blood interface, electrode-tissue contact, catheter ablation footprint, and device design.

Biomarkers

Haemolysis after PFA is characterized by a consistent biochemical triad: elevation of LDH, increase in plasma free haemoglobin, and reduction in haptoglobin. Lactate dehydrogenase levels rise rapidly after ablation and correlate with both the number of pulses delivered and total energy applied.[44,51] As LDH is a universal enzyme found in all cell types, its elevation is not highly specific for haemolysis and may also be linked to cardiac tissue damage. Free haemoglobin is the most specific acute marker of intravascular RBC rupture, increasing three- to five-fold after PFA in proportion to pulse count.[46,48]

Haptoglobin levels decrease in parallel, often below 0.04 g/L, reflecting haemoglobin binding and scavenging.[45,52] Ancillary markers such as indirect bilirubin or urinary haemoglobin are less specific but can support the diagnosis. Adequate pre-ablation hydration markedly reduces biomarker elevations and the risk of AKI.[53]

Altogether, the pattern of LDH↑/fHb↑/Hp↓ constitutes the biochemical fingerprint of PFA-related haemolysis and provides a practical framework for its detection and procedural optimization. Consequently, post-procedure monitoring of LDH, free haemoglobin, and haptoglobin could be considered when haemoglobinuria or AKI is suspected. Pre-procedural biomarker monitoring strategies could include baseline renal function in all patients to establish potential high-risk scenarios and post-procedure creatinine and urinalysis could be considered in high-risk cases.

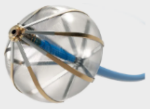
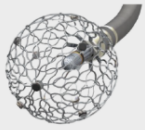
Clinical evidence

Biochemical haemolysis occurs in the vast majority of PFA procedures, irrespective of catheter design or energy settings. Across multicentre studies, LDH and plasma fHb increase in more than 90% of cases, confirming that transient exposure of circulating blood to pulsed electric fields consistently induces RBC electroporation and rupture.[44,51]

Despite this near-universal biochemical phenomenon, clinically significant consequences are rare. Transient haemoglobinuria occurs in 10–20% of procedures, typically resolving within 24–48 h. Severe haemolysis-related AKI has been described only in isolated reports, generally after extensive energy delivery and may be mitigated by more aggressive periprocedural hydration.[44–46]

In the MANIFEST-17K registry encompassing 17 642 patients treated with the pentaspline PFA catheter, five cases (≈0.03%) of AKI requiring temporary haemodialysis were reported, all occurring after a very high number of pulse applications and resolving completely.[4] As these data were generated using a specific PFA platform, the rates of haemodialysis cannot be extrapolated to other catheter technologies or waveforms. In addition, special caution is warranted when combining different PFA catheters. For instance, using both a pentaspline catheter and a focal quadripolar PFA catheter in the same patient, since the delivered doses are cumulative, increases the total energy exposure and raises the risk of haemolysis-related renal impairment.

Overall, clinical evidence suggests that PFA-associated haemolysis is ubiquitous but predominantly subclinical, with renal injury confined to rare, high-dose, or poorly hydrated patients.

Catheter system		Design/ geometry	Mean applications	Haemolysis severity (biomarkers)	AKI incidence/ comments
FARAWAVE™ PFA system by Boston Scientific†		5-spline circular (multielectrode), drip irrigated	60–80	• Highest LDH and fHb rise • Hp↓ 94 ± 40 mg/dL	AKI rare (~0.03% dialysis, MANIFEST-17K, 17 642 patients)
VOLT™ Platform by Abbott*		Balloon in basket design	15–25	• Minimal haemolysis • No significant changes in haptoglobin	None reported
VARIPULSE™ Platform by Biosense Webster†		Variable loop circular, irrigated	40–60	• Moderate LDH rise • Hp↓ 85 ± 32 mg/dL	Occasional mild creatinine rise
PulseSelect™ pulsed field ablation system by medtronic†		Fixed loop catheter	50–60	• Lower LDH/fHb rise • Hp↓ 62 ± 25 mg/dL	No AKI reported
Affera™ mapping and ablation system with sphere-9™ dual-energy catheter by medtronic†		Focal lattice spherical, irrigated	80–100	• Minimal haemolysis • Hp↓ 39 ± 23 mg/dL	None reported

*Data from trials
†Data from real-world evidence

Figure 4 Comparison of haemolysis across PFA systems. Comparative analysis of haemolysis severity and renal risk across major PFA catheter systems. Data summarized from multicentre clinical and preclinical studies.[4,44–47] AKI, acute kidney injury; Hp, haptoglobin; LDH, lactose dehydrogenase; Hb, haemoglobin; fHb, free haemoglobin.

Mitigation strategies

Although biochemical haemolysis is universal after PFA, its clinical impact can be effectively minimized through pre-procedural procedural and periprocedural optimization. Definition of high-risk scenarios should help adopt preventive measures to mitigate associated risks. In this sense, patients with pre-existing renal dysfunction, heart failure limiting intra-procedural or post-procedural hydration, or baseline haematological abnormalities may be particularly vulnerable to the downstream consequences of haemolysis and therefore warrant increased clinical vigilance.[44,54] Consistent with this, available clinical reports suggest that clinically significant AKI occurs predominantly in the setting of extensive energy delivery.[44] This may occur when involving extensive posterior wall or extra-PV ablation or the combined use of more than one PFA catheter. Increased risks could also be associated with poor electrode-tissue contact. As discussed above, experimental and clinical data confirm that haemolysis is dose- and contact-dependent, increasing with higher pulse counts, excessive blood exposure, or poor electrode–tissue coupling.[48,55]

Consequently, maintaining adequate catheter contact reduces intravascular exposure, whereas minimizing number of applications and avoiding unnecessary overlapping lesions are key preventive measures. At present, many PFA catheters lack integrated contact force sensing; however, impedance-based contact assessment is now available in many single-shot and large focal devices. Use of intracardiac echocardiography, to assure electrode-tissue contact prior to ablation, may also play a role in reducing haemolysis.[45,56]

Periprocedural hydration remains the cornerstone of renal protection. In a multicentre series, Mohanty *et al.* showed that administering ≥2 L of isotonic saline virtually eliminated post-PFA haemoglobinuria and prevented haemolysis-related AKI.[53] Experimental data from Yuan *et al.* further suggest that gadolinium-diethylenetriamine-penta-acetic acid (Gd-DTPA) may attenuate erythrocyte electroporation

by stiffening cell membranes, reducing haemolysis both *in vitro* and *in vivo*.[57]

Together, avoidance of excessive lesion delivery, optimized catheter-tissue contact, catheter-specific hemolytic profile awareness, proactive hydration with saline, and potentially biochemical membrane stabilization represent complementary strategies to prevent clinically significant PFA-induced haemolysis and renal complications.

Silent cerebral events

Mechanisms

Left atrial ablation historically carries a risk of cerebral embolic events. While clinically apparent strokes are rare (<1%), MRI studies reveal a much higher incidence of silent cerebral emboli or lesions (SCE/SCL) in up to 14% of RF ablations[58] and around 9% in PFA trials.[59–62] Interpretation of reported SCL rates requires caution, as incidence is highly dependent on study methodology including MRI timing, use of baseline MRI, magnetic field strength, diffusion-weighted imaging protocols, anticoagulation strategy, extent of ablation, catheter exchanges, sheath management, and procedural workflow. Recent registry data confirm MRI evidence of asymptomatic cerebral emboli following PFA, indicating that although catastrophic complications like AEF are avoided, embolic risk may persist.

The origins of SCE/SCL following ablation remain unclear, partly because imaging cannot distinguish between solid and gaseous emboli. Microbubble generation has been observed both anecdotally and during PFA clinical trials and results from electrolysis and gas formation caused by high-amplitude current delivery to blood.[63] Radiofrequency ablation can also produce bubbles through localized overheating.[64] In contrast, while solid particles from RF ablation are known to arise from coagulum deposition, it remains uncertain whether PFA may also generate solid particulates. As such, pinpointing the mechanism (either solid or gaseous) of SCE/SCL remains difficult.

In addition to intra-procedural mechanisms, delayed embolic phenomena may also contribute. Atrial stunning following PFA, characterized by transient mechanical dysfunction and reduced contractility,[65] may promote blood stasis and thrombus formation, thereby representing a potential mechanism for delayed cerebral embolism. Thus, more extensive ablation than necessary should be avoided.

Importantly, it cannot be conclusively stated that the observed rates of SCLs and stroke are solely energy related. Air ingress during catheter or sheath manipulation remains a shared, non-energy related procedural concern across ablation modalities.

Risk factors

Several clinical and procedural factors can significantly influence embolic susceptibility, as previously reviewed.[66] In alignment with air ingress during sheath manipulation, numerous catheter exchanges have been shown to increase the likelihood of silent cerebral infarcts.[67] Suboptimal periprocedural anticoagulation is widely recognized as a major predictor of SCE/SCL formation[68] due to inadequate anticoagulation permitting thrombus formation on foreign surfaces, such as the catheter or sheath. Takami *et al*. demonstrated that microembolic signals occur predominantly during PFA energy delivery using the pentaspline catheter, particularly in the basket configuration and in the presence of overcurrent errors (303 errors), highlighting the importance of catheter configuration and procedural workflow as potential determinants of cerebral embolic risk when using the pentaspline catheter. Overall choice of PFA catheter may influence SCE/SCL occurrence; however, comparisons across technologies should be interpreted cautiously because reported event rates are substantially influenced by a variety of factors including imaging protocols, procedural workflow, anticoagulation strategies, and overall study design.[69–72]

Clinical implications

Recent evidence has produced mixed findings regarding the relative cerebral safety of PFA. In the neurological substudy of the randomized ADVENT trial, MRI-detected SCE/SCL rates were low and did not suggest an excess neurological risk with PFA compared with thermal ablation.[73] Similarly, a recent systematic review and network meta-analysis found no significant difference in SCE incidence between PFA and thermal ablation, although substantial variability was observed across catheter technologies and studies.[71] In contrast, emerging real-world data, including findings from the EMBOL-AF registry,[74] suggest a potentially higher embolic burden with PFA than initially anticipated. Supporting this possibility, a pilot randomized MRI study reported a numerically higher incidence of SCL following PFA than RF ablation (12.9% vs. 6.5%), although the difference was not statistically significant.[75] Taken together, these findings highlight that cerebral embolic risk remains incompletely understood and likely depends as much on procedural workflow, imaging methodology, and catheter design as on the energy source itself.

Despite increasing recognition of MRI-detected silent cerebral events after AF ablation, their clinical and neurocognitive significance remains incompletely understood. Most events are asymptomatic and only detectable through advanced imaging such as diffusion-weighted MRI.[66] Intra-procedural monitoring tools such as transcranial Doppler can identify microembolic signals, but again their clinical relevance is unclear. Prevention relies on strict anticoagulation protocols, minimal catheter exchanges, and careful sheath management. Notably, emerging evidence shows that PFA catheter design influences microembolic burden, underscoring the potential importance of PFA catheter selection.

Pulsed field ablation interactions with implantable devices

As AF ablation expands into older and more comorbid populations, coexistence of PFA technology with cardiac implantable electronic devices (CIEDs) has become increasingly common. Unlike thermal ablation modalities, PFA delivers high-amplitude pulsed electric fields that can interact with nearby metallic structures or highly conductive parts, including CIEDs and left atrial appendage occlusion (LAAO) devices.

Mechanisms

The risk and severity of these interactions are likely influenced by the specific PFA technology used and the type of implanted device. Differences in catheter design, including monopolar vs. bipolar configurations, affect the spatial distribution of the electric field and therefore govern the possible interactions of PFA with CIEDs. Monopolar systems, in which the electric current flows from the ablation electrode on the catheter to a return patch on the back of the patient, generate a broader electric field distribution and may theoretically confer a higher risk of interaction due to greater field dispersion. However, the highest electric field intensities are still concentrated around the catheter in monopolar systems, and it remains uncertain at what

point the electric field intensity is sufficient to induce permanent device damage, or if sustained electric field is the critical component.

Waveform characteristics also play a critical role. Pulse parameters, including duration and pulse delay, will define the spectral frequency content of the PFA signal affecting the electromagnetic interference profile. These factors may affect coupling with device leads and internal circuitry, potentially triggering unintended sensing or device responses. Additionally, the amplitude (voltage or current) and workflow-specific factors may further modulate risk. Accordingly, the interaction profile between PFA and CIEDs is highly system-dependent and platform-dependent.

Cardiac implantable electronic device

Pulsed field ablation has demonstrated both transient and, rarely, permanent interactions with CIEDs. Case reports have described irreversible intracardiac defibrillator (ICD) damage when monopolar PFA was delivered in presumed contact with the SVC coil.[76] Recently, another case of permanent damage to an ICD was reported using the same monopolar PFA system.[77] In contrast to this evidence, controlled preclinical data from an *ex vivo* assessment [44 devices (16 pacemaker, 21 ICDs, 7 CRT-P/D), 1980 PFA applications] demonstrated no change in device settings, functionality, and no macroscopic damage to the devices.[78] Notably, differences in catheter technology likely explain these divergent findings: the reported cases of permanent damage involved a large focal monopolar system, whereas the preclinical study used a bipolar pentaspline catheter. Besides permanent damage to CIEDs, which seems to be extremely rare, PFA can also cause electromagnetic interference changing sensing behaviour of CIEDs and lead–catheter interactions. Potential hazards include CIED oversensing of PFA signals, stunning or damage to tissue surrounding a CIED,[79] induction of an arrhythmia,[80] arcing, or device dislodgement.

Clinical data using bipolar systems further support a favourable safety profile. In the DISRUPT-AF registry ($n = 394$ with CIEDs), no device-related complications or increase in acute adverse events were observed.[81] However, interpretation of these findings is limited by the lack of detailed information regarding catheter-lead proximity during energy delivery, which is likely a key determinant of risk. Overall, these data suggest that contemporary bipolar PFA systems are generally safe in routine workflows, although caution remains warranted in scenarios involving close proximity to device components. This may become more prevalent as PFA is increasingly used for ablation in the right ventricle. Furthermore, as new technologies are released, distance-safety thresholds should be assessed, especially in monopolar systems.

From a practical standpoint, patients with CIEDs undergoing PFA should undergo appropriate pre- and post-procedural device assessment, particularly when energy delivery is anticipated near device components. Special attention should be given to patients who are pacemaker dependent, in whom temporary reprogramming strategies, such as asynchronous pacing, may be considered to minimize the risk of pacing inhibition during energy delivery. In patients with ICDs, temporary suspension of ICD therapies should be performed preprocedurally to prevent inappropriate device therapies. Continuous rhythm and haemodynamic monitoring during energy delivery may also be considered to detect transient device interactions that may not be evident on routine interrogation. Overall, when feasible, unnecessary energy delivery in close proximity to device leads or generators should be avoided until platform-specific safety thresholds are better defined and catheter-lead electrode contact should be altogether avoided.

Left atrial appendage occlusion devices

Patients referred for AF ablation and LAAO devices frequently represent an overlapping cohort, creating scenarios in which PFA could be performed either prior to or following device implantation. In many concomitant cases (e.g. combined PFA and LAAC in one procedure), operators opt to perform PFA prior to LAAO deployment, in part to reduce the risk of device-field interactions. However, a substantial population of patients with pre-existing LAAO devices will subsequently undergo ablation, making this an increasingly relevant clinical consideration.

Emerging preclinical and clinical data suggest that PFA may interact electrically with LAAO devices. An *in vitro* study demonstrated that PFA delivered in close proximity (0–1 mm) to unendothelialized LAAO devices has the potential to cause arcing, observed across both monopolar and bipolar systems. At a separation distance of ∼3 mm, there interactions were no longer observed, suggesting that interactions may be less likely at greater separation distances. However, these findings are derived exclusively from an *in vitro* model and should not be interpreted as a validated clinical safety threshold.[82]

Future perspectives

Several key questions remain unresolved. It is unclear which procedural variables are important to these hazards, including catheter lead distance, or even CIED device manufacturer. Additionally, the safety profile of PFA in patients with newer technologies, such as leadless pacemakers, remains incompletely defined. Expanded clinical registries and prospective studies are needed to better characterize real-world outcomes in patients with CIEDs undergoing PFA. These data will be particularly important as PFA indications expand to include regions such as the superior vena cava, where proximity to device leads may increase the likelihood of interaction.[83]

Comparison to thermal technologies

The clinical adoption of PFA represents a paradigm shift away from conventional thermal modalities—RF and cryoballoon (CB) ablation—driven by a search for more selective and safer energy sources. While thermal technologies rely on conductive heating (>52°C) or freeze-thaw cycling to induce tissue necrosis, PFA utilizes non-thermal IRE as stated above to disrupt cardiomyocyte membrane integrity while largely sparing surrounding collagenous structures. Although neural membranes can be sensitive to electric fields, larger nerves are relatively protected by insulating factors such as the myelin sheath. This selectivity has profound implications for the incidence and management of procedural complications (*Figure 5*). However, as discussed throughout this review, PFA is associated with its own safety profile, including coronary vasospasm and haemolysis-related AKI. Therefore, contemporary comparisons between ablation technologies should consider both the reduction in thermal injury and the emergence of technology-specific adverse events. Moreover, a recent network meta-analysis of randomized trials found broadly comparable conventional safety and efficacy outcomes across RF, CB, laser balloon, PFA, and lattice-tip dual-energy ablation technologies, while identifying differences in procedural efficiency and AF-burden endpoints.[84]

Phrenic nerve injury

Phrenic nerve injury is a well-recognized complication of thermal AF ablation, particularly during CB procedures, where incidence rates of permanent PNI are ∼1.9%.[83] Thermal injury

Complication	Radiofrequency (RF)	Cryoballoon (CB)	Pulsed field ablation (PFA)
Permanent PN Palsy	0.4% (0.1% chronic)	5.4% (1.3% chronic)	< 0.01% (rare reports)
Oesophageal Fistula	0.038%	0.0015%	0 in > 17 000 cases
PV Stenosis (Moderate/Severe)	4.3% / 0.7%	3.8% / 0.5%	Negligable (isolated reports)

Figure 5 Comparative clinical safety of PFA vs. thermal ablation.



Figure 6 Right phrenic nerve stunning during PFA. Fluoroscopic image in the right anterior oblique (RAO) projection demonstrating an elevated right hemidiaphragm following pulsed field ablation (PFA) delivery in the right superior pulmonary vein (RSPV). A 'balloon-in-basket' PFA device and its corresponding guidewire are positioned within the RSPV. A decapolar reference catheter is visible in the coronary sinus (CS).

involves axonal degeneration due to the nerve's anatomical proximity to the right PVs.

In the PFA landscape, permanent PN injury appears exceptionally rare (*Figure 6*).[85] The MANIFEST-17K study, involving over 17 000 patients, reported transient PNI in only 0.06% of cases and zero instances of permanent palsy.[4] While thermal ablation requires continuous PN pacing and diaphragmatic monitoring, PFA-induced PN effects are typically limited to transient 'stunning' or capture during pulse delivery, with rapid functional recovery. However, recent series using sequential compound motor action potential (CMAP) monitoring have reported additional nuance, reporting acute PNI in 26 patients (40.6%).[86] While the majority recovered, incomplete recovery was observed in 24% (6/25) at discharge, and persistent dysfunction was confirmed in one case at 3 months. Although these frequently observed acute CMAP-detected findings may reflect a higher sensitivity of monitoring, their clinical relevance remains uncertain, as this approach may detect subclinical or clinically irrelevant phrenic nerve impairment. However, isolated case reports of persistent palsy have also emerged recently,[87] underscoring the need for further vigilance regarding this adverse event. These complications may be device-specific; certain PFA form factors may stretch the PV towards the nerve, mimicking the mechanical stress seen in CB ablation (*Figure 1*).

Safety domain	Presumed mechanism	Scenarios where risk may present	Intraprocedural warning signs	Preventive measures	Post-procedural monitoring	Level of evidence
Coronary vasospasm	Vascular smooth muscle electroporation, endothelial dysfunction, autonomic effects	CTI ablation, mitral isthmus ablation, ventricular PFA near coronary arteries, high-field exposure adjacent to coronaries	ST-segment elevation, ventricular arrhythmias, hypotension, angiographic vasospasm	Prophylactic nitrates when indicated, coronary anatomy awareness, consideration of alternative energy sources in high-risk locations,	ECG monitoring, assessment for ischemic symptoms, consideration of extended monitoring in selected high-risk cases	Moderate
Haemolysis / AKI	Electroporation of circulating erythrocytes with release of free haemoglobin and LDH	High pulse burden, extensive ablation, poor electrode-tissue contact, baseline haematologic abnormalities	Haemoglobinuria, dark urine, marked biomarker elevation	Adequate hydration, minimise unnecessary applications, optimise tissue contact	Creatinine and urinalysis in high-risk patients; LDH, free haemoglobin, and haptoglobin when AKI is suspected	Moderate
Silent cerebral events/lesions (SCEs/SCLs)	Gaseous and/or solid embolisation, air ingress	Multiple catheter exchanges, suboptimal anticoagulation, sheath manipulation	Usually no immediate clinical signs	Strict anticoagulation, meticulous sheath management, minimise catheter exchanges	Neurological assessment when clinically indicated; MRI primarily in research settings	Low-moderate
Phrenic nerve dysfunction	Neural stunning, electroporation-related injury	Excess ablation near right-sided pulmonary veins and/or superior vena cava	Diaphragmatic capture changes, diaphragmatic weakness, paradoxical diaphragmatic motion	Awareness of phrenic nerve course	Assessment of diaphragmatic function when clinically indicated	Low-moderate
CIED interactions	Electromagnetic interference, sensing disturbances, lead-device interaction, rare device damage	Proximity to a pacing lead or shock coil; high risk in pacing-dependent patients	Pacing inhibition, device behaviour changes or breakage,arrhythmia induction	Appropriate pre-procedural device assessment, avoidance of unnecessary energy delivery near device components	Post-procedural device interrogation and confirmation of normal device function	Low
LAAO device interactions	Electrical coupling between PFA field and metallic device components, potential arcing	Ablation in very close proximity or on LAAO devices	Electrical interaction or arcing (primarily experimental observations)	Avoid direct proximity when feasible and recognise the absence of validated clinical safety-distance thresholds	Standard LAAO follow-up according to local practice	Low

Figure 7 Safety profile of pulsed field ablation: mechanisms and clinical impact. Major safety domains associated with pulsed field ablation (PFA), their proposed mechanisms, and potential clinical consequences. The incidence and severity of these events may vary according to waveform characteristics, catheter design, polarity, lesion location, and procedural workflow. Accordingly, safety observations from individual PFA platforms should not be universally extrapolated to all current or future technologies.

Oesophageal effects

Oesophageal injury, specifically the rare but often fatal AEF, is the most feared complication of thermal ablation. Thermal energy causes indiscriminate protein denaturation and conductive damage to the oesophageal wall. Pulsed field ablation's tissue-selective mechanism offers a significant advantage, as cardiomyocytes can have a lower electroporation threshold than oesophageal tissue and oesophageal tissue is relatively protected by attenuation of the electric field and any potential heating across the atrial-oesophageal interface.[88]

The RF and CB ablations are associated with an AEF incidence of ~0.038% and 0.0015%, respectively ($P < 0.0001$).[89] In contrast, no cases of AEF have been reported to date in more than 17 000 (and more recently estimated up to 500 000) procedures worldwide.[4] This inherent safety allows for more confident ablation along the posterior left atrial wall without the intensive temperature monitoring or mechanical deviation required for thermal modalities.

Pulmonary vein stenosis

Pulmonary vein stenosis (PVS) results from thermal injury to the vascular wall, causing collagen contraction and reactive intimal hyperplasia. In a large RF series, 31.4% of patients showed mild stenosis, 4.3% moderate, and 0.7% severe.[90] Moderate PVS is also more frequent after laser balloon than CB ablation (8.2% vs. 3.8%; $P = 0.03$).[9] The risk of PVS is particularly higher if high-power short-duration RF application is used (10.9% vs. 0.3% in conventional RF application, $P < 0.001$).[91]

Pulsed field ablation preserves the extracellular matrix and structural integrity of the vasculature. Clinical imaging follow-ups consistently show that PV narrowing after PFA is negligible and lacks clinical sequelae, allowing for effective isolation without the risk of long-term cicatricial narrowing.[92] Nevertheless, clinicians should remain vigilant as isolated reports of PV stenosis after PFA have recently been described.[93]

Troponin biomarkers

Myocardial biomarker release has historically served as a surrogate for the volume of tissue necrosis achieved. Pulsed field ablation procedures consistently lead to significantly higher peak levels of high-sensitivity troponin (hs-cTnT), myoglobin, and CK-MB compared to thermal ablation, often two to four times higher.[94]

In thermal ablation, massive troponin release may signal collateral damage. Interestingly, markers of systemic inflammation (CRP) remain comparable, although some studies show CB is associated with greater increases in leukocytes (Delta 2.5 vs. 1.1 times; $P = 0.05$) and CRP (Delta 5.8 vs. 3.4 mg/L; $P = 0.02$) than PFA, suggesting that the heightened myocardial injury in PFA does not translate into increased systemic stress. The overall safety profile of PFA and its principal mechanism-specific adverse effects are summarized in *Figure 7*.[95]

Conclusion

Current clinical experience with PFA highlights several reproducible physiologic patterns that shape its safety profile. Coronary vasospasm remains the most characteristic of these effects, ranging from subclinical vasoconstriction to rare episodes of ischaemia, arrhythmia, or delayed hemodynamic deterioration. Understanding coronary anatomy, optimizing lesion placement,

and using preventive nitrates are the central strategies for reducing risk.

Haemolysis, a direct consequence of RBC electroporation, varies according to catheter design, PFA peak energy, and pulse burden. Although typically benign, progression to acute kidney injury can occur under high energy exposure or inadequate hydration, making dose limitation and fluid administration essential components of procedural planning.

Silent cerebral lesions reflect a combination of energy-related and procedural contributors, including gas formation, air ingress, catheter exchanges, and anticoagulation management. Their clinical implications remain uncertain, but technique-driven mitigation offers meaningful opportunities to reduce microembolic burden.

Across these domains, most physiologic effects are predictable and manageable, while serious complications remain uncommon. Continued refinement of technique and device design will further enhance procedural safety as PFA applications expand.

Authors' contributions

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Sedation and anaesthesia in pulsed-field ablation for atrial fibrillation: mechanisms, procedural requirements, and real-world practice

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Abstract

Pulsed-field ablation (PFA) has rapidly emerged as an important energy source for atrial fibrillation ablation, offering tissue selectivity and procedural efficiency while introducing specific anaesthetic and sedation requirements. This narrative review examines the rationale for anaesthesia and sedation during PFA, the mechanisms underlying pain, involuntary movement, and neuromuscular stimulation, and the implications of catheter design, waveform characteristics, and patient-related factors for peri-procedural management. Available evidence indicates that both deep sedation and general anaesthesia can provide safe and effective procedural conditions when supported by appropriate monitoring, airway rescue capability, and experienced multidisciplinary teams. Deep sedation may offer advantages in workflow, recovery, and patient-centred care, particularly for standard pulmonary vein isolation procedures using contemporary biphasic systems with reduced muscle activation, whereas general anaesthesia remains appropriate for complex procedures, patients with substantial comorbidity, or settings in which complete immobility and airway control are essential. Current real-world practice is highly heterogeneous across regions and institutions, reflecting differences in regulations, staffing models, procedural complexity, and local expertise rather than a universally accepted standard. Overall, anaesthetic strategy in PFA should be individualised according to patient risk profile, expected procedural demands, and device-specific stimulation burden. Further prospective comparative studies are needed to define optimal sedation depth, standardise monitoring and outcome measures, and clarify how emerging technologies may enable lighter yet still effective sedation pathways.

Keywords Sedation • Anaesthesia • Pulsed-Field Ablation • Atrial Fibrillation • Real-World Practice

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Introduction

In this narrative review, we aim to provide a comprehensive analysis of the role of anaesthesia and sedation during pulsed-field ablation (PFA) for atrial fibrillation (AF), with a focus on contemporary sedation strategies, including deep sedation (DS) and general anaesthesia (GA), patient comfort, procedural safety, and optimization of clinical outcomes. We conducted this narrative review based on our clinical expertise and a targeted literature search using more than 100 keywords across major biomedical databases. Studies were selected for relevance, clinical impact, and methodological rigour, and additional references were incorporated following peer-review suggestions. Although a formal systematic protocol was not applied, our approach ensured broad coverage of key developments and evolving practices in the field.

Why we need anaesthesia or sedation during catheter ablation in AF

Historically, anaesthesia and sedation strategies for AF catheter ablation have evolved in parallel with increasing procedural complexity, duration, and technological sophistication. In the early era of AF ablation, when focal trigger ablation and limited pulmonary vein isolation (PVI) predominated, procedures were relatively short and commonly performed under minimal or conscious sedation (CS), primarily to relieve discomfort while preserving patient responsiveness and spontaneous respiration.[1,2] As wide antral PVI became the cornerstone of AF therapy and ablation strategies expanded to include extensive left-atrial mapping, substrate modification, and repeat procedures, workflows grew longer and technically more demanding. These developments highlighted the limitations of lighter sedation and drove a progressive shift towards deeper sedation and GA in many centres.[1,3–7] International data from 2010 to 2019 demonstrate this global transition, with GA emerging as the most frequently used strategy by 2019 (40.5%), followed by CS (32.0%) and DS (27.5%).[1]

Currently, all these three main sedation levels—CS, DS, and GA—are used in AF ablation, with selection guided by patient characteristics, procedural complexity, legal aspects, requirements, and institutional expertise.[1] CS is characterized by a minimally depressed level of consciousness in which patients remain responsive to verbal commands and maintain protective airway reflexes, whereas DS is associated with a more pronounced depression of consciousness, with patients responding only to repeated or painful stimulation and potentially requiring airway support.

Sedation strategy is also influenced by the ablation energy source: radiofrequency ablation (RF) has historically favoured GA, whereas cryoballoon ablation is more commonly performed under CS. In addition, marked regional variation exists, driven by legal constraints, the availability of GA services, and local practice patterns. More recently, PFA has renewed interest in DS as its fast, non-thermal energy delivery may still provoke discomfort while allowing faster recovery and avoidance of intubation, particularly in elderly patients.[7–10] Overall, this historical progression reflects an ongoing effort to align anaesthetic strategy with evolving procedural demands rather than adherence to a single universally preferred approach. (*Table 1*).[1–15]

Patient movement, pain and discomfort, and the shared decision-making between electrophysiologist and anaesthesiologist during PFA procedures

Catheter ablation for AF is a complex procedure requiring a high degree of precision and catheter stability, even in the setting of PFA.[11,12] Even minimal patient movement can significantly impair catheter contact, lesion quality, and procedural safety, particularly during left atrial mapping and ablation.[3,4] Inadequate immobilization may result in prolonged procedure times, suboptimal lesion formation, increased radiation exposure, and a higher risk of an impaired safety profile.[5,6] Pain and discomfort during AF ablation arise from multiple factors; additionally, PFA without adequate analgesia and sedation, despite its non-thermal mechanism, may induce discomfort and involuntary movements due to high-voltage electrical pulse delivery, skeletal muscle activation, and diaphragmatic or thoracic wall contraction.[9,10,13,14] From the patient's perspective, unmanaged pain and distress negatively affect procedural tolerance and

Table 1 Summary of anaesthesia trend

Era	Primary energy source	Primary sedation method	Key medication	Main goal
1998–2005	RF	Conscious sedation	Midazolam/Fentanyl	Basic comfort
2005–10	RF (increasing procedural complexity)	Deep sedation	Midazolam/Fentanyl/ Propofol	Improved tolerance for longer procedures
2010–19	RF (complex left atrial ablations) Cryoballoon	General anaesthesia	Inhaled agents or Propofol/ Fentanyl	Catheter stability and procedural efficiency
2020–24	High-power, short-duration RF Cryoballoon Early PFA	Deep sedation/general anaesthesia	Midazolam/Fentanyl/ Propofol	Efficiency, safety, and reproducibility
≥2025	RF PFA Dual energy approaches	Deep sedation/general anaesthesia	Propofol/Fentanyl /Remimazolam	Rapid recovery, safety, workflow optimization

PFA, pulsed field ablation; RF, radiofrequency

Table 2 Individual priorities and primary risks in anaesthesia/sedation for AF ablation

	Main expectation/goals	Primary risks
Electrophysiologist	Catheter stability, mapping precision, procedural efficacy	Patient movement, reduced catheter contact, longer procedure times, complications
Anaesthesiologist	Airway safety, haemodynamic stability, adequate analgesia/sedation	Hypoventilation, hypotension, aspiration, over-/undersedation
Nurse/EP Lab Staff	Smooth workflows, monitoring, coordination and communication	Communication gaps, delayed response to instability or complications
Patient	Comfort, minimal pain/anxiety, rapid recovery	Pain, anxiety, poor tolerance, dissatisfaction

AF, atrial fibrillation; EP, electrophysiologist.

overall experience.[7,13] The choice between CS, DS, or GA is therefore a critical component of procedural planning and should rely on shared decision-making between electrophysiologists, anaesthesiologists, and patients.[11,12] The decision should be based on patient-related factors (including age, comorbidities, obesity, severe pulmonary disease, sleep apnoea, and anxiety), procedural complexity, expected duration, and institutional experience.[1,6] While electrophysiologists prioritize catheter stability, mapping accuracy, and procedural efficiency, anaesthesiologists focus on patient safety, airway management, and haemodynamic stability.[11,12] Close interdisciplinary collaboration and standardized protocols are essential to anticipate these challenges, manage intra-procedural pain and movement effectively, and optimize procedural success and patient safety in AF ablation. (*Table 2*).[6,9,11,15]

Mechanisms underlying pain and movement during PFA

Pain and involuntary patient movement during PFA arise from the neuromuscular and sensory effects of high-voltage pulsed electric fields (PEFs). When properly designed, PFA delivers ultra-short, high-intensity pulses that preferentially affect myocardial tissue while sparing surrounding structures. However, skeletal muscle fibres and peripheral nerves within the electric field can also be activated, producing visible muscle contractions and nociceptive sensations. The intensity of these effects depends on many factors, including pulse amplitude, duration, number, repetition rate, catheter geometry, and proximity of tissue to the electrodes.[16,17]

At the cellular level, PEFs can elicit action potentials (APs) through multiple mechanisms. Pulses may depolarize nerve or muscle membranes without electroporation, acting directly on voltage-gated ion channels.[18] Alternatively, reversible electroporation can create transient membrane charge imbalances that trigger APs. Understanding the mechanisms of PEF-induced nerve and muscle activation enables electrophysiology teams to anticipate patient responses and tailor sedation strategies accordingly, ensuring both safety and procedural effectiveness.

Catheter configuration and its impact on anaesthetic Requirements

Catheter design is a key determinant of patient movement and pain during PFA, directly influencing anaesthetic requirements. Bipolar catheters confine the electric field between closely spaced electrodes, limiting unintended stimulation of adjacent nerves and skeletal muscles. This localized field reduces involuntary contractions, often allowing procedures to be performed under lighter sedation or CS protocols.[16,17] In contrast, monopolar catheters deliver current from a single active electrode to a distant return pad, generating a broader and less predictable electric field. This increases the likelihood of activating peripheral nerves or skeletal muscles beyond the target myocardium, frequently necessitating deeper sedation or GA to maintain patient immobility and procedural safety.[18] Several patient and procedural factors further modulate neuromuscular activation. Proximity to critical structures, including the phrenic nerve, diaphragm, or chest wall muscles, amplifies contractions and discomfort. Individual patient characteristics, such as body habitus, baseline muscle tone, and pain sensitivity, also influence responses. Procedural variables, including catheter orientation, electrode–tissue contact, and pulse train parameters, can further affect the intensity of muscle contractions.[16,17] Clinically, these considerations may guide sedation strategies. Light sedation to CS may be sufficient when field confinement is optimized and contractions are minimal. Deeper sedation or GA may be required when higher pulse amplitudes, multiple pulse trains, or proximity to major nerves increase the likelihood of involuntary movements. However, to avoid oversimplification, it should be recognized that stimulation burden during PFA is not determined solely by whether a catheter is labelled 'bipolar' or 'monopolar'. Neuromuscular activation is also influenced by electric field distribution, waveform characteristics (mono- vs. biphasic), pulse train design, electrode geometry and contact, and proximity to structures such as the phrenic nerve and diaphragm. Accordingly, sedation requirements reflect a continuum shaped by both device-specific and procedural factors rather than a deterministic bipolar–light sedation and monopolar–GA paradigm.

Current clinical practice landscape

Currently, PFA procedures may be feasible under various sedation strategies ranging from mild CS to GA.[8,9,19–31] However, no standardized sedation protocol has emerged, and practice patterns vary substantially across institutions and geographic regions. European, Middle Eastern, and African practices demonstrate greater variability, with electrophysiologist-driven DS protocols more commonly adopted, particularly in high-volume centres. Many European countries permit appropriately trained electrophysiologists to administer DS independently, supported by specialized nursing staff and anaesthesia consultation availability for airway emergencies.[22,23] Importantly, the choice of sedation strategy reflected institutional practice patterns rather than patient-specific factors or standardized guidelines. Centres using DS reported shorter procedure times and fluoroscopy durations, and, more

Table 3 Sedation monitoring during pulsed field ablation

Study	Region	Sedation type	Specific agents and dosing	Sedation monitoring
EU-PORIA Registry[22]	Europe (multicentre)	Predominantly DS (*n* = 983); GA (*n* = 250)	Not reported for each centre	Institutional standard practice; staffing varied by centre
Iacopino *et al.*[8]	Europe (single centre)	DS with spontaneous respiration	Fentanyl 1.5 mcg/kg; midazolam 2 mg pre-local anaesthesia; ketamine 1 mg/kg ~5 min before first PFA delivery	Anaesthesiologist supervision
Carboni *et al.*[9]	Europe (single centre)	Monitored anaesthesia care (MAC, with propofol) vs. GA	MAC: propofol and fentanyl GA: propofol, sevoflurane; fentanyl and remifentanil (doses per practitioner discretion)	Anaesthesia team delivered MAC or GA per operator preference
Patel *et al.*[21]	United States (Chicago, IL)	Monitored anaesthesia care/DS	Propofol, dexmedetomidine, fentanyl, midazolam (bolus and infusion at practitioner discretion)	CRNA and attending anaesthesiologist; continuous vital signs and end-tidal CO_2 monitoring
Calvert *et al.*[26]	UK (single centre)	CS (EP-delivered)	Midazolam and fentanyl	Anaesthesiologist supervision available for conversion to GA
5S Study[27]	Europe (single centre)	DS	Propofol, midazolam, and fentanyl	Institutional standard practice for procedural sedation without GA in all patients.
Grimaldi *et al.*[28]	Europe (single centre)	DS	Midazolam, ondansetron, dexamethasone, dexmedetomidine, and remifentanil	Anaesthesiologist supervision. Standardized deep sedation with monitoring and sedation scoring
Weyand *et al.*[32]	Europe (single centre)	DS	Propofol. remifentanil, ketamine	Supervision of physician with intensive care expertise
Hiyama *et al.*[33]	Japan (single centre)	DS	Propofol, thiopental, fentanyl, and morphine	Institutional standard practice for procedural sedation without GA in all patients.
Lin *et al.*[35]	China (multicentre)	CS (89.4%)	Not reported for each centre	Anaesthesiologist supervision available for conversion to GA

AF, atrial fibrillation; DS, deep sedation; CS, conscious sedation; CRNA, certified registered nurse anaesthetist; EP, electrophysiologist; GA, general anaesthesia; MAC, monitored anaesthesia care; PFA, pulsed field ablation.

frequently, performed PVI-only procedures. Conversely, GA cases more often included electroanatomic mapping and additional lesion sets such as posterior wall isolation. European Heart Rhythm Association surveys and other multicentre assessments confirm widespread heterogeneity in sedation practices.[19–25] Survey data indicate approximately equal adoption of GA and DS among centres offering PFA, with substantial variation between countries. This geographic variation implies that national practice patterns, regulatory environments, and healthcare system structures influence local sedation protocols. US centres have traditionally favoured GA for AF ablation procedures, while European centres have more commonly employed CS or DS strategies.[24] The introduction of PFA has prompted some US centres to explore DS alternatives. Recent single-centre US reports demonstrate the feasibility and safety of DS for PFA when delivered with appropriate anaesthetic support.[21] Endeavor Health (Chicago, IL) reported outcomes from 40 consecutive patients undergoing PFA under monitored anaesthesia care delivered by a certified registered nurse anaesthetist and attending anaesthesiologist. The protocol utilized propofol, dexmedetomidine, fentanyl, and midazolam (bolus and infusion at practitioner discretion) with continuous vital signs and end-tidal CO_2 monitoring. This series achieved 100% acute PVI with no airway complications or conversions to GA. Asia-Pacific sedation practices reflect regulatory environments and healthcare system maturity levels.[29–36] Japanese centres predominantly employ GA administered by anaesthesiologists, consistent with national medical device approval pathways that emphasize procedural standardization and comprehensive safety monitoring. In contrast, Australian practices mirror European models with greater electrophysiologist autonomy in sedation delivery. China has generated region-specific protocols that balance procedural efficiency with patient safety. Despite differences in historical practice patterns, available evidence suggests comparable clinical outcomes between GA and DS strategies when appropriate monitoring and personnel are available.[22] Institutional protocols serve as the primary determinant of anaesthesia strategy for PFA procedures, and they reflect local resources, particularly anaesthesiology availability and staffing models. Centres with dedicated anaesthesia support may more readily adopt GA or anaesthesia-delivered DS protocols, while centres with limited anaesthesia resources may develop electrophysiologist-delivered CS pathways.[19–25] Some choices remain constrained: individual country regulations may not allow the use of DS agents such as propofol without the presence of a full anaesthesia team. *Table 3* reports all the major studies on sedation monitoring during PFA.

Despite the acknowledged role of operator preference, available studies do not provide robust multicentre data isolating operator experience as an independent predictor of anaesthesia-related complications or long-term outcomes.

Sedation strategies: deep sedation

DS protocols are typically based on titratable hypnotic agents, most commonly propofol (*Table 4*), with or without short-acting opioids (e.g. fentanyl; *Table 5*), and aim to achieve adequate analgesia, amnesia, patient immobility, and respiratory stability while avoiding endotracheal intubation and muscle relaxation, allowing rapid titration and recovery. In the context of PFA, DS requires specific adaptations to account for the characteristically brief but intense neuromuscular and sensory stimulation associated with pulse delivery, including anticipatory analgesia and transient deepening of sedation to ensure immobility. When implemented within standardized protocols and delivered by experienced multidisciplinary teams with appropriate monitoring and airway-rescue capabilities, DS has been shown to provide effective procedural conditions, high patient and operator satisfaction, and a favourable safety profile, supporting its role as a patient-centred alternative to GA in selected individuals. Details of the flowchart for DS and GA regimens are provided in *Figure 1*, *Figure 2* and *Figure 3*.

Propofol-based deep sedation

Propofol has a rapid onset, a short half-life, and requires careful cardiorespiratory monitoring due to its respiration-depressing effects and its dose-related impact on the sinus node and conduction system, potentially resulting in bradycardia and hypotension. Propofol has demonstrated its efficacy and beneficial safety profile in PFA-, cryoballoon-, and RF-based ablation in large studies, with low rates of necessary conversion to GA and a low incidence of sedation-related adverse events.[35] Even for unipolar PFA, which causes more intense skeletal muscle contractions, propofol-based sedation was associated with a safe and effective profile.[36] Additional bolus applications of opioids are advisable in cases of continuous pain during PFA applications. Despite its favourable characteristics, propofol should only be administered by trained and experienced personnel following structured sedation protocols.

Non-propofol deep sedation

Although propofol is considered safe and effective when used by trained personnel, respiratory depression remains a concern. Alternatively, regimens including midazolam, ketamine, dexamethasone, remifentanil, and/or dexmedetomidine may be used in PFA procedures to achieve DS while maintaining spontaneous breathing.[8,28] Non-propofol regimens may offer advantages in selected patients by preserving spontaneous ventilation, reducing the risk of hypotension or apnoea, and allowing for cooperative sedation; however, they may provide less predictable immobility and slower titratability, which are critical considerations during energy delivery. Consequently, non-propofol-based sedation is most often applied in carefully selected patients or as part of multimodal protocols, emphasizing the importance of individualized sedation planning and close anaesthetic monitoring. Finally, the choice of DS strategy should reflect institutional experience, institutional standards, local infrastructure, and individual patient characteristics.

Table 4 Hypnotic/sedative agents and key characteristics

Drug	Typical dosing range (IV)	Onset/offset	Duration	Key advantages in PFA	Key limitations/collateral effects
Midazolam	Bolus 0.5–2 mg (total 1–5 mg)	Onset 2–5 min/ moderate offset	Intermediate	Anxiolysis and amnesia; simple baseline conscious sedation	Respiratory depression; prolonged effect in elderly/ renal dysfunction; insufficient immobility alone
Propofol	Infusion 50–150 µg/ kg/min (± bolus)	Very rapid onset (30–60 s)/rapid offset	Short	Excellent titratability; rapid deepening before PFA pulses; reliable immobility	Hypotension, apnoea, loss of airway reflexes
Dexmedetomidine	Infusion 0.2–1.0 µg/ kg/h	Moderate onset/slow offset	Long (context-sensitive)	Minimal respiratory depression; opioid-sparing	Bradycardia, hypotension; slow recovery; often insufficient alone for PFA
Ketamine	Bolus 0.25–0.5 mg/ kg	Rapid onset/moderate offset	Intermediate	Preserves airway reflexes; strong analgesia; sympathetic support	Emergence reactions; hypersalivation; hypertension
Remimazolam	Bolus 2.5–5 mg; infusion 1–2 mg/ kg/h	Rapid onset/ ultra-rapid offset	Very short	Predictable recovery; minimal accumulation; flumazenil reversible	Limited availability and experience in EP labs

EP, electrophysiologist; PFA, pulsed field ablation.

Table 5 Opioid analgesic and key characteristics

Drug	Typical dosing range (IV)	Onset/offset	Duration	Key advantages in PFA	Key limitations/collateral effects
Fentanyl	Bolus 25–50 µg (repeat as needed)	Rapid onset/ moderate offset	Intermediate	Effective anticipatory analgesia before PFA pulses; familiar agent	Respiratory depression; accumulation with repeated boluses
Remifentanil	Infusion 0.02–0.1 µg/kg/min	Very rapid onset/ ultra-rapid offset	Very short	Precise titration synchronized with PFA pulses; no accumulation	Apnoea, hypotension; requires continuous infusion and close monitoring
Sufentanil	Bolus 5–10 µg or infusion 0.1–0.3 µg/kg/h	Rapid onset/slow offset	Long	High potency; stable analgesia for repeated PFA applications	Accumulation; prolonged respiratory depression

PFA, pulsed field ablation.

General anaesthesia approaches

GA represents the deepest level of anaesthesia, characterized by complete loss of consciousness, absence of responsiveness to painful stimuli, and the requirement for active airway management and ventilatory support.[37,38] The full suppression of voluntary and involuntary movement, including electroporation-induced skeletal muscle contractions, historically favoured GA during early PFA procedures with monophasic waveforms.[39–41] Meanwhile, the use of GA depends on several factors, including country-specific regulations, institutional protocols, patient characteristics, and operator preference.[22,23,25,26,42–48] *Figure 1* and *Figure 3* illustrate the proposed workflow for GA.

Common anaesthetic agents and monitoring requirements

GA during PFA procedures is most often induced using intravenous propofol in combination with short-acting opioids such as fentanyl or remifentanil. Depending on the PFA system and the extent of electroporation-induced muscle activity, neuromuscular blocking agents (e.g. rocuronium) have been administered to achieve complete immobilization.[35,44] Airway management is typically achieved through endotracheal intubation or a laryngeal mask airway (LMA) with controlled mechanical ventilation to ensure stable respiratory conditions throughout the procedure. An LMA is easier to insert and less invasive compared with endotracheal intubation.[49] However, LMA is frequently used without neuromuscular blocking agents (NMBA)s, which may increase the risk of airway reflexes. In the context of PFA, vagal nerve stimulation following pulse delivery may trigger sudden and severe laryngospasm, leading to a potentially life-threatening situation requiring urgent neuromuscular blockade and intubation.[50] Periprocedural monitoring must be continuous throughout the administration of all anaesthetics. This includes electrocardiography, (invasive) blood pressure assessment, pulse oximetry, capnography, and temperature monitoring, in accordance with established GA safety standards.[38,45,51] A neuromuscular-blockade monitor is required when neuromuscular blocking drugs are used, and an agent-specific anaesthetic gas monitor is required when inhalational agents are used.[46,47,51]

Advantages versus disadvantages of general anaesthesia in PFA settings

The principal advantages of GA in the PFA setting include maximal patient comfort, complete elimination of involuntary movement, full control over respiration, and highly controlled procedural conditions for the operator,[48] facilitating transseptal puncture and stable catheter positioning—particularly during energy application with focal PFA catheters—and enhancing 3D mapping precision.[22,24,48] Additionally, patient management during critical intraprocedural situations may be facilitated when PFA procedures are performed under GA. These situations include pronounced vagal responses with profound bradycardia, involuntary diaphragmatic contractions, coughing, and severe hypotension, which may occur after nitroglycerine administration commonly applied prior to cavotricuspid isthmus or mitral isthmus ablation to prevent coronary artery spasm. In such scenarios, GA allows greater control of ventilation and haemodynamics, enabling rapid and effective intervention and potentially improving procedural safety. These benefits must be balanced against relevant disadvantages, including the need for secured airway management and its potential complications, dedicated anaesthesia personnel, increased resource utilization and infrastructural demands, and longer preparation and post-procedural recovery times.[22,48] Additionally, a study comparing GA and DS using a lattice-tip PFA catheter demonstrated similar safety and efficacy, but longer laboratory occupation times with GA.[44] Considering contemporary PFA systems that induce less pronounced muscle contractions and allow shorter procedure times, GA is increasingly applied selectively rather than as a routine standard approach.[22] Finally, in several centres and regions, transesophageal echocardiogram-guided transseptal access when using GA represents standard practice and is considered an important safety measure. Intracardiac echocardiography may serve as an alternative imaging modality; however, its use is typically associated with a substantial increase in procedural costs.

Role of neuromuscular blockade and muscle contraction prevention

Muscle contractions occur during PFA, arising from tissue exposure to high-voltage electric fields. Early monophasic PFA waveforms were associated with pronounced skeletal muscle activation, necessitating GA with deep neuromuscular blockade to ensure patient immobility and procedural precision.[50]

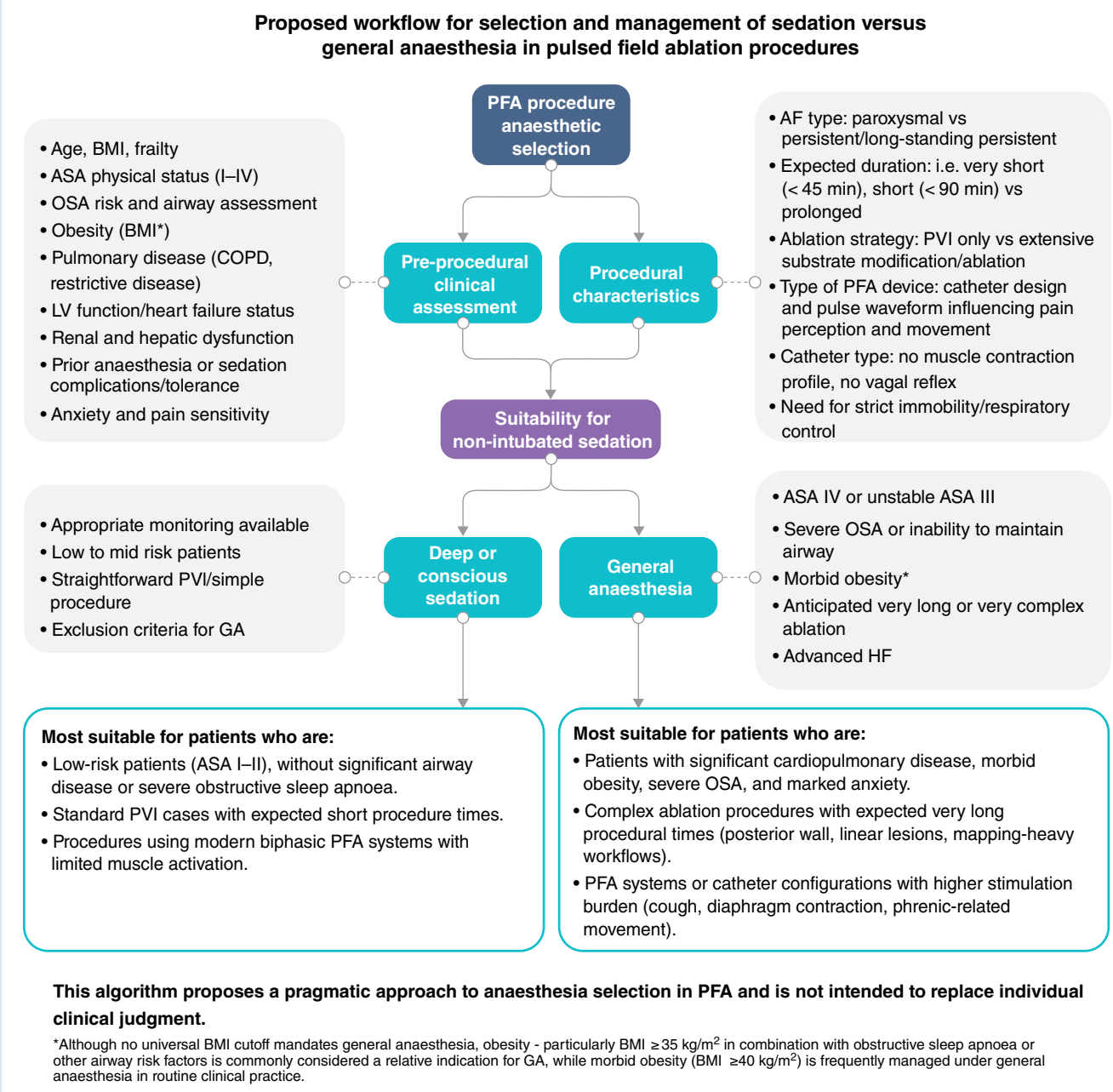


Figure 1 Proposed workflow for selection of anaesthesia/sedation strategy in pulsed-field ablation procedures.

Activation of nerves innervating muscles is thought to be the most likely mechanism of muscle stimulation, rather than direct muscle fibre stimulation.[52] Through stimulation of motor neurons innervating muscles, acetylcholine (ACh) is released at the neuromuscular junction, causing muscle fibre depolarization with a resultant increase in intracellular calcium release, leading to actin–myosin interactions and muscle contraction. The obvious consequences include diaphragmatic contraction and chest-wall movement causing coughing (also the result of a reflex arc), resulting in catheter movements, ablation-mapping shifts, and increased risk of complications such as perforation and tamponade.[53–57] Non-depolarizing NMBAs interrupt this sequence by occupying nicotinic ACh receptors on the postsynaptic membranes of the neuromuscular junction, preventing membrane depolarization and unwanted muscle contraction during critical stages of the procedure. In contrast, contemporary biphasic waveforms have been specifically engineered to mitigate these effects.[53] Experimental data demonstrate that short phase duration and interphase intervals, combined with longer interpulse intervals, significantly attenuate muscle contractions and pain without compromising lesion efficacy (*Figure 4*).[58] By increasing frequency (up to 10 kHz) with short pulses (<0.5 μs), sensory, motor, and pain thresholds are increased, thus minimizing stimulation of nerves and muscles during electroporation-based treatments.[59] These waveform refinements reduce neuromuscular excitability by limiting charge accumulation across excitable tissues, thereby improving procedural tolerability. Clinical studies and first-in-human experiences confirm that modern biphasic PFA systems exhibit substantially

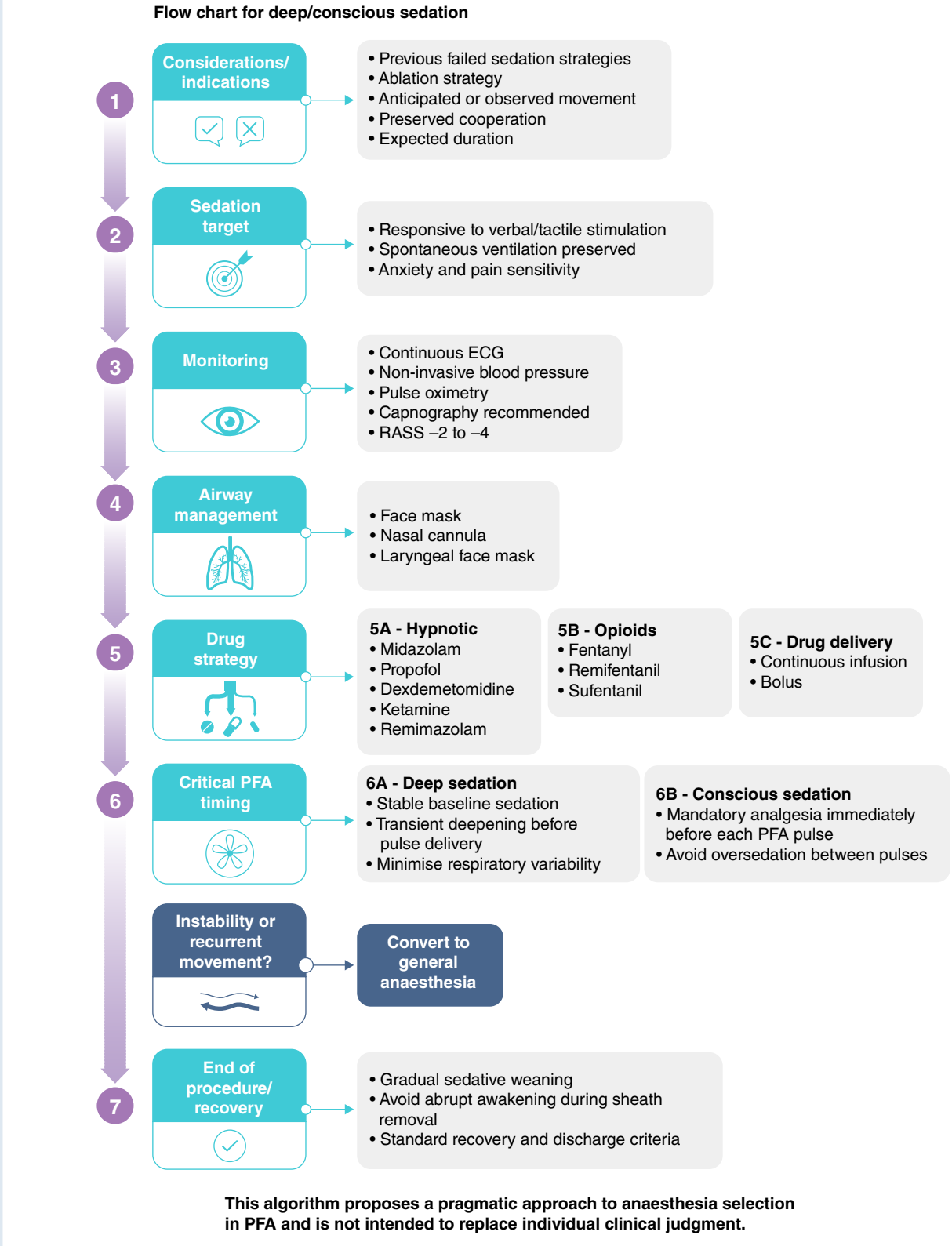


Figure 2 Proposed management of conscious sedation/deep sedation strategy in pulsed-field ablation procedures.

reduced skeletal muscle activation compared with historical monophasic platforms.[24,60] While GA can improve procedural precision through controlled ventilation and reduced motion,[61] there is significant evidence that DS can provide comparable outcomes.[35] As a result, the routine use of NMBAs is no longer universally required for PFA; instead, deep-sedation protocols

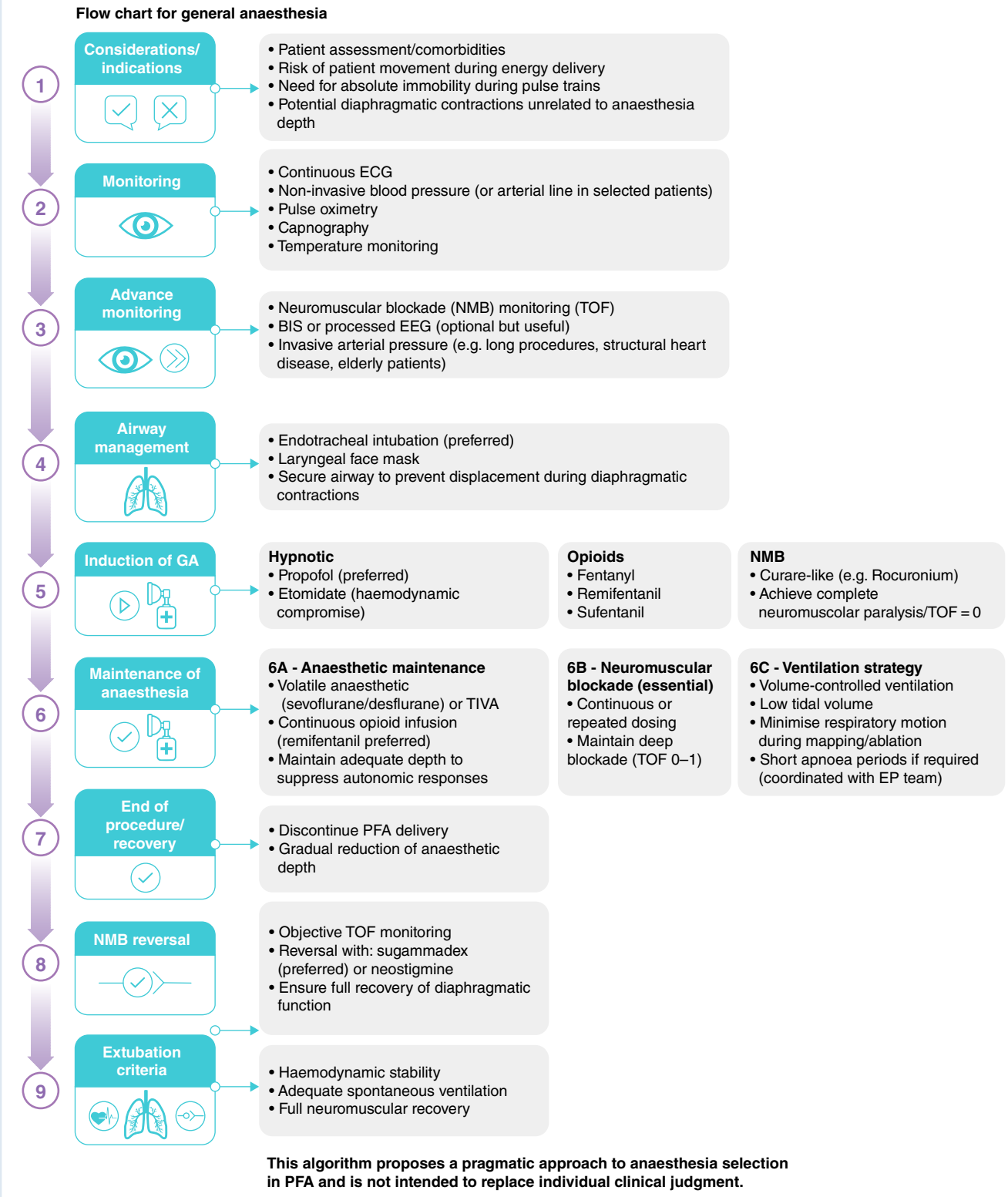


Figure 3 Proposed management of general anaesthesia strategy in pulsed-field ablation procedures.

—often incorporating short-acting hypnotics and opioids—are increasingly favoured. It is important to note that the use of NMBAs, normally employed to facilitate optimal tracheal intubation conditions (and not for continuous endotracheal-tube tolerance during an EP procedure), risks undetected phrenic nerve injury, and protection strategies should be used.[62,63] NMBAs may still be selectively employed as part of full anaesthesia-supported intervention in cases of excessive patient movement or

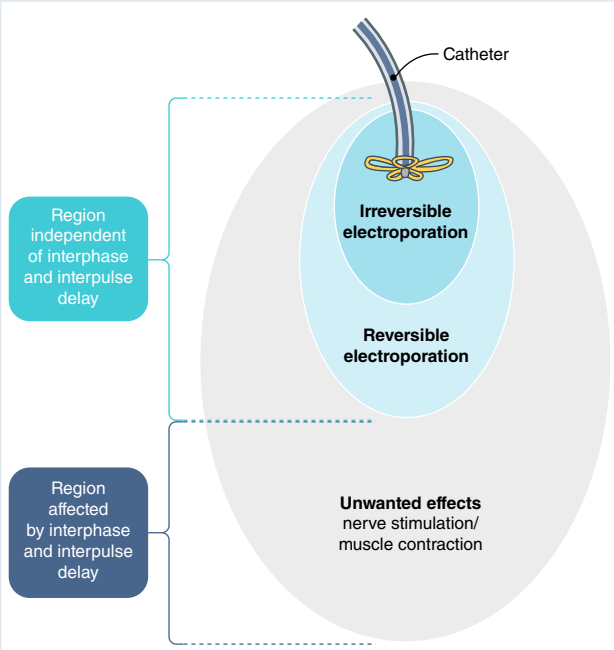


Figure 4 Schematic illustration of regions in and around the treatment site, showing areas dependent on and independent of the interphase (d1) and interpulse (d2) delays. The spatial extent of nerve excitation exceeds that of cell membrane electroporation, reflecting the lower activation thresholds required for neuromuscular stimulation compared with those for electroporation.[58]

discomfort, or when patient factors are not amenable to deep sedation—such as obesity, difficult airway, or significant comorbidity. GA with secured airway control remains appropriate in selected patients, such as those with severe obstructive sleep apnoea, limited cardiopulmonary reserve, or anticipated prolonged procedures, but it is no longer considered routine. It is clear that the routine use of NMB during biphasic PFA delivery is diminishing, representing a substantial departure from earlier PFA workflows that relied heavily on GA. The advent of nanosecond-waveform PFA, with its further reduction in muscle contraction and pain stimulation, will likely make CS an achievable goal.[64]

Intra-procedural management and monitoring

Sedation strategy, airway management, and oxygenation

Airway management under DS generally relies on spontaneous ventilation with supplemental oxygen via nasal cannula or face mask, with or without an oropharyngeal airway. High-flow nasal oxygen offering CPAP may be advantageous in selected patients by maintaining oxygenation during deeper sedation required for certain phases of a PFA procedure. Continuous capnography is recommended[65] to detect early respiratory compromise and to assist in titration of sedatives and analgesics, ensuring that the patient remains spontaneously ventilating—an essential aim during sedation. Processed EEG (e.g. BIS, PSI, entropy)[66,67] can further assist in titration of sedatives[68,69] and clinical recognition of sedation depth using validated scales such as the Richmond Agitation–Sedation Scale.[70] Where deeper sedation leads to inadvertent respiratory compromise (i.e. apnoea or loss of airway), the sedationist must manage the interim period by down-titrating sedatives and maintaining oxygenation through immediate airway manoeuvres (e.g. jaw thrust, airway opening techniques, bag-valve-mask ventilation), or by using a supraglottic airway device, until spontaneous ventilation is re-established. Anaesthesia support must be readily accessible if required. The use of IV lignocaine/lidocaine 1–2 mg/kg minutes before PFA energy delivery may mitigate coughing, whether reflex-mediated or directly stimulated.[71,72]

Pain and nociception monitoring

Despite reduced muscle contractions, electroporation remains a potent nociceptive stimulus. Pain perception during PFA has been reported even under CS, highlighting the importance of adequate analgesia in the absence of overt movement.[64] Objective nociception monitoring may offer additional value during deeply sedated PFA procedures. Indices such as the Analgesia Nociception Index and the Nociception Level Index reliably detect nociceptive responses under anaesthesia and sedation, often preceding haemodynamic changes.[73,74] Nociception-guided analgesia has also been associated with improved postoperative pain outcomes and reduced opioid consumption.[75] Integrating these technologies may allow individualized analgesic titration, improving comfort while avoiding oversedation—particularly valuable for short PFA procedures.

Haemodynamic stability

Biphasic PFA may still provoke transient autonomic responses, including brief fluctuations in blood pressure or heart rate. Continuous non-invasive or invasive haemodynamic monitoring should be selected based on patient risk profile. Balanced sedation strategies and judicious use of vasoactive agents help maintain stability, particularly in patients with structural heart disease.[24,76]

Recovery phase considerations

One major advantage of DS for PFA is rapid recovery. Short-acting sedative and analgesic agents facilitate early awakening, neurological assessment, and mobilization. Post-procedural pain is typically mild, but systematic assessment remains important—especially when nociception-guided strategies were used intra-procedurally.

Tailoring anaesthesia to patient and procedural needs

No universally validated algorithm exists for anaesthesia selection during PFA procedures.[22,24] However, contemporary practice integrates multiple factors to guide individualized decision-making as reported in the proposed workflow (*Figures 1–3*). The main decision factors are:

- *The American Society of Anesthesiologists (ASA) Physical Status Classification:* ASA classification is widely used for pre-procedural risk stratification, grading patients from ASA I (healthy) to ASA VI based on systemic disease severity. In atrial fibrillation ablation, the ASA score assists in estimating anaesthetic risk and guiding the selection of CS, DS, or GA, as well as the required level of monitoring and anaesthesiology involvement. Higher ASA classes (≥III) are associated with increased susceptibility to

Table 6 Literature overview of published experience focused on sedation protocol during PFA for AF

Study/Year	PFA technology/setting	Sedation/ anaesthesia	Drug details/primary drug regimen	Sample size	Study type	Key findings
Grimaldi *et al.* (Europace 2023)[28]	Variable-loop biphasic PFA, PVI only	DS	Midazolam, ondansetron, dexamethasone, dexmedetomidine, remifentanil	29	Prospective, single-centre	Adequate sedation depth (RASS −1 to −5); high satisfaction; no procedural complications
Iacopino *et al.* (Europace 2023)[8]	Pentaspline PFA, PVI only	DS	low-dose fentanyl + midazolam + ketamine in spontaneous respiration	66	Prospective, single-centre	100% PVI; high patient and operator satisfaction; no major anaesthesia-related complications
Rillig *et al.* (Europace 2024)[35]	PFA with lattice-tip catheter, PVI/PVI+	GA vs. DS	GA: remifentanil infusion + bolus of propofol, then continuous infusion of both DS: bolus on fentanyl and propofol then continuous infusion of propofol	63 (23 vs. 40)	Retrospective, multicentre	Comparable acute PVI success; shorter lab occupancy with DS; low conversion to GA
Weyand *et al.* (Journal of Clinical Medicine 2024)[32]	Focal PFA, PVI/PVI+	DS	Continuous infusion of propofol and remifentanil	30	Retrospective, single-centre	High procedural efficacy; safe DS
Iacopino *et al.* (Journal of Cardiothoracic and Vascular Anesthesia 2024)[79]	Pentaspline PFA, PVI only	DS	Midazolam, fentanyl, ketamine	117	Prospective, single-centre	100% PVI; high satisfaction; effective pain control; no major sedation-related complications
Wahedi *et al.* (Journal of Cardiovascular Electrophysiology 2024)[80]	Pentaspline PFA vs. Cryo, PVI only	DS	Continuous propofol, midazolam, sufentanil	50 (PFA) + 50 (Cryo)	Prospective, single-centre	100% PVI without conversion to GA; dose of sufentanil required was significantly higher in PFA group; rate of complication similar between groups
Galuszka *et al.* (Journal of the American Heart Association 2024)[37]	Pentaspline PFA vs. Cryo vs. RF, PVI only	DS	Propofol, midazolam and fentanyl	429 (PFA) + 412 (Cryo) + 208 (RF)	Retrospective, single-centre	Total doses of propofol and fentanyl comparable between PFA and Cryo, higher than in RF.
Metzner *et al.* (Heart Rhythm 2024)[81]	PFA and RF with lattice tip catheter, PVI/PVI+	GA/DS	Intravenous propofol, midazolam and fentanyl	25 (18/7)	Prospective, single-centre	DS seemed feasible
Hirokami *et al.* (Heart Rhythm 2024)[82]	PFA and RF with lattice tip catheter, PVI/PVI+	GA/DS	GA: muscle relaxants + endotracheal intubation DS: propofol, midazolam, fentanyl	55 (15/40)	Retrospective, multicentre	100% PVI; 4 linear ablations in DS group required a switch of ablation energy
Sochorová *et al.* (Circulation 2025)[83]	Pentaspline PFA, PVI/PVI+	DS#1 vs. DS#2 vs. GA (TIVA)	DS#1 continuous remimazolam-ketamine DS#2 intermittent	127 (43 vs. 42 vs. 42)	Randomized, single-centre	Remimazolam-ketamine DS superior to propofol-opioid regimens (either boluses

Continued

Table 6 *Continued*

Study/Year	PFA technology/setting	Sedation/ anaesthesia	Drug details/primary drug regimen	Sample size	Study type	Key findings
			propofol-opioid boluses TIVA: continuous propofol-opioid with secured airway			or continuous) with fewer adverse sedation events
Chen *et al.* (Interventional Journal of Cardiology 2025)[84]	Variable-diameter circular catheter, PVI/ PVI+	GA/DS/CS	*Not specified*	159 (45/5/ 109)	Prospective, multicentre	Effectiveness comparable between CS and GA/DS, longer procedure times under CS.
Calvert *et al.* (Journal of Interventional Cardiac Electrophysiology 2025)[26]	Pentaspline PFA, PVI/ PVI+	GA vs. DS	GA: Propofol CS: Midazolam + Fentanyl	23 (15 vs. 8)	Prospective, single-centre	2 patients switched from CS to GA; better post-op experience with CS; higher level of pain and anxiety with CS
Patel *et al.* (Journal of Interventional Cardiac Electrophysiology 2025)[21]	Circular loop catheter/ Pentaspline PFA, PVI only	DS	Propofol, dexmedetomidine, fentanyl, midazolam	100	Retrospective, single-centre	100% PVI, no airways complications, no conversions from DS to GA
Van der Graaf *et al.* (Journal of Interventional Cardiac Electrophysiology 2025)[71]	Circular loop catheter, PVI only	GA vs. CS	GA: fentanyl, propofol, opioid continuous infusion CS: atropine, lidocaine, fentanyl, diazepam	175 (132 vs. 43)	Retrospective, single-centre	No conversion to GA; no CS patients experienced complications; 100% PVI
Nakahara *et al.* (Heart Rhythm Supplement 2025)[85]	Variable loop catheter PFA	GA vs. DS	*Not specified*	24 (12 vs. 12)	Prospective, single-centre	Minimal catheter movement with GA; 2 DS patients needed remapping due to movement
Carboni *et al.* (Europace Supplement 2025)[20]	Pentaspline PFA, PVI/ PVI+	GA vs. DS	*Not specified*	478 (341 vs. 137)	Prospective, multicentre	High patient and operator satisfaction; procedural feasibility of DS across centres.
Tilz *et al.* (Europace Supplement 2025)[86]	Balloon in Basket PFA, PVI only	DS vs. DS/CS	*Not specified*	146 (91 vs. 55	Prospective, multicentre	No adverse events associated with movement in both CS/DS groups; no outcomes differences
Chun *et al.* (Europace 2025)[22]	Pentaspline PFA, PVI/ PVI+	GA vs. DS	*Not specified*	1233 (250 vs. 983)	Prospective, multicentre	Fluoroscopy time shorter with DS; no differences in long term outcome
Tilz *et al.* (Heart Rhythm O2 2025)[87]	Balloon in Basket PFA, PVI/PVI+	CS	Metamizole, fentanyl, midazolam	14	Prospective, Single-centre	100% PVI; high-level of satisfaction
Sciacca *et al.* (Heart Rhythm 2025)[10]	Variable-loop catheter PFA, PVI only	DS	Propofol, Midazolam, Fentanyl	61	Prospective, Single-centre	Positive patient feedback
Compagnucci *et al.* (Heart Rhythm 2026)[88]	Pentaspline PFA, PVI/ PVI+	GA vs. DS	GA: propofol with mixed strategies (desflurane,	1188 (745 vs. 443)	Prospective, multicentre	High level of both patient- and

Continued

Table 6 *Continued*

Study/Year	PFA technology/setting	Sedation/ anaesthesia	Drug details/primary drug regimen	Sample size	Study type	Key findings
			midazolam, fentanyl/ remifentanil) DS: mixed approach (propofol, ketamine, midazolam, primarily fentanyl)			operator-reported positive outcomes across GA and DS strategies

CS, conscious sedation; DS, deep sedation; GA, general anaesthesia; PFA, pulsed field ablation; PVI, pulmonary vein isolation; PVI+, pulmonary vein isolation with additional lesion set; RF, radiofrequency.

sedation-related complications and may warrant more controlled anaesthetic approaches and closer peri-procedural surveillance.

- *Patient Comorbidities:* Pre-operative assessment should explicitly evaluate respiratory and cardiac comorbidities, as these increase risk during spontaneous-breathing sedation.[22,24,33] Patients with significant airway risk, severe obstructive sleep apnoea, or advanced heart failure (HF) typically warrant GA for airway control and haemodynamic stability.[33,34]
- *Procedural Complexity:* More complex procedures may favour GA to ensure patient immobility and optimal procedural conditions.[8,19,22,24,28] However, substantial variability exists across geographic regions. In contrast, shorter and more straightforward PVI procedures in low-risk patients may be suitable for DS.[8,28]
- *Catheter Type and Waveform Effects:* PFA systems vary in their stimulation profiles. Devices producing pronounced muscle contractions, cough reflex, or vagal responses necessitate deeper anaesthesia.[8,19,22,24,28] Emerging nanosecond PFA systems that reduce muscle contractions may allow lighter sedation in selected patients, though clinical validation is ongoing.[36]

In practice, these factors interact: procedural stimulation and complexity determine the minimum sedation depth required for catheter stability, while patient comorbidity and local resources determine the safest way to deliver it. The following section summarizes the clinical evidence base that supports this individualized approach, with particular attention to outcomes and patient experience under GA and DS.

Literature overview of clinical evidence

Clinical evidence informing anaesthesia selection for PFA is largely pragmatic rather than prescriptive. Across pivotal randomized trials[77,78] and post-approval clinical programmes, anaesthesia was most often selected per local practice (GA or DS) rather than mandated by protocol (*Table 6*). Taken together, these programmes show that both GA and DS are feasible in randomized settings. Prospective registries and multicentre real-world series[22,89–92] or post-approval surveillance datasets[93,94] provide the clearest picture of contemporary sedation practice. Importantly, clinical effectiveness and low rates of major collateral injury were preserved across centres using different anaesthesia strategies, with patient selection (e.g. severe pulmonary disease, sleep apnoea) influencing the choice of GA. Single-centre and observational studies specifically addressing anaesthesia/sedation provide practical protocols and direct comparisons (*Table 6*). Early prospective single-centre studies described standardized DS regimens using midazolam/fentanyl with ketamine adjuncts,[8,92] or midazolam/remifentanil with dexmedetomidine.[28] More recent observational registries comparing CS (or DS without airway instrumentation) versus GA for certain PFA platforms (including over-the-wire circular and lattice-tip systems) report comparable acute isolation success, suggesting both approaches can be safe and effective when protocols, monitoring, and selection criteria are rigorously applied. From the patient perspective, DS is practical for PFA, improving workflow and patient experience without compromising safety. Positive patient feedback highlights that sedation quality strongly influences acceptance and willingness for repeat intervention.[10,20] In the largest reported assessment of pentaspline PFA to date—evaluating both patient- and operator-reported outcomes across GA and DS strategies—both approaches were associated with uniformly high satisfaction (*Table 6*).[88] Overall, the available literature supports a tailored approach: PFA can be performed under monitored CS/DS or under GA with airway control, with selection driven by patient

comorbidity, anticipated procedural complexity, and local resources. We acknowledge that a substantial portion of the currently available clinical data refers to a single PFA technology. This largely reflects the present state of the evidence, as the majority of published clinical experience—including registry data—pertains to the most mature and widely adopted platform. These data also highlight the need for prospective, comparative studies focusing on patient experience, efficiency, different technologies, and rare adverse events, which are addressed further in subsequent sections.

Emerging trends and technological advancements

Technological innovation is rapidly reshaping anaesthetic needs in PFA. One of the most important developments is pulse modulation, which aims to reduce skeletal muscle activation by adjusting waveform shape, polarity, pulse timing, and field distribution. Particularly, the adoption of biphasic pulse configurations with optimized timing parameters has substantially reduced muscle contractions and improved procedural tolerability. These refinements are essential to incorporate into next-generation systems to meaningfully decrease involuntary contractions, thereby reducing the depth of anaesthesia required for safe and controlled ablation. Evolution of current and future PFA systems could also lead to technology-specific procedural characteristics as potential determinants in selecting the most appropriate sedation strategy. Technological integration is also improving sedation delivery. Processed EEG monitoring, advanced capnography, and nociception indices now permit finer titration of sedatives and analgesics, reducing oversedation risk.[95,96] Alongside waveform optimization, there is increasing interest in the future role of CS-only protocols. As PFA becomes less painful and more movement-sparing, selected procedures may be performed using CS without compromising comfort, safety, or catheter stability. Early experiences in certain PFA systems, including conscious non-propofol-based sedation cohorts in recent PFA studies,[8,28,97] suggest feasibility and good patient tolerance, although broader validation is still needed. Differences in sedation protocols may also significantly influence post-procedural recovery profiles and, consequently, the feasibility of same-day discharge following AF ablation. Optimized, fast-recovery sedation strategies could facilitate safe early mobilization and monitoring, supporting same-day discharge in carefully selected patients.[98–100]

Pharmacological innovation is another expanding frontier. Remimazolam, an ultra–short-acting benzodiazepine with predictable kinetics and rapid reversal, has emerged with the potential to offer a more haemodynamically stable and deeper sedation alternative to midazolam, and may even be comparable to propofol for EP procedures requiring titratable sedation, with the added advantage of a specific antagonist (flumazenil).[83] Meanwhile, ketamine, although less studied in PFA, provides strong analgesia, preserves respiratory drive, and may complement low-dose opioid or benzodiazepine strategies.[79] Together, these evolving technologies and pharmacological agents signal a future in which PFA can be performed more efficiently, more comfortably, and with reduced reliance on propofol-based deep sedation or resource-demanding GA.

Future directions and research needs

Despite growing clinical experience, significant uncertainties remain regarding optimal sedation and anaesthesia strategies for PFA. A major gap is the lack of evidence defining the ideal anaesthesia depth, including objective thresholds for movement suppression, pain control, coughing, and haemodynamic stability. Current studies vary widely in assessment methods making comparisons across systems difficult. Standardized safety endpoints, such as hypoxia, use of necessary airway manoeuvres, hypotension, and recovery times, are also inconsistently reported. A related limitation is the absence of standardized measures for pain and movement in PFA trials. The field would benefit from consensus scoring tools that capture both procedural discomfort and electroporation-induced muscle activation. Objective tools—such as accelerometry, EMG-based movement indices, EEG-based depth monitoring and nociception, or validated pain scales—should be incorporated into future study designs to allow meaningful comparison between technologies, catheters, and sedative regimens. Further, there is a need to develop predictive models that guide anaesthesia planning based on patient characteristics (frailty, sleep apnoea, HFpEF, obesity), procedure type, and catheter configuration. Machine learning and artificial intelligence tools may help determine which patients are appropriate for CS and which require deeper support.[101,102] Randomized trials or large-scale multicentre registries will be essential to compare sedation practices across institutions, evaluate rare adverse events, and identify best practices. Remimazolam represents a compelling candidate for future PFA workflows, but its role remains largely unexplored in electrophysiology. Finally, future PFA device innovation should integrate anaesthesia considerations directly into system design. This includes waveform refinement for minimal muscle activation, quieter or shorter pulse sequences, catheters engineered for movement-resistant stability, and real-time communication between ablation systems and anaesthetic monitors. Collaboration between engineers, electrophysiologists, and anaesthesiologists will be essential to build PFA platforms that are inherently compatible with lighter, safer, and more streamlined anaesthesia strategies.

Key points and practical takeaways

- *Who is best suited for DS:*
  - Low-risk patients (ASA I–II), without significant airway disease or severe obstructive sleep apnoea.
  - Standard PVI cases with expected short procedure times.
  - Procedures using modern biphasic PFA systems with limited muscle activation.
- *Who is best suited for GA:*
  - Patients with significant cardiopulmonary disease, morbid obesity, severe OSA, marked anxiety.
  - Complex ablation procedures with expected very long procedural times (posterior wall, linear lesions, mapping-heavy workflows).
  - PFA systems or catheter configurations with higher stimulation burden (cough, diaphragm contraction, phrenic-related movement).
- *Sedation strategy must match expected neuromuscular stimulation:*
  - Catheters/pulse trains producing more intense contractions (diaphragmatic or chest-wall contractions) → DS with careful titration or GA.
  - Contemporary biphasic waveforms often allow DS; emerging ultra-short or nanosecond pulses may make CS viable.
- *Monitoring requirements that are non-negotiable for DS:*
  - Continuous ECG, pulse oximetry, blood-pressure monitoring.
  - Continuous capnography should be adopted to detect early hypoventilation.
  - Immediate ability to perform airway manoeuvres (jaw thrust, airway adjuncts, BVM ventilation).

- Trained staff capable of managing inadvertent apnoea or loss of airway.
- *Monitoring requirements for GA:*
  - Full ASA-standard monitoring including capnography, neuromuscular-blockade monitoring (when NMBs are used), and temperature control.
  - Controlled ventilation via ETI or LMA, with awareness of LMA-related airway reflex risks in PFA.
- *Pain is not eliminated by reduced muscle activation:*
  - PFA remains a strong nociceptive stimulus; anticipatory analgesia is important.
  - Consider nociception-guided analgesia indices (e.g. ANI, NOL) when available.
- *Recovery considerations:*
  - DS enables rapid awakening and turnover; ideal for high-throughput PVI workflows.
  - GA may prolong recovery but ensures maximal immobility and airway control.
- *Local resources drive real-world choices and strongly influence strategy:*
  - Availability of anaesthesia support, workflow pressures, and national regulations decisively shape sedation strategy.
  - Centres with limited anaesthesia availability may rely more on electrophysiologist-directed DS workflows.
  - Centres with full anaesthesia support may use GA more liberally for efficiency and haemodynamic control.

Conclusion

(a) *What is established*
   (a) Both DS and GA provide safe and effective procedural conditions for PFA, with comparable acute success and mid-term arrhythmia outcomes.
   (b) Adequate monitoring—e.g. continuous capnography and immediate airway-rescue capability—is essential for safe DS.
   (c) Patient-specific factors (airway, comorbidities, anxiety), procedural complexity, and institutional expertise remain central to sedation selection.

(b) *What is device-/centre dependent*
   (a) Required anaesthesia depth varies by PFA system, waveform, catheter geometry, and expected nerve/muscle stimulation.
   (b) Airway strategies (DS with spontaneous breathing vs. GA with LMA/ETT) differ across centres depending on staffing and regulatory frameworks.
   (c) Anaesthesia-delivered vs. electrophysiologist-led sedation is strongly shaped by local infrastructure, availability of anaesthesia personnel, and national norms.

(c) *What remains uncertain*
   (a) The optimal anaesthesia depth for different PFA systems is not yet defined; objective thresholds for movement suppression and analgesia are lacking.
   (b) No standardized metrics exist for movement burden, cough reflex, pain scores, or haemodynamic perturbations during PFA.
   (c) The future role of remimazolam, multimodal DS protocols, or ultra-short waveform PFA enabling true CS requires dedicated study.
   (d) Prospective randomized comparisons of GA vs. DS—focusing on patient experience, workflow efficiency, and rare adverse events—are still needed.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Treatment of paroxysmal and persistent atrial fibrillation with pulsed field ablation

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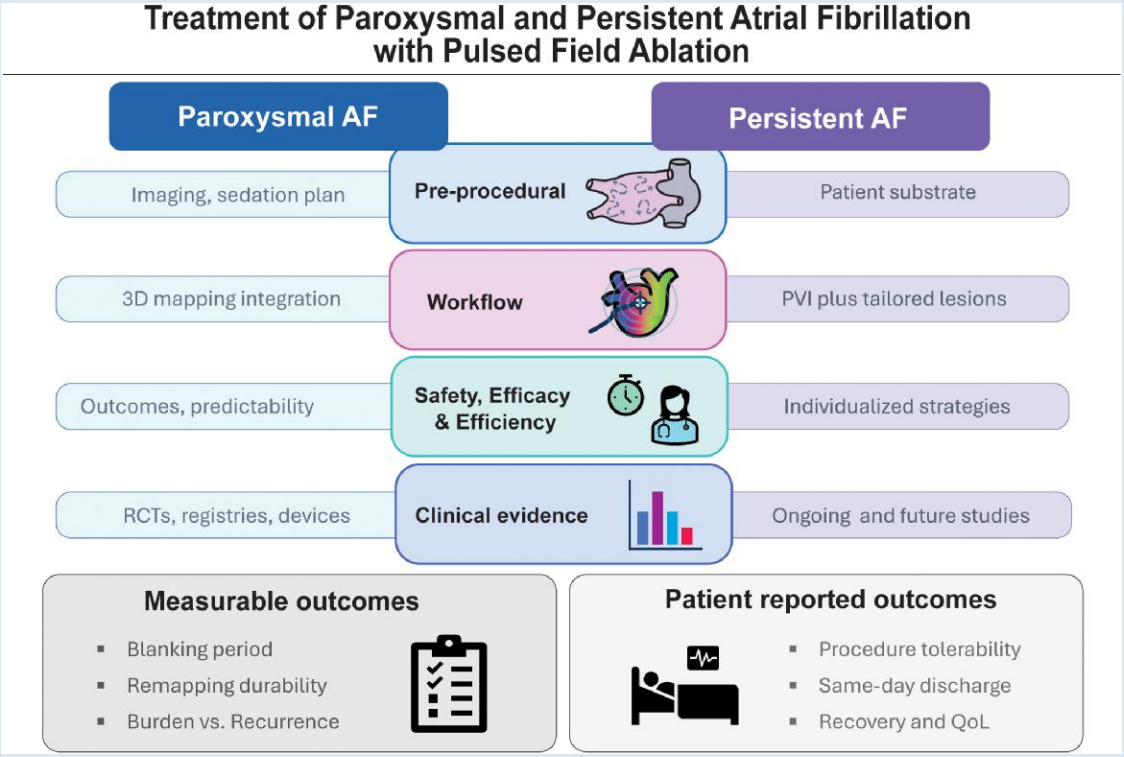
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Abstract

Pulsed field ablation has emerged as a novel energy source for atrial fibrillation ablation, offering preferential myocardial ablation with a favourable safety profile. Contemporary paroxysmal AF clinical studies demonstrate 12-month freedom from atrial arrhythmia recurrence in approximately 75-85% of patients, with major complication rates generally ranging from 1 to 3%. Compared with thermal ablation, PFA offers comparable efficacy and streamlined procedural workflows. In persistent AF, PVI remains the foundation of ablation, while additional adjunctive strategies are increasingly evaluated. Current evidence suggests that PFA can achieve 12-month arrhythmia-free outcomes generally ranging from approximately 60-75% in persistent AF populations. Major procedure-related complications typically occur in <3% of cases, supporting the feasibility of broader lesion sets with an acceptable safety profile. However, the incremental benefit of adjunctive ablation beyond PVI and the optimal lesion set for persistent AF remain to be assessed further Outcome assessment after PFA requires consideration of evolving endpoints. The clinical relevance of the traditional post-ablation blanking period is being re-evaluated, while continuous rhythm monitoring and AF burden are increasingly incorporated alongside conventional recurrence endpoints. Patient-reported outcomes are an important component of PFA evaluation. Compared with thermal ablation, PFA is associated with improved procedural tolerability, reduced analgesic requirements, rapid recovery, and the potential for same-day discharge. These features, together with favourable efficacy and safety outcomes, may contribute to broader adoption of PFA across both paroxysmal and persistent AF populations.

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Graphical Abstract



Keywords Pulsed field ablation • Atrial fibrillation • Paroxysmal atrial fibrillation • Persistent atrial fibrillation • Procedural workflow • Safety • Procedural efficacy • Mid and long term efficacy • Clinical evidence • Measurable outcomes • Blanking period definition for PFA • PVI durability • AF burden • Patient reported measurable outcomes • Post-ablation recovery and return to activity • Patient-reported outcomes and quality of life

Introduction

Pulsed field ablation (PFA) has emerged as a largely non-thermal energy modality that utilizes the principle of irreversible electroporation to achieve myocardial tissue ablation. By preferentially targeting cardiomyocytes while sparing adjacent structures such as the oesophagus and phrenic nerve and avoiding pulmonary vein stenosis, PFA offers the potential for improved safety and procedural efficiency for atrial fibrillation (AF) ablation. Early clinical experience and growing evidence suggest that PFA may overcome several limitations of conventional ablation technologies, with shorter procedure times, a favourable safety profile, and promising efficacy outcomes.

As PFA technology rapidly evolves, its application across different AF populations—including paroxysmal AF (PAF) and persistent AF (PersAF)—is being actively investigated. Key considerations include patient selection, procedural workflows, procedural efficacy, safety and efficiency, integration with advanced three-dimensional mapping systems, and durability of lesion formation. In parallel, there is increasing interest in measurable clinical outcomes of AF ablation, ranging from arrhythmia recurrence and AF burden to patient-reported quality of life and recovery trajectories.

This document provides a comprehensive overview of PFA in contemporary AF management. It explores procedural strategies in PAF and PersAF, evaluates clinical and patient-centred outcomes, and highlights current evidence as well as ongoing research efforts. Together, these insights aim to inform clinical decision-making and guide future developments in the field of AF ablation.

PFA in paroxysmal AF

Introduction

Pulmonary vein isolation (PVI) represents the procedural cornerstone and primary endpoint of catheter ablation for PAF.[1] Conventional radiofrequency (RF) and cryoballoon (CB) PVI technologies rely on thermal tissue injury and are therefore associated with the risk of collateral damage to adjacent structures. PFA has emerged as a predominantly non-thermal energy modality and is regarded as a potentially transformative technology for AF ablation, particularly in PAF, with rapid adoption into clinical practice.[2] This section focuses on established devices currently used in routine clinical practice.

Pre-procedural considerations

Imaging

The EHRA clinical consensus document alludes to the importance of cardiac computed tomography (CT) or magnetic

resonance (MR) imaging for anatomic and substrate delineation in complex AF and ventricular tachycardia (VT) ablation procedures.[3] In general, pre-procedural imaging remains institution- and workflow-dependent and may include no dedicated imaging, cardiac MR imaging, or CT. Its use should not differ from thermal ablation protocols. Given the availability of large-diameter, anatomy-based single-shot PVI catheters, omission of systematic pre-procedural imaging is feasible and widespread. Similar to thermal energy PVI procedures, to exclude left atrial thrombus, transoesophageal echocardiography, intra-cardiac echocardiography (ICE), or cardiac CT is recommended in patients with a CHA_2DS_2-VA score ≥ 1 who have not received continuous oral anticoagulation (OAC) for at least 3 weeks.[1] OAC is generally managed uninterrupted or with omission of the morning dose on the day of the procedure and resumption in the evening.

Sedation vs. general anaesthesia

A systematic review and meta-analysis of 12 302 patients undergoing catheter ablation for AF showed that there was no significant difference in recurrence of atrial tachyarrhythmias between general anaesthesia (GA) and sedation.[4] Similarly, a prospective registry of 1002 patients showed that conscious sedation is as safe and effective as GA in AF ablation, particularly with cryoablation. The choice of anaesthesia appears to be driven by patient characteristics and institutional factors without affecting long-term outcomes such as AF recurrence or complication rates.[5]

Skeletal muscle activation during PFA generally necessitates deep sedation or GA to ensure patient comfort and catheter stability, even though conscious sedation has been used successfully with some PFA platforms.[6] Initial European experience has demonstrated feasibility and safety of deep sedation with both bipolar and monopolar PFA systems.[7,8] Importantly, the sedation strategy is typically guided by national regulations and institutional practice.[9] While GA is frequently adopted in the United States, deep sedation is commonly used in several European countries and supported by a well-trained electrophysiology team.

Procedural workflow and 3D mapping integration for PVI

For PVI-only procedures, the introduction of single-shot technologies led to a shift from point-by-point RF ablation towards anatomy-based approaches, which was rapidly adopted in early PFA systems.[10] After femoral venous access and transseptal puncture, contemporary anatomy-based PFA systems enable rapid PVI using multielectrode catheters delivering high-voltage pulses. Catheter positioning may be guided by fluoroscopy alone or combined with ICE or 3D mapping. Energy delivery at the PV ostium or antrum, often with catheter rotations, results in acute elimination of PV potentials. Anticholinergic agents or RSPV first isolation may mitigate vagal reflexes.[11–13] More recent PFA platforms integrate advanced 3D mapping and/or ICE to assess catheter positioning and tissue contact, facilitating tailored strategies, including substrate-based targets beyond the PVs or the posterior LA wall. Owing to its favourable safety profile, PFA has generally reduced or obviated routine use of oesophageal temperature monitoring in many centres, although practices vary. Although some strategies support fluoroscopy-guided workflows,[14] 3D mapping is increasingly adopted, providing anatomical visualizations, catheter navigation, lesion prediction, impedance-based contact assessment, and identification of low-voltage areas.[15,16] While PFA-based PVI can be performed with minimal mapping, 3D mapping may facilitate lesion documentation, confirmation of isolation, and voltage assessment. In the MANIFEST-REDO study, the use of imaging or 3D mapping during *de novo* PVI was associated with greater PVI durability.[17] However, to date, no RCT has been carried out to show improved clinical success with routine 3D mapping in PFA, supporting its role as an adjunct.[18]

Clinical studies

Clinical evidence for PFA in PAF includes RCTs, large real-world registries, and procedural refinement studies addressing lesion durability.

Randomized controlled trials

RCTs available with the pentaspline catheter consistently demonstrate non-inferiority of PFA compared with thermal ablation. In ADVENT,[18] PFA achieved comparable 12-month freedom from atrial arrhythmia recurrence vs. RF and CB ablation, with high acute PVI rates and a favourable safety profile despite limited operator experience with PFA. In single Shot Champion, experienced operators confirmed non-inferiority of single-shot PFA vs. CB ablation, with a signal towards improved efficacy.[19] Continuous monitoring with implantable loop recorders (ILRs) showed comparable AF burden.[20] Most recently, the BEAT PAROX-AF trial was published demonstrating comparable PVI success rates with the pentaspline PFA vs. focal RF energy (77, 2% vs. 77, 6%) in experienced centres using the CLOSE protocol (*Table 1*). Importantly, after RF ablation, PV stenosis was noted in 12 patients ($n = 2 > 70\%$, $n = 10 > 50\%$, 11.3%). Clinical efficacy outcomes with the pentaspline catheter in all RCTs were comparable, while procedural metrics and safety favoured PFA (*Figure 1*).

Registry and real-world studies

Large multicentre registries covering different workflows extend these findings to routine practice, reporting near-universal 100% acute PVI, elimination of major thermal complications, and mid-term single-procedure arrhythmia-free survival of ~70–>80%, depending on monitoring strategy.[21,22]

Durability optimization: the olive strategy

Procedural techniques can influence PVI durability. In a single centre study with the pentaspline catheter, the 'olive' strategy (2 PF applications in a smaller basket configuration placement into the PV ostium) seemed to improve lesion durability without compromising safety based on invasive remapping suggesting reduced PV reconnection and no increase in complexity or complications[23] (*Figure 2*).

Novel PFA devices

The role of emerging PFA technologies including balloon-based systems, basket and circular catheters with or without guidewires, spherical arrays, large-footprint, and small-tip devices, as well as hybrid platforms allowing switching between RF and PFA remains to be defined and warrants evaluation in large-scale randomized and real-world studies[24–31] *Table 2* refers to major PFA device categories and technical details.

Safety

Despite overall improvements in AF ablation, patient safety remains central in AF ablation.[33] Due to its near non-thermal mechanism, PFA shows significantly reduced collateral injury. Large-scale data report no atrio-oesophageal fistula, no clinically relevant PV stenosis, and an extremely low risk of phrenic nerve palsy. Post-procedural haemolysis after PFA for AF treatment is believed to be common and occurs across different types of PFA

Table 1 Randomized clinical trials of pulsed field ablation vs. thermal ablation

	ADVENT (2023)	SINGLE SHOT (2025)	BEAT PAROX-AF (2026)
Comparator	RF/CB	CB	RF
Patients (n)	305	210	292
Mean Procedure time (min)	PFA 105.8 ± 29.4 Thermal 123.1 ± 42.1	PFA 54.8 ± 22.7 CB 73.2 ± 26.7	PFA 59 ± 22 RF 98 ± 33
Mean Fluoroscopy time (min)	PFA 21.1 ± 11.0 Thermal 13.9 ± 12.8	PFA 14.6 ± 7.2 CB 15.1 7.9	PFA 12 ± 6 RF 7 ± 6
Acute PVI success	>99%	100%	100%
Primary Efficacy Endpoint	Freedom from a composite of initial procedural failure to achieve pulmonary vein isolation with the use of the randomly assigned treatment method only, documented atrial tachyarrhythmia lasting 30 s or longer after the 3-month blanking period, the use of class I or III antiarrhythmic drugs or cardioversion after the 3-month blanking period, the use of amiodarone at any time, or repeat ablation at any time during the 1-year follow-up period	The first recurrence of any atrial tachyarrhythmia (atrial fibrillation, flutter, or tachycardia) lasting at least 30 s during the period from Days 91 to 365 after the ablation procedure	Single-procedure success rate after 12 months defined as the absence of ≥30 s atrial arrhythmia recurrence, class I/III antiarrhythmic drug resumption after a 2-mo blanking period, or any repeat ablation
Primary Safety Endpoint	A composite of prespecified device- and procedure-related serious adverse events within 7 days after the procedure. Atrioesophageal fistula and pulmonary vein stenosis were included as serious adverse events regardless of the timing of occurrence	A composite of cardiac tamponade leading to pericardiocentesis, persistent phrenic-nerve palsy lasting more than 24 h, serious vascular complications leading to intervention, stroke or transient ischemic attack, atrioesophageal fistula, or death within 30 days	Composite safety endpoint of at least one adverse event per patient
Monitoring method	TTM: weekly (3–12 mo) + when symptomatic ECG: 3, 6, and 12 months Holter: 72 h at 6 and 12 months	Continuous rhythm monitoring after ablation with implantable cardiac monitors	Telephone follow-up at 1 month, in-person follow-up at 2, 6, and 12 months. Weekly self-recorded single-lead ECGs with hand-held ECG (AliveCor Kardia) and symptom-driven recordings
Primary efficacy	PFA 73.3% Thermal 71.3%	PFA 62.9% CB 49.3%	PFA 77.2% RF 77.6%
Primary safety	PFA 2.1% Thermal 1.3%	PFA 0.95% CB: 1.9%	PFA 4.8% RF 7.6%

Summary of main outcome reports.
PFA, pulsed field ablation; RF, radiofrequency current; CB, cryoballoon; CC, complication class; FU, follow up.

platforms.[34] Haemolysis and occasional haemodialysis (≈0.02%) have been reported, associated with insufficient catheter–tissue contact and high application numbers; specific catheter designs may mitigate this risk.[35,36] Nevertheless, this threshold may not accurately reflect clinically meaningful haemolysis following PFA. The absence of clinical predictors or laboratory surrogates suggests that the rare risk of renal injury must be balanced with the well-established benefits of PFA when lesions are delivered in moderation while optimizing tissue contact.[37] With growing familiarity with over-the-wire workflows, cardiac tamponade rates are reduced. Cerebrovascular events remain within expected ranges. Recently, a very low incidence (≈0.1–0.16%) of coronary vasospasm and sudden cardiac death has been reported, including delayed and coronary proximity independent cases, warranting further investigation.[38] Please refer to chapter 5 of the PFA supplement for additional details on safety topics.

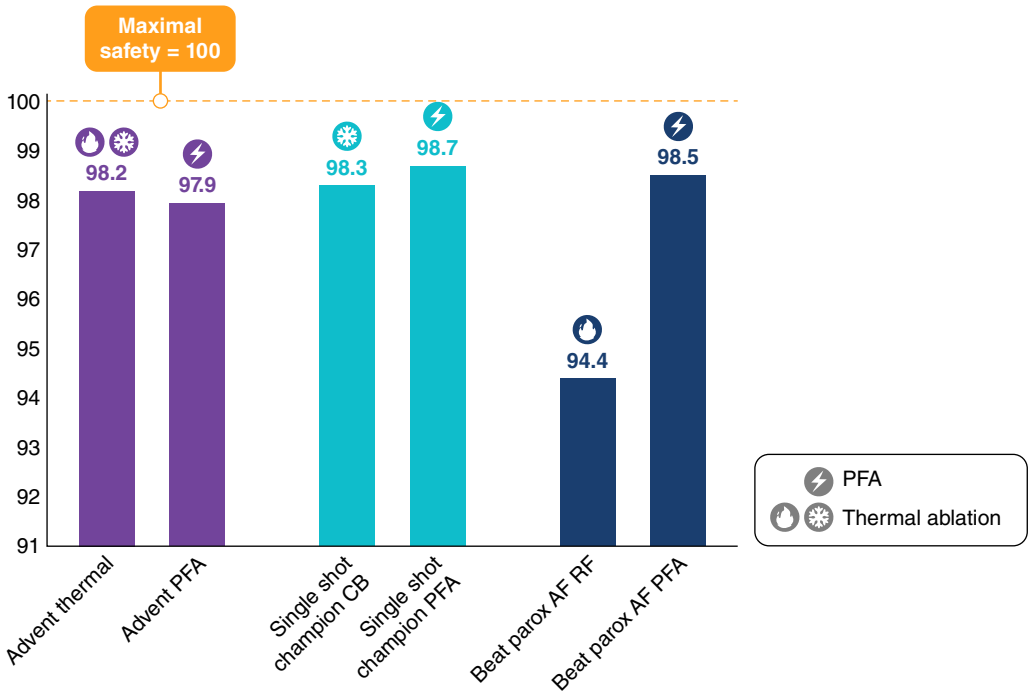


Figure 1 Safety profiles based on the proposed EHRA Complication Score. Based on the proposed EHRA complication score, safety indices derived from recent randomized controlled trials comparing pulsed-field ablation with thermal ablation confirm and quantitatively support the improved safety profile of PFA. Maximal safety would render a score of 100.

Procedural and laboratory efficiency

The majority of novel PFA devices enable faster PVI compared to thermal ablation.[19,39] Even if performed by operators with limited PFA experience, shorter procedure times were consistently reported.[18] Owing to the timing of irreversible electroporation and electrical stunning, post-ablation waiting periods may be omitted without compromising acute endpoints, improving procedural efficiency and throughput. PFA seems to improve electrophysiology laboratory efficiency through short learning curves, predictable, short procedure times, and the feasibility to use deep sedation. These advantages are driven by reduced operator dependency, rapid energy delivery, simplified catheter manipulation, and the omission of post-ablation waiting periods. Consequently, this may result in more efficient laboratory scheduling, increased patient throughput, and the potential for reduced waiting times.

Mid- and long-term efficacy

Clinical success depends on follow-up strategy, ranging from ~60% with continuous monitoring to 70–>80% with intermittent monitoring. In early real-world practice, PFA-based PVI achieves 12-month success rates comparable to CB or RF ablation. Interestingly, AF burden assessed by loop recorders appears similar following pentaspline catheter PFA and CB PVI.[19] Future improvements may result from enhanced PVI durability, identification of PVI non-responders, and a deeper mechanistic understanding of AF. AF burden should be considered a complementary and increasingly important endpoint, particularly in trials with continuous monitoring, but standard definitions remain necessary for comparability across studies and technologies.

Conclusion

PFA enables PVI with short procedure times, high reproducibility, robust efficacy, and excellent safety profile. The success of PFA in PAF is primarily driven by the reliable achievement of durable PVI rather than by a fundamentally different ablation target. Further improvements in efficacy will therefore depend on identifying and addressing arrhythmogenic substrates beyond the pulmonary veins.

PFA in persistent AF

Pre-procedural considerations

The 2024 ESC Guidelines recommend catheter ablation for PersAF patients resistant or intolerant to antiarrhythmic drug therapy (Class I/Level A), in selected heart failure patients with reduced ejection fraction (Class IIa/Level B), or even as first-line option (Class IIb/Level C), to improve symptoms and reduce AF burden/progression in appropriately selected patients pursuing rhythm control, within a shared decision-making strategy, and a strict comorbidity optimization within AF-CARE (risk factors and stroke prevention).[40]

Although the optimal ablation strategy is still under investigation, pre-procedural planning may help to individualize lesion-set complexity (PVI-only vs. PVI+) based on PersAF duration (<6 months vs. >6 months), presence of concomitant flutter, and atrial cardiomyopathy.

Anticoagulation typically consists of uninterrupted or minimally interrupted periprocedural OAC, and long-term OAC continuation currently still follows CHA_2DS_2-VA recommendations irrespective of apparent rhythm outcome.[1,40]

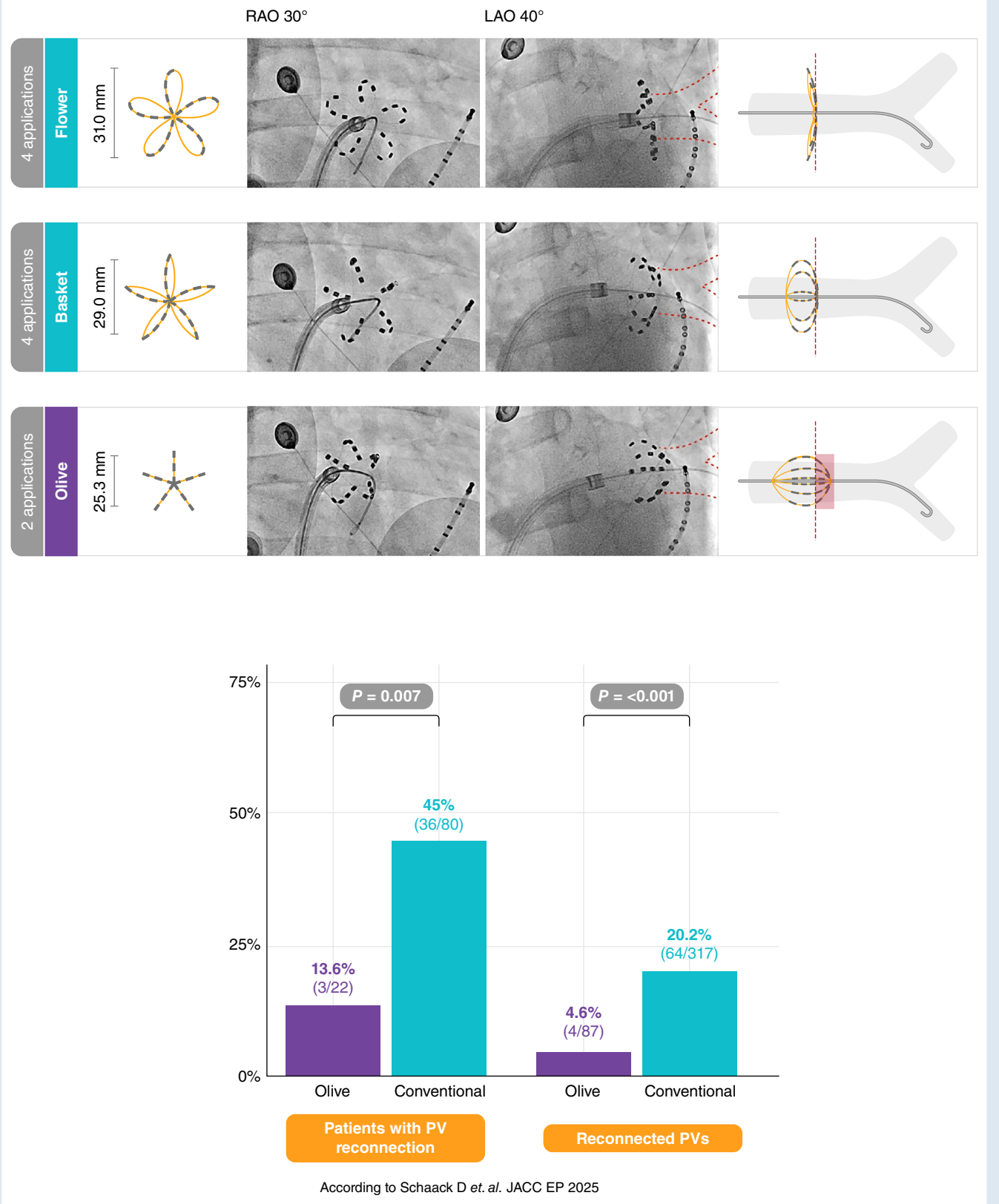


Figure 2 The 'olive' strategy workflow showing different pentaspline catheter configurations and applications. Durability data obtained from remapping studies using the 'olive' strategy.[23]

Table 2 List of different commercially available PFA systems with technical details[32]

	Farapulse™	PulseSelect™	Varipulse™	Volt™	Sphere 360™	Sphere-9™	Omnypulse™	Faraflex™	STSF Dual Energy™	TactiFlex Dual Energy™	Farapoint™
Manufacturer	Boston Scientific	Medtronic	Biosense Webster	Abbott	Medtronic	Medtronic (Affera)	Biosense Webster	Boston Scientific	Biosense Webster	Abbott	Boston Scientific
Catheter architecture/ strategy	Multielectrode single-shot	Multielectrode single-shot	Multielectrode single-shot	Multielectrode single-shot	Multielectrode single-shot	Focal lattice-tip dual-energy catheter	Focal PFA catheter	Focal PFA catheter	Focal dual-energy RF/PFA catheter	Focal dual-energy RF/PFA catheter	Focal PFA linear catheter
Diameter	31/35 mm	25 mm	25–35 mm	28 mm	34 mm	9 mm	12 mm	9 mm	3.5 mm	4 mm	3.5–4 mm
Catheter size	12 F	9 F shaft/9.8 F array	8.5 F	13 F	8 F	8 F	7.5 F	8 F	8 F	8 F	8 F
Over-the-wire	Yes	Yes	No	Yes	Yes	NA	NA	NA	NA	NA	NA
Steerability	NA	NA	NA	NA	NA	Bidirectional	Bidirectional	Bidirectional	Bidirectional	Bidirectional	Bidirectional
Pulse amplitude/ duration	1.8–2.0 kV/µs	1.5 kV/µs	1.8 kV/µs	1.5–1.8 kV/µs	1.3–2.0 kV/µs	2 kV/ µs(Pfrev: 32 A/<10 µs; EU only)	1.2–1.5 kV/ µs	2 kV/µs	1.0–1.5 kV/ µs	1.9–2.2 kV/ µs	1.4–2.0 kV/ µs
PFA Ablation mode	Bipolar	Bipolar	Bipolar	Bipolar	Monopolar	Monopolar	Bipolar	Monopolar/ bipolar	Monopolar	Monopolar	Bipolar
Waveform	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic
Dedicated 3D mapping	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Finally, application of PFA may be painful, and these procedures are most commonly performed under GA or deep sedation.[41]

Procedural workflow

Evidence from PersAF cohorts shows that PFA delivers high acute PVI and procedural efficiency; however, strategy selection (PVI-only vs. PVI+) is currently still controversial and frequently individualized. Current guidelines only recommend PVI as the cornerstone of AF ablation in PersAF. In the absence of unequivocal evidence of improved efficacy, additional lesions such as posterior wall and other linear lesions or AF mapping-based focal ablation strategies are not recommended in routine clinical practice by current guidelines.[42–44]

In short-duration PersAF (<6 months), with limited substrate and PV-centric triggers, PVI-only strategy with PFA achieves rapid, wide-area lesions with high acute and durable isolation and consistent procedural efficiency. Comparative PersAF series indicate broadly similar acute success against RF or cryo, with shorter procedure times, and favourable safety profile.[43,45]

When long-standing PersAF (>6 months), extensive low-voltage zones, or non-PV drivers are present, the ablation strategy may include adding posterior wall isolation (PWI) and selected lines (roof, anterior, mitral isthmus) in some centres; however, its routine application is not recommended in current guidelines. Many data indicate feasibility of PVI + PWI using pentaspline-PFA, with encouraging 1-year outcomes that depend on lesion completeness and workflow standardization, however without proven superior efficacy.[42–45]

PFA can close gaps, complete roof/anterior lines, and target macro-re-entrant circuits. However, mitral-isthmus (MI) durability with a pentaspline PFA catheter is limited. In a long-term follow-up of a PersAF cohort, no patient had durable MI block at redo, and most recurrences were peri-mitral flutter related, often requiring coronary-sinus and/or vein-of-Marshall adjuncts to achieve final block, underscoring the need for mapping-guided lesion delivery and, where necessary, hybrid energy/epicardial approaches.[46,47] While substantially higher lesion durability was reported following linear lesions with combined PFA and RF using a dual-energy lattice-tip catheter[2,8,48] data on durability of PFA-only linear lesions with dedicated catheter designs and waveforms are still awaited. Importantly, given the electrical tissue 'stunning' caused by reversible effects of PFA, acute linear block appears to be a poor surrogate for durable transmural lesion creation and further studies are needed to establish objective criteria for durable lesion creation with PFA.[28,49]

Safety

One of the most critical advantages of PFA is the marked reduction of classic thermal complications (atrio-oesophageal fistula, PV stenosis, and persistent phrenic palsy). Large real-world datasets and trials demonstrate low major-complication rates and support rapid adoption.[21,50] Nonetheless, PFA-specific effects (e.g. haemolysis, coronary spasm) warrant vigilance, limit the number of applications, and protocolized monitoring, particularly when applying PFA near coronary arteries.[51,52]

In PersAF, PFA shows a favourable safety profile compared to RF and CB, with significantly less risk of durable phrenic palsy than CB, and an almost zero risk of atrioesophageal fistula, which is particularly reassuring for PWI, or for the ablation of posterior wall circuits.[21,42,44,45,50]

It is worth noting that some rare complications may only become visible with very large-scale adoption. This has been reflected in large real-world registries with the pentaspline PFA catheter such as MANIFEST-17K[50] and MANIFEST US.[35]

Procedural efficacy

At 1 year, freedom from atrial arrhythmia after PFA for PersAF is at least comparable to best-practice thermal strategies.[43–45] With continuous monitoring, 12-month freedom from atrial arrhythmia recurrence was 52.0% when account for any episode ≥30 s and 71.6% when using a 0.1% burden threshold. In a randomized trial with the dual-energy lattice-tip catheter, 12-month freedom from a composite of atrial arrhythmia recurrence, use of rhythm control therapies, and acute procedural failure was 73.8%, which was non-inferior to current RF technology (65.8%).[53] However, continuous-monitoring experience in a PersAF-dedicated programme reported sustained AF-burden reduction and lesion-durability signals, enabling more granular characterization of late recurrences than intermittent follow-up.[42] In long-standing PersAF or markedly remodelled atria, endocardial PFA alone may be insufficient. For MI lines specifically, durability limitations with pentaspline PFA highlight a pro-arrhythmic risk of peri-mitral flutter when block is incomplete, reinforcing the role of 3D mapping, epicardial adjuncts (CS/VOM-ethanol), and/or hybrid energy to secure durable conduction block.[47] More recently, the AVANT-GUARD randomized controlled trial compared the safety and efficacy of PVI with pentaspline catheter vs. AAD in first-line PersAF. At 1 year, the study showed that patients treated with PVI have superior freedom from recurrent atrial tachyarrhythmia and comparable safety outcomes.[54]

3D Mapping integration beyond PVI

Versatility and scalability across diverse patient groups are prerequisites if PFA is to become the default modality for all AF ablations; current evidence supports its application not only in PAF but also in PersAF[55] In PersAF, substrate-directed strategies, such as PWI and broader lesion sets, are under active evaluation; early experience indicates they can be delivered safely and efficiently with PFA, although incremental clinical benefit over PVI alone remains unproven and awaits dedicated randomized trials. Beyond PVI, PFA has indeed been extended to more complex lesion architectures. In a prospective series of 215 patients (with approximately two-thirds undergoing redo procedures), pentaspline-catheter PFA achieved acute PWI in 100% of cases with a low major-complication rate (0.9%), and at redo, posterior wall durability was confirmed in 85% of patients.[56] Despite a lower 1-year arrhythmia-free survival (53%) in that cohort, likely reflecting advanced substrate and the redo context, the demonstration of procedural safety and lesion durability in a challenging population is encouraging. More recently, a large prospective persistent-AF study employing PVI plus PWI with PFA reported favourable safety and effectiveness, further broadening the standard scope of PFA strategies.[42] In contrast to the high durability typically seen for PVI and PWI with the pentaspline catheter, MI block and left-atrial appendage or coronary-sinus isolation are often no longer observed on 3-month remapping, highlighting limited persistence of some extra-PV targets.[46,47] These shortcomings likely relate more to catheter geometry, originally optimized for PVI, and line orientation than to electroporation itself. As the device ecosystem expands, with varied footprints, focal tools, and adjustable or hybrid energies, treating complex PersAF substrates should become more feasible, enabling more reliable transmural lines and lesion sets.

The fact that electro-anatomical mapping (EAM) becomes pivotal once the planned lesion set extends past PVI is widely

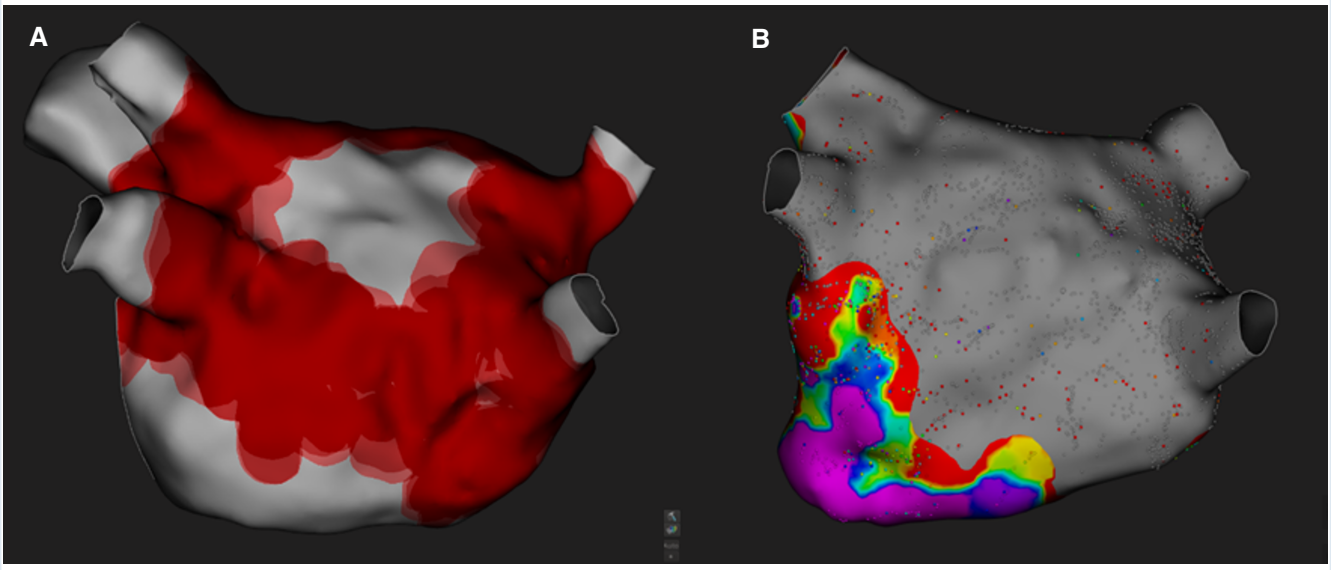


Figure 3 Posterior view of the left atrium in a PersAF patient after PWI performed with an Opal™ FaraNAV™ 31 mm (Boston Scientific, St Paul, MN, USA). (*A*) PFA lesion tags defining posterior wall boundaries. (*B*) Voltage map showing the posterior 'box lesion' type after PFA ablation.

accepted. CT–EAM fusion helps define PWI boundaries and visualize the mitral isthmus; high-density voltage mapping identifies macro/micro reentrant circuits, and eventually low-voltage substrate for eventual targeted homogenization; activation mapping and differential pacing verify roof/anterior/MI block and expose epicardial breakthroughs.[42,44,45,47] Systematic tagging of applications and documentation of validation criteria improve reproducibility and support team-wide consistency, an approach aligned with learning-curve observations from other energy platforms (*Figure 3*).

For MI lines, EAM and eventually ICE help manage tissue thickness heterogeneity. Despite all this, adjunctive epicardial and/or vein-of-Marshall strategies should sometimes be planned upfront, when anatomy is unfavourable, or when conduction recurs and complete block cannot be obtained.[46,47]

Upcoming studies on persistent AF ablation

Definitive randomized evidence that PVI+ substrate modification (e.g. PWI, roof/anterior lines) with PFA improves hard outcomes vs. PVI-only in PersAF is lacking. Multiple on-going randomized controlled trials are now targeting this exact question. In this context, the results of the PersAF cohort of the Beat AF Trial should bring in a near future, important insights on this crucial question.[57,58]

In addition, while PFA shows high PVI durability with the pentaspline catheter, this effect for linear lesions particularly on the MI and coronary-sinus targets remains uncertain. In this setting, evidence is still emerging on which catheter geometries, dosing paradigms, and (for hybrid energy systems) energy combinations maximize efficacy while preserving selectivity in PersAF substrate. The dual-energy lattice-tip randomized control trial showed feasibility and non-inferiority at 1 year, but longer-term PersAF-specific, head-to-head data are needed.[53]

Table 3 summarizes currently published studies treating Persistent AF patients exclusively. Finally, real-world, multicentre registries and national programmes should continue, and future analysis will be key not only to evaluate generalizability and health system impact of PFA in PersAF ablation but also to understand learning curve, efficiency, safety signals for potentially rare events, and cost-effectiveness analysis of this energy at high scale.[59]

Measurable outcomes after PFA procedures

Blanking period definition for PFA

A substantial proportion of patients exhibit early recurrences (ERs) of atrial tachyarrhythmia within the first 3 months after catheter ablation of AF. Following thermal ablation, ERs were reported in ~30%–40% of patients under intermittent monitoring[60–65] and 60% with ILRs.[66,67] ERs may be promoted by a transient proarrhythmic state resulting from acute atrial injury,[68,69] inflammation[68–70] and autonomic nervous system alterations[71] caused by thermal lesions. It has therefore become conventional practice to use a post-ablation blanking period during which ERs are not considered treatment failure and do not warrant reintervention. Nevertheless, numerous studies have shown that ERs are predictive of late recurrences[60,61,66,67,72–74] and long-term AF burden.[62,66] Crucially, the prognostic significance of ERs is strongly dependent on timing.[61–64,66] In thermal ablation studies, 12-month freedom from late arrhythmia recurrence averaged ~70–80% among patients without ER compared to 50–60%, 30–40%, and <10% among patients experiencing ER within the first, second, and third month post-ablation, respectively.[61–64,66] Given these findings, the traditional 90-day blanking period was shortened to 8 weeks in the 2024 consensus statement on AF ablation.[1]

Compared to thermal ablation, PFA lesions exhibit spared vascular and nervous tissue, preserved extracellular matrix,

increased apoptosis (vs. necrosis), and less inflammatory cell infiltration.[75–79] The early post-PFA period may thus entail a milder and/or shorter proarrhythmic state. In the Single Shot Champion trial,[19] ILR-detected ERs within 90 days occurred in substantially fewer patients randomized to PFA compared to CB ablation (38.1% vs. 58.1%, $P < 0.001$). Likewise, AF burden within the blanking period was lower in the PFA group (3.2 ± 0.8% vs. 5.5 ± 1.0%, $P < 0.001$), whereas it did not significantly differ within Days 91–365 (1.4 ± 0.4% vs. 1.9 ± 0.4%, $P = 0.17$). In ADVANTAGE AF Phase 2,[42] ILR monitoring showed an early peak in arrhythmia burden within 30 days post-ablation, which was predictive of post-blanking healthcare utilization. In studies using intermittent rhythm monitoring, the incidence of ERs within 90 days post-PFA ranged from 6.0% to 31.6%,[80–86] generally lower than in comparable thermal ablation cohorts,[60–64] and ERs were independent predictors of late recurrence. To our knowledge, two studies reported monthly rates of ER after PFA with the pentaspline[83] or a circular PFA catheter.[84] Combining data from these two studies (631 patients, 54.7% paroxysmal AF), 90-day ERs occurred in 22% of patients. Twelve-month freedom from late recurrence was 79% among patients without ER, compared to 25% among those with ER. Patients with ER in the first, second, and third month after PFA exhibited 59%, 29%, and 9.9% freedom from late recurrence.

Some authors have suggested that the blanking period could be redefined as 1 month after PFA,[83] or even be eliminated entirely.[87] The blanking period does appear to be less relevant and shorter post-PFA, as ERs are less prevalent by approximately 20 percentage points compared to thermal ablation, and ERs within the second and third months post-PFA are associated with high rates of late recurrence. However, ERs in the second month may still be transient in ∼30% of patients. It therefore appears reasonable to keep using a 2-month blanking period pending further data. Adopting different endpoints for PFA vs. thermal ablation would also hinder comparisons between ablation technologies. Additional data, including detailed analysis of ILR data from recent PFA trials, may help clarify this area of uncertainty.

Finally, device-specific and monitoring-specific data are still needed before adopting PFA-specific endpoints. In our opinion, current evidence supports maintaining the consensus 8-week blanking period in clinical practice as well as for comparability purposes. However, recurrences in Month 2 (and especially Month 3) warrant particular attention (e.g. intensified monitoring) because they carry high predictive value for late recurrence.

Durability from remapping data

Achieving durable PVI is crucial to any AF ablation strategy, even though other mechanisms are also involved in AF recurrence post-PVI, especially in persistent AF.[88,89] In that regard, first-generation PFA systems already appear equivalent or superior to the more mature thermal ablation technologies. *Figure 4* summarizes PVI durability as reported in first-in-human studies for different commercially available and investigational PFA systems.[25,27,28,90–98] Notwithstanding methodological heterogeneity between trials, and workflow optimization not prespecified by protocol, per-vein PVI durability with PFA reached ≥90% with most systems. For comparison, in systematic remapping studies of thermal ablation systems, including second-generation CB and contact force-sensing RF catheters, per-vein PVI durability averaged 71% (95% CI, 69–73%) with RF and 79% (95% CI, 74–83%) with CB ablation.[99] In a recent meta-analysis[100] comparing PFA to thermal PVI with systematic remapping data, per-vein PVI durability was significantly superior with PFA by ∼20 percentage points compared to both RF and CB ablation ($P < 0.001$). On a patient level, complete isolation of all PVs was durably achieved in 81.9% of patients with PFA compared to 54.4% with RF and 48.8% with CB ablation.

Real-world data from large-scale PFA registries, including MANIFEST-REDO ($n = 427$)[17] and EU-PORIA ($n = 144$),[101] found substantially lower PVI durability rates averaging 71%. Nevertheless, real-world comparative data remain in favour of PFA: in a multicentre retrospective analysis of 870 propensity score-matched patients undergoing *de novo* AF ablation, per-vein PVI durability among 145 re-interventions was significantly higher following index ablation with PFA (80.9%) compared to CB (72.5%) and RF ablation (65.2%), $P = 0.01$.[102]

Data are scarce on the durability of non-PV lesions. In ADVANTAGE-AF Phase 2,[103] durable isolation of the posterior wall was observed in 10 of 16 (62.5%) patients undergoing repeat ablation. For comparison, in the CAPLA trial,[104] the same was achieved in 5 of 16 (31.3%) patients following contact force-enabled RF ablation. Other ablation sites, such as the mitral isthmus, may remain more challenging due to their anatomical characteristics.[105,106] In a recent study[107] of 236 patients undergoing AF ablation with left atrial appendage isolation, coronary sinus isolation, and mitral isthmus ablation with the pentaspline PFA catheter, acute success was 100%, 62.2%, and 100%, respectively. Systematic remapping at 3 months revealed durable isolation/block in only 4.6%, 1.3%, and 5.5%, respectively. These findings highlight the potential discrepancy between acute electrical effects of PFA and long-term results for non-PV targets. This is likely reinforcing the need for optimized catheter design. In contrast, in 122 patients undergoing systematic remapping after linear lesions with a lattice-tip dual-energy ablation catheter, durable block was achieved in 82% at the left atrial roof, 68% at the mitral isthmus, and 87% at the cavotricuspid isthmus.[28] A small real-world study of 39 patients undergoing remapping during repeat ablation or left atrial appendage occlusion after linear ablations with the lattice-tip catheter found comparable results.[48] Of note, both studies used various combinations of RF and PFA, making direct comparisons with other systems difficult.

Predicting durable lesion creation has been an ongoing challenge with both thermal ablation and PFA. Reversible effects of PFA ('reversible electroporation') may further complicate this task. Catheter-tissue contact most likely impacts PFA lesion creation, and the use of ICE to assess contact was shown to substantially improve lesion durability.[108] Ongoing efforts including optical lesion assessment[109] and contact sensing enabled PFA catheters[110] may further improve durable and predictable lesion creation.

Arrhythmia burden vs. arrhythmia recurrence

Ablation failure has been conventionally defined as atrial tachyarrhythmia recurrence ≥30 s beyond the blanking period. However, very short and sporadic arrhythmia episodes are unlikely to significantly alter the quality of life, cardiac haemodynamics, autonomic nervous system function, or cause adverse remodelling or stroke. Moreover, since many patients experience improvement in clinical status despite arrhythmia recurrences, time-to-first-recurrence analysis fails to adequately characterize response to therapy. There is now consistent evidence from both thermal ablation and PFA trials that this arbitrary endpoint is poorly correlated with meaningful clinical outcomes.[103,111,112] Atrial arrhythmia burden, defined as the proportion of time spent in AF during a specified monitoring

Table 3 Summary of published studies on Persistent AF

	SPHERE Per-AF (2024)	ADVANTAGE AF Phase 1 (2025)	ADVANTAGE AF Phase 2 (2025)	AVANT GUARD (2026)
Manufacturer	Medtronic	Boston Scientific _	Boston Scientific	Boston Scientific
Comparator	Contact-force RF ablation	NA	NA	Antiarrhythmic drug therapy
Study type	RCT	Single Arm	Single Arm	RCT
PFA catheter	Sphere-9 lattice-tip dual-energy catheter	FARAWAVE pentaspline catheter	FARAWAVE + FARAPOINT linear catheter	FARAWAVE pentaspline catheter
Patients	420	260	255	310
Ablation cohort	First-time ablation only	First-time ablation only	First-time ablation only	First-line rhythm-control
Ablation strategy	PVI only	PVI+ posterior wall ablation	PVI+ posterior wall ablation +CTI linear PFA (when indicated)	PVI+ posterior wall ablation
Primary Efficacy endpoint	Composite of freedom from treatment failure (arrhythmia recurrence, cardioversion, AAD initiation/ escalation, or repeat ablation)	A composite of acute success of PVI and PWA; post–3-month blanking freedom from documented recurrence of AF/ AFL/AT; freedom from reablation for AF/AFL/AT; freedom from any direct current cardioversion for AF/AFL/AT; and freedom from use of new or escalated doses of class I/III AADs or any post-blanking amiodarone	A composite of acute success of PVI and PWA; post–3-month blanking freedom from documented recurrence of AF/ AFL/AT; freedom from reablation for AF/AFL/AT; freedom from any direct current cardioversion for AF/AFL/AT; and freedom from use of new or escalated doses of class I/III AADs or any post-blanking amiodarone	A composite of acute success and Long-term defined as freedom from the use of amiodarone through 12 months and freedom from the following after the blanking period: at least 30 s of symptomatic atrial fibrillation, flutter, or tachyarrhythmia; at least 1 h of asymptomatic atrial fibrillation, flutter, or tachyarrhythmia; electrical cardioversion or ablation for atrial fibrillation, flutter, or tachyarrhythmia; and the use of class I or III antiarrhythmic drugs (in the PFA group only)
Primary Safety Endpoint	A composite of pre-specified device-related or procedure-related serious adverse events, including death, atrio-oesophageal fistula, stroke, myocardial infarction, cardiac tamponade/perforation, PV stenosis, phrenic nerve paralysis, transient ischemic attack, thromboembolism, major vascular access complications/ bleeding, heart block, gastroparesis, severe pericarditis, or new or extended	Rate of predefined safety events: myocardial infarction, stroke, transient ischemic attack, thromboembolism, pulmonary oedema, unresolved phrenic nerve palsy/paresis, serious vascular access complications, heart block, or gastrointestinal disorders occurring within 7 days of the index procedure; death, cardiac tamponade/ perforation, or pericarditis; or other PFA system/procedure–related cardiovascular or pulmonary adverse	Rate of predefined safety events: myocardial infarction, stroke, transient ischemic attack, thromboembolism, pulmonary oedema, unresolved phrenic nerve palsy/paresis, serious vascular access complications, heart block, or gastrointestinal disorders occurring within 7 days of the index procedure; death, cardiac tamponade/ perforation, or pericarditis; or other PFA system/procedure–related cardiovascular or pulmonary adverse	The primary safety endpoint was device- or procedure-related serious adverse events among patients in the combined PFA group

Continued

Table 3 *Continued*

	SPHERE Per-AF (2024)	ADVANTAGE AF Phase 1 (2025)	ADVANTAGE AF Phase 2 (2025)	AVANT GUARD (2026)
	hospitalization for a cardiovascular or pulmonary adverse event	event within 30 days of the index procedure and PV stenosis or atrio-oesophageal fistula occurring before the 90-day follow-up	event within 30 days of the index procedure and PV stenosis or atrio-oesophageal fistula occurring before the 90-day follow-up	
Monitoring strategy	Continuous—implantable cardiac monitor	Continuous—implantable cardiac monitor	Continuous—implantable cardiac monitor	Continuous—implantable cardiac monitor
Mean Procedure time (min)	PFA: 101 ± 30.8 RF: 126 ± 49.2	103 ± 34.8	105 ± 36	87 ± 33
Primary efficacy	PFA: 73.8% RF: 65.8%	**63.5%**	73.4%	PFA: 56% AAD: 30%
Primary safety	PFA: 1.4% RF: 1.0%	**2.3%**	2.4%	PFA: 5.1%

period and expressed as a percentage of the recording time,[20] provides a continuous measure of rhythm status over any period of time, allowing to quantify response to therapy over time. Arrhythmia burden was shown to correlate much more closely with meaningful outcomes including AF-related symptoms, quality of life,[111,113,114] healthcare utilization,[103,111,115] heart failure hospitalization, new-onset heart failure,[112,116,117] stroke,[115,118–120] and all-cause mortality.[112,115,117] The duration of the longest episode of uninterrupted arrhythmia is strongly associated with arrhythmia burden and also correlates with meaningful outcomes.[103,111,113,115,119,120]

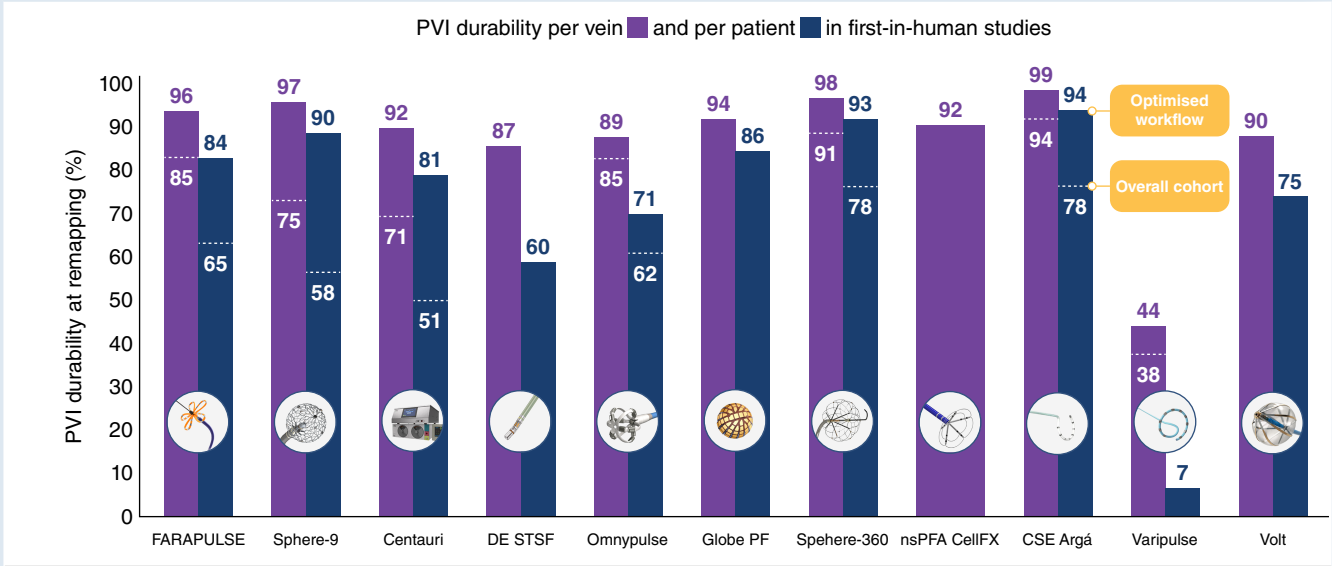
The optimal thresholds to define ablation success may be specific to the clinical setting and should be relevant for outcomes. In a seminal analysis,[111] the CIRCA-DOSE investigators found arrhythmia burden >0.1% and longest episode duration >1 h to best correlate with increased healthcare utilization (composite of emergency department visits, hospitalizations, cardioversions, and re-ablation) within 12 months after thermal PVI for paroxysmal AF. Interestingly, quality of life at 12 months was meaningfully altered only at higher thresholds of >5% arrhythmia burden and >24 h longest episode duration. These findings have been largely reproduced in PFA trials. In ADVANTAGE AF Phase 2,[103] 12-month healthcare utilization sharply increased when ILR-based post-ablation arrhythmia burden exceeded 0.1% (RR, 11.0; 95% CI, 6.1–19.9) and when the longest episode duration exceeded 1 h (RR, 10.2; 95% CI, 5.6–18.5) (*Figure 5*). Using the traditional 30-second recurrence definition, 12-month freedom from atrial arrhythmia was 51.1%. However, 12-month effectiveness was 71.6% with ≤0.1% arrhythmia burden and 70.0% with no episode >1 h. Notably, 94% of these persistent AF patients exhibited no episode with >24 h duration post-ablation. Quality of life improved evenly across categories of residual burden and longest episode duration. Other PFA trials reported arrhythmia burden from intermittent rhythm monitoring. In the ADVENT trial,[121] 12-month post-ablation arrhythmia burden <0.1% was associated with the lowest healthcare utilization and greatest improvement in quality of life. Residual burden <0.1% was more commonly achieved with PFA compared to thermal ablation. In the single-arm PULSED AF study evaluating a circular PFA catheter,[122] persistent AF patients exhibited significant improvement in quality of life across all categories of residual burden, while paroxysmal AF patients experienced greater improvement with lower residual burden (<10%). This finding is consistent with ADVANTAGE AF Phase 2 and ADVENT and highlights the dependence of failure thresholds on clinical background and the relevance of quantifying response to therapy on a continuous scale.

Therefore, current evidence shows that arrhythmia burden is a more clinically meaningful rhythm endpoint than the traditional ≥30-second recurrence, and it is our opinion that future trials should, at least, consider burden as a complementary endpoint, particularly when continuous monitoring is used. Nevertheless, traditional definitions (based on intermittent monitoring) remain necessary for comparability across studies, technologies, and real-world data.

Patient-reported measurable outcomes

Introduction

Beyond procedural efficacy and safety, patient-reported measurable outcomes (PROMs) are increasingly recognized as



Studies	IMPULSE/PEFCAT 1 & 2	Reddy *et.al*	ECLIPSE AF	SmartfIRE	Omny-IRE	PULSE EU	Reddy *et.al*	Reddy *et.al*	BURST AF	Inspire & Admire	Volt CE
Energy	PF	PF & RF	PF	PF & RF	PF	PF	PF	PF	PF	PF	PF
Timing of remap	75 or 90 days	90 days	90 days	75 days	75 days	90 days	75 days	90 days	90 days	Within 12 mo	Within 12 mo
Mandated remap	Subset	Yes	Yes	Subset	Subset	Yes	Subset	Yes	Yes	Redo	Redo
Population	PAF	PAF/PerAF	PAF/PerAF	PAF	PAF	PAF	PAF	PAF	PAF/PerAF	PAF	PAF/PerAF
N (of remap)	*N* = 110	*N* = 122	*N* = 80	*N* = 30	*N* = 29	*N* = 43	*N* = 74	*N* = 30	*N* = 88	*N* = 36	*N* = 8

Figure 4 PVI durability in first-in-human studies for different PFA systems. PVI durability per vein (blue) and per patient (green; proportion of patients with all PVs durably isolated) as assessed by invasive remapping ≥75 days after index ablation. For trials with concomitant workflow optimization, solid bars refer to the optimized workflow sub-cohort (AdmIRE trial for the Varipulse studies) and dashed white lines refer to the overall cohort (pooled population if multiple studies). Per patient, PVI durability is likely more clinically relevant but was not reported in all studies. Of note, the methodology differed between trials as indicated, particularly the remapping conditions (systematic, subset, or repeat ablation only; the latter typically enriches the population in PV reconnections). Other first-in-human studies did not report PVI durability data and are not included. PAF denotes paroxysmal atrial fibrillation; PerAF, persistent atrial fibrillation; PF, pulsed field; PVI, pulmonary vein isolation; RF, radiofrequency.

important indicators of clinical value following AF ablation. Contemporary AF management guidelines emphasize symptom relief, functional recovery, and health-related quality of life (HRQoL) as central treatment goals, particularly where rhythm-control strategies are pursued primarily to improve patient well-being rather than survival alone.

Observational data demonstrated that PFA, through its non-thermal mechanism and relative myocardial selectivity, may have the potential to influence patient experience across multiple domains including anaesthetic requirements, procedural tolerability, post-procedural recovery, return to activity, and quality of life.[10,123–125]

Anaesthesia, procedural tolerability, and pain management

AF ablation has traditionally been performed under either conscious/deep sedation or GA, with practice varying according to operator preference, institutional workflow, and ablation modality. Early clinical adoption of PFA frequently utilized GA, particularly during first-in-human studies and early experience with integrated and variable-loop systems. However, contemporary real-world data indicate that PFA can be successfully performed using a range of anaesthetic strategies, including GA, deep sedation, and selected conscious sedation pathways.[10,50,126]

Observational studies have demonstrated the feasibility of deep sedation protocols employing short-acting agents such as propofol, midazolam, fentanyl, and adjunctive ketamine, with high rates of acute PVI and low rates of airway intervention or conversion to GA.[50] In one cohort, deep sedation was associated with 100% acute procedural success for PVI with no airway complications or conversions to GA.[127] Other studies report high patient satisfaction and favourable sedation depth metrics (e.g. Richmond Agitation-Sedation Scale, visual analogue pain scores), with no requirement for invasive airway support.[128,129] In the randomized COOPERATIVE-PFA trial, deep sedation with continuous remimazolam and ketamine achieved a lower rate of the composite of hypoxemia, hypotensive, and hypertensive events compared to both GA and propofol-opioid-based deep sedation, with similar levels of patient satisfaction.[41]

Transient skeletal muscle capture may occur during PFA energy delivery and remains an important determinant of intraprocedural comfort. The degree of myostimulation appears dependent on waveform design, pulse sequencing, catheter geometry, and energy delivery strategy. Biphasic waveforms and multielectrode circumferential catheter designs may reduce muscle stimulation compared with earlier monophasic or focal delivery systems.[125]

Conscious sedation and mild sedation protocols have also been explored, with feasibility in selected patients,[130] though intraprocedural pain perception may be higher and comfort lower in these situations. Overall, comparative data indicate that analgesia and sedation requirements are generally higher with PFA than with thermal modalities, though sedation-related complications remain uncommon.[131] Notably, different PFA platforms

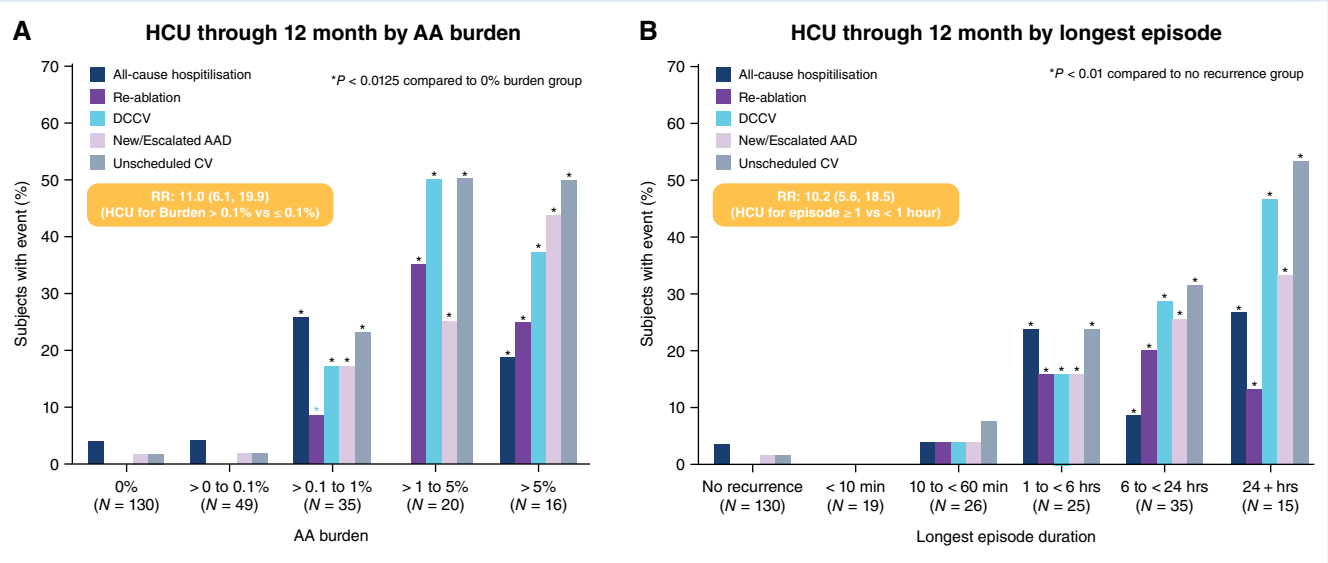


Figure 5 Correlation between healthcare utilization and arrhythmia burden. Healthcare utilization (HCU) as a function of atrial arrhythmia burden (*A*) and longest episode duration (*B*) assessed by implantable loop recorder 12 months after PFA for persistent AF in the ADVANTAGE AF Phase 2 trial. AA denotes atrial arrhythmia; AAD, antiarrhythmic drug; CV, cardiovascular visit; DCCV, direct current cardioversion. Reproduced with permission from Reddy et al.

may have different sedation requirements, and focal-tip PFA catheters have been used successfully under conscious sedation.[6]

Compared with thermal ablation, PFA avoids tissue heating or freezing and may therefore reduce nociceptive stimulation related to thermal injury, oesophageal irritation, and collateral tissue inflammation. Early observational experience suggests lower post-procedural chest discomfort and less odynophagia after PFA than after RF or CB ablation.[123,124]

There remains substantial international variation in sedation pathways. In some healthcare systems, delivery of deep sedation requires dedicated anaesthetic personnel, which may influence the scalability and accessibility of PFA programmes despite favourable procedural efficiency.[10]

Same-day discharge

Same-day discharge (SDD) following AF ablation is increasingly adopted as a patient-centred and resource-efficient care pathway. Successful SDD depends not only on procedural safety but also on patient confidence, symptom burden, early mobilization, and perceived readiness for discharge. Consensus statements support SDD in appropriately selected patients with structured follow-up pathways.[132] While further prospective trials on SDD strategies are warranted, current meta-analysis data show that SDD after AF ablation was associated with low prevalence of post-discharge complications, re-hospitalizations/ER visits and mortality, and a similar risk compared with overnight stay.[133]

The procedural efficiency and favourable early recovery profile of PFA make it particularly suited to SDD protocols. Patients undergoing PFA frequently report minimal post-procedural chest discomfort, limited swallowing symptoms, and rapid mobilization after vascular haemostasis.[123,134]

Recent multicentre observational analyses have compared SDD rates and outcomes between PFA and thermal ablation, and suggest that SDD is more commonly achieved after PFA. One prospective study showed that 80.4% of PFA patients were discharged on the same day, compared with 57.7% after RF ablation, with lower 30-day readmission rates in the PFA cohort.[135] Patient clinical characteristics were not significantly different between the two groups, and all procedures were undertaken under GA in both groups. The overall complication rates and use of closure devices were also not significantly different between groups, and therefore, the differences in SDD rates were postulated to be due to shorter procedural times and less perceived concern about delayed complications.

Another large comparative cohort reported higher SDD rates in PFA patients, with similar rates of major and minor complications between PFA and RF SDD groups, supporting the safety of SDD after PFA.[136] In this study, the use of vascular closure devices was higher in the PFA group, but it was also felt that operators' lower concern with adverse events was a major driving factor. We acknowledge, however, that these data are observational, influenced by local sedation practice, discharge pathways, patient selection, and institutional workflow.

Post-ablation recovery and return to activity

Rapid recovery following AF ablation is a clinically meaningful patient-centred outcome. During the first post-procedural week, patients treated with PFA generally report mild and transient symptoms, most commonly related to vascular access sites rather than intrathoracic discomfort.[123,124]

Compared with historical RF cohorts, lower rates of post-procedural chest symptoms have been described following PFA, potentially reflecting reduced atrial tissue inflammation and the absence of thermal collateral injury.[124,125] Many patients resume self-care activities within 24 h and return to light physical activity within several days, with early return to work commonly reported in observational practice[134] (*Figure 6*).[137]

Psychological recovery is increasingly recognized as an important component of PROMs after AF ablation. Although formal comparative data remain sparse, some patient experience

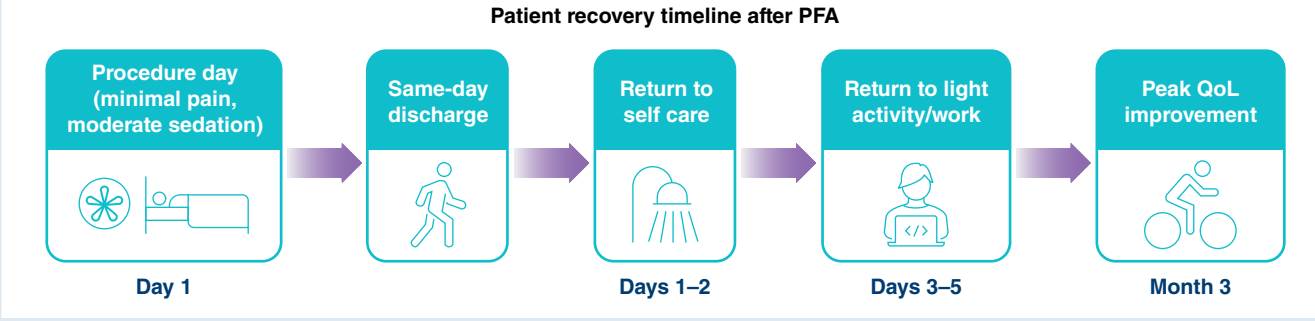


Figure 6 Patient recovery timeline from procedure day to return to light activity/work and peak quality of life improvement following a PFA procedure, from discharge to return to self-care and light activity/work.

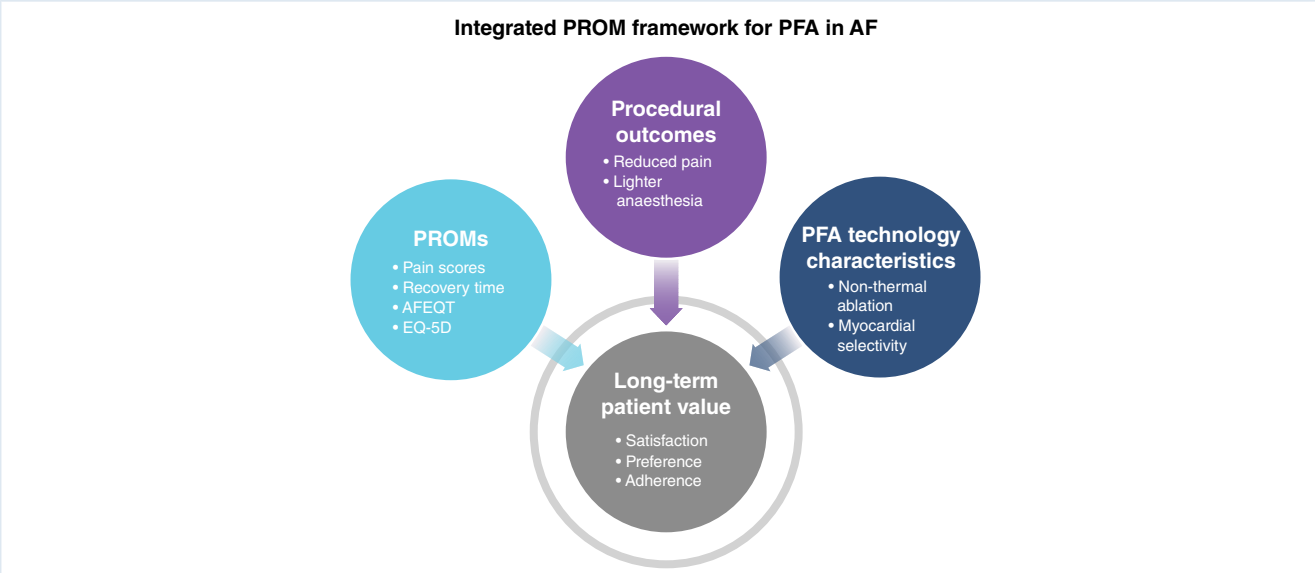


Figure 7 Integrated patient-reported outcome measures framework for PFA in AF leading to long-term patient value.

studies suggest reassurance regarding the perceived safety profile of PFA, particularly with respect to oesophageal and phrenic nerve complications that have historically concerned patients undergoing thermal ablation.[10]

Patient-reported outcomes and quality of life

The principal patient-centred objective of AF ablation is reduction in arrhythmia-related symptoms and improvement in quality of life. Validated AF-specific instruments such as the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire are well established for assessing treatment benefit.

Emerging PFA trial and registry data demonstrate clinically meaningful improvements in AFEQT scores following successful ablation, including reductions in palpitations, fatigue, exercise limitation, and treatment concern. Improvements are typically evident by 3 months and may be sustained through 12 months of follow-up.[123,138]

Generic HRQoL measures, including EQ-5D domains, have also shown improvement following PFA, particularly in physical functioning and usual activities.[138] The magnitude of benefit appears broadly consistent with that observed after successful thermal ablation, although direct comparative PROM studies remain limited, and therefore it remains uncertain whether improvements in quality of life are PFA-specific or mainly reflect successful rhythm control.

Overall patient satisfaction after PFA appears high in contemporary cohorts. Reported drivers of satisfaction include shorter procedures, rapid recovery, low symptom burden, and willingness to undergo repeat treatment if required (*Figure 7*).

Conclusions

In an era of multiple competing ablation technologies, patient experience is likely to become an increasingly important differentiator in treatment selection. Notwithstanding the observational nature of most data available, current evidence suggests that PFA offers a favourable PROM profile, with encouraging signals regarding procedural tolerability, early recovery, SDD feasibility, and post-ablation quality of life.

Conclusion and future perspectives

PFA represents a significant advancement in the field of AF management, offering a novel, non-thermal approach that addresses many limitations of conventional ablation technologies. Across both paroxysmal and persistent AF populations, PFA has demonstrated a compelling combination of procedural efficiency, safety, and promising efficacy. Its unique mechanism of irreversible electroporation enables preferential myocardial ablation while minimizing damage to surrounding structures, translating into a more predictable safety profile and potentially reducing procedure-related complications.

In paroxysmal AF, PFA has shown high acute success rates for PVI, with encouraging mid- and long-term durability supported by remapping data. In persistent AF, where substrate complexity often necessitates more extensive ablation strategies, PFA is being explored beyond PVI, including adjunctive linear and focal lesion sets. While early results are promising, further evidence is needed to define optimal workflows and lesion strategies in this more challenging population.

Importantly, the evaluation of outcomes after PFA is evolving beyond traditional endpoints such as arrhythmia recurrence. Metrics including AF burden, lesion durability, and patient-reported outcomes—such as procedural tolerability, recovery time, and quality of life—are becoming increasingly central to assessing procedural success. The potential for SDD and faster return to normal activity underscores the broader impact of PFA on patient experience and healthcare resource utilization.

Looking ahead, continued technological refinement, integration with advanced three-dimensional mapping systems, and standardization of outcome measures will be critical. Ongoing and future clinical trials will help clarify the role of PFA in persistent AF, optimize ablation strategies, and establish long-term efficacy and safety. As evidence accumulates, PFA is poised to improve outcomes in AF ablation, with the potential to deliver more efficient, patient-centred, and durable rhythm control solutions.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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The perspective of combining pulsed field ablation and left atrial appendage closure

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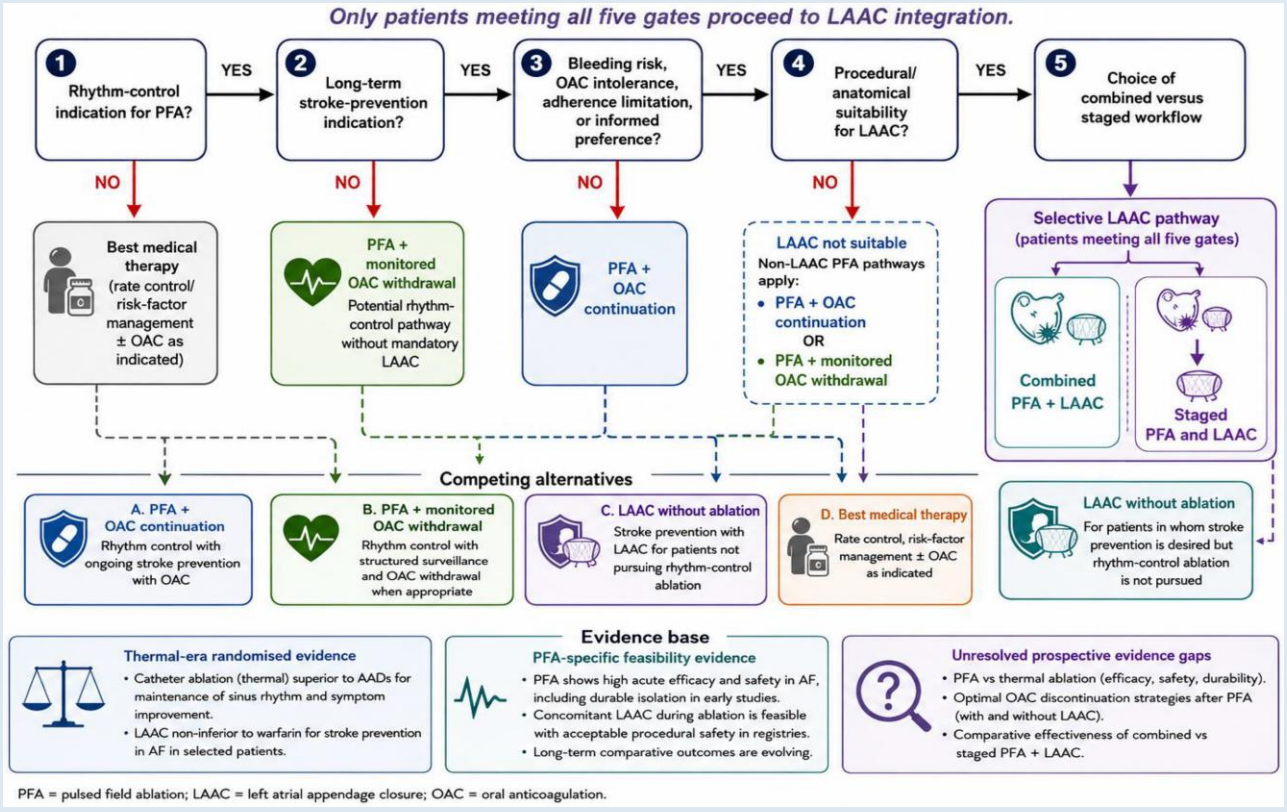
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Abstract

Pulsed field ablation (PFA) and left atrial appendage closure (LAAC) are increasingly discussed as complementary strategies in atrial fibrillation (AF) care, addressing rhythm control and long-term thromboembolic risk. The rationale is attractive, but the current evidence base is uneven. Randomized evidence for LAAC around AF ablation is strongest for thermal-ablation-era workflows, particularly the OPTION trial, which showed lower non-procedure-related major or clinically relevant non-major bleeding with LAAC than with oral anticoagulation (OAC) and non-inferiority for death, stroke, or systemic embolism. Dedicated PFA-specific evidence remains limited to feasibility studies and early observational experience, and no trial has demonstrated that combined ablation-LAAC procedures are clinically superior when the ablation component is performed with PFA rather than radiofrequency or cryoballoon ablation. In parallel, OAC-withdrawal trials after apparently successful ablation, including OCEAN and ALONE-AF, have reported low thromboembolic event rates in selected lower-risk populations, whereas CLOSURE-AF cautions against simple extrapolation of LAAC benefit to older, frailer patients at high stroke and bleeding risk. This review therefore positions combined PFA-LAAC as a potential option for carefully selected patients rather than an established routine strategy. We summarize procedural workflow, patient selection, trial populations, device-platform considerations, reimbursement and organizational issues, and the main uncertainties that should guide future prospective studies.

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Graphical Abstract



Decision framework for PFA and LAAC integration. This shows five sequential decision gates: (i) rhythm-control indication for PFA; (ii) long-term stroke-prevention indication; (iii) bleeding risk, OAC intolerance, adherence limitation, or informed preference; (iv) procedural/anatomical suitability for LAAC; and (v) choice of combined vs. staged workflow. It also highlights competing alternatives: PFA plus OAC continuation, PFA plus monitored OAC withdrawal, LAAC without ablation, and best medical therapy. Finally, it labels the evidence base as thermal-era randomized evidence, PFA-specific feasibility evidence, and unresolved prospective evidence gaps. The figure should not be interpreted as implying that PFA-LAAC is clinically superior to radiofrequency- or cryoballoon-based combined workflows.

Why combine pulsed field ablation and left atrial appendage closure?

Catheter ablation has become a cornerstone in the management of symptomatic atrial fibrillation (AF), supported by randomized evidence showing improved rhythm control and quality of life (*Table 1* and *2*). Advances in ablation technology have accelerated the adoption of pulsed field ablation (PFA), which uses irreversible electroporation rather than thermal injury and has demonstrated non-inferior efficacy to conventional thermal ablation in paroxysmal AF, with a favourable safety profile in large registries and contemporary consensus and review documents.[1–6]

Stroke risk after AF ablation is not determined solely by documented AF recurrence. It also reflects age, comorbidities, atrial cardiomyopathy, endothelial dysfunction, inflammation, and non- left atrial appendage (LAA) sources of embolism.[7,8] Current guidelines therefore recommend long-term anticoagulation according to the thromboembolic risk profile rather than perceived ablation success alone.[9–11]

Oral anticoagulation (OAC) remains the standard stroke-prevention strategy in AF. Left atrial appendage closure (LAAC) is an alternative for selected patients, particularly those with an indication for stroke prevention and a contraindication to long-term OAC or unacceptable bleeding/tolerance issues. Contemporary guidance emphasizes careful referral, anatomical assessment, shared decision-making, and structured follow-up imaging after LAAC.[12] Earlier LAAC trials and long-term follow-up established non-inferiority to warfarin in selected populations, while PRAGUE-17 provided randomized data vs. direct oral anticoagulants (DOACs) in high-risk patients.[13–15]

Combining PFA and LAAC may reduce cumulative procedural exposure by using one venous access, one transseptal access, and one anaesthetic episode. This logistical argument applies to combined ablation-LAAC in general; it does not establish a PFA-specific clinical advantage over radiofrequency or cryoballoon-based combined workflows. The concept is clinically plausible, but it should not be interpreted as proven routine care. The current task is to identify the patients for whom incremental benefit is likely to outweigh procedural risk and to distinguish evidence derived from thermal-ablation-era trials from still-limited PFA-specific data.

Table 1 Trial populations and implications for combined PFA-LAAC

Trial	Population	Strategy	Primary endpoint(s)	Selected absolute outcomes	Relevance to PFA-LAAC
OPTION	1600 post-ablation patients; CHA_2DS_2-VASc ≥2 men or ≥3 women; mean CHA_2DS_2-VASc 3.5; low mean HAS-BLED 1.2	AF ablation plus LAAC vs. AF ablation plus OAC; ablation was RF/cryo, not PFA	Safety: non-procedure-related major or clinically relevant non-major bleeding. Efficacy: death, stroke, or systemic embolism at 36 months	Bleeding 8.5% vs. 18.1%; efficacy composite 5.3% vs. 5.8%; ischaemic stroke 1.2% vs. 1.3%	Supports LAAC as an alternative after ablation in selected patients; does not establish routine PFA-LAAC
COMBINATION	202 patients with non-valvular AF undergoing combined catheter ablation and LAAO in 14 high-volume centres; 194 completed the trial; mean age 67.3 years; 56.7% male.	Ablation-first vs. occlusion-first; contact-force RF catheter ablation and plug-like LAAO devices; not PFA-specific.	Composite of thromboembolic events including stroke or TIA, device-related thrombus, clinically relevant bleeding, and cardiovascular rehospitalization or death; rhythm outcomes.	Event-free survival 83.5% vs. 71.1% favouring occlusion-first; chronic peri-device leak 5.2% vs. 15.5%; device-related thrombus 1.0% vs. 8.2%; freedom from AF 77.3% vs. 63.5%.	Challenges a default ablation-first sequence for plug-like devices; should not be extrapolated directly to PFA-LAAC, but makes sequence a patient-, device-, and platform-specific decision.
CHAMPION-AF	3000 AF patients suitable for anticoagulation; mean age 71.7 years; mean CHA_2DS_2-VASc 3.5	LAAC vs. NOAC; not ablation-specific	CV death, stroke, or systemic embolism; non-procedure-related bleeding	Efficacy 5.7% vs. 4.8% (non-inferior); non-procedure-related bleeding 10.9% vs. 19.0%	Expands evidence for LAAC vs. NOAC in selected OAC-eligible patients; not PFA-specific and not an ablation trial
CLOSURE-AF	888 patients in primary analysis; older and high risk; mean age 77.9; CHA_2DS_2-VASc 5.2; HAS-BLED 3.0	LAAC vs. physician-directed best medical care including DOACs when feasible	Stroke, systemic embolism, major bleeding, or CV/unexplained death	Primary events 16.8 vs. 13.3 per 100 patient-years; not non-inferior	Cautions against extrapolating LAAC benefit to frail high-risk populations without careful selection
OCEAN	1284 patients at least 1 year after successful ablation; selected, no recurrent atrial tachyarrhythmia; mild-to-moderate risk	Rivaroxaban vs. aspirin; no LAAC	Stroke, systemic embolism, or new covert embolic stroke at 3 years	Primary event 0.31 vs. 0.66 per 100 patient-years; not significant; fatal/major bleeding 1.6% vs. 0.6%	Low event rates suggest OAC withdrawal may be reasonable in selected patients; not generalizable to high-risk patients
ALONE-AF	840 patients without documented recurrence at least 1 year after ablation; mean CHA_2DS_2-VASc 2.1	OAC discontinuation vs. continued DOAC; no LAAC	Stroke, systemic embolism, or major bleeding at 2 years	Composite 0.3% vs. 2.2%; ischaemic stroke/systemic embolism 0.3% vs. 0.8%; major bleeding 0% vs. 1.4%	Supports OAC discontinuation in carefully selected lower-risk post-ablation patients; does not remove the need for LAAC in selected higher-risk patients

AF, atrial fibrillation; CV, cardiovascular; DOAC, direct oral anticoagulant; LAA, lef atrial appendage; LAAC/LAAO, left atrial appendage closure or occlusion; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation; PFA, pulsed field ablation; RF, radiofrequency; TIA, transient ischaemic attack.

Table 2 Disaggregated clinical interpretation of major trials

Trial	Stroke/systemic embolism	Bleeding	Mortality	Clinical interpretation
OPTION	Ischaemic stroke 1.2% vs. 1.3%; haemorrhagic stroke 0.4% vs. 0.4%; systemic embolism 0.3% vs. 0.1%	Non-procedure-related major or clinically relevant non-major bleeding 8.5% vs. 18.1%; ISTH major bleeding 3.9% vs. 5.0%	Death from any cause 3.8% vs. 4.5%	Main difference was bleeding; thromboembolic events were low in both arms.
COMBINATION	Primary composite included thromboembolic events including stroke or TIA; trial was not powered for isolated stroke/systemic embolism.	Clinically relevant bleeding was included in the composite; periprocedural complications were similar between sequence groups.	Cardiovascular rehospitalization or death was included in the composite; one non-cardiac death was reported.	Sequencing trial: occlusion-first reduced chronic peri-device leak and device-related thrombus vs. ablation-first with plug-like devices; not PFA-specific.
CHAMPION-AF	Stroke 3.6% vs. 2.5%; systemic embolism 0% vs. 0.1%	Non-procedure-related bleeding 10.9% vs. 19.0%; non-procedure-related ISTH major bleeding 5.1% vs. 6.4%	CV death 2.7% vs. 2.7%	Non-inferiority for composite efficacy with lower bleeding, but with a numerically higher stroke signal.
CLOSURE-AF	Stroke 2.6 vs. 2.7 per 100 patient-years; systemic embolism 0.3 vs. 0.1 per 100 patient-years	Major bleeding 7.4 vs. 6.2 per 100 patient-years	CV/unexplained death 9.5 vs. 7.7 per 100 patient-years	High competing risk population; no net advantage of LAAC over best medical care.
OCEAN	Stroke or systemic embolism 0.8% vs. 1.1%; new covert embolic stroke 0% vs. 0.3%	Fatal or major bleeding 1.6% vs. 0.6%; clinically relevant non-major bleeding 5.5% vs. 1.6%	All-cause death 1.6% vs. 1.1%	Low thromboembolic event rates and more bleeding with rivaroxaban in this selected population.
ALONE-AF	Ischaemic stroke/systemic embolism 0.3% vs. 0.8%; TIA 0.6% vs. 0%	Major bleeding 0% vs. 1.4%; clinically relevant non-major bleeding 1.4% vs. 1.9%	No all-cause mortality in either group	Composite advantage driven primarily by bleeding reduction.

CV, cardiovascular; ISTH, International Society on Thrombosis and Haemostasis; LAAC, left atrial appendage closure; PFA, pulsed field ablation; TIA, transient ischaemic attack.

Procedural workflow and technical considerations

Patient selection

Patient selection should start with two independent questions: first, whether the patient has a clear indication for catheter ablation; second, whether LAAC is a reasonable alternative to long-term OAC. A combined procedure is most defensible when both answers are affirmative and when the risks of staging are clinically relevant. This includes patients with symptomatic AF undergoing ablation who have moderate-to-high thromboembolic risk, clinically important bleeding vulnerability, previous major or recurrent clinically relevant bleeding, OAC intolerance, difficulty maintaining long-term OAC adherence, or a strong preference to avoid lifelong OAC after informed discussion. The selection threshold should be higher in very frail patients, patients with complex LAA anatomy, active LAA thrombus, prohibitive vascular or transseptal risk, or limited life expectancy.

Single procedure vs. staged approach

A single-procedure strategy may reduce hospital visits, repeated transseptal puncture, and repeat anaesthesia. A staged strategy remains appropriate when LAA anatomy is uncertain, when pre-procedural imaging is incomplete, when post-ablation oedema may complicate sizing, when the centre has limited combined-procedure experience, or when the stroke-prevention decision should be deferred until rhythm outcome and OAC tolerance have been reassessed. Neither strategy is intrinsically superior for all patients. Conversely, a staged strategy exposes patients to a second procedure and to an interval between ablation and LAAC during which adverse events may occur, although the available evidence for this point remains limited.[16]

Order of procedures

When a combined approach is selected, procedural sequence should be treated as an unresolved and device-specific issue rather than as a fixed rule. In many contemporary PFA-LAAC workflows, operators perform PFA before LAAC because this

allows unrestricted left atrial catheter manipulation and avoids delivering PFA close to a newly implanted LAA device. However, the COMBINATION randomized clinical trial, which compared ablation-first with occlusion-first strategies in patients undergoing combined catheter ablation and left atrial appendage closure (LAAO), reported higher event-free survival, lower chronic peri-device leak, and less device-related thrombus with an occlusion-first strategy using plug-like LAAO devices.[17] This evidence should be reconciled with PFA-specific practice because COMBINATION was not a PFA trial, used contact-force radiofrequency ablation, and may not be directly generalizable to all LAAO devices or PFA platforms. Contemporary PFA statements note that combined PFA and LAAO is feasible but emphasize that routine use remains controversial.[18,19] Therefore, sequence selection should consider expected ablation targets, LAA anatomy, device type, likelihood of post-ablation oedema, and whether further PFA delivery near an implanted device would be required. A PFA-first approach may be reasonable when ablation near the LAA ridge or left pulmonary veins is anticipated and no device is yet present; an occlusion-first approach may be considered when LAA sealing and device stability are the dominant concerns and further PFA close to the device can be avoided.

Transseptal access and imaging

A single transseptal puncture is usually sufficient. The puncture should support pulmonary vein access and coaxial access to the LAA. Transoesophageal echocardiography (TEE) and intracardiac echocardiography (ICE) are both used for transseptal guidance, device sizing, deployment, leak assessment, and pericardial effusion screening. The imaging modality influences anaesthesia strategy: TEE often favours general anaesthesia or deep sedation, whereas ICE may facilitate non-general anaesthesia workflows in experienced centres.

Pulsed field ablation-related oedema and sizing

Pulsed field ablation may produce acute atrial tissue oedema. If oedema is present or suspected, post-ablation measurements may underestimate the true LAA landing-zone dimensions after oedema resolves. For combined procedures, operators should assess LAA dimensions before ablation when feasible, integrate pre-procedural computed tomography (CT) or pre-ablation high-quality echocardiographic measurements with intraprocedural imaging, and avoid relying on a single post-ablation measurement when anatomy is borderline. Within manufacturer-specific instructions for use, operators should avoid undersizing and consider an appropriately larger or oversized device when clinically justified to reduce the risk of late peri-device leak or device instability. This should not be interpreted as evidence that PFA solves sizing or sealing limitations related to LAAC; late peri-device leak and device stability remain important follow-up endpoints.

Interaction with existing intracardiac material

Available data and consensus statements suggest that PFA can generally be performed safely in patients with intracardiac devices, but ablation immediately adjacent to device leads or LAAO devices should be avoided where possible. Electroporation-related interaction should be regarded as a broader device-field interaction concern for any implanted LAAO device, not as a phenomenon limited to lobe-and-disc platforms. Device geometry may modulate risk, and disc protrusion may influence catheter access or local field distribution, but visible arcing has also been reported during PFA applications delivered near an implanted LAAO device.[18–20] Pulsed field ablation should therefore not be delivered in direct contact with, or immediately adjacent to, any implanted LAAO device when avoidable. These observations support careful device-specific planning and reinforce the need to choose the procedural sequence so that PFA applications near the LAA ridge, left pulmonary veins, or an implanted LAAO device are minimized.

Post-procedural follow-up

Post-procedural antithrombotic therapy should follow device-specific recommendations, local protocols, and patient bleeding risk. Follow-up imaging with TEE, cardiac CT, or both is needed to confirm device position, exclude device-related thrombus, and assess peri-device leak. Follow-up should also include rhythm surveillance, because LAAC does not treat AF recurrence and because stroke mechanisms after ablation are not exclusively LAA-mediated.

Clinical evidence: separate thermal-era evidence from pulsed field ablation-specific evidence

Historical and registry experience with combined ablation and left atrial appendage closure

Combined AF ablation and LAAC was first evaluated mainly with radiofrequency or cryoballoon ablation and early-generation LAAC devices. Single-centre and multicentre observational studies, as well as broader analyses of LAAC combined with other cardiac procedures, demonstrated procedural feasibility and generally low annual stroke rates after combined procedures.[21–24] These studies were clinically important but non-randomized, often heterogeneous in ablation technique, device type, antithrombotic regimen, and follow-up intensity. Registry experience with contemporary WATCHMAN FLX and Amulet devices is reassuring, but observational comparisons are vulnerable to selection bias.[25,26]

OPTION: the strongest post-ablation left atrial appendage closure evidence, but not pulsed field ablation-specific

OPTION randomized 1600 patients with AF undergoing catheter ablation and an elevated CHA_2DS_2-VASc score to LAAC or OAC. At 36 months, LAAC reduced non-procedure-related major or clinically relevant non-major bleeding (8.5% vs. 18.1%; hazard ratio 0.44) and was non-inferior for death, stroke, or systemic embolism (5.3% vs. 5.8%). International Society on Thrombosis and Haemostasis (ISTH) major bleeding, including procedure-related bleeding, was numerically lower with LAAC (3.9% vs. 5.0%) and met non-inferiority but not superiority. Ischaemic stroke was uncommon and similar (1.2% vs. 1.3%), as was haemorrhagic stroke (0.4% in both groups).[27]

The interpretation of OPTION should be precise. The trial supports LAAC as an alternative to OAC in selected post-ablation patients, but it does not prove superiority for individual thromboembolic endpoints, and it did not use PFA. OPTION enrollment occurred in a thermal-ablation-era workflow. Therefore, its

results can inform but not validate combined PFA-LAAC as a routine strategy. Timing and rhythm sub-analyses are hypothesis-generating and support procedural feasibility, but dedicated PFA studies remain required.[28,29]

Pulsed field ablation-specific combined evidence

Pulsed field ablation-specific evidence for concomitant LAAC is currently limited. Early feasibility studies of PFA with concomitant LAAC and single-centre experience suggest that workflows are technically feasible and that acute safety is acceptable in experienced centres.[30,31] However, these data are not powered for stroke, systemic embolism, death, major bleeding, device-related thrombus, or long-term peri-device leak. They also do not demonstrate that combined procedures are clinically superior when performed with PFA rather than radiofrequency or cryoballoon ablation. The manuscript therefore treats PFA-LAAC as an emerging strategy rather than an established standard.

Competing strategies: oral anticoagulation withdrawal, left atrial appendage closure without ablation, and high-risk medical therapy

OCEAN and ALONE-AF challenge the assumption that all successfully ablated patients necessarily need either lifelong OAC or LAAC. In OCEAN, 1284 patients at least 1 year after successful AF ablation were randomized to rivaroxaban or aspirin. Rivaroxaban did not significantly reduce stroke, systemic embolism, or new covert embolic stroke compared with aspirin; stroke or systemic embolism occurred in 0.8% vs. 1.1%, while fatal or major bleeding occurred in 1.6% vs. 0.6%.32 In ALONE-AF, discontinuing OAC in 840 patients without documented recurrence after ablation reduced the composite of stroke, systemic embolism, and major bleeding compared with continuing OAC (0.3% vs. 2.2% at 2 years), driven largely by bleeding; ischaemic stroke or systemic embolism remained rare (0.3% vs. 0.8%).[32]

These OAC-withdrawal studies enrolled selected patients, generally with lower thromboembolic risk than many LAAC candidates, and used protocolized rhythm surveillance. They should not be extrapolated to patients with high CHA_2DS_2-VA scores, limited monitoring, recurrent AF, or substantial atrial cardiomyopathy. Conversely, CLOSURE-AF cautions that LAAC benefit should not be assumed in frail, older, high-risk populations. In CLOSURE-AF, patients had a mean age of 77.9 years, a mean CHA_2DS_2-VASc score of 5.2, and a mean HAS-BLED score of 3.0; LAAC was not non-inferior to physician-directed medical therapy for the composite of stroke, systemic embolism, major bleeding, or cardiovascular/unexplained death.[33]

Pulsed field ablation, anticoagulation, and the residual-risk problem

Pulsed field ablation may improve ablation safety and efficiency, but it does not by itself define long-term antithrombotic strategy and should not be assumed to improve outcomes of combined procedures beyond what has been shown for ablation-LAAC workflows in general. The central unresolved question is whether better rhythm outcomes will meaningfully reduce thromboembolic risk enough to change the threshold for OAC continuation or LAAC. Stroke after AF ablation may still occur because of silent recurrence, atrial cardiomyopathy, vascular disease, left atrial mechanical dysfunction, or non-cardioembolic mechanisms.[7,8]

Guidelines remain conservative: in patients with a long-term stroke-prevention indication, OAC decisions after ablation should be based on thromboembolic risk rather than rhythm status alone.[9–11] Newer trials suggest that this approach may be too broad for selected lower-risk patients with durable rhythm control and rigorous monitoring, but they do not yet define a universal off-OAC strategy.[32,34]

Combined PFA-LAAC may therefore be most relevant for patients in whom ablation is clinically indicated and long-term OAC is problematic, not for all patients undergoing PFA. A patient with low thromboembolic risk and excellent rhythm control may not need LAAC. A patient with very high stroke risk, advanced frailty, and high procedural risk may be better served by optimized medical therapy. The gap between these extremes is where shared decision-making and future evidence matter most.

Practical patient-selection framework

A pragmatic selection algorithm can be framed as sequential gates rather than a binary rule. This framework should be adapted to local guidelines, reimbursement restrictions, and patient preference (refer to *Graphical Abstract*).

Decision gate	Clinical indicators favouring progression	Clinical consequence
Gate 1: Is ablation indicated?	Symptomatic AF despite medical therapy, first-line ablation in appropriate patients, tachycardia-mediated cardiomyopathy, or patient-centred rhythm-control indication.	No combined procedure if ablation itself is not justified.
Gate 2: Is stroke prevention needed?	CHA_2DS_2-VA score indicating long-term stroke prevention; atrial cardiomyopathy or prior stroke may strengthen concern.	Low-risk patients generally do not require LAAC.
Gate 3: Is long-term OAC problematic?	Prior major bleeding, recurrent clinically relevant bleeding, high bleeding risk not easily modifiable, intolerance, adherence problems, renal impairment affecting OAC use, or strong informed preference.	If OAC is well tolerated and bleeding risk is low, incremental LAAC benefit may be smaller.
Gate 4: Is procedural risk acceptable?	Favourable LAA anatomy, no active LAA thrombus, acceptable vascular and transseptal risk, sufficient life expectancy, centre expertise.	Avoid or stage LAAC in frail patients with high periprocedural risk or uncertain anatomy.
Gate 5: Combined or staged?	Combined if both procedures are clearly indicated, imaging is adequate, and centre workflow is mature. Staged if anatomy, oedema, antithrombotic plan, or patient preference requires reassessment.	Combined PFA-LAAC should be a selected pathway, not default practice.

Sex-specific considerations

To date, combined ablation-LAAC studies have not demonstrated a consistent sex-specific difference in the performance of the combined strategy itself. However, available trials and registries were not primarily powered for sex-stratified assessment of procedural outcomes such as device-related thrombus, peri-device leak, stroke, bleeding, or mortality. This is relevant because trial eligibility thresholds and thromboembolic-risk schemes often differ by sex, whereas procedural endpoints are usually reported for the overall cohort. Future studies should therefore pre-specify sex-stratified analyses and report device, imaging, and antithrombotic outcomes separately for women and men.

Device landscape and cross-platform limitations

The evidence base should not be generalized across devices without qualification. Pulsed field ablation systems differ in catheter geometry, electrode configuration, waveform, dosing logic, mapping integration, and susceptibility to safety interruptions. Left atrial appendage closure devices differ in landing zone, sealing mechanism, protrusion into the LAA ostium, anti-thrombotic regimen, and imaging requirements. These differences matter when combining procedures. In particular, apparent procedural advantages of one PFA platform or one LAAO design should not be extrapolated to other systems without platform-specific evidence.

Device/domain	Examples or categories	Combined-procedure considerations	Evidence caveat
PFA platforms	Multi-spline/pentaspline catheters, circular catheters, balloon systems, focal solid-tip catheters, lattice-tip or large-footprint catheters, dual-energy PFA/RF systems	Lesion geometry, catheter manipulation, remapping workflow, sheath exchanges, and interaction with LAA devices differ by platform.	OPTION did not include PFA; early PFA-LAAC studies should not be extrapolated across all PFA systems, and no comparative evidence has shown clinical superiority of PFA-LAAC over RF- or cryoballoon-based combined workflows.
Endocardial plug-type LAAC	WATCHMAN FLX/FLX Pro and related plug-type systems	Designed to sit within the appendage ostium/landing zone; may reduce disc protrusion into the left atrium but does not remove the possibility of device-field interaction. PFA delivery in direct contact with or immediately adjacent to any implanted LAAO device should be avoided where possible.	Most randomized post-ablation LAAC evidence is WATCHMAN-based. Visible arcing has been reported near an implanted LAAO device, so apparent geometry advantages should not be over-interpreted.
Lobe-and-disc LAAC	Amulet and related lobe-and-disc systems	Disc protrusion may influence catheter access, PFA field distribution, or system safety interruption near left pulmonary veins in some anatomies. The same avoidance principle applies: do not deliver PFA close to any implanted LAAO device when avoidable.	Encouraging registry data exist, but randomized post-ablation evidence is less extensive than for WATCHMAN-based OPTION; device-field interaction concerns are not exclusive to disc-based devices.
Epicardial/ surgical LAA exclusion	AtriClip and surgical/epicardial approaches	Different procedural pathway, imaging follow-up, and antithrombotic assumptions; not directly comparable with percutaneous LAAC.	Not a substitute evidence base for percutaneous concomitant PFA-LAAC.

Reimbursement challenges and opportunities in Europe

Policy, funding, and organizational considerations

Despite growing evidence around the safety and feasibility of the concomitant approach, the lack of supporting funding frameworks and policies can significantly delay the integration of concomitant procedures into routine clinical practice. In Europe, reimbursement decisions are decentralized and influenced by national and, in some cases, regional health technology assessments (HTAs), heterogeneous reimbursement frameworks, and payer decisions,[35] which determine how hospitals

and clinicians are remunerated and often result in fragmented implementation and heterogeneous patient access.[35]

The flexibility of systems to accommodate the concomitant approach varies widely,[36,37] and financial sustainability may require intervention at various levels, ranging from reimbursement mechanisms to HTA processes and national policy decisions. In some countries, a critical element in adopting combined LAAC and AF ablation is defining it as a unified clinical entity within existing procedural coding systems. While AF ablation and LAAC each have established codes, some European coding systems require adjustments for their simultaneous use. When it comes to funding, in many diagnosis-related group (DRG)-based systems, reimbursement is limited to the dominant procedure per hospital admission, with the second one, often involving a high-cost device, adding substantial unreimbursed expense. Countries operating under DRGs, global budgets, fee-for-service, or mixed models may require alternative mechanisms to align incentives for concomitant procedures, ranging from the establishment of dedicated procedural codes or DRGs to add-on payments for devices or other targeted funding mechanisms.

Dedicated HTAs that assess the combined approach may also support adoption in selected countries. However, HTA outcomes are not always binding for reimbursement policy,[38] and funding decisions may also be influenced by statements from national commissioners (e.g. NHS England), inclusion into Health Benefit Catalogues, or national clinical guidance (e.g. issued by NICE in the UK, the Haute Autorité de Santé in France, and Socialstyrelsen in Sweden). National policy, consensus documents, or clinical guidance could support the combined approach by clarifying key aspects such as funding eligibility and patient selection. Increased adoption of concomitant procedures may also pose organizational questions that should be addressed, including operator training, multidisciplinary coordination, and cath-lab and anaesthesia capacity.

Current international reimbursement landscape

While in the United States, concomitant LAAC and AF ablation reimbursement has been introduced in 2024,[39] reimbursement across Europe remains fragmented. In Switzerland, a DRG for concomitant AF ablation and LAAC was introduced at the beginning of 2026,[40] but other DRG-based systems, such as Germany or Italian private accredited hospitals, reimburse one procedure per hospital admission, creating economic disincentives for concomitant rather than staged interventions. Other DRG-based systems, such as France and England, allow add-on payments for AF ablation and/or LAAC devices, which partially offsets, but does not fully eliminate, the financial disincentives for concomitant procedures. Global budget systems, such as Spain or Italian public hospitals, allow discretionary allocation of funds to cover all hospital activity, including concomitant procedures, while other European countries, such as Belgium and Croatia, have mixed reimbursement systems in which devices are funded separately from procedural costs. In many European countries, reimbursement for LAAC is restricted to patients with contraindications to long-term oral anticoagulation, thereby excluding a substantial proportion of patients enrolled in the OPTION trial.

Therefore, across Europe, the integration of concomitant LAAC and AF ablation into routine clinical practice will depend not only on the accumulation of further clinical evidence but also on reimbursement pathways and national policies evolving to reassess and reflect the value of combined interventions. Clear reimbursement frameworks, as seen in the US, can accelerate the adoption of integrated AF management strategies.

Limitations and uncertainties

The current evidence base has important limitations. First, the strongest randomized post-ablation LAAC evidence comes from OPTION, which used radiofrequency and cryoballoon ablation rather than PFA. Second, PFA-specific combined data are early and underpowered for clinical endpoints. Third, no comparative study has shown that combined ablation-LAAC procedures are clinically superior when performed with PFA rather than radiofrequency or cryoballoon ablation. Fourth, trial populations differ substantially: OPTION enrolled post-ablation patients with relatively low bleeding risk, CHAMPION-AF enrolled OAC-eligible patients not specifically linked to ablation, CLOSURE-AF enrolled older, high-risk patients with major competing risks, and OCEAN/ALONE-AF enrolled selected patients without documented recurrence after ablation. Fifth, composite endpoints can obscure clinically important differences between stroke, bleeding, and mortality. Sixth, device-platform differences limit generalization across PFA systems and LAAC devices. Seventh, sex-specific analyses are limited and usually underpowered, despite sex-related differences in trial eligibility thresholds and thromboembolic-risk scoring. Finally, cost-effectiveness and reimbursement assumptions are country-specific and likely to change as technology, trial evidence, and payment systems evolve.

Future perspectives

Future studies should evaluate combined PFA-LAAC with device-neutral, platform-specific reporting. At minimum, prospective studies should report ablation technology, LAAC device type, imaging modality, procedure sequence, transseptal strategy, acute complications, device-related thrombus, peri-device leak, rhythm monitoring intensity, OAC discontinuation protocol, and disaggregated clinical endpoints, including sex-stratified outcomes. Trials should compare combined PFA-LAAC not only with ablation plus continuous OAC but also with ablation plus structured OAC withdrawal or monitoring-guided OAC re-initiation. Comparative studies should also test whether PFA-LAAC offers any clinical advantage over radiofrequency- or cryoballoon-based combined workflows rather than assuming benefit from procedural efficiency or the safety profile of PFA alone.

CHAMPION-AF has now reported that LAAC was non-inferior to non-vitamin K antagonist oral anticoagulant (NOAC) therapy for cardiovascular death, stroke, or systemic embolism and reduced non-procedure-related bleeding in OAC-eligible patients.[41] This supports a broader discussion of LAAC as a potential alternative to NOACs in selected patients, but it does not answer the ablation-specific or PFA-specific question. CLOSURE-AF simultaneously reminds the field that high-risk frail patients may have competing risks that can offset expected LAAC benefit.[33] Together, these trials argue for more precise patient selection rather than universal expansion.

Conclusions

Combined PFA and LAAC is a technically plausible and increasingly relevant strategy for selected patients with AF who require rhythm control and have a clinically meaningful reason to avoid long-term OAC. Current randomized evidence supports LAAC around AF ablation mainly from thermal-ablation-era data, while PFA-specific evidence remains limited and does not yet establish superiority over radiofrequency- or cryoballoon-based

combined procedures. The strategy should therefore be presented as an emerging, patient-selected pathway requiring prospective validation, not as routine standard care.

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Final approval of manuscript

All authors.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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PULSED FIELD ABLATION FOR CARDIAC ARRHYTHMIAS SUPPLEMENT

The future of PFA in cardiac ablation procedures

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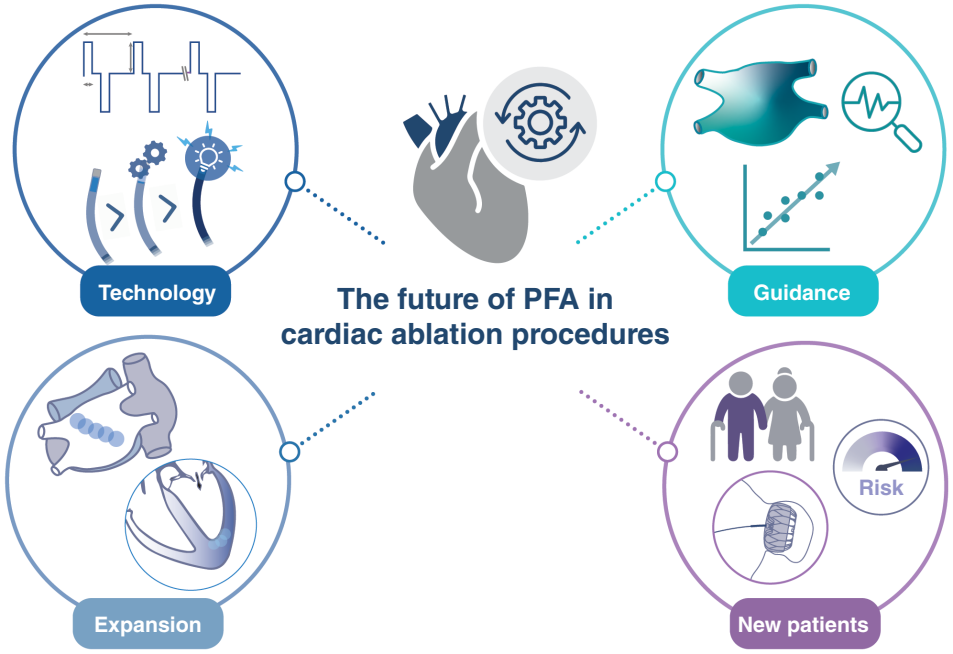
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Abstract

Pulsed field ablation (PFA) has rapidly emerged as a major development in catheter ablation, with increasing clinical adoption driven by procedural efficiency and a favorable safety profile compared with thermal energies. This article summarizes the future directions of PFA in electrophysiology, focusing on technological innovation, and how these advances are expected to expand PFA clinical indications. Additionally, this article provides a perspective on current gaps and future challenges of PFA. A perspective on future developments in new waveforms, catheter architectures, and integration with electroanatomical mapping systems for PFA is summarized. The document discusses novel waveform configurations and catheter design concepts that may improve lesion quality, procedural versatility, and safety. Additionally, this article also reviews how parallel advances in electroanatomical mapping integration, artificial intelligence, and robotic navigation are expected to enhance procedural guidance and enable individualized therapy. This manuscript summarizes the potential applications of PFA beyond pulmonary vein isolation and how emerging evidence supports its feasibility for linear atrial lesions, substrate modification, treatment of complex atrial tachycardias, and ventricular arrhythmia ablation. In addition, this article provides insights on how PFA may facilitate catheter ablation in new patient populations including elderly patients and those with higher procedural risks. Finally, this manuscript provides an outlook at major remaining challenges and knowledge gaps for PFA. The lack of homogenous procedural endpoints definitions and lesion durability assessment are discussed. Furthermore, this article highlights the need for standardized terminology and reporting in an environment where the high heterogeneity between available commercial systems complicates comparison across technologies.

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Graphical Abstract



Keywords Pulsed field ablation • Future • Waveform • Catheter design • Electroanatomical mapping • New patient groups • Terminology • Standarization • Clinical trials

Introduction

Pulsed field ablation (PFA) has undergone exceptionally rapid development in recent years, transitioning from an experimental energy source to a clinically established modality in cardiac electrophysiology. PFA has generated considerable interest as an alternative to conventional radiofrequency and cryothermal ablation. The rapid widespread clinical use has been accompanied by an unprecedented technological innovation, with multiple dedicated platforms now available and large-scale trials rapidly defining its role in atrial fibrillation treatment.

This article provides an overview of the future perspectives of PFA in cardiac electrophysiology. It first examines the potential technological evolution of PFA with a focus on new waveforms, advances in catheter design, and procedural integration with 3D mapping systems. Subsequently, the article explores new and emerging indications, highlighting the progressive expansion of PFA beyond pulmonary vein isolation (PVI) in atrial fibrillation to more complex arrhythmia substrates and broader clinical applications with a specific focus on future applications in the ventricle. Additionally, new patient groups benefiting from PFA are examined. Finally, the article addresses the remaining scientific and clinical challenges associated with PFA, including remaining knowledge gaps, standardization of protocols and reporting and discussing the current challenges for system comparison. Finally, an outlook about ongoing and future clinical trials is provided. With the remarkable innovation pace in PFA, the aim of this article is to provide a structured synthesis of key directions for future developments, research and clinical adoption of this disruptive ablation technology.

Technological evolution of PFA: shaping energy delivery and guidance

New waveforms

From the early years of PFA exploration, there was already some awareness that waveform design would have a major influence on lesion creation as well as safety and procedural workflow. The early development of the first PFA system initially explored the use of a monophasic square waveform; although this was effective in isolating the pulmonary veins, prominent skeletal muscle stimulation was noted, which compelled the use of general anaesthesia and paralytics.[1] Transition to biphasic waveform delivery for the second half of the PEF CAT study[2] showed how skeletal muscle activation was noticeably reduced, thereby making deep sedation a feasible option for operators. Subsequent studies showed that biphasic PFA may also have other additional safety advantages over monophasic PFA; in a porcine study, monophasic PFA delivered on the T wave of the cardiac cycle consistently triggered ventricular fibrillation, whereas this was not seen with biphasic delivery.[3] Nowadays, most contemporary clinical platforms deliver groups of biphasic square wave pulses with individual pulse duration in the short microsecond range.

As our knowledge of PFA continues to mature, other aspects of waveform design are under active investigation. Specifically, other pulse durations beyond the microsecond duration domain are under study (see *Figure 1A*). In preclinical and early first-in-human studies, sub-microsecond PFA in the nanosecond range has been shown to be effective in creating transmural myocardial lesions in the atrium and pulmonary veins with

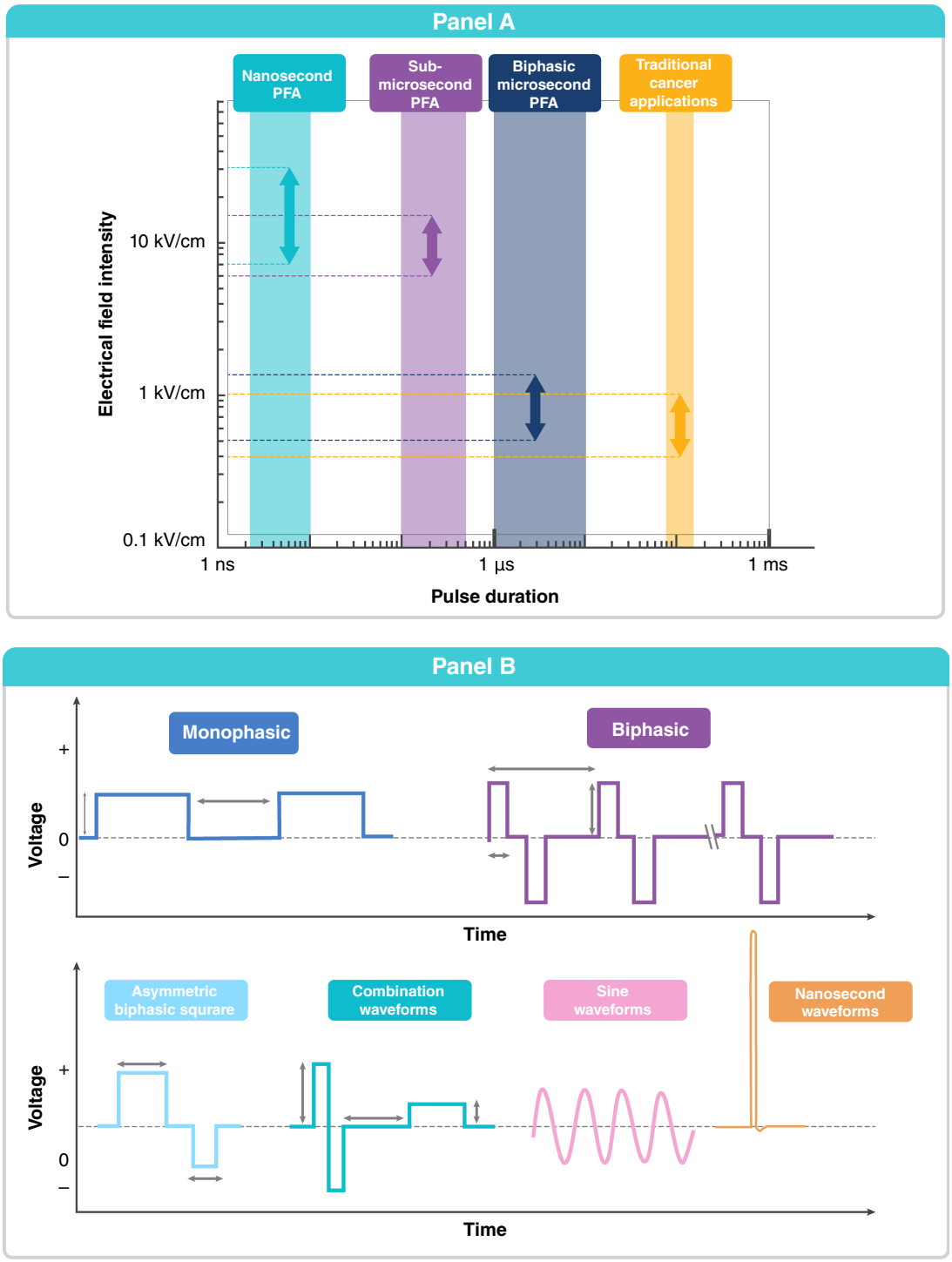


Figure 1 *A*) Summary of main pulse duration domains for irreversible electroporation applications. *B*) Summary of the main waveforms explored for PFA applications.

both endocardial as well as surgical approaches.[4–6] Additionally, exploratory large animal studies have also demonstrated the feasibility of nanosecond PFA for ventricular myocardial ablations.[7–9] Effects on cells have been studied since the early 2000s suggesting specific effects on intracellular structures and demonstrating their ability to induce electroporation of intracellular structures.[10,11] From a clinical perspective, nanosecond PFA may induce skeletal muscle contraction to a lesser extent than microsecond PFA, which may widen options for intraprocedural sedation. Nanosecond pulses could require considerably increased voltage levels delivered by the PFA generator potentially involving technological challenges

regarding isolation and impedance matching for the correct pulse transmission to the target tissue. Additionally, the effects of submicrosecond pulses may substantially differ between purely nanosecond pulses of a few nanosecond duration to submicrosecond pulses in the order of hundreds of nanoseconds. Other ongoing uncertainties that will require further study include the extent of microbubble formation and long-term lesion durability.

Besides pulse duration, future developments may involve using alternative waveforms different from biphasic square pulses or even combinations of different pulse types (see *Figure 1B*). The use of sine waveforms has been investigated as an alternative means of PFA delivery. Preclinical chronic porcine data demonstrated durable PVI and linear lesion formation without clinically significant pulmonary vein stenosis, detectable microbubbles, electrical arcing, thrombus, charring, or major collateral injury.[12] In the BURST-AF study, coherent sine-burst electroporation achieved 94.1% per-vein durability, 94.4% durability of additional posterior wall and cavotricuspid isthmus lesions, and 92.6% freedom from atrial arrhythmias at 6 months.[13] Additionally, altering the symmetry of biphasic square waveforms, different amplitudes or durations between the positive and the negative parts of the biphasic pulse, has also been explored; in a pilot study utilizing an asymmetric biphasic square waveform (positive phase 5 µs, negative phase 3 µs), successful PVI was achieved in 10 patients, with no atrial arrhythmia recurrences or complications over 6 months.[14] Other pulse parameters including interpulse delay may be important determinants of lesion creation as well.[15–17]

In summary, there is a plethora of PFA parameters that factor into ablation efficacy and safety; furthermore, waveform delivery parameters must be considered in context with the ablation catheter that is being used. It is therefore contingent upon the medical community and industry to be aware of the complexities and nuances behind these parameters and to ensure systematic testing prior to clinical implementation.

Next-generation PFA catheters: optimizing energy delivery

Besides new developments on PFA waveforms, the second most important element allowing PFA evolution is the catheter design. While some contemporary PFA systems are based on repurposed catheter designs, next-generation PFA catheters are expected to evolve to purpose-built PFA designs incorporating features that should address current limitations in efficacy, precision, side effects and workflow efficiency.

A central concept in future catheter development is the device form factor and the associated tissue surface area treated during a PFA application. Contemporary PFA systems include small-focal, large-focal, regional and single-shot platforms adapted for focal, linear or wide-area lesion creation or for circular PVI.[18] Regarding single-shot devices, while current systems already enable rapid PVI, the realization of a 'true single-shot' device, one application-one position, remains a current design challenge. Furthermore, anatomical variability and complex arrhythmogenic substrates support the need for adaptable and multifunctional designs capable of adapting to diverse scenarios and anatomies. Next-generation catheters capable of dynamically adopting multiple shapes to provide large area or focal ablation functionalities would represent a paradigm shift.

Another potential area of innovation is precise electric field control for shaping lesion size and limiting collateral effects. Although PFA preferentially ablates cardiac tissue, electric field propagation beyond the target region, particularly towards near sensitive structures, can produce undesired collateral effects like excessive neuromuscular stimulation and associated pain or coronary spasm. Advancements in electrode configuration allowing electric field confinement or electric field shielding strategies could enable a more spatially confined ablation minimizing unintended effects on nearby tissues.[19]

Fabrication materials, especially electrode materials, are another area of potential future innovation where traditional metallic electrodes may be supplemented or replaced by novel conductive polymers that offer enhanced flexibility, improved tissue contact, and superior biocompatibility. Parallel to material innovation, fabrication techniques are likely to undergo a transition from manual assembly to scalable manufacturing processes such as printed electronics and additive manufacturing. These approaches will allow precise control over electrode geometry and enable the integration of complex electronic and sensing components directly into the catheter structure. Multifunctional electrodes capable of simultaneous sensing and energy delivery could represent an advantage in future designs.

With the expected evolution of software tools, future PFA catheters are also expected to incorporate ultra-high-density electrogram recording capabilities. Enhanced signal quality and spatial resolution could improve procedural outcomes and reduce arrhythmia recurrence rates.[20] Beyond electrograms, the integration of multiparametric sensing—encompassing temperature, impedance, contact, force, optical information or even tissue metabolic activity—could provide comprehensive real-time feedback on tissue status during ablation.

An additional area where improvements in catheter architecture may be implemented is eliminating the need for electrode irrigation. Although PFA relies on a non-thermal mechanism for tissue ablation, irreversible electroporation, the application of high pulsed electric fields on biological tissues can induce considerable short-duration rises in temperature by the Joule heating effect. PFA system optimization should ensure that the thermal profile of any PFA platform does not exceed the thresholds for thermal damage. Accordingly, some contemporary systems require considerably high electrode irrigation rates to ensure lesion formation without unintended thermal effects.[21] Future improvements in waveform design and purpose-built catheters could overcome the need of irrigation generalizing irrigation-free catheter designs.

The convergence of these technologies with artificial intelligence (AI) and robotic systems may further transform future catheter-based interventions. AI algorithms could support operators by optimizing pulse delivery and guiding optimal catheter positioning. Lastly, although robotic navigation is not a new concept,[22] the rapid advancements in robotic systems may enable this concept rapidly evolving towards a future of semi-automated or fully automated ablation procedures.

Finally, sustainability considerations are becoming increasingly relevant.[23,24] The development of reusable or partially reusable catheters, along with environmentally conscious manufacturing processes, could reduce medical waste and overall healthcare costs without compromising safety or performance.

The role of mapping with PFA: future guidance on PFA procedures

Initial implementations of PFA technology did not include dedicated integrations of the ablation catheter into the electroanatomical mapping systems, and procedures were guided by traditional imaging techniques, mainly visualization of the catheter under fluoroscopy or rudimentary integration into mapping systems. Nowadays, although some systems are still extensively

used without the support of electroanatomical mapping, the rapid development of PFA has led most contemporary platforms to incorporate dedicated, purpose-built catheter solutions specifically designed for PFA delivery.

As optimal clinical implementation of PFA relies heavily on accurate and reproducible procedural guidance, electroanatomical mapping is expected to play an increasingly important key role in future developments.[25,26] The integration of electroanatomical mapping into PFA workflows should focus on several key domains, including accurate catheter positioning within complex cardiac anatomies, reliable assessment of catheter–tissue interaction, robust evaluation of lesion formation, and comprehensive characterization of the underlying substrate, among others.[27] Mapping technologies may evolve from a primarily navigational role towards a more active contribution to real-time decision-making and individualized ablation strategies—an evolution that is likely to become even more relevant as the clinical indications for PFA expand toward increasingly complex atrial and ventricular substrates.

Accurate catheter positioning represents a foundational element in the role of mapping in PFA, as PFA efficacy is highly dependent on catheter position and orientation, spatial consistency, and anatomical alignment within complex cardiac structures.[28,29] Ablation efficacy is determined by the intersection of the target tissue with the volume where the electric field intensity exceeds the lethal threshold for cardiac tissue specific for each PFA system. Future developments are likely to include high-accuracy anatomical acquisition tools, improved modelling tools for accurate depiction of the predicted PFA field distribution, or integration of intracardiac echocardiography for more precise catheter rendering—particularly for non-linear and multi-spline designs. In addition, improved visualization of sheaths and guidewires may contribute to further reductions in fluoroscopy usage.

The assessment of catheter-tissue interaction constitutes a complementary aspect of procedural guidance beyond spatial positioning alone. Although the value of traditional contact force metrics is still under study and may not provide additional benefits for every PFA design, effective PFA lesion formation will be optimized by minimizing the distance between the catheter and myocardial tissue.[30] Future mapping implementations are therefore expected to focus on the refinement and validation of PFA-specific indicators of tissue interaction, such as impedance-based parameters, providing real-time feedback on contact quality and enabling operators to optimize energy delivery without relying on paradigms derived from thermal ablation technologies.

Defining robust lesion assessment strategies and procedural endpoints remains one of the most significant challenges in the broader adoption of PFA. Conventional markers of ablation efficacy, including acute voltage reduction or immediate conduction block, may not fully reflect the unique temporal and electrophysiological effects associated with PFA lesions.[31] Electroanatomical mapping is therefore expected to play an increasingly important role in interpreting lesion formation and distinguishing transient from durable effects. In this sense, future systems may include optimized real-time algorithms able of analysing and extracting electrogram features such as morphology and recovery dynamics of unipolar electrograms that could help predict areas of reversible or irreversible electroporation after pulse delivery.[32–35] Another important element that may be integrated into future mapping systems relates to the ability for energy delivery titration. Nowadays, PFA lesion formation is governed by procedural workflow optimization rather than energy delivery titration. Although several PFA-specific indices integrating variables such as voltage, contact force, and application count have been proposed,[36–39] the validity of their predictive performance is still to be proven in the clinical setting. Increasing understanding of PFA mechanisms may lead to the development of novel system-specific predictors that most likely will not only rely on traditional parameters used in thermal ablation but also on new concepts specifically developed for PFA.

Mapping systems also offer the potential to integrate substrate characterization into PFA decision-making, supporting a more individualized approach to ablation, particularly in patients with persistent atrial fibrillation. Although no individualized ablation strategy has yet demonstrated clear superiority over antral PVI alone,[40,41] the increased procedural efficacy and safety profile associated with PFA may lower barriers to evaluating more advanced mapping-guided strategies. These improvements could include novel algorithms, AI–assisted analysis, or panoramic mapping techniques, among others. In this setting, mapping may contribute not only to procedural execution but also to strategic planning and patient-specific optimization of PFA therapy.

Continued integration of mapping-derived information into PFA procedures will be essential to establish reproducible standards, refine procedural endpoints, and support the safe and effective expansion of PFA across a broader range of clinical indications.

New indications: expanding the clinical horizon of PFA

Beyond pulmonary vein isolation: extending PFA to complex atrial arrhythmias

PVI remains the cornerstone of catheter ablation for AF. However, recurrence and the need for repeat ablation remain frequent, especially in persistent AF, prompting consideration of strategies beyond PVI to address non-pulmonary vein triggers and atrial substrate.[42]

PFA increases the procedural practicality of ‘beyond-PVI’ approaches. Energy delivery is rapid and repeatable, enabling efficient extension of ablation beyond PVI, such as linear lesion sets and targeted substrate modification (e.g. low-voltage areas).[43] Myocardial preferentiality provides a rationale for broader substrate modification with a favourable collateral profile, supporting more extensive atrial lesion sets beyond antral PVI.[44] Future expansion is likely to focus on defined atrial arrhythmia substrates and anatomical isthmuses. Typical flutter is a prime target for linear PFA at the cavotricuspid isthmus (CTI), with emerging data showing high acute block and procedural efficiency.[45] For perimitral flutter, PFA may enable a more durable mitral isthmus block, with coronary sinus applications as a potential adjunct to address epicardial connections. Similarly, complex post-ablation atrial tachycardias (roof- and perimitral circuits and scar-related re-entry) may be addressed through mapping-guided linear sets and focal consolidation.[46] Key limitations for these indications include defining robust procedural endpoints, ensuring chronic durability of linear block, and establishing adequate dosing workflows associated with lesions beyond PVI. Given the favourable safety profile, interest in extending ablation beyond PVI has increased.[47]

In parallel, platform evolution is lowering barriers to complex procedures. New catheter generations and system refinements increasingly combine PFA delivery with 3D mapping

integration, enabling navigation and lesion deployment beyond antral PVI within familiar workflows. This availability of 3D-guided PFA broadens the technical scope for complex atrial arrhythmias, while iterative refinements in catheter design and platform integration aim to improve applicability and procedural consistency. As mapping-linked PFA is adopted more widely, incremental improvements in catheter design and software integration may support more consistent coverage of complex atrial substrates; the clinical impact, however, requires prospective validation.[48–50]

Device development is also diverging into complementary tool classes, which include single-shot multielectrode geometries (basket/flower and circular designs, including size-adaptable variants) and focal or large-footprint platforms.[51] Single-shot designs are optimized for rapid, standardized antral coverage and can be redeployed to adjacent atrial regions—most commonly the left atrial posterior wall.[42,51] Focal and large-footprint concepts support line completion and regional substrate modification under mapping guidance, particularly in redo procedures.[51] Notably, lattice-based platforms have enabled reversible electroporation mapping with transient conduction block to help localize critical sites in re-entrant atrial tachycardias; early clinical experience suggests feasibility and reproducibility with moderate sensitivity, but further evaluation is required before broader adoption.[52]

Current pulse protocols have been primarily developed and validated for antral PVI, not for systematic beyond-PVI lesion sets. Proprietary pulse protocols limit cross-platform comparison and impede systematic optimization, but emerging directions include alternative pulse structures and delivery algorithms aimed at improving lesion homogeneity, lesion depth and procedural control.[51,53] In selected settings, hybrid workflows with energy toggling (switching between PFA and radiofrequency) can be useful as a pragmatic bridge—for example, when completing depth-limited segments or closing residual gaps during early adoption and in anatomically challenging redo scenarios—but their role is likely to diminish as PFA catheter form factors, mapping integration, and dosing concepts for beyond-PVI targets mature.[53]

With continuing advances in catheter design, mapping integration, and energy delivery concepts, 'beyond-PVI' atrial ablation is moving further into focus and may improve long-term procedural effectiveness; however, robust long-term outcome data for systematic extension strategies remain limited.[40,41]

PFA in the ventricle

Catheter ablation of ventricular arrhythmias (VAs) remains limited by several features intrinsic to ventricular substrate. Compared with atrial tissue, the ventricular myocardium is thicker, often scarred or infiltrated by fat, and may contain intramural or epicardial circuits that are difficult to reach with conventional radiofrequency (RF) ablation. In addition, VA ablation frequently requires treatment of extensive substrate, and procedural endpoints such as acute noninducibility do not always predict durable success. These limitations are particularly relevant in scar-related ventricular tachycardia (VT), in which inadequate lesion depth, incomplete transmurality, and inability to access protected substrate may all contribute to recurrence.

The main appeal of PFA in the ventricle is not simply novelty but the possibility of safer energy delivery with deeper scar penetration and reduced collateral injury relative to thermal energy delivery. Nonetheless, there are some key aspects that will require further clarification. PFA induces immediate electrogram (EGM) attenuation or disappearance, which may represent transient electrophysiological stunning (reversible electroporation) rather than irreversible myocardial ablation. As such, acute arrhythmia suppression or non-inducibility may potentially result from reversible electroporation effects within the targeted substrate, rather than permanent lesion formation. Thus, traditional procedural endpoints, such as EGM elimination, non-capture with high output pacing, noninducibility, and the use of waiting periods to confirm lesion durability, may be less reliable when applied to PFA. These limitations highlight a gap in our current understanding of lesion durability in ventricular PFA and underscore the need for alternative validation strategies.

While feasibility and procedural safety are becoming increasingly evident, the question of true effectiveness, defined as durable substrate modification and sustained arrhythmia control, remains to be fully established.

Lesion characterization from animal and *in vivo* data

Experimental studies consistently suggest that PFA lesion formation is less attenuated by scar than RF ablation and may also traverse tissue interfaces containing collagen or fat more effectively.[1] In a swine model of healed myocardial infarction, PFA created more homogeneous and better demarcated lesions than RF, with greater depth and a higher rate of transmurality.[54] Lesion extension through collagen and fat towards the epicardium with preservation of intramural blood vessels or nerve bundles was observed with PFA but not with RF. Other animal work confirmed that lesion depth in scarred myocardium may still be somewhat smaller than in healthy myocardium but remains substantial and generally superior to RF in infarct substrate.[54–56] Additional work demonstrated penetration of both infarct and iatrogenic scar, with depths up to 8.6 mm in some sections, while QRS-gated delivery eliminated ventricular arrhythmias that were occasionally provoked by ungated pulse delivery.[56]

Another important observation from preclinical work is the repetition dependence for lesion depth. Repeated applications increase lesion depth and size, which may be particularly important in thick myocardium or complex structures (e.g. septum, papillary muscles).[57,58] In ventricular models, this approach has achieved lesion depths of 6–9 mm and, in bipolar configurations, transmural lesions exceeding 14 mm without overt thermal injury.

Catheter configurations, feasibility, safety, and effectiveness

Small-footprint focal PFA systems

The earliest structured clinical data for ventricular PFA come from focal PFA delivered through contact force-sensing catheters. PFA was feasible across multiple ventricular locations to treat premature ventricular contractions (PVCs), with acute and chronic success both reported at 85%.[59] Irritative ventricular firing occurred in 55% of patients; of note, acute remapping findings suggested that at least some early lesions included a reversible component rather than immediate permanent substrate elimination.

A broader two-centre ventricular arrhythmia experience including both PVC and scar-related VT confirmed that focal PFA is technically feasible and acutely effective, with an overall acute success of 84%.[60] Yet this study also illustrated the difference between acute feasibility and true effectiveness. While 3-month suppression of PVCs remained good at 81%, only 52% of patients with scar-related VT were free of recurrent VA at follow-up. In addition, three patients developed transient conduction system block due to unexpected electric current leakage from proximal shaft electrodes, underscoring that

purpose-built catheter design, not just waveform, critically affects safety.

The most recent major development is the introduction of high-voltage focal PFA systems designed specifically for scar-related VT.[61] The first-in-human VCAS study represents a strong clinical signal that ventricular PFA is moving towards meaningful substrate ablation. In 26 patients with scar-related VT, acute procedural success was achieved in 92%, 6-month freedom from recurrent VT or ventricular fibrillation (VF) or Implantable Cardioverter Defibrillator (ICD) shock was 81.8%, and VT/VF burden fell by 98%. Most importantly, in a subgroup undergoing paired endocardial and epicardial mapping, transmural tissue homogenization after endocardial-only PFA was acutely observed in all evaluated patients.

Large-footprint focal PFA systems

The next step in the evolution of ventricular PFA has been the development of large-footprint catheters (see *Figure 2*), which may permit high-density mapping and delivery of RF and/or PFA energy. Initial small studies showed that this strategy is feasible in complex ventricular substrate and may enable faster and broader substrate modification than focal catheters.[62,63] In an early-feasibility study of 18 patients with recurrent VT, 3-month ventricular-arrhythmia-free survival reached 78%; however, coronary spasm occurred in most patients undergoing epicardial PF delivery, although all episodes resolved with nitrates.[63]

The multicentre AVAAR registry provided the first larger-scale real-world assessment of a large-footprint focal PFA system. Among 126 patients, acute success was 84% and arrhythmia-free survival at a mean of 5.6 months was 72%.[64] These outcomes support procedural feasibility and suggest reasonable short-term efficacy in a difficult population. However, this registry also reported safety events: major complications occurred in 6%, including thromboembolic events and one ventricular fibrillation episode related to catheter insulation breach, while minor complications included transient ST changes, haemolysis, mechanical left bundle branch block, and chordal injury without sequelae. Overall, large-footprint focal systems may potentially improve feasibility by enabling rapid mapping and wider lesion sets, but their true effectiveness still depends on whether the created lesions are truly transmural and durable, especially in non-ischaemic cardiomyopathy where trabeculation, variable wall thickness, and intramural substrate remain major obstacles.

Future perspectives

Reversible electroporation offers a compelling, still largely exploratory concept for arrhythmia mapping by enabling transient and localized electrical silencing of arrhythmogenic substrate without causing permanent tissue injury.[52,65] This strategy has the potential to evolve into a novel functional mapping tool for VT (*Figure 3*), bridging the gap between substrate identification and ablation; however, its role will depend on improved control of energy delivery and validation in dedicated clinical studies.

Future progress in ventricular PFA will also depend on establishing reliable procedural endpoints that accurately reflect durable lesion formation rather than transient electrophysiological effects. In parallel, optimization of energy delivery and dosing strategies, together with the development of dedicated catheter designs specifically engineered for ventricular anatomy and substrate complexity, will be essential to enable tailored PFA titration for different tissue characteristics and to consistently achieve sufficient lesion depth and transmurality.

New patient groups

Pulsed field ablation signifies one of the most substantial innovations in the field of cardiac electrophysiology, with an unprecedented adoption into clinical practice largely because of advantages in procedural efficiency and safety when compared to thermal ablation. In addition to PFA becoming the preferred initial ablation modality for paroxysmal and persistent AF, there has been an organic reappraisal of patient groups being offered

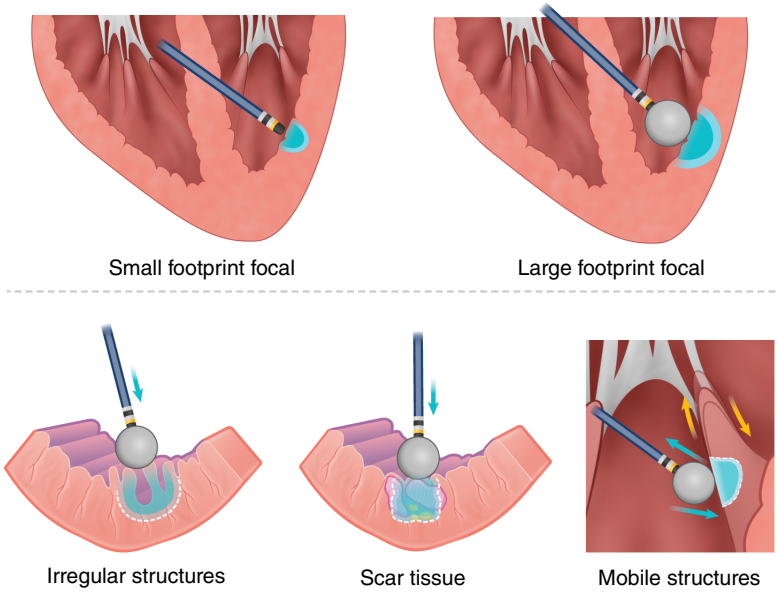


Figure 2 PFA applications in the ventricle.

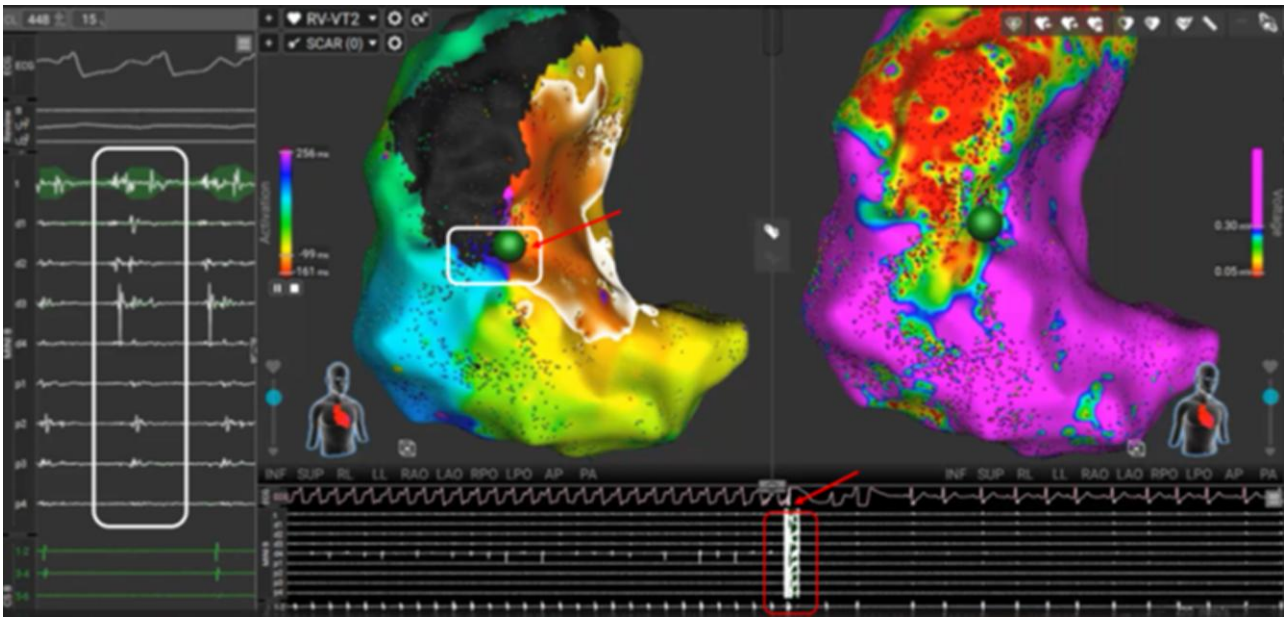


Figure 3 Reversible electroporation for ventricular arrhythmia mapping. The VT activation map (left panel) demonstrates a figure-of-eight re-entry pattern, with mid-diastolic potentials identified at the VT isthmus (white rectangle). Application of reversible electroporation at this critical isthmus (red arrow) results in termination of the VT.

intervention. This reappraisal has centred on the concept of the risk-benefit ratio of intervention, whereby clinicians and patients balance the anticipated magnitude of benefit against the anticipated magnitude of risk associated with intervention, an analysis that is unique to various patient groups (see *Figure 4*).

(A) **Asymptomatic patients.** It is estimated that more than one third of patients with AF are asymptomatic. Patients with asymptomatic AF have been considered to be a group with a lower perceived benefit of intervention, as the core benefit of catheter ablation is improvement in symptoms and quality of life, and a group who is at lower risk of adverse AF-associated complications. However, large studies have demonstrated comparable rates of all-cause mortality, cardiovascular mortality, and stroke/systemic embolism in those with symptomatic and asymptomatic AF,[66] and recent interventional studies have demonstrated that the benefit of early rhythm control was maintained in the absence of symptoms (hazard ratio for primary outcome in asymptomatic patients of 0.76, 95% CI 0.57–1.03 vs. 0.79 in symptomatic patients, 95% CI 0.64–0.98).[67] This suggests that an intervention with a low magnitude of risk (e.g. PFA) may be beneficially employed in asymptomatic patients to improve clinical outcomes, with consideration of patient preferences as part of the shared decision-making process.

(B) **Elderly patients.** Elderly patients (≥ 75 years) represent a high-risk subgroup, in terms of adverse AF-associated cardiovascular outcomes (e.g. death, disabling stroke, major bleeding, and cardiac arrest)[68,69] and adverse procedural outcomes (higher rates of AF recurrence and higher risk of interventional complication).[70] However, PFA appears to be associated with a beneficial risk-benefit ratio, as PFA is not associated with reduced efficacy in the elderly subgroup (e.g. preserved benefit) and confers a lower risk of procedure-related complication (e.g. reduced risk). As such, in contrast to thermal ablation, it can be expected that PFA will be offered to an increasing number of elderly patients.

(C) **Patients at elevated procedural risk.** Patients with increasing numbers of cardiovascular comorbidities are often not offered invasive intervention out of concern of prohibitive procedural risk. In contrast to thermal ablation, PFA is capable of minimally thermal and selective tissue injury, minimizing the risk of collateral damage (e.g. to the phrenic nerve or oesophagus) and avoiding the negative effects of thermal energy (e.g. coagulum formation or pulmonary vein stenosis). As such, PFA offers a novel opportunity for invasive intervention for the subset of patients considered too high risk for complications related to thermal ablation.

(D) **Structural atrial pathology and longstanding persistent AF.** Patients with more advanced atrial structural pathology are known to manifest more advanced forms of AF (e.g. longstanding persistent AF) and experience an inferior freedom from recurrent atrial tachyarrhythmia compared to ablation for paroxysmal atrial fibrillation (e.g. attenuated benefit of intervention).[41] Moreover, patients with atrial myopathy and more persistent forms of atrial fibrillation have a greater burden of comorbidities and experience higher rates of peri-procedural complications (e.g. increased risk of intervention).[71] In this subgroup PFA offers a potential efficacy advantage[72,73] as it is able to better penetrate and homogenize the scarred myocardium associated with atrial myopathy.[74] Given the favourable efficacy and safety profile associated with PFA, it can be expected that PFA will be increasingly offered to patients with structural atrial pathology and more advanced forms of AF.

(E) **Concomitant AF and left atrial appendage occlusion**. The OPTION trial demonstrated the benefit of combined AF ablation and left atrial appendage occlusion (LAAO) for patients at high risk of stroke.[75] While these procedures were most often staged, there is increasing interest in the more patient-centric concomitant AF ablation and LAAO. When concomitant procedures are performed with thermal energy, there is a risk of significant oedema in the left atrial appendage-pulmonary venous ridge, which can lead to early LAAO device migration or a later peri-device leak. PFA causes less tissue swelling than thermal ablation, suggesting it may be the preferred energy modality for concomitant LAAO.

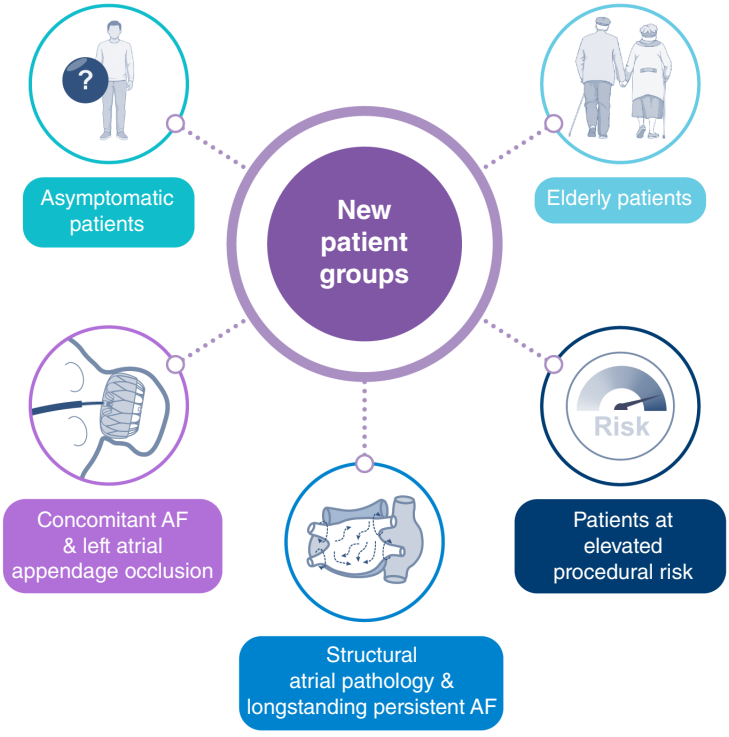


Figure 4 Summary of main new patient groups for future PFA applications.

Remaining challenges in PFA: scientific and clinical aspects

Knowledge gaps: unresolved questions in PFA

PFA has progressed rapidly from biophysical concept to clinical routine, driven by procedural efficiency and a favourable collateral profile. However, several scientific and clinical uncertainties remain, and these gaps may become more consequential as PFA expands beyond PVI.[51]

A core unresolved issue is the definition of 'dose' in PFA and how delivered parameters translate into durable tissue injury. Lesion formation reflects interactions between waveform, electrode geometry, tissue thickness, and catheter–tissue coupling; a uniform dosing paradigm to compare different PFA systems is unlikely. Current pulse protocols have been primarily developed and validated for antral PVI, whereas systematic dosing for extended atrial targets and other chambers is still evolving.[18] Repeated applications are often used to increase lesion depth and width, but the dose–response relationship and the possibility of dose titration for durable transmurality remain incompletely defined.[18] Accurate real-time *in vivo* field distribution remains difficult to predict, as local anatomy and tissue anisotropy may alter electric-field penetration and lesion geometry, particularly in thicker regions and for linear block.[18,51,76]

A second gap concerns intra-procedural assessment of lesion creation. It is not yet possible to reliably distinguish long-term failure due to incomplete target ablation from failure driven by reversible electroporation or acute reversible effects.[51] Transient conduction impairment and reversible effects further complicate endpoint interpretation, and validated real-time markers that predict chronic durability are still lacking when broader atrial coverage and linear block are pursued. Lesion heterogeneity at borders may leave functional gaps that are not apparent on acute testing.[18,51] Furthermore, the dynamics of recovery of reversible effects are not yet accurately defined and the validity of a universal optimal waiting period for all PFA systems is yet to be established.[32,35]

Long-term tissue response warrants further characterization. While preferential myocardial effects are supported, precise cardiomyocyte death mechanisms remain incompletely defined. The balance between acute cell death, triggered by catastrophic membrane disruption in areas receiving the highest PFA dose, and delayed cell death processes, including apoptosis and pyroptosis induced by calcium overload, ATP depletion, mitochondrial injury, and related mechanisms in lower-dose regions, remains poorly defined. A better understanding of these differential cell death pathways may provide important insights into lesion maturation, healing kinetics, and the evolution of post-ablation inflammatory responses. Additionally, the impact of repeated PFA exposures during consolidation or redo procedures remains incompletely defined across different atrial substrates and scar composition. Whether PFA produces distinct chronic scar architecture—and how this relates to organized atrial tachycardias—remains insufficiently characterized.[18,51]

Energy-related bioeffects represent an additional gap that becomes more relevant with broader use. Haemolysis and microbubble formation can arise from electrode–blood interactions and waveform-dependent electrochemical or thermal processes; importantly, no quantitative clinical threshold linking haemolysis severity to acute kidney injury has been established.[77] Clinical studies indicate that PFA-induced haemolysis

is common but usually subclinical. Plasma-free haemoglobin levels typically peak in the range of 30 to 60 mg/dL after AF ablation procedures, although higher values may occur with increasing numbers of pulse application.[78,79] Microbubble generation is shaped by waveform properties, supporting the concept that waveform optimization may be required as indications broaden.[77,80] Effects on coronary arteries, especially delayed events although very rare need more mechanistic studies to establish the real impact in clinical practice.[81] Additionally, the role of combining different energy sources for increasing therapeutic effects also remains to be proven as current evidence is limited to a single preclinical study.[82]

Knowledge gaps also persist in special patient groups (i.e. populations under-represented in pivotal datasets). For example, in patients with cardiac implantable electronic devices, electrical field interactions with leads and generators remain insufficiently studied, and more systematic peri-procedural and long-term device evaluation is required.[83]

Finally, device and waveform innovation is outpacing biological validation. Many commercial waveforms remain non-disclosed, limiting mechanistic comparison and systematic optimization.[51] Computational work suggests that catheter geometry can alter current density and lesion precision, but optimization remains challenging without chronic lesion correlation and greater transparency of pulse protocols.[84] Reversible electroporation concepts illustrate the opportunity—and uncertainty—of using sub-lethal pulsing for functional mapping before irreversible lesion delivery; early experience suggests feasibility, but broader evaluation is required.[18]

Overall, addressing the existing knowledge gaps will require sustained efforts spanning both fundamental research and clinical investigation. While understanding of PFA has advanced considerably in recent years, unresolved issues continue to position it as a dynamic and promising area for future research and innovation. Ongoing collaboration among academic researchers, clinical specialists, and industry partners will be essential to ensure steady and well-integrated progress in the field.

The need for a common language: standardization of PFA systems and reporting

The rapid adoption of PFA has ushered in a 'bioelectric' revolution in cardiac electrophysiology demonstrating high procedural efficiency and a favourable safety profile compared to thermal modalities. However, the rapid implementation has outpaced the development of standardized definitions and reporting frameworks resulting in significant heterogeneity in how PFA systems, parameters and procedural endpoints are described and reported across studies and clinical reports.[85] This ambiguity makes it difficult to synthesize data and establish long-term clinical benchmarks for this maturing technology.

Why is standardization challenging in PFA?

Standardization is primarily hindered by the proprietary and often undisclosed nature of PFA waveforms.[84,86] Manufacturers utilize distinct 'pulse recipes' or profiles that vary widely in pulse amplitude, width (ranging from nanoseconds to milliseconds), numbers, frequency, and waveform polarity (monophasic vs. biphasic).[18] Furthermore, diverse catheter architectures, ranging from over-the-wire circular arrays to focal lattice-tip and 'balloon-in-basket' designs, drastically alter the resulting electric field distribution and energy density in tissue.[18] Some designs may even exhibit an electric field shielding effect in certain tissue areas potentially requiring more electric current delivered.[84] Unlike RF ablation, where 'Power' and 'Duration' are universal metrics, PFA lacks a unified dose metric that accounts for these complex waveform and hardware interactions.[87,88]

Why is it needed?

Standardization is essential for comparability across platforms and clinical trials.[86] Without harmonized reporting, clinicians cannot determine if varying outcomes or complication rates are inherent to PFA as a modality or specific to a particular waveform or catheter footprint. For example, side effects such as haemolysis (which appears dose-dependent) or coronary spasm are recognized as PFA class effects, but lack of standardization in reporting of clinically significant thresholds makes system comparison difficult. Transparency is also critical because PFA systems are constantly evolving. Moreover, standardization is critical for the development of multimodal clinical registries that leverage AI to interpret data across different institutions.

Common mistakes and misleading concepts

Several misconceptions in PFA extend beyond theoretical misunderstandings and influence how results are reported, interpreted and compared across studies.

The most prevalent reporting mistake in studies is relying on acute isolation and signal loss as a surrogate for durable lesion formation.[35] While the disappearance of bipolar electrograms is a standard endpoint in thermal ablation, in PFA it often reflects 'cellular stunning' or reversible electroporation rather than permanent cell death.[18,35] Emergent research suggests that unipolar signals may be a more reliable indicator of durable irreversible lesions than bipolar signal elimination. Recent experimental and clinical studies suggest that the most informative unipolar electrogram markers following PFA are abolition of the terminal S-wave, reduction of unipolar voltage to $\leq$0.4 mV, prominent ST-segment elevation, and dynamics of these abnormalities over time.[32–35] Finding reliable acute endpoints to report in PFA remains an open challenge. As a result, acute procedural success is systematically overestimated.

A second major misconception is the implicit assumption that 'PFA is PFA', leading to aggregation of results across fundamentally different systems. In reality, lesion formation depends on electric field distribution, pulse amplitude, duration, number of pulses and trains, polarity and vectoring, catheter geometry and electrode configuration. These parameters are highly system-specific and often proprietary, resulting in markedly different biological effects, including lesion depth and safety profiles.

Another misleading concept is that PFA is completely non-thermal[74] or independent on catheter-tissue contact, contributing to inconsistent reporting of safety endpoints and procedural variables. From a reporting standpoint, this misconception leads to a lack of standardized monitoring of surrogate markers such as microbubbles, temperature rise and difficulty attributing complications such as thromboembolism or coagulation to specific mechanisms.

Collectively, these misconceptions do not simply reflect gaps in mechanistic understanding but lead to heterogeneous and often non-comparable datasets.

Finding a common language

To find a common language, recent consensus guidelines propose a harmonized nomenclature[85,86]:

- PFA profile: The specific, disclosable pulse parameters of a system (such as amplitude, width, and shape).

- PFA application: A single successful delivery of all programmed pulse trains at a single catheter position.
- Catheter classification: Defining catheters as focal (≤4 mm tip), large-tip focal (4–12 mm), or regional (4–12 mm), or regional (>12 mm) to better characterize their tissue footprint.

Committees now call for minimal technical disclosure in all published manuscripts, including pulse amplitude, vectoring (monopolar vs. bipolar), duty cycle and total energy delivered. Only through such transparency and the use of protocol-mandated remapping studies for new devices can the field transition from empirical workflows to a predictable and standardized PFA therapy.

System comparison: why is comparing PFA systems so hard?

Why is comparing PFA systems so hard—but still so important for future scientific progress as well as better safety and procedure outcomes?

As described previously, there are numerous variations among the different PFA systems regarding PFA waveform, energy delivery pattern, dosing, catheter characteristics, available intraprocedural feedback information, surrogates for lesion durability, etc.[51,86,89] Furthermore, design variables such as waveforms are continuously optimized while this information is not publicly available among PFA systems. Even if manufacturers disclosed waveform characteristics, each waveform is intrinsically linked to a specific catheter design, preventing direct comparison between different waveforms within a standardized experimental model.

Reliable biological models for acute assessment of lesion formation, particularly for distinguishing reversible from irreversible electroporation and evaluating PFA durability, are limited, as PFA effects require an intact *in vivo* system and sufficient time for lesion maturation. Acute changes in local electrograms and conduction properties, such as signal attenuation or conduction block, are not reliable procedural endpoints limiting the feasibility of comparing different PFA systems in simple experimental models.

The above-mentioned factors make evaluation of acute treatment effects as well as direct comparison between PFA systems very difficult at this stage, representing a key limitation of the technology. A potential way forward is to develop a standardized framework that enables comparison of PFA systems based on available device data and shared evaluation criteria.

Availability of PFA waveform and energy information as well as common standards for energy description and delivery should be a mandatory first step forward.[86] Although this information alone would not be enough, it could be a first step for developing a basic model for acute system comparison. Next step will be further development of *in vitro* models and surrogates for measuring *in vivo* safety, tissue-effects and lesion durability.

From a clinical perspective, while standarized metrics are currently under investigation, some procedural parameters could be proposed for system comparison. Potential acute surrogate endpoints for durable electroporation and clinical response include distribution of applied electric field, tissue proximity indicators, local unipolar and bipolar post-ablation signal changes, impedance response or a combination of these factors. However, the underlying details of these parameters are typically not disclosed for each system, which again complicates direct comparison. In addition, patient-specific factors, such as differences in cardiac anatomy, target tissue thickness and local fibrosis, cause a variable individual response to PFA and to different PFA systems in both healthy and abnormal hearts.

Lastly, very limited data are available directly comparing different PFA systems in head-to-head studies looking at long-term clinical endpoints, such as freedom from arrhythmias. Therefore, comparison of different PFA systems is now based on data from different studies that are not directly comparable. Long-term head-to-head comparisons including procedural safety, remapping data to assess lesion durability and comparison of clinical outcomes should be prioritized. Safety parameters may include risk of clinically significant haemolysis, vasospasm, significant thrombus and stroke formation, as well as the risk of malignant arrhythmias. Outcome parameters may include both biomarkers, noninvasive imaging, patient-reported outcomes and arrhythmia recurrence.

The EP community together with the industry are encouraged to combine forces to enable meaningful comparison of different PFA technologies. Only then is it possible to further optimize PFA energy delivery and get safe and durable lesion formation. The ultimate aim is to improve clinical outcomes consistently, regardless of patient characteristics, operator, or ablation system.

Clinical trials: what future studies must address?

So far, clinical evidence in PFA can be considered relatively mature for initial PFA systems while robust data is still under development for more recently approved systems. Large registries and pivotal trials on AF ablation with PFA show high procedural success rates (i.e. PVI) with low major complications (0.7–2%) and 1-year freedom from atrial arrhythmia for paroxysmal AF between 65 and 85% approximately, depending on the system studied.[47,90–94] It is important to highlight that cross-trial comparison is limited by differences in efficacy definitions, monitoring intensity, inclusion of antiarrhythmic drug escalation or repeat ablation in composite endpoints.

Recent trials have been designed aiming at indication extension to cover the broad spectrum of AF: since the first pivotal trial of a PFA technology for the treatment of drug-refractory paroxysmal AF in 2024,[95] studies have been published covering also drug-refractory and first-line persistent AF (ADVANTAGE-AF, phases I and II, NCT05443594, PULSED AF NCT04198701, VOLT-AF NCT06223789, SPHERE Per-AF NCT 05120193, AVANT-GUARD study NCT06096337).[72,73,91,96–98] Ongoing research is extremely active with a focus on indication expansion, managing repeat procedures, assessing new catheter technologies and performing head-to-head comparisons with traditional thermal ablation, yet there are still several domains where PFA clinical evidence requires further research. The extension to more complex forms of AF brings the need to assess the safety and performance of additional lesion sets beyond PVI: while ablation of the posterior wall with PFA has been already studied in recent trials,[73] assessment of other lesions, which are common to the treatment of persistent AF or repeat ablations, such as the mitral isthmus, LA roof or superior vena cava still needs to be comprehensively assessed through upcoming clinical trials. Additionally, the development of focal and large-focal PFA catheters allows the creation of linear lesions to manage supraventricular tachycardias (SVT) such as cavo-tricuspid isthmus (CTI)-dependent atrial flutter and macro-reentrant atrial tachycardias. For SVTs other than CTI-dependent flutter, only small series have been published to date, showing very high acute success (98%) and 6-month recurrence of 10%,[99] while a more complete assessment of these arrhythmias should be integrated in future pivotal trials.

From the safety perspective, PFA has demonstrated a favourable profile so far, generally outperforming conventional

thermal ablation. However, some particular effects such as haemolysis and coronary spasm, although rarely associated with clinically relevant adverse events, need a full understanding in this context. Current studies are thoroughly assessing the real occurrence of such complications and studying procedure-specific mitigation strategies. For the prevention of renal failure, protocols are investigating dedicated hydration workflows to be undertaken in the periprocedural setting. For coronary vasospasm, upcoming clinical studies should better assess through imaging acute and potential chronic extent of this phenomenon with PFA but also with traditional thermal energy.

From the effectiveness perspective, attention should be given both to long-term follow-ups and, where possible, to remapping data to assess lesion durability. Monitoring strategies are also evolving with the use of implantable cardiac monitors (ICM) that allow continuous retrieval of arrhythmia recurrence information without the need for scheduled in-clinic follow-ups, facilitating long-term follow-ups especially after one year. Use of ICM has become a standard for new IDE studies, opening the pathway to use AF burden-based outcomes, and link burden thresholds to clinical events that may constitute a paradigm shift in the overall management of AF. The first long-term follow-up publication for PFA (up to 4 years) was recently reported for the pentaspline catheter.[100] On the other hand, lesion durability assessment through 3D remapping procedure should be part of every first-in-human clinical study and will likely remain a key point of trial design as PFA technology is optimized. Lesion durability data will also be informative for dosing optimization, which is considered important for the consolidation of standardized protocols to maximize effectiveness.[18,44,101–103]

The role of improved imaging techniques such as intracardiac echocardiography and advanced 3D mapping to support PFA procedures is also an important field where upcoming studies should focus. Integrating novel 3D mapping tools with PFA may enhance procedural precision, but future studies should establish the impact on long-term outcomes. In particular, the integration of advanced mapping tools such as electrographic flow mapping is object of ongoing randomized clinical studies evaluating this novel, personalized approach for treating persistent AF in combination with PFA.[104] Further exploration of similar approaches with focal catheters in complex cases such as repeat ablation will allow assessing if personalized therapy planning can improve long-term outcomes and efficiency.

Lastly, PFA therapy of ventricular arrhythmias is a promising field of application. To date, several prospective cohorts of patients have been studied showing good acute success.[60,61,64,105,106] Lesion depth and durability, long-term effectiveness and complication assessment will be key elements to evaluate in upcoming clinical studies to better assess the value of this technology in this area.

Conclusions

While PFA has rapidly transformed the cardiac electrophysiology field, the future ahead of this technology remains promising and will be shaped by ongoing technological refinement, expansion into broader and more complex arrhythmia indications and advancements in research to close current mechanistic knowledge gaps. Although PFA is increasingly regarded as the leading ablation technology of the future, it remains uncertain whether it will completely replace conventional thermal energy sources.

Despite its rapid clinical adoption, significant challenges remain in PFA, particularly regarding the standardization of efficacy and safety endpoints and cross-system comparison across different technologies. Another important challenge in the evolving PFA landscape is education within the electrophysiology community. The novel concepts associated with PFA mechanisms and platform-specific procedural considerations will need to be progressively incorporated into future electrophysiology training programmes and standardized educational pathways.

PFA has reshaped the landscape of catheter ablation, but its long-term consolidation will depend on continued technological refinement, rigorous long-term evaluation, and careful integration into evidence-based clinical practice.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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