

Complexity and Perplexity of Pulsed Field Ablation: An Engineering Perspective

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Abstract

Pulsed field ablation (PFA), recently introduced as a non-thermal and selective method for cardiac ablation, was associated with great promise, hope and expectation, but also raised some concerns and left some questions unanswered, in particular with respect to waveform. To better understand the challenges associated with the design and development of safe and efficient PFA systems, the underlying mechanism of electroporation at the membrane, cellular and tissue levels is described. The three interdependent components of each system, that is, the waveform, the catheter and the generator, are then addressed. The effect of the different waveform parameters on treatment outcomes is reviewed, and the consequences of a potential mismatch of the three components in the development of a safe and efficient PFA system are highlighted.

Keywords

Pulsed field ablation, electroporation basics, engineering perspective, optimisation, development

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Pulsed field ablation (PFA), recently introduced as a non-thermal and selective method for cardiac ablation, is associated with great promise, hope and expectation, but also raises some concerns.^{1–3} Unfortunately, from a scientific and engineering perspective, PFA is associated with a poorly defined design and parameter space due to the nature of the treatment, which includes load variability and requires multi-parameter optimisation with several potentially conflicting constraints. The device, that is, the waveform, the catheter and the pulse generator, forms the trinity of PFA. They must be developed together and function as a whole that is greater than the sum of its parts. An ever-increasing number of newly developed pulse generators and catheters with different waveforms raises important questions. Are they comparable and does a certain combination have specific side effects? Are these specific or the same for all systems? Do we need to ask the same questions and conduct the same studies for each new PFA system?

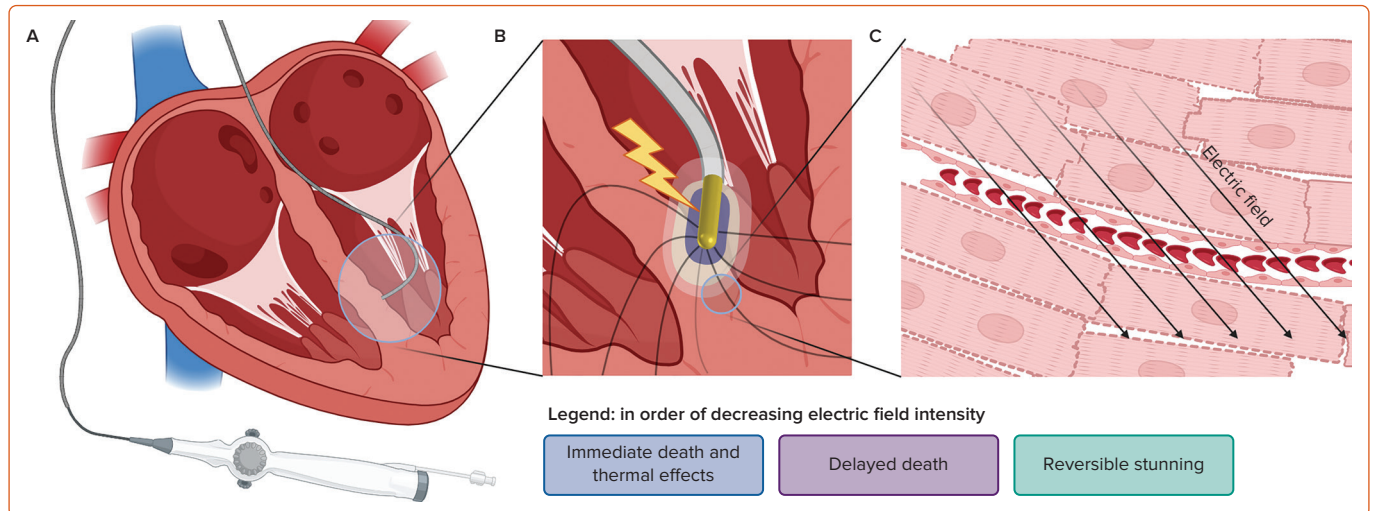
To better understand the challenges of developing a PFA system, we will first describe the phenomenon of electroporation that underlies PFA at the membrane, cellular and tissue levels. We will then look at the waveform, the catheter and the pulse generator, which must be considered and developed as a unit to be fully functional. Even small changes in one of the three components can cause the whole system to fail or at least operate suboptimally. Only by understanding these aspects can we fully assess the challenges and recognise how narrow the path to success can be.

Basic Description and Understanding of Electroporation

Cell Membrane: Increased Conductivity and Cell Depolarisation

The cell membrane separates the inside of the cells from the outside. It has a very selective permeability for ions and molecules, which enables the cell to survive even in a sometimes somewhat unstable environment. In excitable cells, ion channels and pumps ensure that the cells can generate and transmit action potential. The cell membrane can be regarded as a capacitor from an electrical point of view and thus represents a barrier for electrical current (at low frequencies). During and after electroporation, the conductivity of the cell membrane is greatly increased and the membrane remains permeable to ions and other molecules for up to several minutes after treatment.^{4,5} Even though this persistent increase in permeability for ions (e.g. Na, Cl, Ca, K, etc.) is smaller than during the pulse delivery itself, it is sufficient to cause and maintain cell depolarisation, which can be transient (triggering action potential) or can result in sustained depolarisation.^{6–8} Increased transient membrane permeability results in the stunning of excitable cells (rendering them unexcitable or causing conduction block).⁹ This depolarisation can result in immediate disappearance of local electrograms and transient phrenic nerve paresis.^{10–13} Given that the membrane damage caused by electroporation is followed by membrane repair, this can lead to cells regaining the ability to react to an electrical stimulus within a few minutes, depolarising and conducting an action potential.^{14,15} For a given pulse

Figure 1: Pulsed Field Ablation at Different Scales



A: Organ level. The catheter is positioned in the blood pool in contact with the myocardium. **B:** Tissue level. The electric field is strongest around the ablation catheter. The magnitude rapidly drops with increasing distance from the surface, as indicated by the contours. Electric current (indicated by black lines) flows from the catheter to the surface electrodes. **C:** Cellular level. An electric field is present in the tissue, consequently also in the capillaries and small blood vessels. Sufficient field strength causes electroporation of the membrane of the cardiomyocytes, but also of the other cells present in the tissue, such as vascular endothelial cells and red blood cells. Through membrane electroporation, additional conductive pathways are created, enabling the current to pass through the cytoplasm. Created in BioRender. Kos, B (2025) <https://BioRender.com/7sa2cxl>.

duration and number of pulses, the most important parameter that determines the level and intensity of electroporation is the amplitude of the electric field to which the cell is exposed.

Electroporation at the Cellular Level: Reversibility

As a consequence of cell membrane electroporation and increased membrane permeability, there are several downstream effects, including changes in gene regulation and protein expression.⁵ Historically, electroporation was separated into reversible and irreversible, with the only clear determination between the two represented by whether the cells survive the treatment or later die via one of the cell death pathways.¹⁶ Reversible electroporation is typically associated with applications such as drug and gene delivery, in which transient permeabilisation of the cell membrane enables therapeutic agents to enter the cell before the membrane permeability returns to normal physiological conditions and the cell therefore recovers.^{17–20} Irreversible electroporation, in contrast, leads to changes in the membrane or sustained disruption, which leads to cell death via diverse cell death pathways.^{21–23}

Membrane resealing alone, however, does not guarantee cell survival. Cell death is a dynamic process, and different pathways of cell death can occur in the same lesion at different times, locations and distances from the catheter.^{24,25} The electric field closest to the catheter and electrodes is the highest and then drops rapidly with distance from the catheter.²⁶ It is therefore plausible to speculate that necrotic or pyroptotic cell death predominates in the lesion core (where the field is strongest), while apoptotic mechanisms may be more prevalent at the lesion periphery.

Tissue Level: Electric Field Distribution and Cell–Cell Interactions

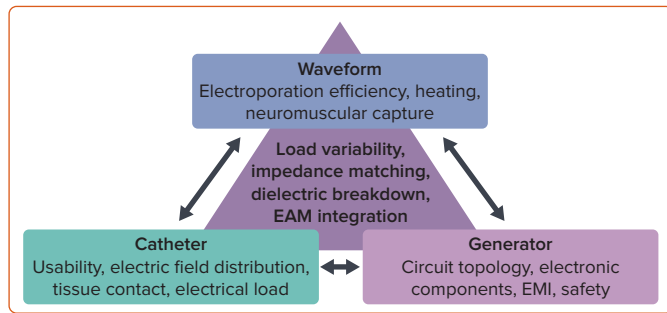
To achieve therapeutic electroporation in tissue, an electric field has to be established in the tissue, which is usually achieved by bringing electrodes in contact with the tissue. In cardiac electrophysiology, this is most commonly achieved in a minimally invasive way using a catheter approach (Figures 1A and 1B). The cells of the tissue are organised and embedded in the extracellular matrix. Several different cells coexist in the same volume of

tissue, nerves pass through, and vessels bring oxygen (and nutrient-rich blood) to every cell in the body. Electroporation occurs at the membrane cell level, as described above, and all cells can be electroporated, including (but not limited to) cardiomyocytes, fibroblasts, neurons, endothelial cells and erythrocytes (Figure 1C). In addition to the effects on individual cells described in the previous sections, cell–cell interactions are at least transiently disrupted, leading to leaky vessels, which results in oedema formation.²⁷ All of these effects occur simultaneously due to high-voltage pulse delivery, but they have different dynamics of resealing and recovery.

The membrane conductivity increase due to electroporation also leads to an increase in tissue admittance (i.e. a decrease in tissue impedance). This means that the electrical load is changing during the delivery of pulses in a non-linear fashion.^{28,29} Based on previous *in vivo* studies on gene transfer and drug delivery, it is well established that pulsed electric fields transiently reduce tissue perfusion and increase vascular permeability, including temporary disruption of the blood–brain barrier.^{30–32} These changes lead to a reduction of tissue cooling due to diminished or absent capillary blood flow, and promote oedema formation. The resulting oedema further decreases tissue impedance following pulse delivery and contributes to the early stages of wound healing and tissue repair.^{33,34} Additionally, reduced perfusion and elevated interstitial fluid pressure caused by oedema may impair the contractile function of cardiomyocytes.

While PFA was initially described as more selective for cardiac tissue based on *in vitro* data, this is not mirrored by *in vivo* studies and their findings of a lethal electric field.^{35–37} An interesting observation is that PFA can ablate through scarred tissue.³⁸ Scarred tissue, which is mostly acellular, has a significantly higher conductivity than healthy myocardium.^{39,40} Scarred tissue seems to present a lower barrier for the electric field, however, with the increase of conductivity due to electroporation, the electroporated myocardium becomes similarly conductive as the scarred tissue, which results in the ability of PFA to ablate through the scar.²⁶

It is important to note that electroporation is a physical mechanism of cell membrane disruption that can affect all cell types. For PFA, the most relevant cells are of course cardiomyocytes, but other cells such as

Figure 2: The Pulsed Field Ablation Trinity

For a successful system the three system components (i.e. the catheter, waveform and generator) have to work together to achieve reliable success. However, design choices for each of the components affect the requirements and functioning of the other two. EAM = electro-anatomical mapping; EMI = electromagnetic interference.

erythrocytes, neurons, cardiac fibroblasts and cells of the cardiac conduction system can also be electroporated. All of the electroporation effects on the cells described above can also be observed in these cells, leading, for example, to haemolysis, spasm of the cardiac arteries, phrenic nerve paresis, and disruption of the cardiac conduction system.^{41–50} It is not yet clear to what extent these effects are reversible, and what affects the extent of injury and rate of recovery of their normal function.

While the electric field decreases rapidly with distance from the catheter surface, it is important to consider that the electric field at a given point in the tissue (*Figure 1B*) depends on the geometry of the catheter, the tissue and its electrical properties, and the configuration of the return electrode. If all of these factors are kept constant, the electric field depends on the voltage.

The Trinity of PFA: Waveform, Catheter and the Pulse Generator

Pulsed field ablation depends on the successful delivery of a sufficiently strong electric field in the target tissue. As shown in *Figure 2*, the waveform, catheter and pulse generator must function together as a whole, greater than the sum of its parts. The waveform must effectively irreversibly electroporate the targeted cells (i.e. cardiomyocytes) of the arrhythmogenic substrate and avoid, as much as possible, heating and bubble formation, minimise neuromuscular capture (pain and muscle contraction) and reduce or minimise stunning and/or reversible electroporation.⁵¹ For atria and specifically for pulmonary vein isolation (PVI), 2–5-mm-deep lesions are sufficient to create transmural lesions and effectively isolate the pulmonary veins. However, for targeting ventricular substrate, this is not sufficient because greater depth is required. In the following sections we take a look at the three components of the trinity.

The Waveform

Early electroporation research was performed using monophasic 100 µs pulses.⁵² Nanosecond pulses and sub-microsecond pulses were then intensively researched, because they looked promising for causing interesting biological effects.⁵³ Later, Arena et al. suggested using biphasic short pulses with the intention of reducing the contrast in tissue conductivity and neuromuscular stimulation.⁵⁴ Several first-in-human studies of PFA were performed using monophasic pulses, but those quickly switched to biphasic pulses.⁵⁵ A biphasic waveform has many parameters, all of which have the possibility of affecting the treatment outcomes.^{56–58} *Figure 3A* shows a compact and complete set of waveform parameters. A single treatment waveform can be composed of several trains. Each individual train can be composed of a single or several bursts

of pulses. A single burst can contain one or several biphasic pulses. The total duration of a treatment then depends on the number of trains, the duration of each train and the delay between trains.

Figure 3B shows how the different parameters of the pulses affect treatment. An increase in pulse amplitude greatly increases irreversible electroporation and heating, and causes a small increase in all other outputs.^{10,24,25,37,59,60} Increasing pulse width causes a large increase in electrochemical reactions, pain, neuromuscular capture and arrhythmogenicity.^{61–63} Increasing the number of pulses causes a large increase in electrochemical reactions, by increasing the total amount of charge delivered, and a small increase in all other parameters.

The shape of the pulses has a very important effect: we know that longer monophasic pulses are more efficient in electroporating cells and that monophasic pulses delivered at a relatively low repetition rate should be the preferred choice.^{25,37} However, monophasic pulses cause electrochemical reactions and severe neuromuscular capture and pain.^{22,55,64–66} Biphasic pulses dramatically reduce electrochemical reactions, but also decrease all other parameters except heating, which is unaffected by pulse shape, and depends only on the total energy and rate of pulse delivery.^{37,62–64,67} Increasing interpulse delay reduces heating slightly, but also greatly increases pain, neuromuscular capture and arrhythmogenicity.^{62,63,67} Intertrain delay has an effect on the heating: a long pause between pulse trains enables cooldown of the tissue by blood (and to a smaller extent by catheter irrigation).⁶⁸

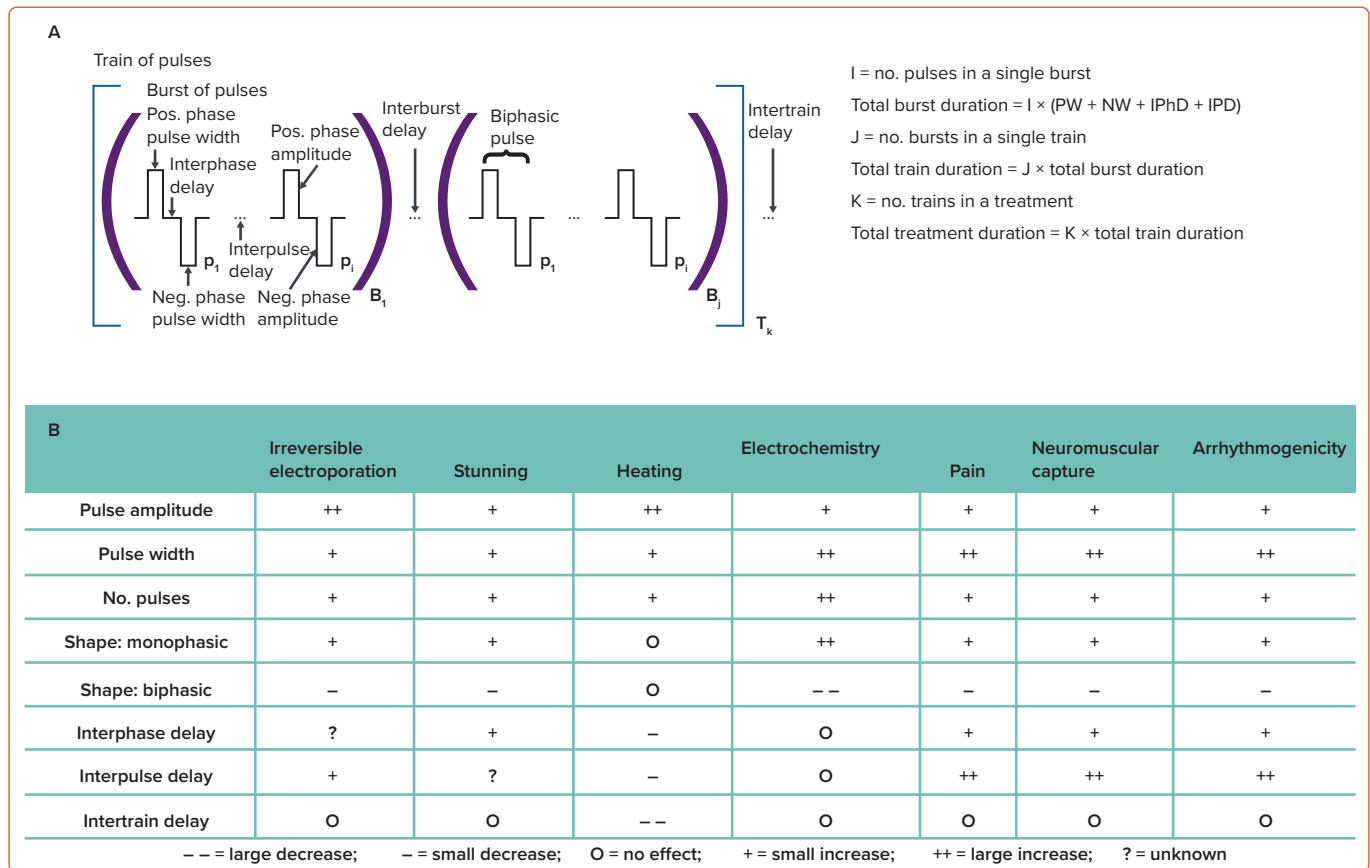
The Catheter

The catheter must be manoeuvrable, should be introduced through a small-diameter sheath, able to conduct a high-voltage electric signal from the generator to electrodes, and sustain the high voltage in the limited space of the connecting cables and catheter. The catheter design can be unipolar, meaning that the pulses are delivered between the active electrodes on the catheter and a grounding electrode on the surface of the patient; or bipolar, indicating that the pulses are delivered between electrodes on the same catheter. The electrodes on the catheter have to provide an effective distribution of electric field in the tissue, and minimise local heating and stray fields that are generated in the blood pool (risk of haemolysis) and also in tissue distant from the target area causing nerve and muscle stimulation (neuromuscular capture). In this respect unipolar PFA delivery should reduce haemolysis but also increase neuromuscular capture compared to bipolar delivery. Regardless of the specific catheter design, the constrained shaft (internal space) can cause the delivered waveform to the tissue to deviate from the waveform at the output of the generator resulting in reduced voltage and altered pulse shape (*Figure 4A–C*).

Most commercial radiofrequency (RF) or PFA cardiac catheters have catheter cabling that acts as a low-pass filter with a frequency cut-off around 2 MHz. As a result, pulse rise and fall times are prolonged by approximately 200 ns. Consequently, square wave pulses longer than 1 µs undergo minimal distortion, while a biphasic pulse requires at least a 200 ns interphase delay (i.e. the pause between the positive and negative phases) to maintain charge balance. However, in such a system, a 200 ns pulse loses 50% of its power and takes on a triangular shape (*Figure 4C*). Therefore, to enable efficient nanosecond pulse delivery, catheter cabling and active delivery electrodes must be optimised accordingly.

In contrast to RF ablation, PFA does not depend on conductive diffusion transfer to achieve ablative effect in tissue. In fact, blood is a tissue with

Figure 3: Definition of Waveform Parameters and Their Effects



A: Schematic diagram of all waveform parameters and total duration of treatment. B: Effects of different waveform parameters on important efficacy and safety endpoints. IPHD = interphase delay; IPD = interpulse delay; NW = negative pulse width; PW = positive pulse width.

some of the highest conductivity in the human body.^{69,70} This means that electric fields will spread through blood in a generally similar way as through the myocardium. During the pulse delivery itself conductivity of tissue increases. Given the conductivity increase factor for cardiac tissue reported in the literature, the conductivity of myocardial tissue affected by electroporation becomes similar to that of blood.³⁷ Consequently, when the catheter is not in direct contact with the myocardium, the depth of the resulting lesion is reduced. This reduction in lesion depth is usually at least equal to the distance between the catheter and the myocardium.⁷¹ It is important to note that in PFA – in contrast to RF ablation – achieving good contact is more important than contact force for ensuring optimal lesion size.^{72–78}

The Pulse Generator

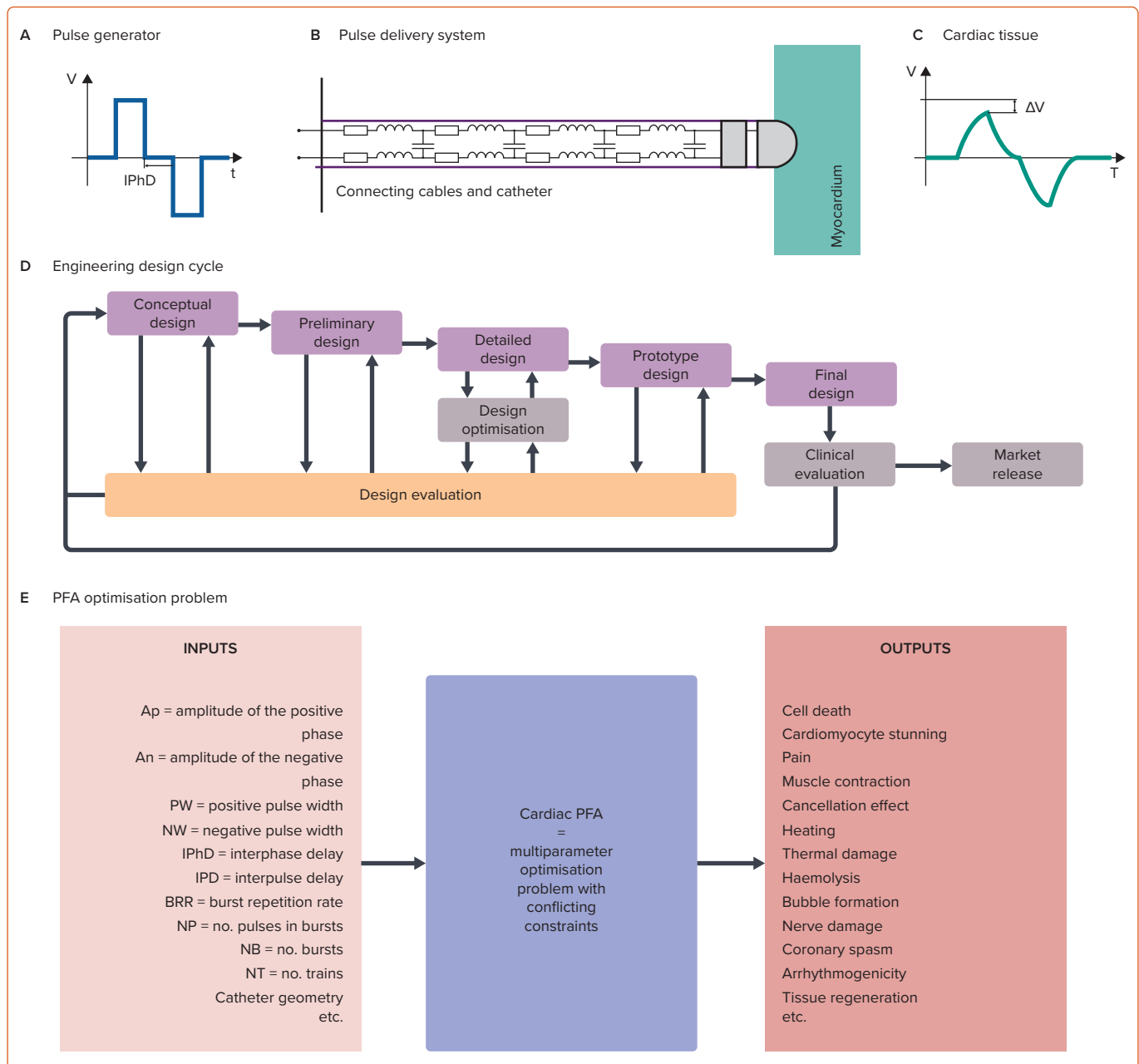
Like most new medical devices, the main design of the current PFA systems was locked for several years before they were approved for the market. Figure 4D shows a typical design cycle of a medical device.⁷⁹ This cycle is very long, given that many steps are required to develop such a treatment. At each step of the process, detailed evaluation is performed and some parameters of the system are locked. First, new hardware must be developed, which must then be tested for electrical safety and electromagnetic compatibility. Then the preclinical tests are carried out, followed by clinical trials. During this period it is difficult to change the hardware because it has already passed previous tests, therefore the outcome is often already known at the beginning of the cycle. However, there was a lack of sound knowledge about this treatment when the first decisions were made. Therefore, many of the existing PFA systems were modified at very late stages (Figure 4D).^{56–58} However, during this development cycle, many new insights have been gained in preclinical

and clinical trials and in the widespread adoption of the technology. This can constitute a basis for a new design cycle. Unfortunately, many of these findings cannot be used collectively to improve PFA because the waveforms of PFA systems are not publicly disclosed and shared between systems. Hence, our knowledge is only partially assembled and far from complete.

After a decade of studies, we now know that shorter pulses attenuate unwanted muscle contractions and nerve stimulation, but this also reduces the efficiency of the treatment, which can be compensated for by applying higher voltages.^{25,54,61,62,80} A compromise between side effects and efficiency is therefore being sought, which has led to the development of generators with high voltage and short pulses. However, the higher the voltage and the shorter the pulses, the more difficult it becomes to develop such pulse generators and, above all, to ensure that the device is safe for the patient and the operator and does not interact with other devices in crowded electrophysiology laboratories.

The development of silicon carbide switches has now made it possible to develop high voltages faster, and in shorter pulses, which attenuates muscle contractions and nerve stimulation.⁸¹ However, faster pulse rise times also increase peak leakage currents, peak electromagnetic interference and peak voltages across the reinforced insulation.⁸² Designers in this area should pay particular attention to this, given that PFA waveforms generate atypical interference. Typical medical devices generate continuous leakage currents and electromagnetic interference. However, PFA systems generate high peak and low RMS (root mean square) leakage currents and quasi-peak electromagnetic interference due to their fast rise and fall times and long delays between pulses and

Figure 4: Development of a Pulsed Field Ablation System: From Concept to Reality



A–C: The change of a biphasic 200 ns pulse on its way from the generator (A) through the pulse delivery system (B). The pulse generator (A) produces a waveform with a defined amplitude (V) and interphase delay; however, due to the influence of resistive, inductive and capacitive components in the catheter and connecting cables (B), the pulse shape is distorted. In particular, the amplitude reaching the cardiac tissue (C) is reduced (ΔV) and the interphase delay is shortened and the rise and fall times are increased. D: The engineering design cycle: there are many stages from a conceptual to a final design. At each stage the design is subject to evaluation. During the detailed design, optimisation is carried out. At each stage, the process can be started from the beginning, with lessons learned informing design decisions. E: The pulsed field ablation optimisation problem is a multi-parameter optimisation with multiple inputs coming from the waveform, catheter and generator, and many outputs. Some of the outputs are desirable, others should be avoided.

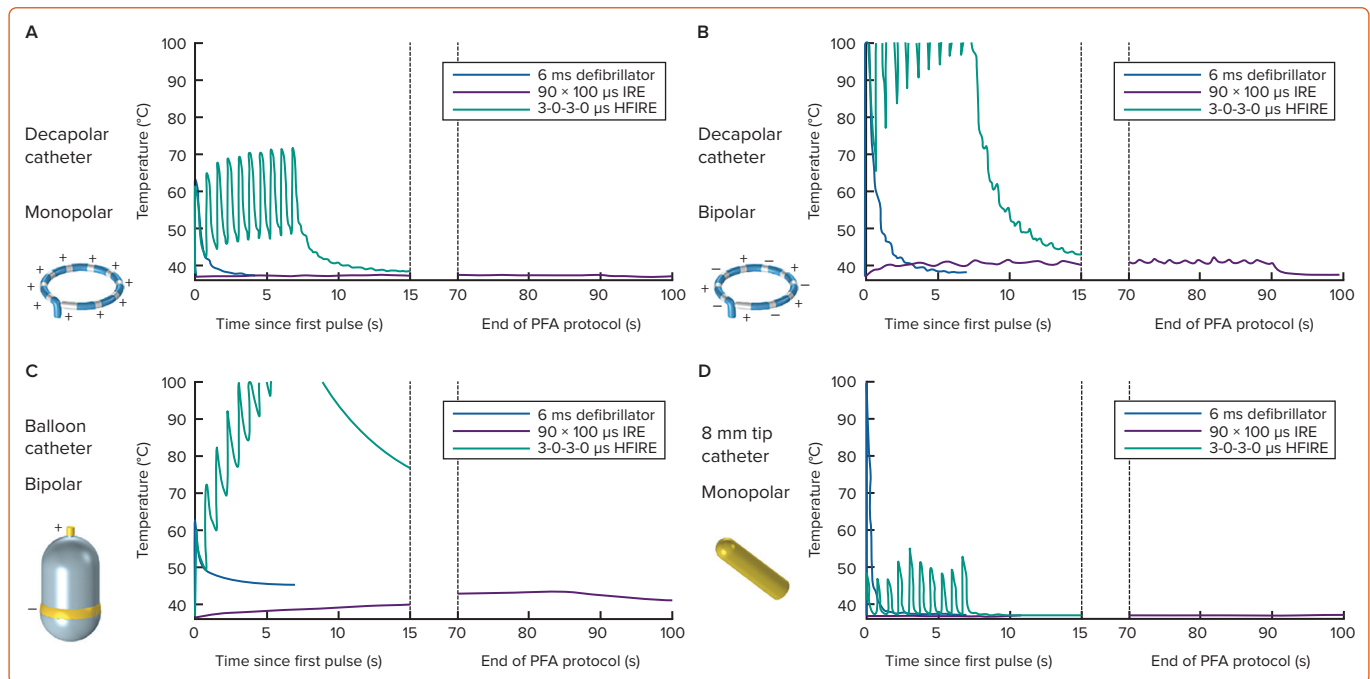
bursts. Such a device can pass the standardised leakage current and electromagnetic compatibility (EMC) tests, given that the medical device standard requires measurements only of low-frequency leakage currents that can lead to cardiac arrest and quasi-peak EMC.^{83,84} However, this does not mean that the high peak leakage current cannot affect the patient's untargeted tissue and that high electromagnetic spikes cannot interfere with some of the neighbouring devices.

In addition, transient overvoltages occur across the reinforced insulation in PFA systems during PFA delivery, hence it is not sufficient to base the insulation design on the steady-state operating voltage alone. These transient overvoltages must be considered when designing the reinforced

insulation.⁸⁵ Fortunately, existing standards for medical devices include methods for calculating insulation requirements that take into account such transient conditions. High-voltage pulses with fast rise times, as used in PFA, can lead to electrical discharges and electric arcing. During arcing, the current can increase significantly, which poses a risk to the patient's health and can lead to damage to the components of the pulse switch. To mitigate these risks, current- and energy-limiting circuitry should be incorporated into the PFA system to prevent arcing and protect critical switching elements.⁸⁶

Compared with RF ablation signals, PFA signals have significantly higher amplitudes (in the order of kilovolts), while measurement signals used for

Figure 5: Time Course of Electrode Surface Temperature



The graphs show the temperatures for all waveforms for four different catheter configurations. A: Decapolar ring catheter in a monopolar configuration. B: Decapolar ring catheter in a bipolar configuration. C: Balloon catheter in a bipolar configuration. D: 8 mm tip catheter in a monopolar configuration. Voltage: (A–C) 2,000, 1,900, 2,800 V for the 6 ms, IRE, and HFIRE protocols, respectively; (D) 2,100, 1,000, 1,300 V for the 6 ms, IRE, and HFIRE protocols, respectively. 6 ms = a single 6 ms monophasic exponentially decaying defibrillator pulse; HFIRE = high-frequency irreversible electroporation (10 trains of a single burst of 333 biphasic pulses with a 3 μs positive pulse width, 0 μs intraphase delay, 3 μs negative pulse width and 0 μs interpulse delay); IRE = irreversible electroporation (90 × 100 μs monophasic pulses delivered at 1 Hz); PFA = pulsed field ablation.

mapping, temperature and force detection are typically in the millivolt range. This large difference in signal magnitude makes electrical isolation within the confined wiring of cardiac catheters and connectors particularly challenging. In addition, switching between high-voltage and high-current PFA pulses and low-voltage and low-current measurement of intracardiac electrogram (iECG) signals in switching units presents a further design and engineering challenge.

Another unmet need is periprocedural guidance of PFA. It is impossible to reliably predict durable lesion based on bipolar iECG signal attenuation and voltage maps due to transient stunning of the cardiomyocytes (i.e. reversible electroporation). Early systems were not (well) integrated into mapping systems for catheter visualisation; and contact assessment was not available. Given that the lack of contact reduces lesion depth, the reliability and durable efficacy were limited. Clinical experience now shows that repositioning and following the protocols as prescribed by manufacturers is essential to achieve PVI.^{87,88}

Pulse generation technology and catheter technology have changed significantly since the initial development of the hardware, and we have much more data on the clinical efficacy and side effects of specific pulse waveforms and electrical geometries. This could mark the beginning of a new cycle of PFA systems, 2.0.

Effects of Mismatched Waveform and Catheter Design

The shape of the electrodes, and the positioning of and spacing between the electrodes on the catheter can be precisely defined and fixed (circular loop catheter) or have a variable geometry (pentaspline and variable loop catheters).¹ These influence not only the distribution of the electric field, but also the load – that is, how much current will flow through the wires in the catheter shaft during pulse delivery. The

currents can easily be in the range of 10–30 A, which corresponds to a high instantaneous power.

The different sizes of the catheter, the shape (e.g., flower or basket), and vectoring (between splines, bipolar or unipolar) determine the distribution of the electric field, as well as the load – the amount of current the generator must provide. The distribution of the electric field also determines the size and depth of the lesion, but due to the different waveforms used, the same electric field threshold cannot be used to compare different catheters. A catheter (as a load) in contact with the tissue behaves differently to a catheter in the blood pool, that is, in slight or partial contact with the tissue. Furthermore, the form factor of the catheter will also affect lesion size dependence on contact force.

PFA catheters are available in very different shapes and sizes. Although the manufacturers do not provide information on the waveforms, various protocols with preclinical results are described in the literature. To illustrate the effects of mismatched waveforms and catheters, we used numerical modelling to examine all possible combinations of three catheters and three waveforms described in the literature.

The three catheters were a generic decapolar loop catheter, an 8 mm spherical tip catheter, and a custom bipolar balloon catheter.^{47,89,90} Each catheter was tested with three pulse protocols: a single 6 ms monophasic exponentially decaying defibrillator pulse; 90 × 100 μs monophasic pulses delivered at 1 Hz (i.e. irreversible electroporation; IRE); and 10 trains of a single burst of 333 biphasic pulses with a 3 μs positive pulse width, 0 μs intraphase delay, 3 μs negative pulse width and 0 μs interpulse delay (i.e. high-frequency irreversible electroporation; HFIRE).^{65,66,90} Pulse amplitudes were adjusted for each configuration to achieve transmural lesion depth (3 mm in the schematic atrium). More details on the modelling are available in the *Supplementary Material*.

Electrode surface temperatures varied significantly across combinations. Generally, the HFIRE waveform resulted in the highest surface temperature rise, due to the fact that the required amplitude was the highest, and also because the waveform has a 100% duty factor (defined as the total time in the 'on' position divided by the total duration of the pulse train). In these configurations the monopolar deliveries resulted in lower electrode surface temperatures (*Figure 5A and D*). The 8 mm tip catheter resulted in the lowest average electrode surface temperature, however, the total surface area of the electrode was also the largest, and it enables only point-by-point ablation, whereas the other electrode configurations theoretically represent a single-shot approach. The lowest surface temperatures were observed with the long IRE protocol, which has a very low duty factor and a long total duration. It is therefore almost completely mitigated by blood flow cooling (or by diffusion in *Figure 5C*, in which blood flow is blocked by the balloon). The investigated balloon also had a very high surface temperature in the HFIRE configuration, due to the mismatch between the surface area of the two delivery electrodes: namely, the tip electrode was much smaller than the ring electrode positioned at the PV ostium. Therefore, the tip electrode has a much higher local current density and resultant higher heating.

Conclusion

A well-designed PFA system should be safe and efficient. Currently available systems (i.e. those that are approved or are being developed

and tested) were mostly developed for AF treatment, that is, to achieve PVI. PFA offers unique opportunities: for the first time we do not need to compromise on effectiveness in PVI for safety. This should enable us to test hypotheses that are driving the treatment of paroxysmal and persistent AF patients with much better precision than was previously possible. At the same time, given that PFA is at least as effective as RF ablation and cryo-balloon ablation but has superior efficiency, this will enable the treatment of increasing volumes of patients early after their initial diagnosis.^{91,92} □

Clinical Perspective

- A successful pulsed field ablation (PFA) procedure depends on the seamless integration of three key system components: the waveform, the catheter and the generator, which must be designed and calibrated to work in harmony for optimal therapeutic effect.
- A basic understanding of the mechanisms of electroporation is crucial to ensure consistent, safe and effective PFA treatment in different clinical scenarios. Failure to do so may result in treatment inconsistencies and unexpected outcomes.
- Current PFA workflows are not interchangeable between different devices, meaning that what works for one system should not be adopted for another without adequate research and clinical validation.

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