Breaking the Rhythm: Atrial Fibrillation and the Potential of Pulsed Field Ablation

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Abstract

Background: Atrial fibrillation is a common and serious heart condition. Pulsed field ablation is a new treatment option for atrial fibrillation.
Methods: Sources were identified via PubMed search with important key terms such as “atrial fibrillation,” “pulsed field ablation,” and “pulsed field ablation clinical trials.” Pertinent information was taken from relevant literature to be included in this paper.
Results: Pulsed field ablation has many theoretical advantages over traditional ablation, including increased safety and tissue specificity. Animal models and preliminary data suggest a favorable side effect profile, but existing clinical data is limited and has yet to establish greater efficacy or safety for pulsed field ablation when compared to thermal ablation in humans.
Conclusion: Pulsed field ablation is an innovative technology that may be of considerable benefit to patients with atrial fibrillation, but further research is necessary to conclude its efficacy and safety compared to existing ablation techniques.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is a major source of morbidity and mortality in healthcare today. This paper begins with a review of AF. This includes epidemiology, etiology, pathophysiology, symptoms, diagnosis, treatment, and prognosis. Next, pulsed field ablation (PFA) is reviewed. This section covers the history, mechanism, advantages, and disadvantages of PFA. A summary of the major animal studies and clinical studies that have been done is included as well. The section concludes with what the future of PFA holds and what further action is needed.

2. Atrial Fibrillation

2.1. Epidemiology AF is the most common cardiac arrhythmia worldwide. Currently, AF affects about 1% of the global population, but its prevalence is expected to increase two to threefold by the year 2050.[1] AF can occur in any patient, but it is more likely when certain risk factors are present. Age has been found to be the most significant risk factor for AF.[2] The Framingham Heart Study found that the increase in the likelihood of AF compared to patients aged 50-59 is 4.98-fold in patients aged 60-69, 7.35-fold in patients aged 70-79, and 9.33-fold in patients aged 80-89.[3] Sex is also a factor in AF; males are generally more likely to develop AF than females.[2] One study found the incidence of AF per 1000 people to be 4.67 in men and 2.71 in women.[4] This trend can be partially attributed to the higher burden of underlying risk factors for heart disease in men. Studies have revealed that the incidence of AF may also vary across races.[2] One study noted the incidence rates of AF per 1000 people to be 11.23, 6.07, 5.77, and 3.94 for White, Hispanic, Black, and Chinese patients respectively. This is likely influenced by sociocultural and environmental factors rather than biological differences.[5]

2.2. Etiology The exact cause of AF is most often unknown on an individual patient basis, but there are many factors that have been shown to play a role in the disorder. For example, there are certain genetic mutations that have been implicated in the development of AF. Mutations in genes that control ion channels in cardiomyocytes have been proven to be a cause, as they

interfere with normal cardiac depolarization and repolarization.[2] Having a family history of AF was associated with an odds ratio of 1.85 for development of AF compared to patients without a family history.[6] Cardiovascular diseases such as coronary artery disease, hypertension, and myocarditis have also been implicated in the development of AF. Other health problems that are linked to AF development include neurological disorders, endocrine disorders, and obstructive sleep apnea. Lifestyle factors like sedentary lifestyle, obesity, smoking, and alcohol consumption can also cause or exacerbate AF. Oftentimes, however, AF arises idiopathically or in the absence of obvious risk factors. Though the pathogenesis of AF is incompletely understood, all of these factors ultimately stress or damage the heart, causing atrial tissue to take on certain electrical or physical abnormalities. These abnormalities lead to the development of AF.[1, 7]

2.3. Pathophysiology AF is an irregular and rapid heart rate caused by dyssynchronous contraction of the atria, resulting in a quivering motion.[2] The origin of the arrhythmia is either electrical remodeling or structural remodeling, which occur when the heart experiences stress or damage. In electrical remodeling, cardiomyocytes take on new, unique electrical properties that result in abnormal behavior like faster refractory periods or slower conduction times. Structural remodeling of the atria, also called atrial cardiomyopathy, occurs when cardiomyocytes undergo changes to their physical structures. The two modes of remodeling are mediated by any of a number of specific changes to cardiac tissue. These include inflammation, altered ion channels, increased presence of myofibroblasts, oxidative stress, malfunctions of the autonomic nervous system, or activation of the renin-angiotensin-aldosterone system. Sometimes, patients with AF have electrophysiological abnormalities in their tissue without undergoing remodeling, typically due to genetics; this expedites the process of developing AF.[7]

There are two main hypotheses about the basic mechanism of AF. The first hypothesis is that there is a single ectopic focus area of muscle in the atria that contracts rapidly. The second hypothesis is that there are multiple wavelets of electrical activity that result in multiple reentrant circuits throughout the atria. It has also been hypothesized that patients experience a combination of the two mechanisms. According to this theory, the atria experience ectopic firing in a single location that later spreads to multiple locations. The origin is often proximal to the pulmonary veins of the left atrium due to the atypical cellular properties of this region. These ectopic beats then develop into multiple wavelets of electricity in the atria. Finally, the wavelets turn into reentrant circuits, which occur when a signal follows a self-sustaining loop in the myocardium, causing the irregular rhythm to repeat itself. In healthy tissue, when an atrial cell attempts to initiate a heartbeat, nearby cells are still in their refractory periods and do not conduct the impulse. However, in a heart that has experienced electrical remodeling, nearby cells may have refractory periods short enough that they are able to conduct another signal, allowing the ectopic beat to propagate. If this impulse finds a loop-shaped pathway of cells that are ready to conduct again, a reentrant circuit results; this then results in an indefinite period of sustained AF.[8]

Another important characteristic of AF's pathophysiology is that once the disorder begins, it remains and often continues to worsen. The phrase "atrial fibrillation begets atrial fibrillation" was introduced to describe this phenomenon. This can occur in a variety of ways. For example, tachycardia associated with AF promotes further electrical remodeling by causing cells to shorten their refractory periods, allowing for more reentrant circuits. The atria are also unable to fully contract when in AF, which can induce structural remodeling by causing progressive dilation

that leads to further fibrosis of cardiac tissue. This leads to slower conduction and allows more runs of AF to occur.[8]

2.4. Symptoms There is a wide spectrum of presenting symptoms in AF. Patients may be asymptomatic, in severe hemodynamic distress, or somewhere in between.[1] AF most commonly presents with sensations of dyspnea, heart palpitations, and fatigue.[9] Other symptoms include feelings of chest pain or pressure, exercise intolerance, lightheadedness, dizziness, syncope, difficulty concentrating, sleep disturbances, loss of appetite, and weakness.[1] Interestingly, AF severity does not always correlate with symptom severity; a patient with mild AF can have severe symptoms while a patient with advanced AF can have mild symptoms. Certain groups tend to experience more severe symptoms, such as patients with an anxiety disorder, female patients, and non-White patients.[9]

2.5. Diagnosis The diagnostic process of AF consists of multiple steps. The physician starts by taking a medical history and family history, then inquiring about lifestyle habits and symptoms. A physical exam follows and is important for identifying physical signs of AF as well as potential etiologies. The official diagnosis is made with an electrocardiogram. This may occur during an acute AF episode or when looking at the data collected on a portable Holter heart monitor. An electrocardiogram of AF will have no defined P-waves, irregular QRS complexes, and tachycardia. If a diagnosis of AF is made, other tests such as a blood test, an echocardiogram, or an MRI may be used to look for causes of the condition as well as existing damage.[10]

AF is divided into four categories based on the length of episodes. Paroxysmal AF is when episodes last less than a week and end without treatment. Persistent AF is when episodes last more than a week and require treatment to terminate. Long-standing persistent AF is when AF is sustained for more than a year. Permanent AF is when AF is expected to continue indefinitely and no further attempts to restore normal sinus rhythm (NSR) are made. AF is further subclassified as valvular, meaning the patient has comorbidities involving the heart valves, or non-valvular. Differential diagnoses are atrial flutter, atrial tachycardia, Wolff-Parkinson-White syndrome, and other cardiac arrhythmias as these can present as AF.[1]

2.6. Treatment There are many treatment options available for AF. Treatment can be categorized into four groups: stroke prevention, rhythm control, rate control, and management.

Strokes are one of the most feared complications of AF. They are more common in patients with AF because AF causes stasis of blood in the left atrium, which may lead to blood clots. These clots have the potential to exit the heart and cause thromboembolism in the brain. Medications are one way to prevent stroke.[11] Vitamin K antagonists such as warfarin were the first anticoagulants used for stroke prevention in AF, but require frequent monitoring and lifestyle adjustments, which can be difficult for patients. They are, however, still used today in select cases.[3] Direct oral anticoagulants are a more recently developed option for stroke prevention, and have the advantage of not requiring dose monitoring; examples include dabigatran, rivaroxaban, and apixaban. Aspirin may also be used to prevent stroke. Procedures can also be effective for stroke prevention. Left atrial appendage occlusion, done with a Watchman device or an Amplatzer device, is a newer approach in which a device is implanted in the heart via catheter. The device blocks off the left atrial appendage, the area of the heart where most blood clots originate, with a parachute- or cylinder-shaped mesh.[11]

Rhythm control is another mode of treatment in which an attempt to restore NSR is made. Patients who have been in AF for an extended period of time typically cannot return to NSR, so rhythm control is only used early on in the progression of the condition. Class I antiarrhythmics, such as flecainide and propafenone, block sodium channels. Class III antiarrhythmics, such as dronedarone and sotalol, block potassium channels. The regulation of these channels helps regulate the heartbeat.[12] There are also several procedures available for rhythm control. Patients may undergo direct current cardioversion to restore NSR, although this is only a temporary measure and does not address the underlying cause. Catheter ablation is another method of restoring NSR in which very hot or very cold temperatures are used to destroy AF-causing tissue. A newer technique of ablation called pulsed field ablation will be discussed in detail in the next part of this paper. Similarly, the Maze procedure creates scar tissue in the atria in order to correct abnormal conduction pathways.[13]

Rate control may be used in addition to rhythm control or when restoration to NSR is not desired. The goal of rate control is to keep patients out of AF with rapid ventricular response and consists of controlling the rapid heart rate often seen in AF. This can be achieved with nondihydropyridine calcium channel blockers, such as diltiazem and verapamil, which slow the sinoatrial and atrioventricular nodes. Beta blockers like atenolol and bisoprolol slow the conduction of electrical signals through the heart as a means to slow heart rate.[3]

Finally, management of AF through lifestyle changes is also important in controlling the condition. Weight loss, increased physical activity, smoking and drinking cessation, decreased caffeine consumption, dietary changes, treatment of other conditions, and improved sleep quality are all evidence-based options to reduce the burden of AF.[3]

2.7. Prognosis The prognosis of AF is highly variable. In general, AF is not immediately life-threatening and a patient can live with AF for many years. However, AF has been associated with a twofold increase in the likelihood of premature death due to the severe complications that may arise, including stroke, heart failure, heart attack, sudden cardiac death, dementia, and cognitive impairment.[2] Patients may also experience a decreased quality of life due to uncomfortable or painful symptoms, reduced ability to function, or anxiety about the condition. AF has no cure and continues to advance with time, eventually becoming permanent. However, treatment is able to reduce AF burden and complications.[14]

3. Pulsed Field Ablation

3.1. History The main cellular mechanism of pulsed field ablation (PFA) is called electroporation. This first appeared in agriculture and the food industry before it was used in medicine. Its first medical application came in 1982 when it was used to introduce exogenous DNA into human cells. Clinical applications began in oncology with procedures like electrochemotherapy, gene electrotransfer, and tumor ablation. Electroporation was introduced into cardiology later in the 1980s to ablate the atrioventricular node and treat various supraventricular arrhythmias. This was unsuccessful owing to severe complications and a lack of control over the procedure. Electroporation was abandoned as a treatment option for arrhythmias by the 1990s when researchers concluded that thermal ablation was more ideal.[15] Recent technological advances such as new catheter designs, improved sources of energy, and customizable parameters have allowed electroporation to be reconsidered as a treatment for AF and other arrhythmias. The PFA procedure was initially investigated in 2011, with clinical studies

beginning in 2018.[16] The PulseSelect PFA system by Medtronic received a Breakthrough Device designation from the FDA in 2018 and was FDA-approved on December 13th, 2023.[17] The Farapulse system by Boston Scientific received its Breakthrough Device designation in 2019 and was approved for use on January 31st, 2024. These are the only two PFA systems currently approved for clinical use in the United States.[18]

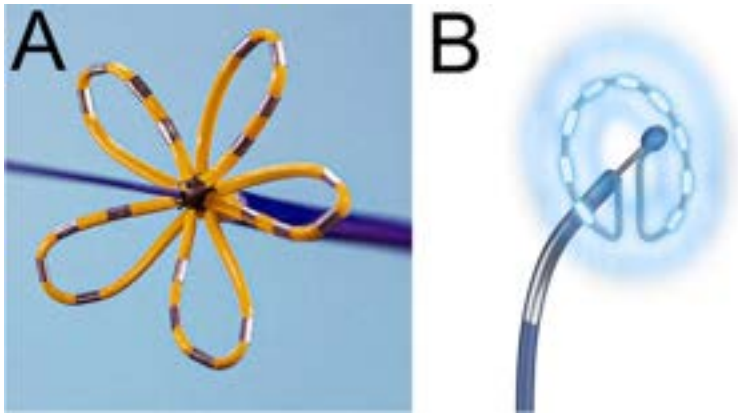

Figure 1: The two approved PFA catheters in the United States. A is the Farapulse catheter tip and B is the PulseSelect catheter tip. Adapted from “Innovations in Atrial Fibrillation Ablation” Journal of Interventional Cardiac Electrophysiology (2023).[19]

3.2. Mechanism/Parameters PFA requires three main pieces of equipment: a generator to deliver pulses, a catheter to perform the ablation, and a sheath to guide the catheter to the heart.[20] There are two PFA systems available for use: PulseSelect and Farapulse. The PulseSelect catheter is 25 millimeters wide, has nine electrodes, and is a fixed loop shape. The Farapulse catheter comes in 31 or 35 mm sizes, has twenty electrodes, and can be configured into a basket or flower shape.[21] The ablation procedure is called pulmonary vein isolation (PVI) and generally involves these broad steps: putting the patient under general anesthesia, inserting the sheath into the femoral vein, guiding it through the body and into the inferior vena cava, entering the right atrium, puncturing the atrial septum to enter the left atrium, directing the catheter through the sheath, and finally isolating the pulmonary veins.[22] It is a very similar method to that of traditional thermal ablations, which instead use heat as in radiofrequency ablation (RFA) or cold temperatures as in cryoballoon ablation (CBA).[23]

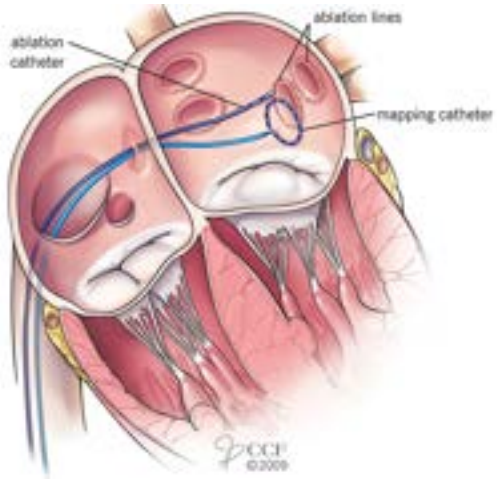

Figure 2: Typical pulmonary vein isolation procedure using RFA. Adapted from “Pulmonary Vein Isolation” Cleveland Clinic Journal of Medicine (2009).[24]

During the procedure, two electrodes on the catheter release very short pulses of high voltage electricity, generating an electric field.[23] These electric fields are then rapidly applied to cardiomyocytes in the location to be ablated, typically around the pulmonary veins.[25] Cell membranes are lipid bilayers with proteins that serve as channels for ions or molecules. A consistent transmembrane voltage is maintained across these channels. The electric fields of the catheter disrupt this voltage, causing the cell to form large pores.[15] These openings in the membrane allow normally impermeable material to enter and leave the cell, resulting in a variety of reactions, such as lipid peroxidation, disruption of osmotic homeostasis, damage to organelles, and more.[26] This process of using electric fields to create pores in cells is called irreversible electroporation (IRE) and it ultimately results in cell death.[25] Because the pulmonary veins are most often the source of AF, using IRE to isolate cells of the pulmonary veins from atrial cells is typically effective at correcting the arrhythmia.[23]

One unique aspect of PFA is that it has many customizable parameters. While still not entirely understood, optimal ranges are being investigated and these parameters show potential to make the practice of AF ablation safer and more precise. One such parameter is voltage amplitude, which refers to the maximum voltage delivered during a pulse and determines the strength of the electric fields. The typical range of voltage amplitude is between 250 and 1250 volts per centimeter. Proceduralists choose voltage amplitude based on the competing risks; voltage that is too high may cause ectopic tissue damage and voltage that is too low may not achieve the desired effect of tissue ablation. Pulse cycle length is another modifiable parameter, referring to how long a single pulse lasts. The pulses used in PFA are short, often ranging from 5 microseconds to 70 microseconds, though at times they may range from nanoseconds up to milliseconds in length.[27, 28] The pulse needs to be short enough that any heat can quickly dissipate but long enough that IRE takes place.[23] Pulses can also be set to be bipolar or monopolar. In a bipolar pulse, there are two active electrodes in close proximity. A monopolar pulse has one active electrode with a pathway to a distant, less active electrode.[29] Other parameters that can be customized during the procedure are the choice of a biphasic or monophasic pulse, pulse width, pulse shape, interphase delay, interpulse delay, duty cycle, number of pulses per pulse train, and number of pulse trains. The ideal ranges of these

parameters are still being explored and further research is needed to determine the optimal settings.[23]

3.3. Advantages PFA has many theoretical advantages over thermal ablation. First, PFA should be safer. Because PFA does not use extreme temperatures and does not require direct contact between the catheter and heart tissue, it is hypothesized to have a more favorable safety profile than thermal ablation. PFA should also be more precise than thermal ablation, as demonstrated by the fact that lesions created by PFA have precisely demarcated boundaries, while lesions from thermal ablation tend to have blurry edges. PFA also has many customizable parameters and may therefore be more versatile for technically complex ablations. Various aspects of the pulse can be adjusted for each patient, which allows proceduralists to better tailor the therapy for specific clinical scenarios. Additionally, PFA has excellent tissue specificity. Thermal ablations use either heat or cryoablation, which do not select for a specific structure and instead damage all nearby tissues indiscriminately. Many complications of thermal ablation involve damage to non-cardiac tissues, like atrioesophageal fistula, pulmonary vein stenosis, coronary artery injury, and phrenic nerve palsy.[23] In contrast, each tissue in the body has its own electric field threshold, so PFA can select for specific types of tissue. PFA deliveries can have voltage amplitude and other parameters modified so they specifically ablate cardiac tissue, protecting adjacent structures such as the esophagus, pulmonary veins, coronary arteries, and the phrenic nerve.[30] Lastly, PFA procedure times are typically shorter than those of thermal ablations. One PFA delivery can be done in a single heartbeat, and only three to four deliveries are needed to create a lesion. The actual isolation of a vein can be accomplished in one or two minutes. This quick process could bring total procedure times from over 180 minutes for thermal ablation down to 60-90 minutes for PFA. Less time under anesthesia means less time for complications to occur, especially in older patients who are more likely to have AF and therefore more likely to require treatment. Additionally, a faster procedure means more ablations can be performed, making treatment more accessible and readily available to patients. It is important to note that these advantages are only in theory and have not yet been entirely proven in clinical studies.[23, 31]

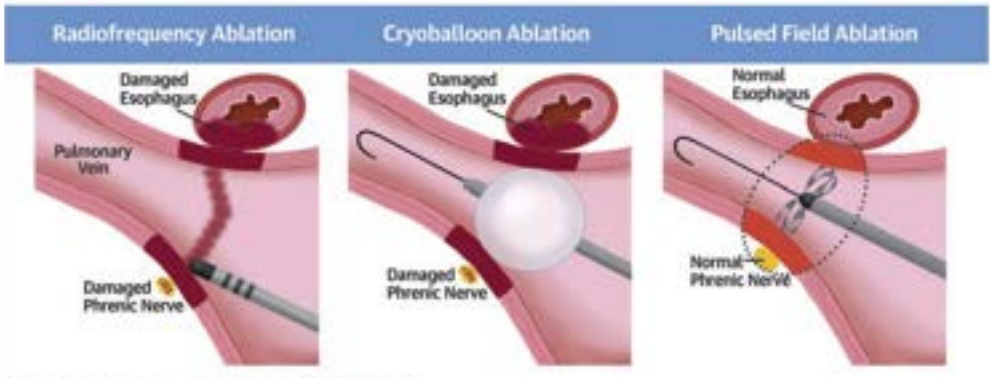

Figure 3: Tissue specificity of RFA, CBA, and PFA. RFA and CBA both show damage to adjacent structures, while PFA damage is contained to the intended area. Adapted from “Single-Shot Techniques for Pulmonary Vein Isolation in AFib: From Cryoablation to Pulsed Field Ablation” Journal of the American College of Cardiology (2019).[32]

3.4 Disadvantages PFA also has drawbacks compared to thermal ablation, including lack of information, a difficult procedure, expensive price, and safety concerns. First, the clinical information available on PFA is very limited. There have been relatively few studies on PFA in comparison to the amount on thermal ablation, and these studies are generally not randomized, large-scale or long-term. Researchers have conducted only one randomized controlled trial (RCT) testing PFA in humans. Due to this lack of information, there is no standardized protocol for how to set the parameters or perform the procedure. The cellular mechanism of IRE is also still not entirely understood. In contrast, thermal ablation has a multitude of studies available, a standardized approach, and thorough understanding of its mechanism.[16] PFA is also a difficult procedure to implement. It requires specialized training that may take physicians some time to acquire. Furthermore, a study on the costs of PFA, RFA, and CBA found the average total price a hospital pays for one procedure to be highest for PFA. This means hospitals may be unwilling or unable to afford PFA.[33] Lastly, there are some complications more commonly seen in PFA than in thermal ablation, including coronary artery spasms, pulmonary artery hemorrhage, and phrenic nerve stunning. Thermal ablation, in contrast, has already been widely implemented and its complications are well understood.[16]

3.5. Animal Studies Animal models have been used to perfect PFA techniques and evaluate its effectiveness. Neven et al. performed IRE on 5 porcine models with varying amounts of energy. The 30-joule lesions were 3.2 mm deep, the 100-joule lesions were 6.3 mm deep, and the 300-joule lesions were 8.0 mm deep.[34] Semenov et al. tested the effect of different pulse durations, 10 nanoseconds and 4 milliseconds, on ion channels in rat embryos. It was found that the 10-nanosecond pulses created smaller and more uniform pores in the cells than the 4-millisecond pulses. However, efficiency of IRE was about the same with both pulse lengths.[35] These two studies show the extent to which changing one parameter affects procedural outcomes. Hirano et al. used PFA in 36 porcine models. Measurements of electrical activity at the site of ablation revealed that bipolar voltage went from 4.11 millivolts pre-ablation down to 0.24 millivolts post-ablation.[36] Stewart et al. compared PFA and RFA in six porcine models. Electrogram amplitudes were brought below 0.5 millivolts in 67.5% of PFA deliveries versus 27.0% of RFA deliveries. PFA also eliminated bipolar voltage in 100% of ablations, slightly more than RFA at 92.0%.[37] These two studies demonstrate that PFA has been successful at preventing electrical conduction in cardiac tissue. This suggests that properly placed, PFA could be effective at stopping the abnormal conduction pathways of AF.

Animal models have been further used to compare the safety of PFA to the safety of thermal ablation. De Pre et al. conducted a study on PFA by performing IRE on the ventricles of 4 porcine models. Of 103 arteries proximal to the lesions that were made, only 6 experienced narrowing, and all affected arteries had under 50% area stenosis. 5 porcine hearts had the left anterior descending artery treated directly with PFA; none had any stenosis. This trial shows the tissue specificity of PFA in practice.[38] Padmanabhan et al. studied PFA in canine models. Successful lesions were created in 20 out of 21 locations of PFA. Only 1 canine experienced ectopic myocardial damage and none had damage to adjacent structures. Both the efficacy and tissue specificity of PFA are shown in this study.[39] Koruth et al. conducted a comparison of PFA and RFA. Out of 36 porcine models treated with PFA and 6 treated with RFA, pulmonary vein stenosis and nerve damage were only seen in those that received RFA. This study not only evaluates the safety of PFA on its own but also in comparison to traditional methods, and the results suggest that PFA is safer than RFA.[40] Sugrue et al. ablated the Purkinje fibers without

significantly affecting electrical conduction in the bundle of His or the anterior fascicle bundle, which went from a bipolar voltage of 5.9 millivolts pre-ablation to 5.4 millivolts post-ablation, indicating that even directly adjacent structures are safe from ablation when PFA is used.[41] Song et al. looked at PFA in 84 rabbits. The pulses were applied directly to the esophagi at a voltage typically used on cardiomyocytes. 16 weeks after the ablation, no injury to the esophagus was present, including no esophageal ulcer or fistula, suggesting that when the voltage of PFA is set for cardiomyocytes, even direct pulses will not cause undesired damage.[42]

3.6. Clinical Studies Reddy et al. conducted the only RCT on PFA in human subjects. 305 AF patients were randomized to PFA and 302 to thermal ablation. Researchers were not blinded to treatment assignment. The study revealed that treatment success with PFA was 73.3% and success with thermal ablation was 71.3%. Serious adverse events occurred in 2.1% of patients treated with PFA and 1.5% of patients treated with thermal ablation. The study concluded that PFA was noninferior to thermal ablation ($p < 0.001$), however superiority would not have been proven had that been the pre-specified endpoint. This trial reveals that the differences between PFA and thermal ablation are not as major as previous studies may have indicated.[43]

Numerous other human studies have been done on PFA, but most are very limited due to lack of randomization and limited sample size. Another Reddy et al. study performed PFA on 22 patients with symptomatic paroxysmal AF. PVI was achieved in 100% of ablations and was effective in 86%.[44] Another study evaluated the Sphere-9 catheter, a lattice-tip PFA catheter, involving 76 patients with paroxysmal or persistent AF. Either only PFA or a combination of PFA and RFA was used. The overall complication rate was 1.3%, the most prevalent complications being with the vascular system, and there were no severe complications. The data indicates that PFA is generally more effective than thermal ablation, both by itself and in combination with RFA.[45] The IMPULSE, PEFCAT, and PEFCAT II trials each enrolled patients with symptomatic paroxysmal AF. A pooled analysis of these trials found that the percentage of patients that experienced significant complications was 2.5%, none of which had esophageal or nerve injuries. Acute PVI was achieved in 100% of patients. Follow-up appointments found that 84.8% of pulmonary veins were still isolated at three months and 81.1% of patients were free of AF at one year.[46] Cochet et al. tested the Farapulse catheter in 41 patients. 18 patients were treated with the Farapulse catheter; none had esophageal lesions, but 33% experienced aortic lesions. Of those treated with thermal ablation, 43% had esophageal lesions and 43% had aortic lesions. This study reveals that PFA is capable of damaging structures close to the ablation site, but not any more than RFA.[47] Nakatani et al. found that late gadolinium enhancement in the atria was 60% higher after PFA. However, most abnormal scarring healed within 3 months, while the beneficial scars from the ablation remained. Both methods of ablation caused damage to heart function, but only PFA patients showed improvement as time went on.[48] The inspIRE Trial tested the CARTO catheter and found it resulted in 100% acute success of PFA.[49] The PULSED AF pilot trial tested the PulseSelect catheter on 38 patients with paroxysmal or persistent AF. Immediate PVI success was 100% and there were no safety events reported at the 30-day follow-up.[50] Gunawardene et al. discovered that PFA is capable of inducing coronary spasm when ablating the mitral isthmus line.[51] The MANIFEST-PF survey was a retrospective study on 1758 patients who underwent PFA. Its main findings were that the rate of major complications, pericardial tamponade and stroke, was 1.6% and the rate of minor complications, vascular complications and transient ischemic attack, was 3.9%.[52] The PULSED AF trial showed PFA to be effective at one year in 66.2% of patients with paroxysmal AF and 55.1% of patients with

persistent AF. The rate of major safety events was 0.7%.[53] Rocca et al. used score-matching to compare patients treated with PFA and thermal ablation. Complication rates were 3.4% with PFA, 5.5% with RFA, and 8.6% with CBA. Freedom from AF at one year was seen in 79.3% patients with PFA, 72.4% with RFA, and 74.7% with CBA.[54] The MANIFEST-17K retrospective survey assessed the safety of PFA in 17642 patients. The major complication rate was 0.98% and the minor complication rate was 3.21%. The major complication of hemolysis with renal failure was noted in 5 patients.[55] The majority of clinical studies have suggested that PFA is both effective and safe, especially in patients with paroxysmal AF, but most of these are limited and should not be taken as fact. Many single-arm trials have tested the efficacy and safety of PFA but further RCTs directly comparing PFA and thermal ablation are needed.

3.7 Future Directions PFA's theoretical advantages give it great potential as an effective and safe treatment for AF. However, not enough concrete evidence has been collected to back these advantages up. More large-scale, long-term, and randomized trials are needed to confirm PFA's promise. Further studies directly comparing PFA to thermal ablation are needed as well. In the future it may also be beneficial to evaluate the effects of PFA in different types of patients, for example comparing the outcomes of PFA in paroxysmal AF and persistent AF. As more information is collected, a standardized protocol and an easier-to-learn procedure will need to be developed if PFA is to be implemented as a common treatment. Finding a way to lower costs would also assist in making PFA a widely performed procedure. Further investigation into procedural techniques and the technology behind PFA will also be useful for improving outcomes and understanding PFA's mechanism of action.

4. Conclusion

AF is a prevalent and grievous heart condition. PFA presents a promising treatment modality due to its theoretical and practical advantages, for instance a safer and faster procedure. Animal studies and limited human data suggest that PFA has favorable safety and comparable efficacy in comparison to thermal ablations. However, in the only major RCT comparing PFA to thermal ablation, there was not a large difference between the two techniques. Further studies are required to identify which patients would benefit the most from this emerging treatment as well as the ideal procedural technique. Overall, PFA is an innovative approach to the treatment of AF and it will be interesting to see what the future holds.

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