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Review Article

Pulsed-Field Ablation For The Treatment Of Left Atrial Tachyrhythms In The Context Of Hfpef: Putting Water On Fire?.

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Abstract

Adverse left atrial (LA) remodeling, dilatation, and scar tissue formation facilitate atrial fibrillation (AF), a common comorbidity in heart failure (HF) with preserved ejection fraction (HFpEF). Poor compliance of the left ventricle facilitates these alterations. Treating concurrent HF requires treating atrial tachyrhythms with catheter ablation (CA), according to an increasing quantity of clinical data and medical guidelines. This advice is challenging because thermal CA techniques, such as cryoablation and radiofrequency ablation, both work by creating more scar tissue. For patients who already have significant scarring from HFpEF, AF therapy with thermal CA may increase the burden of atrial scarring.Thus, thermal CA may serve as the "gasoline" for the LA's slowly smoldering "fire," speeding up the recurrence of AF. Using high-voltage irreversible electroporation, pulsed-field ablation (PFA) is a non-thermal CA approach that can break up arrhythmogenic foci and reentrant microcircuits without leaving a large scar. By acting as "water" instead of "gasoline," PFA may lessen the severe fibrosis response to thermal CA that predisposes to AF.PFA may therefore improve the longevity and effectiveness of CA for AF in HFpEF, which may in turn reduce the likelihood of procedural issues from successive CAs.The clinical principles underlying HFpEF and AF are briefly discussed in this article, followed by an overview of the available evidence regarding PFA's potential as a better CA method for AF in the context of coexisting HFpEF.

Keywords : *electrophysiology; chronic fibrosis; heart failure; atrial fibrillation; nonthermal; catheter.*

INTRODUCTION

Heart Failure

Sixty-four million people worldwide suffer from heart failure (HF), a clinical illness [1]. About six million adults over twenty develop heart failure (HF) in the US alone [2]. Between 2012 and 2030, there is a projected 46% increase in the prevalence of heart failure in the United States. The longer lifespans of people and better chronic disease care are the causes of the rise in prevalence [3].Furthermore, the United States will diagnose 550,000 new cases year on average [4].There are now better options for treating HF at all stages and its aftereffects. As a result, in 2023, 9% of Americans lost their lives to heart failure [2].Surgery, drugs, gadgets, and/or lifestyle modification are used to treat HF. Since lifestyle modifications target the underlying cause of unfavorable left ventricular (LV) remodeling, they represent the first treatment opportunities. Regular exercise, effective stress management, and—above all—adequate nutrition—as demonstrated by diets like the Mediterranean diet—are the main focuses of these modifications [5].Another important factor in preventing HF is reducing sedentary behavior and removing risky exposures like alcohol and smoke. Medication and lifestyle modifications are frequently used to treat chronic illnesses.Risk factors for cardiovascular disease can be managed with a variety of pharmacological medications, including sodium-glucose cotransporter-2 inhibitors, beta-adrenergic antagonists, and angiotensin-converting enzyme inhibitors.The third approach for managing HF is the use of devices, especially in light of the risk of cardiogenic shock. In addition to sophisticated mechanical circulatory devices for acutely reduced heart function, such as Impella® heart pumps, extracorporeal membrane oxygenation, and HeartMate and BiVACOR® ventricular assist devices, these

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devices include cardiac contractility modulation [6], cardiac resynchronization therapy, and intra-aortic balloon pumps. By stimulating the heart with non-conductive electrical impulses, cardiac contractility modulation causes the heart's tissue to contract and pump blood.An intravascular device called Impella® is temporarily inserted into the ventricular cavity and used centrifugal flow to pump blood across the corresponding semilunar valve into the relevant great artery, improving the apparent cardiac output while lowering cardiac work. People with pulmonary problems, frequently in addition to cardiogenic shock, can benefit from extracorporeal membrane oxygenation (ECMO). A centrifugal pump pulls blood that is high in carbon dioxide from the right atrium and/or caval bodies and deposits it in a bladder box or bubble collector.After that, the pump forces the blood into a sequence of chambers (which are chosen based on the sweep speed) where a gas blender and oxygenator are used to remove carbon dioxide and perform oxygenation. A heat exchanger regulates the blood's temperature. The blood is then returned to the body through either the arterial system (known as VA-ECMO; requires an additional device for left ventricular venting unless paired with a TandemHeart device) or the venous system (known as VV-ECMO).

Lastly, ventricular assist devices can be utilized as destination therapy or as a bridge to transplantation in a unilateral or bilateral manner.Surgery is the fourth and last treatment option for heart failure. For secondary heart failure, surgical alternatives include valve replacements or repairs; nonetheless, orthotopic heart transplantation is the sole cure for HF when valvular disease is absent. There are dangers and possible consequences associated with transplantation. Medication and lifestyle modifications are the recommended course of treatment because they are inexpensive and non-invasive.However, the prevalence of advanced heart failure medications will continue to climb due to necessity as the average age of HF patients continues to rise. Although regenerative medical techniques and swine organ transplants are becoming more popular, none of them have yet to show clinical value.

Atrial Fibrillation

Forty million people worldwide suffer with atrial fibrillation (AF), the most prevalent kind of arrhythmia [7]. Because of longer life spans, the prevalence is predicted to rise further in the years to come. In 2017, AF caused more than 287,000 fatalities worldwide [8]. About six million people in the US have AF, and between 2011 and 2018, it was the cause or contributing factor in 276,373 deaths [9].By 2030, the prevalence of AF is expected to rise, according to the US Centers for Disease Control and Prevention [7]. Drugs that regulate heart rate and rhythm, direct-current cardioversions, catheter ablations—possibly with implanted devices—and surgical ablations are all used to treat atrial fibrillation.People receiving medication treatment may take a single class of drugs or a mix of drugs from other classes. Betaadrenergic antagonists, non-dihydropyridine calcium channel blockers, and occasionally digoxin are the drugs used to control heart rate. Among the drugs used to control rhythm are potassium and sodium channel blockers. Cardioversions can be carried out pharmacologically or by direct-current electrical shock. In electrical cardioversion, either two paddles are inserted into the mediastinum during open surgery, or two transcutaneous pads are initially applied to the patient's chest. After that, the heart receives a brief high-voltage current pulse.The purpose of the shock is to cause all of the heart's cells to voluntarily depolarize so that the intrinsic conduction system, which normally depolarizes all of the cardiac cells at the fastest rate, may seize control of the heart and produce sinus rhythm.

Ablation Techniques for Atrial Fibrillation

There are two types of catheter ablation techniques: thermal and non-thermal. The mainstay of care for AF that is resistant to pharmaceutical suppression has historically been thermal ablation. Inserting the catheter into a vascular (usually venous) access site in the arm or groin is the first step in thermal catheter ablation techniques. After that, the catheter travels through the venous system until it passes through the inferior vena cava and into the right atrium. The foramen ovale is used to access the left atrium (LA) from the right atrium, avoiding the right ventricle and lungs. In order to destroy cardiac tissue that permits or spreads reentrant microcircuits and arrhythmogenic foci, the ablation catheter in the LA projects heat using radiofrequency energy or necrosis-inducing cold using circulating liquid nitrogen.It should be mentioned that depending on the transmurality and substrate complexity, arterial and subxiphoid epicardial access are also used. A single ablation session for long-standing persistent AF without pharmacologic substrate suppression produced only a 57% success rate [10], which is defined as no recurrent AF 12 months after the procedure, according to meta-analyses on thermal catheter ablation. Additionally, the authors of the same study stated that the success rate rose to 71% following two or more ablations.Open cardiac surgery is necessary for surgical ablations, which are most frequently carried out as one of the numerous MAZE, hybrid MAZE, or "cut-and-sew" MAZE operations. This type of ablation involves physically cutting off sections of the right atrium, superior vena cava, pulmonary venous inlets, and/or LA with a knife. A suture is then used to reconnect the severed tissue [11]. Radiofrequency ablation or intracardiac cryoablation are other methods for producing ablation lines. Abnormal electrical impulses from ectopic cardiac tissue cannot disturb the regular heartbeat because electrical currents cannot pass through the resulting scar tissue. According to research, up to 90% of patients who have

the MAZE-III surgery are free of AF after a year [12].As a result, surgical ablations are probably more effective than thermal catheter ablation, which has a success rate of 65–82%.

Correlation between Heart Failure and Atrial Fibrillation

Despite being separate chronic illnesses, heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are positively correlated.

This is because HFpEF can result in irreversible dilatation, fibrosis, and remodeling of the LA, all of which can lead to AF. Additionally, risk factors such coronary artery disease, acquired diabetes mellitus, and hypertension are shared by the two comorbid illnesses. In two different studies [13,14], it was discovered that between 33% and 65% of people with HFpEF have concomitant AF.The underlying pathophysiology of AF in the context of HFpEF is described in the current review study. Additionally, we will compare the results of thermal catheter ablation and pulsed-field ablation (PFA) as AF treatments and go over the benefits and drawbacks of PFA. Lastly, we will discuss the evidence that suggests PFA is theoretically superior to thermal catheter ablation for patients who have both HFpEF and AF.

The HFpEF and AF Fire

Heart Failure with Ejection Fraction Preserved

The clinical definition of heart failure (HF) is any structural or functional defect of the heart that hinders the ventricles from receiving or expelling enough blood volume to meet the body's perfusion needs [15]. A prolonged, ineffective cough, orthopnea, exhaustion, lower extremity edema, decreased exercise tolerance, and dyspnea during daily activities are physical signs of heart failure [16]. High jugular vein pressure, tachycardia, right ventricular heaving, pulsus or electrical alternans [17], and a shifted cardiac apex [16] are clinical indicators of heart failure. The LV ejection fraction (EF) is one method that can be used to classify HF. The percentage of the heart's blood that is expelled with each beat is known as the EF.The main technique for measuring EF is non-invasive cross-sectional imaging, which is mainly carried out using magnetic resonance imaging (MR), computed tomography, or echocardiography. Transthoracic ultrasound is the preferred technique since it is quick, easy, and highly reproducible. Direct viewing of the LV cavity with contrast during cardiac catheterization (ventriculogram) can also be used to evaluate EF.In mathematics, EF is computed by dividing the LV end-diastolic volume by the LV stroke volume, which is the volume of blood pumped out of the LV as indicated by end-diastolic volume minus end-systolic volume. The fraction is then multiplied by 100. Heart failure with reduced ejection fraction (HFrEF), heart failure with recovered ejection fraction (HFrecEF), heart failure with mid-range ejection fraction (HFmrEF), and heart failure with HFpEF are the four categories of heart failure. An LVEF of less than or equal to 40% is referred to as HFrEF.Having an LVEF between 41 and 49% is known as HFmrEF.Having an LVEF of more than 40% after previously having one of less than or equal to 40% is known as HFrecEF. Finally, having an LVEF of 50% or above is referred to as HFpEF.HFpEF will be the specific topic of this article. The failure of the LV to fully relax and remain partially constricted results in HFpEF. Since HFpEF is a relatively novel clinical entity, it poses considerable problems in terms of pharmacologic therapy and diagnostic precision. Patients with HFpEF rarely share the same demographics as those with HFrEF because the former group is more likely to be female, have no obstructive coronary disease, and may be older, which results in a larger relative load of comorbidities.The clinical phenomena of HFpEF is explained by a number of molecular explanations, but titinopathy is the most widely accepted. The largest protein in the entire body and the largest protein in sarcomeres is called titin. The diastolic spring of the cardiomyocyte is primarily driven by titin, which has been thoroughly investigated in relation to HFpEF [18].Although the LV's systolic function is unaffected, poor relaxation of the LV results in an inadequate filling of the LV with blood. While maintaining the numerical fraction for EF, a decreased end-diastolic volume with normal systolic function results in a lower cardiac output that cannot satisfy the body's metabolic needs [19].Additionally, the successive cardiac chambers experience an imbalance in pressure because to the LV's excessive rigidity, which leads the LA to dilate and build up scar tissue [20].Due to its favorable link with the risk of adverse events such thrombosis, LA fibrosis is important [21]. Furthermore, tachyrhythms can result from LA fibrosis; for this reason, people with HFpEF are often diagnosed with AF. LA is widely recognized as a primary target for AF treatment [21]. Age, AF, renal illness, hypertension, and acquired diabetes mellitus are risk factors for HFpEF. Patients with HFpEF had a mortality risk of 8% for those under 70 and 12% for those 71 and older. Remarkably, a concomitant illness claims the lives of 17% of people with HFpEF [17].

Atrial Fibrillation in HFpEF Context

More than 40 million people worldwide suffer from AF, the most prevalent kind of arrhythmia [7]. Once contractile atrial cardiomyocytes, usually found in the LA close to the pulmonary vein inlets, develop the ability to self-excite and depolarize, enabling them to start an action potential in place of the intrinsic cardiac pacemaker cells. This is the first step in the cellular mechanism of atrial fibrillation (AF). A depolarization wavefront can be facilitated throughout the atrial myocardium once a small number of the now-autorhythmic cardiomyocytes have depolarized [22]. Because of the conductive tissue's spatial separation and the very brief refractory period, many

of these wavefronts can coexist naturally. Usually represented as spiral wavelets, these wavefronts are caused by distinct foci of ectopic electrical activity and can occasionally combine to appear as synchronized atrial electrical activity. The atria mechanically quiver instead of contracting uniformly due to the disorganized electrical activity, which raises the risk of thromboembolism in AF [23]. Clinically, the lack of distinct P-waves and uneven RR intervals on a 12-lead surface ECG are indicators of this condition [23].There are four stages of AF [24,25]: paroxysmal (stage 3A), persistent (stage 3B), long-standing persistent (stable 3C), and permanent (stage 4). One of the two main theories used to treat AF is rhythm regulation. In order to create sinus rhythm, it entails the use of cardioversions, catheter ablations, surgical ablations, and antiarrhythmic drugs (mostly class 1 and class 3 agents) [26]. Ratecontrol is the alternative therapy option for AF. Slowing the ventricular rate without restoring sinus rhythm is the aim of rate control. Class 2 and class 4 agents are used for this [27].Treating AF concurrent with HF requires controlling tachyrhythms with catheter ablation, according to growing clinical data and medical guidelines [28, 29]. Based on results from recent randomized trials that show catheter ablation is superior to medication therapy for rhythm control, catheter ablation of AF in patients with HFrEF has now achieved a Class 1 indication [30,31]. One might assume that HFpEF is not far behind.Radiofrequency and cryoablation frequently cause myocardial fibrosis because they use thermal energy as their mode of action. With a varied success rate in preserving sinus rhythm—which has been reported to reach 56% two years after thermal ablation—this treatment is an acceptable alternative for patients with AF who do not have HFpEF [29]. Because patients with HFpEF complicated by AF may benefit from a catheter ablation modality that does not induce additional macroscopic scar tissue, additional consideration should be given to thermal ablation, which has long been the only option for catheter-based rhythm management for AF.Due to the increased pressure exposure from the LV procedure, patients with HFpEF have a higher burden of fibrosis in theLA.Therefore, for individuals with significant LA scar tissue, treating AF with a thermal ablation approach may increase the amount of scar tissue burden. This may be compared to putting "gasoline" into the "fire" that is slowly consuming the LA.

Ablation by Pulsed Field

PFA is a "non-thermal" ablation technique that is becoming more and more popular worldwide for the treatment of AF, albeit tiny temperature changes have been seen, depending on the pulse frequency and voltage.Although there are other commercial PFA systems available worldwide, the FARAPULSETM system has recently received approval from the Food and Drug Administration and has been seen more frequently in invasive cardiac electrophysiology labs around the United States. PFA promotes cell death in intracellular organelles and membrane cells by using irreversible electroporation. By causing holes in the cell membrane, the electrical impulses destabilize the membrane and cause necrosis or apoptosis, which results in celldeath[32,33]. Phospholipid bilayer membranes are the specific focus of PFA's mode of action. Lethal membrane damage is produced by introducing intra-membrane current flow by high-voltage electrical pulses. All membranes in the high-voltage electric field are theoretically susceptible to this damage, albeit tissue types differ in their susceptibilities to PFA and the precise PFA parameters can be adjusted. In addition to being monopolar or bipolar, PFA electrical pulses can also be made to be monophasic or biphasic and adjusted for the impulse length. Although there is currently no common protocol directing operators, several distinct investigations [34–36] have demonstrated that short biphasic pulses have higher success rates than monophasic impulses.In a similar vein, the operator chooses the precise voltage [34].The majority of publicly available recorded PFA techniques use roughly 10–90 pulses per session, each lasting 100 microseconds, an electric field of roughly 500–3000 V/cm, and a frequency of 1–10 Hz, even though there is no unified protocol that is accessible to the public [34]. The theoretical benefits of a non-thermal catheter ablation technique may demonstrate that PFA is preferable than radiofrequency and cryoballoon catheter ablation, despite the paucity of data regarding its efficacy for comorbid AF in the context of HFpEF (Table 1). Thermal ablation raises the likelihood of developing atrial fibrillation again and causes more atrial fibrosis.PFA has a better profile of procedural risks and side effects than thermal catheter ablation, which is its first and main advantage. PFA's non-thermal method effectively reduces the likelihood of thermal problems like pulmonary vein stenosis, fistula formation, and perforation [37–39]. The second benefit of PFA is that, in contrast to thermal ablation, which requires consideration of the sink effect, electrical impulses are unaffected by nearby high-velocity blood arteries [40]. When radiofrequency ablation is used, blood vessels can lower the surrounding structures' temperature; when cryoablation is used, the temperature can rise.In conclusion, PFA offers a means of treating pharmacologically resistant AF, lowering worries about the patient developing iatrogenic diseases or the LA scar load getting worse. PFA may also reduce the number of surgeries required for recurrent AF and the rate of ablation failure for AF. In the end, PFA might serve as "water" to put out the LA's AF-prone "fire," which is blazing slowly. The ability to use both thermal and non-thermal ablation procedures enhances the arsenal of invasive electrophysiologists. Future research should compare results in this particular patient subgroup of AF with HFpEF in order to eventually

provide medical recommendations for an improved ablation technique.

CONCLUSIONS

When compared to thermal ablation, PFA may be a better option for treating AF in the context of HFpEF. The evidence supporting this potential benefit is that thermal ablation causes fibrosis, which can result in recurrent AF and act as the "gasoline" for the "fire" of LA-driven AF. As "water" to the "fire," PFA, on the other hand, uses non-thermal energy and, as a result, has a lower chance of recurrent AF and higher risk factors. Even though PFA has great potential for treating AF in the context of HFpEF, further data from specialized clinical trials is required to support its application.

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