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REVIEW ARTICLE

Ablation Therapy for Persistent Atrial Fibrillation

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Abstract: Atrial Fibrillation (AF) is the most common form of electrical disturbance of the heart and contributes to significant patient morbidity and mortality. With a better understanding of the mechanisms of atrial fibrillation and improvements in mapping and ablation technologies, ablation has become a preferred therapy for patients with symptomatic AF. Pulmonary Vein Isolation (PVI) is the cornerstone for AF ablation therapy, but particularly in patients with AF occurring for longer than 7 days (persistent AF), identifying clinically significant nonpulmonary vein targets and achieving durability of ablation lesions remains an important challenge.

Keywords: Atrial fibrillation, ablation, pulmonary vein isolation, cryoballoon, radiofrequency, left atrium.

1. INTRODUCTION

Atrial Fibrillation (AF) is the most common form of electrical disturbance in the heart and contributes to significant patient morbidity and mortality. With the population aging, the prevalence of AF is expected to rise to an estimated 6-12 million people by 2050 in the United States and 17.9 million people by 2060 in Europe. The worldwide prevalence of atrial fibrillation has also increased by 33% during the last 20 years [1]. AF is associated with increased overall mortality, particularly due to heart failure [2]. Catheter ablation for AF to maintain sinus rhythm improves the quality of life and may reduce mortality, particularly in patients with congestive heart failure [3, 4].

The pathophysiology and natural history of persistent AF (peAF) remain incompletely understood. PeAF occurs in the setting of electrophysiological and structural alterations of atrial myocardium termed "structural remodeling," resulting in the substrate for AF. Although initially adaptive to external stressors, cardiomyocytes develop adverse structural remodeling and eventually fibrosis that promotes atrial reentry later in the disease process [5, 6]. Moreover, pre-existing comorbidities, such as hypertension, obstructive sleep apnea, heart failure, obesity, and chronic kidney disease, exacerbate the atrial remodeling that perpetuates AF [7, 8]. Patients with peAF develop more advanced adverse atrial remodeling and fibrosis compared with patients with paroxysmal AF, which makes treatment of peAF more challenging [9].

Ablation therapy has emerged as an important therapy for AF due to its superior efficacy as compared with antiarrhythmic medications [10, 11]. It helps to break the vicious cycle of AF begetting AF in atrial myocardium [12]. Pulmonary vein isolation (PVI) remains the cornerstone of AF ablation based on the early observation that AF is often triggered by atrial ectopic beats arising from the pulmonary veins [13, 6]. Recurrent AF after ablation often occurs as a result of a lack of durable PVI long-term [14]. Furthermore, particularly in patients with peAF, PVI may not be adequate in achieving long-term maintenance of sinus rhythm [15, 16] due to adverse atrial remodeling that often necessitates the search for other ablation targets [17-19].

Even inexperienced centers and with high volume electrophysiologists, rates of success of ablation in patients with peAF are approximately 50-65% after one ablation procedure [20-22]. There is some additional success rate for those patients undergoing redo ablation [23, 24], although improvement of symptoms and reduction of AF burden reduces the rate of redo ablations for those patients who experience arrhythmia recurrence. Improving the rate of success of ablation in patients with peAF currently depends on two main factors: identifying other possible ablation targets in the remodeled atria [25], and perhaps more importantly, achieving more durable PVI [14]. In this paper, we will review novel approaches and technologies that have been developed to achieve these goals.

2. TRIGGER MAPPING: LESSONS FROM PAROXYSMAL AF

In addition to the antral tissue surrounding the pulmonary veins, non-PV foci have been evaluated as feasible targets for ablation. Santangeli *et al*. demonstrated that up to 11% of patients have reproducible sustained AF from non-PV foci; indeed, recurrences are often related to these focal non-PV triggers [26]. Non-PV triggers include the periannular regions of the mitral and tricuspid valves, the crista termi-

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nalis, eustachian ridge, interatrial septum, left atrial posterior wall, left atrial appendage, Superior Vena Cava (SVC), coronary sinus or ligament of Marshall. The P wave characteristics of the Atrial Premature Depolarizations (APDs) that initiate episodes of AF can help indicate the location of the trigger. For example, an SVC focus may trigger AF-initiating APDs that have P waves with a larger negative component in V1 as compared with APDs arising from right PV focus, and a mitral annular focus may trigger AF-initiating APDs that have biphasic notched P waves in the precordial leads and low-amplitude P waves in limb leads [26]. Kubala *et al*. developed and verified an algorithm based on P-wave morphology and intra-atrial multipolar activation patterns to help identify non-PV trigger sites of origin. Using the results of 450 intracardiac and electrocardiographic recordings, the locations of non-PV triggers of AF could be appropriately assessed in 96% of those recordings using detailed P-wave characteristics in specific leads, such as P-wave amplitude and polarity [27].

Isoproterenol is often used to elicit non-PV triggers, especially when AF recurs following PVI ablation in the absence of PV reconnection [28]. As a cardiac beta1 and beta2 adrenoreceptor agonist, isoproterenol leads to an increase in diastolic and intracellular calcium, which in turn decreases action potential duration and atrial refractory periods, automaticity, and triggered activity [29] . Various protocols of isoproterenol dosing and infusion times have been proposed [30-32], and some centers incorporate atrial burst pacing along with isoproterenol [33-35], but practices vary. In the effect of empirical left atrial appendage isolation on long-term procedure outcome in patients with persistent or longstanding persistent atrial fibrillation undergoing catheter ablation (BELIEF) trial, isoproterenol was used to identify non-PV foci after PVI ablation. It was felt to be an inadequate tool in overall ablation success as compared with empirical isolation of the left atrial appendage [36].

Non-PV triggers initiate paroxysms of AF but are possibly even more clinically significant in patients with peAF [37]. In some patients with peAF, PVI, along with ablation of non-PV triggers can improve long-term ablation success [38]. Identifying and eliminating non-PV triggers can be a cumbersome and imperfect process [39].

3. THE TRANSITION FROM ATRIAL FIBRILLATION TRIGGERS TOWARD ATRIAL SUBSTRATE ABLATION

The identification of atrial myocardium as an anatomic and electrophysiologic substrate for the perpetuation of AF leads to the suggestion that ablation of scar areas of the atrium is an important goal after PVI in patients with peAF [40]. Indeed, the original surgical literature proposed the Cox-Maze III approach of isolating the posterior left atrial wall and performing linear scar in both atria [41]. In the early 2010s, it was common practice for electrophysiologists to perform substrate-based ablation with the linear roof or mitral isthmus ablation lines or ablation of complex fractionated atrial electrograms (CFAEs) in patients with peAF [21, 42]. In the first multicenter randomized trial to study the addition of linear ablation lines and CFAE ablation to PVI in patients with peAF, the multicenter randomized Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF II) study showed no advantage in freedom from AF or atrial arrhythmias when additional ablation beyond PVI was performed [43].

Since the publication of STAR AF II, investigators have explored more precise methods of targeting atrial substrate. One approach is to identify fibrotic regions with a bipolar voltage of <0.5 mV on electroanatomic mapping and to then isolate these regions using an encircling box lesion set [44] or to homogenize these regions until no electrically active myocardium remains [45]. Another approach is to demonstrate atrial scar using LGR MRI and to ablate these regions during the ablation procedure [46].

Over the last few years, there has also been a resurgence of interest in isolating the posterior left atrial wall, which is a common location for scar regions felt to be important for the maintenance of AF [47]. Posterior wall isolation commonly involves creating a linear roofline and the line connecting the lower pulmonary veins following PVI to create a box-shaped lesion. Isolation of the posterior wall in addition to PVI provides longer recurrence-free survival without the use of an antiarrhythmic drug as compared with PVI alone [48-49]. These findings were supported in a meta-analysis of 5 studies with almost 600 patients, which importantly also found comparable procedure-related complications and procedural time when posterior wall isolation was performed [50]. In contrast to these data, the POBI-AF investigators recently found that empirical complete posterior wall box isolation did not improve the rhythm outcome of catheter ablation among 217 patients with peAF [51]. The indications and possible benefits of posterior wall isolation remain hotly debated in the field.

4. FOCAL AND ROTATIONAL DRIVERS OF AF

The traditional multiple wavelet hypothesis assumes that AF results from randomly propagating waves lacking any organization. Recently, however, data have demonstrated that wave propagation during AF is not random but contains components that depend on self-organized drivers, or rotors, that spin at high frequency and promote the complex patterns of fibrillatory conduction as they propagate through the atria [52].

Ablating these rotors has been proposed as an alternative strategy for ablation in patients with peAF - especially when the AF has persisted for a long time. Using noninvasive signal processing prior to the ablation procedure, Haissagurerre *et al*. demonstrated that the number of AF drivers increased with the duration of AF (*e.g.,* 3 drivers in AF lasting 1-2 months, 4 in AF lasting 4-6 months, 6 in AF of >6 months) and that ablation was more successful in patients with peAF compared to patients with longstanding peAF. Accordingly, the rate of AF termination declined as the duration of continuous AF increased - from 85% for AF lasting less than or equal to 3 months to 15% for AF lasting more than 12 months [53].

The technique of focal impulse and rotor modulation (FIRM) ablation was addressed in the Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation (CONFIRM) trial [54]. In this study, Narayan *et al*. identified localized electrical rotors or focal impulse sources in 92 patients with paroxysmal or persistent (72%) AF whose comorbidities included hypertension, diabetes mellitus, prior stroke/transient ischemic attack, coronary artery disease, and hyperlipidemia; these patients were treated in a 2-arm 1:2 design by FIRM-guided ablation followed by conventional ablation, or by conventional ablation alone. The acute endpoint of AF termination or consistent slowing was achieved in 86% of FIRM-guided cases *versus* 20% of conventionally treated patients. FIRM-guided cases had higher freedom from AF (82.4% *versus* 44.9%) during a median of 273 days of follow-up. The lower success rate in conventional ablation is thought to be related to the high number of sources in the right atrium, which are not targeted with conventional ablation, as well as an increased number of source locations associated with peAF compared to paroxysmal AF.

Other studies have investigated the distribution of AF driver domains in patients with peAF [55]. In a prospective study of 29 patients with peAF or longstanding peAF, Gianni *et al*. identified and ablated rotors using FIRM mapping. All sources were successfully ablated, and the overall success rate defined by AF slowing or AF organization was 41%, with no major procedure-related adverse events. After a mean 5.7 months of follow-up, freedom from AF or another atrial tachyarrhythmia without antiarrhythmic drugs was only 17% [56]. In contrast, Mohanty *et al*. compared PVI plus FIRM ablation with PVI plus posterior wall isolation and non-PV trigger ablation in patients with peAF and longstanding peAF and found that only 24% of patients with FIRM-guided ablation remained arrhythmia-free at 24 months follow up (compared with 48% in the PVI plus posterior wall plus non PV trigger group) [57]. Data regarding FIRM-guided ablation continues to emerge but remains limited by the specialized nature of FIRM mapping and the lack of standardized ablation strategy.

5. OTHER MAPPING SYSTEMS TO IDENTIFY AF DRIVERS

A number of other mapping systems have been used to pinpoint focal activity and electrical rotors in patients with peAF [58, 59]. Honarbakhsh *et al*. used a whole-chamber multielectrode basket catheter to record unipolar signals and create wavefront maps using proprietary software. Drivers were defined rigorously and mapped pre-and post-PVI and were targeted with ablation. In this small study, drivers that had also been identified on pre-PVI maps were more commonly associated with AF termination [58].

Noninvasive identification of AF drivers has also been proposed. The noninvasive epicardial and endocardial system uses up to 224 MRI-compatible unipolar ECG electrodes in special arrays that are placed on patient's torso followed by thoracic contrast MRI. Based on the MRI data, the 3D epicardial and endocardial biatrial geometry is reconstructed. During the ablation, multiple local unipolar electrograms are projected onto the atrial surfaces to represent the spatially distributed reentrant electrical activity of the atrium [59]. Another noninvasive mapping system, the ECVUE, processed reconstructed electrograms to demonstrate both focal and reentrant activity. It showed that 77% of patients with peAF were free of AF recurrence at 1-year follow-up when they had ablation of these targets followed by PVI and finally left atrial linear ablation if AF persisted. Of note, these patients had a significantly higher rate of atrial tachycardia (49%), necessitating administration of antiarrhythmic medication or an additional procedure [60].

Recently, a novel noncontact imaging and mapping system that uses ultrasound to reconstruct atrial anatomy and measure charge density was proposed to guide ablation of peAF [61]. Charge density mapping was able to discern various activation patterns, including complex patterns termed localized irregular activation, a repetitive multidirectional entry, and exit conduction through a confined zone. This novel ultrasound imaging and charge density mapping system safely guided ablation on non PV targets in peAF patients with 73% single procedure and 93% second procedure freedom from AF at 12 months [61].

With newer imaging modalities, mechanisms that induce and sustain arrhythmias in patients with peAF are better understood. Verma *et al*. suggested that acute AF termination is likely secondary to ablation of focal activation sites rather than rotational activation sites [62]. This may change our ablation strategy to only focal activation sites instead of ablating all detected drivers, which may decrease the rate of AT burden. Choosing the ideal imaging modality and ablation strategy would be the key to achieving higher success rates in patients with peAF.

6. EFFECTIVE TECHNOLOGY FOR MORE CONSISTENT AND DURABLE ABLATION LESIONS

Perhaps the most important factor in preventing AF recurrence in all types of AF is the durability of ablation lesions, specifically, the durability of PVI. Advances in technology are ongoing in the quest to have more consistent and durable lesions and to result in even safer, shorter, and more effective procedures. Current, up-to-date ablation technologies include cryoablation, radiofrequency and other balloons, use of contact force, and pulse-field ablation. We will briefly review advancements in each of these technologies.

7. CRYOBALLOON ABLATION

Cryoballoon (CB) ablation has increased in popularity as compared with conventional RF ablation due to studies demonstrating its efficacy [63, 64], predictability, and shorter procedure times [65]. In the CIRCA DOSE trial, the freedom from recurrent atrial arrhythmias as detected by implantable loop recorder was 52.2% in patients who underwent PVI with cryoballoon using a standard 4 min lesion duration [64]. When cryoballoon ablation was performed in patients with peAF with a goal of PVI, the CRYO4PERSIS-

TENT AF trial demonstrated a 60.7% freedom of atrial arrhythmias at 12 months post-ablation [22].

CB technology is adapting to PV anatomy and is emerging as a substrate-based tool as well. Akkaya *et al*. identified a 29.7% recurrence rate during 3-year follow-up in patients with peAF treated with the second-generation CB [66]. This relatively high success rate is an improvement from prior studies using other ablation techniques that showed less than 60% success rate [67]. In addition to PVI, cryoballoon ablation has been used for additional substrate ablation. Nordsieck *et al*. recently found that patients treated with left atrial posterior wall ablation using the CB were less likely to require an additional procedure as compared with patients treated with conventional radiofrequency ablation or hybrid surgical ablation [68]. CB technologies are rapidly evolving and will likely result in even safer and more effective ablation options in the coming years.

8. RF BALLOONS

Advances in balloon technology have also resulted in the development of balloon-based RF systems [69, 70]. Such technologies offer single shot circumferential RF ablation using a balloon placed at the ostium of each pulmonary vein. Recent studies showed comparable clinical efficacy and safety of hot balloon ablation when compared to CB-based ablation [71, 72]. However, long-term data on the results of RF balloon ablation for PVI have not yet been established.

9. CONTACT FORCE

The advent of Contact Force (CF) sensing RF catheters has resulted in more consistent and durable ablation lesions and in even safer procedures [73, 74]. In a randomized multicenter trial of 128 patients with peAF undergoing the first-time ablation, although CF sensing-guided ablation did not change 12-month outcomes, lower force as defined by CF sensing resulted in significantly more gaps [75]. The recently published Prospective Review of the Safety and Effectiveness of the THERMO COOL SMART TOUCH SF Catheter Evaluated for Treating Symptomatic PersistenT AF (PRECEPT) trial found that the CF sensing catheter was very safe and effective in patients with peAF [76].

10. PULSED ELECTRIC FIELDS

Recent data have highlighted the emerging role of pulsed electric fields [PEF), which use irreversible electroporation to perform cardiac ablation in pigs [77] and humans [78]. PEF may provide tissue-specific effects and further reduce the risks of complications associated with the use of thermal energy [79, 80]. PEF has been proposed as an emerging therapy for PVI ablation and left atrial substrate ablation in patients with peAF [81]. Optimally designed catheters and mapping systems meant to provide PEF for durable AF ablation are under active development [82, 83].

CONCLUSION

AF ablation is a highly effective treatment strategy for patients with all types of AF. PVI remains the cornerstone for AF ablation therapy. In patients with peAF, identifying clinically significant non-PV targets and achieving durability of ablation lesions remain important challenges.

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CONFLICT OF INTEREST

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