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EDITORIAL

Focal Ablation of Atrial Fibrillation: The Target Remains Elusive

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Abstract

Contemporary technology using mapping tools and algorithms in animal and computer models has suggested discrete atrial fibrillation (AF)-sustaining mechanisms in the form of electric rotors as focal areas of AF perpetuation. When these focal sites were targeted, ablation initially appeared promising in reducing the recurrence rates of AF. However, many other investigators have been unable to reproduce this kind of success with focal impulse and rotor modulation (FIRM)-guided ablation, and have cast doubts on the effectiveness of this novel technique that could have led to a paradigm-shift in our approach to AF ablation. A single randomized trial that was recently published in a high-impact cardiology journal indicating poor results of rotor ablation was subsequently retracted amidst a cloud of controversy and doubt about the flaws and conflicts of current medical publishing. Thus, until further evidence from ongoing and future randomized studies becomes available, the target of focal ablation for AF patients continues to remain elusive. ***Rhythmos*** 2017;12(2):21-25.

Key Words: atrial fibrillation; acute atrial fibrillation; persistent atrial fibrillation; catheter ablation; rotors; focal impulses; focal fibrillation waves; pulmonary vein isolation

Abbreviations: AF = atrial fribrillation; FIRM = focal impulse and rotor modulation; PV = pulmonary vein; PVI = pulmonary vein isolation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia with continuously increasing trends in its incidence, [1] associated with increased morbidity and mortality and incurring high societal impact and financial cost. [2, 3] Rhythm control strategies with antiarrhythmic drugs have been disappointing, while the advent of ablation techniques has ushered in a new era in the management of this arrhythmia. [2-6] Current ablation methods comprise pulmonary vein (PV) isolation (PVI) techniques with either radiofrequency energy or cryoenergy application that may eliminate or limit the arrhythmia triggers. [2, 6, 7] These methods have been mainly proposed for paroxysmal AF, while for persistent or longstanding persistent AF, additional ablation steps targeting the arrhythmia substrate have been performed by several investigators. [8] However, even with the best available technological advancements, the efficacy of ablation is hampered by moderate success rates and increased number of complications. The ablation procedures are demanding lengthy and tedious, and are

still plagued by high recurrence rate,[6] unlike the usual ablation procedures of other supraventricular or idiopathic ventricular tachycardias, which are routinely and practically cured with focal ablation with very high success, low complication and recurrence rates. [9] Thus, there has been a continuing search for a more effective way to approach this common arrhythmia with a similar strategy, however, to date this quest has not been very fruitful.

The most important tool to investigate a possible focal approach to AF ablation can only be found by better understanding of its pathogenesis and pathophysiology mechanisms, which has certainly not been an easy task over the years. Modern and sophisticated technology using mapping tools and algorithms in animal and computer models has suggested discrete AF-sustaining mechanisms in the form of electric rotors spinning at high speed and producing gradients in the spatial distribution of dominant atrial frequencies, with the highest frequency domain corresponding to the rotor location. [10-12] When these high frequency domain sites were targeted, ablation initially appeared promising in reducing the recurrence rates of AF. [13, 14]

However, many other investigators have been unable to reproduce this kind of success with focal impulse and rotor modulation (FIRM)-guided ablation, and have cast doubts on the effectiveness of this novel technique that could lead to a paradigm-shift in our approach to AF ablation. [15, 16] Furthermore, other investigators have been insisting for a long time that localized rotors and focal impulse sources of AF are based on false premises, as they have never been able to prove their existence in their own experiments, as they could only visualize focal AF waves rapidly dispersing and without spatial stability. [17, 18]

Rotors and Focal Impulses

It's been quite a while since Jalife and colleagues have described rotor activity in optical mapping studies in experiments in isolated hearts, as well in computer simulation studies. [10] These investigators believe and assert that studies at the whole-heart level support the hypothesis that maintenance of both paroxysmal and persistent AF may depend on the periodic activity of a small number of rotors in the posterior left atrial wall-PV region. [11] These rotors activate the atria at exceedingly high frequencies and result in fibrillatory conduction.

This idea of AF maintained by fibrillatory conduction emanating from a small number of high-frequency reentrant sources (rotors), was further supported by the work of Narayan and colleagues by developing a technique of rotor elimination as a therapeutic strategy for AF. [14] These investigators postulated that atrial rotor activity was critical in maintenance of ongoing fibrillatory activity, and could be identified and successfully ablated. They developed novel mapping techniques (Topera Solution, Abbott, Chicago) that allowed for the identification and localization of rotor sources. Initially, they recruited 92 patients with paroxysmal or persistent (72%) AF undergoing 107 procedures and tested their technique followed by the conventional method in 27 patients and compared it with the conventional method alone applied in 65 patients. [14] Localized rotors or focal impulses were detected in 98 (97%) of 101 procedures with sustained AF, each exhibiting 2.1 ± 1.0 sources. AF termination (in a median of 2.5 min) or slowing was achieved in 86% of focal impulse and rotor modulation (FIRM)-guided cases vs 20% of control cases ($p < 0.001$). Ablation time was similar in the two groups (52-58 min). During follow-up (median 9 months) after a single procedure, FIRM-guided cases had higher freedom from AF (82.4% vs 44.9%; $p < 0.001$). Extended follow-up to 2.4 years indicated that patients receiving FIRM-guided ablation maintained higher freedom from AF after 1.2 ± 0.4 procedures (median 1) (77.8% vs 38.5%, $p = 0.001$) and a single procedure ($p < 0.001$) and higher freedom from all atrial arrhythmias ($p = 0.003$). [19] Thus, early clinical investigations of rotor elimination appeared quite promising. [14, 19, 20] Furthermore, the same investigators in a retrospective analysis of rotor sites in patients having PVI suggested the success of that procedure might in fact have been due to fortuitous elimination of rotors, rather than PVI *per se*. [21] These results were considered promising enough that industry rushed to embrace the strategy.

Rotor Opposing Studies

Other investigators have consistently been opposing the idea of existing rotors as a pathogenetic mechanism in AF, [22] while others have presented poor results of rotor ablation in clinical studies. [15, 16] Allessie and colleagues have mapped AF activity in a number of models, and have not seen AF-sustaining rotors refuting the findings described by Jalife et al, calling into question the basic pathophysiology in targeting such rotor or focal impulse sources during ablation.[22] Instead of rotors as the drivers of AF, Allessie et al have observed by direct high-resolution mapping of fibrillatory tissue a quite different physiology pointing into longitudinal dissociation of propagating wavefronts between epi- and endocardial atrial layers. [17] These investigators demonstrated many narrow wavelets propagating simultaneously through the atrial wall with their lateral boundaries formed by lines of interwave conduction block, predominantly oriented parallel to the atrial musculature. The highest degree of interwave conduction block was found in the PV area. These investigators believe that electric dissociation of

neighboring atrial muscle bundles is a key element in the development of the substrate of human AF.

In another study, the same investigators found focal fibrillation waves widely distributed over both atria (with the right atrium having ~4-fold higher incidence of focal waves in persistent than during acute AF). [18] The majority (90.5%) occurred as single events, while repetitive focal activity (>3) happened in only 0.8%. The authors believe that these data favor epicardial breakthrough rather than a cellular focal mechanism as the underlying mechanism. Often, conduction from a site of epicardial breakthrough was blocked in 1 or more directions. This generated separate multiple wave fronts propagating in different directions over the epicardium. They concluded that focal fibrillation waves are due to epicardial breakthrough of waves propagating in deeper layers of the atrial wall, providing a constant source of independent fibrillation waves originating over the entire epicardial surface, offering an adequate explanation for the high persistence of AF in patients with structural heart disease.

Furthermore, a number of recent clinical studies have reported poor results in patients undergoing rotor ablation either as a stand-alone strategy or in conjunction with PVI.[15, 16] Gianni et al reported their results of rotor ablation in 29 patients with persistent AF. Rotors were identified in all patients, with a mean of 4 ± 1.2 per patient (62% were left atrial). [15] All sources were successfully ablated, but overall acute success rate was 41% and short-term efficacy (mean 5.7 months) of a single-procedure with freedom from atrial arrhythmia without antiarrhythmic drugs was only 17%.

Buch et al performed FIRM-guided ablation in 43 patients treated for AF (56% paroxysmal, 67% having had prior AF ablation) at 2 academic medical centers, targeting rotors, along with PVI in 77% of patients. [16] They identified rotors in all patients (mean 2.6 ± 1.2 per patient, 77% in left atrium), but acute procedural success was 47% with a 9.3% complication rate. At 18 ± 7 months of follow-up, 37% were free from documented recurrent AF after a 3-month blanking period; only 21% were free from documented atrial tachyarrhythmias and off antiarrhythmic drugs.

On top of this big controversy, a recent event with a recalled randomized study came to stir the waters and instill more controversy and trigger wide discussion in the electrophysiology community about heavily conflicted interests (http://www.medscape.com/viewarticle/868778). OASIS (Outcome of Different Ablation Strategies In Persistent and Long-Standing Persistent Atrial Fibrillation) (https://clinicaltrials.gov/ct2/show/NCT02533843?term=OASIS&rank=15) was the first randomized study comparing three ablation strategies in persistent or long-standing nonparoxysmal AF that showed that targeting electrical rotors was associated with very poor results. It included 113 patients from two US centers and one German center undergoing first-time AF ablation to FIRM-only (n=29; 28% female), FIRM plus PVI (n=42; 33% female), or PVI plus posterior wall and non-PV trigger ablation (n=42; 31% female). FIRM mapping was repeated until all rotors were identified and ablated or AF organized into atrial tachycardia or converted to sinus rhythm. Focal drivers or rotors were detected in all FIRM patients (mean 4 per patient FIRM-only; 4.2 FIRM-PVI). Rotor mapping and ablation prolonged the procedure duration, which averaged 131 min with PVI plus posterior wall and non-PV trigger ablation vs 222 min with FIRM-alone and 233 min with FIRM plus PVI (P<0.001). No procedure-related adverse events occurred with FIRM-alone, but the arm was stopped early for futility after a relatively high rate of recurrence. At 12 months of follow-up, the primary end point of freedom from any recurrent atrial arrhythmias without antiarrhythmic drugs occurred in 14% of patients with FIRM-only, 52% with FIRM plus PVI, and 76% with standard PVI plus posterior wall and non-PV trigger ablation (log rank P<0.0001). The study results were presenting at a late breaking news session at the Heart Rhythm Society Meeting in 2016 (http://www.medscape.com/viewarticle/863139) and was simultaneously published in the American College of Cardiology Journal, but was subsequently retracted (http://www.medscape.com/viewarticle/868778) (http://www.sciencedirect.com/science/article/pii/S0735109716328273). [23]

Drivers of Intramural Reentry

Other investigators have put forth the theory of intramural reentry as the basic mechanism for AF maintenance. [24, 25] Based on ex vivo experimental results and clinical studies, they hypothesize that there exists localized intramural reentry that maintains AF in humans which is anchored to patient-specific microanatomic tracks of varying number, size, and distribution. They assert that there is a limited number of localized intramural microanatomic reentrant AF drivers anchored to heart-specific 3-dimensional fibrotically insulated myobundle tracks, which remain hidden to current clinical single-surface electrode mapping. They propose that simultaneous endocardial-epicardial mapping coupled with high-resolution 3D structural imaging may be able to reveal these drivers. [26] They believe that this theory may unify the findings from many clinical electrode mapping studies and that better understanding of microanatomic reentrant AF driver fingerprints could lead to more reliable identification of these drivers and targeted AF ablation strategies.

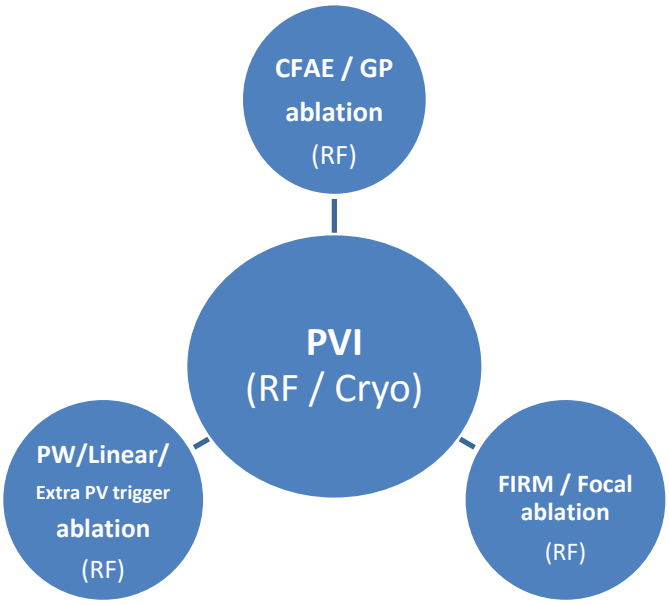

Figure 1. The core of all AF ablation techniques is pulmonary vein isolation (PVI), whether AF is paroxysmal or persistent. PVI is effected via radiofrequency or cryoenergy application. However, many investigators have suggested and applied more extensive (adjunctive) ablation targeting the substrate in patients with persistent AF, including ablation of areas of complex fractionated atrial electrograms (CFAE) or ganglionated plexi (GP) (both considered cardiac autonomic denervation), ablation of the posterior wall (PW) and/or applying linear lesions in the left atrium. Current guidelines though recommend use of extra ablation techniques on top of complete PVI only upon recurrences of AF. With the advent of focal impulse and rotor modulation (FIRM)-guided ablation, hopes rose high that this type of focal ablation could be applied for all types of AF with or without PVI, however problems with reproducibility of initially promising results and lack of randomized trial results have curtailed initial enthusiasm. CFAE = complex fractionated atrial electrograms; cryo = cryoenergy; FIRM = focal impulse and rotor modulation; GP = ganglionated plexi; PAF = paroxysmal atrial fibrillation; persAF = persistent atrial fibrillation; PVI = pulmonary vein isolation; PW = posterior wall; RF = radiofrequency (energy)

Conclusion and Perspective

Pulmonary vein isolation (PVI) remains the cornerstone of all ablation techniques for patients with either paroxysmal or persistent AF (Fig. 1). Although from the beginning of AF ablation procedures, this was apparent for the paroxysmal type of AF, the RASTA (Randomized ablation strategies for the treatment of persistent atrial fibrillation) and STAR AF (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial - Star AF II Study) studies suggested that PVI alone is a best first step even for persistent AF. [27, 28] Other additional steps and adjunctive approaches to AF ablation, including testing for, and ablating macroreentrant flutter(s) and non-PV trigger sites, and/or targeting the arrhythmia substrate with linear ablation or ablation of complex fractionated atrial electrograms (CFAE) could be part of an individualized approach. [8, 29] Electrical and anatomic remodeling of the atria may be the at the core of the arrhythmia problem, and the degree of atrial fibrosis denoting the extent of anatomical remodeling (so called "fibrotic atrial cardiomyopathy"), which is harder to reverse as compared to reversible electrical remodeling, may determine the success of ablation, at least for the cases of persistent AF. [30]

With regards to the utility of focal ablation of rotors or focal impulse areas or other drivers such as intramural reentry drivers, this remains a moot point at this juncture. Ongoing and future studies may offer more data on this issue. The REAFFIRM (Randomized Evaluation of Atrial Fibrillation Treatment With Focal Impulse and Rotor Modulation Guided Procedures) trial, estimated to finish in 2018, is an industry-sponsored, randomized, multicenter study comparing the efficacy of PVI + FIRM ablation to PVI alone (ClinicalTrials.gov; NCT02274857). Until then, great controversy clouds the efficacy of focal ablation for AF patients, and its target continues to remain elusive.

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