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EDITORIAL

Focal Rotor/Driver Ablation for Atrial Fibrillation: a Dream Come True?

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The success of catheter ablation of atrial fibrillation (AF) remains modest despite the use of a variety of techniques, because the real target remains elusive.[1] Even the endpoint of AF ablation is still under debate. It is not yet known whether isolation of the pulmonary veins (PVI), currently having a reproducible modest success rate when performed at the antrum and guided by electrophysiological mapping, is what is needed or additional foci should be routinely targeted. Some investigators have suggested that it is the ganglionated plexi (GPs) that mostly provide the triggers to the pulmonary veins, and GPs should be the primary targets during ablation.[2] Others have focused on ablation of complex-fractionated atrial electrograms (CFAEs) claiming successful outcome;[3] some have combined PVI with ablation of CFAEs.[4] In cases of persistent AF, additional ablation lines and/or posterior atrial wall debulking have been applied to enhance the success rate of the procedure. Until recently, no focal ablation was ever reported to have any success in this patient population.

Recently, Narayan et al devised an optical computational approach and mapped localized electrical rotors and focal impulse sources in 49 patients with AF. Patients with persistent AF (n=30) had more sources than those with paroxysmal AF (2.1±1.0 vs 1.5±0.8, P=0.02), related to shorter cycle length (163±19 ms vs 187±25 ms, P<0.001).[5] The majority of sources were found in the left atrium and only about a quarter of sources were localized in the right atrium. In a subsequent case report, the authors presented a patient with persistent AF who failed prior left atrial radiofrequency Maze and endocardial ablation procedures.[6] Use of this novel computational mapping disclosed one AF rotor in the right atrium and another in the left atrium. Brief 3–5-minute ablation applications at each rotor terminated AF, which remained noninducible on testing, while no AF recurrence was reported over the next 6 months.[6] In another study by the same group, the investigators localized rotors or focal sources (mean 2.1 sources) in 98 (97%) of 101 patients with sustained AF and then proceeded with ablation aiming at these targets.[7] This novel approach with focal impulse and rotor modulation (FIRM) was applied in 36 patients and compared with conventional ablation performed in the other 71 patients. The endpoint of ablation was AF termination or consistent slowing, which was achieved in 86% of FIRM-guided cases versus 20% of conventional cases (p<0.001). FIRM ablation alone at the primary source terminated AF in a median 2.5 min. During follow-up (median 273 days), after a single procedure, 82% of FIRM-guided cases vs 45% of

conventional cases were free from AF. Adverse events were similar between the two groups. The authors concluded that AF is sustained by several meandering waves (rotors) or focal impulse sources and FIRM ablation at these specific sources acutely terminated or slowed AF, and improved outcome. In another small series of 12 patients, FIRM mapping identified focal AF sources (average of 1.9±0.8 per patient) in either atria and FIRM-guided ablation achieved AF termination (n=8) at about 5 minutes or AF organization (n=4). [8]

These recent reports by Narayan's and other groups show, for the first time, stable rotors to be the drivers of AF and guided ablation of these drivers can result in termination of AF after a relatively short application.[5-9] Although it is not entirely clear whether the AF driver in these patients are focal discharge or rotors, the reports by Narayan et al,[7] if and when reproduced by other teams, have the potential to revolutionize the field of AF ablation. Of course this entails a complex method of panoramic simultaneous mapping of electrical activation with use of a basket catheter and hence there will be hurdles in its applicability. However, this novel, albeit intricate, approach suggests that one or few drivers of AF, capable of maintaining AF, can be effectively identified and successfully eliminated by their targeted ablation.

It remains unclear whether these rotors and focal sources could be identified by other means rather that this complex computational mapping. Nademanee et al introduced complex fractionated atrial electrograms (CFAEs) as ablation targets rather than PVI in patients with AF.[3] In a cohort of 121 patients with refractory AF (57 paroxysmal and 64 chronic), CFAEs were found in 7 of 9 regions of both atria, mostly in the interatrial septum, pulmonary veins, roof of left atrium, and left posteroseptal mitral annulus and coronary sinus ostium. Ablation at these areas resulted in termination of AF without need for cardioversion in 115 of the 121 patients (95%). At 1-year of follow-up, 110 (91%) patients were free of arrhythmia recurrence, 92 after one ablation procedure and 18 after two procedures. Sanders et al performed spectral analysis and endocardial mapping of dominant activation frequency (frequency with the highest amplitude) during AF in 32 patients undergoing AF ablation (19 paroxysmal, 13 permanent).[10] Ablation at a dominant frequency site resulted in significant prolongation of the arrhythmia cycle length, while no change was observed in sites with absent dominant frequency. Importantly, AF terminated during ablation in 17 of 19 patients with paroxysmal AF, but not permanent AF. The authors concluded that spectral analysis and frequency mapping can identify localized sites of high-frequency activity during AF and ablation at these sites can result in prolongation of the AF cycle length and termination of paroxysmal AF, indicating their role in the maintenance of AF. Takahashi et al from Haissaguerre's laboratory have also reported on focal ablation in a series of 40 patients with chronic AF.[11] The investigators first performed PVI and roof line ablation; then, they proceeded with electrogram-based ablation in the left atrium and coronary sinus. The authors identified the percentage of continuous electrical activity and the presence of a temporal gradient of activation as independent predictors of favorable ablation regions They concluded that catheter ablation at sites displaying a greater percentage of continuous activity or a temporal activation gradient is associated with slowing or termination of chronic AF. These reports emphasize the importance of local electrogram analysis in the ablation process. Whether this type of analysis could offer some insight into the localization of focal sources or mechanisms of AF and direct focal ablation without the need of PVI or other complex procedures remains dubious for the time being.

The work with rotors and local drivers of AF goes back to several years, when investigators put forth the hypothesis that maintenance of AF, regardless whether it is paroxysmal or persistent, may depend on the periodic activity of a limited number of rotors in the left atrial-pulmonary vein junction, which activate the atria at very high rates resulting in fibrillatory activity.[12-14] High resolution optical mapping techniques allowed for experiments which have shown spatiotemporal organization during AF and in some cases rotors seem to be the drivers that maintain AF. Rotors may form when a wave breaks upon interacting in its path with the heterogenous structural and/or electrophysiological substrate. Thus, it seems that wavebreak, leading to wavelet formation and rotor initiation, is crucial for AF maintenance. There appears to be an ionic basis in the initiation, control and modification of rotors and fibrillatory conduction and termination, with involvement of both sodium and potassium currents.[14] Experiments have indicated that inhibition of sodium current (I_{Na}) may induce rotor and AF termination by 3 different mechanisms (by enlarging the core of the rotor, decreasing rotor anchorage to functional obstacles leading to further meandering and final extinction, and by reducing the number of secondary wavelets that generate new rotors). Certain potassium currents (I_{Kur} and I_{to}) have also been suggested to prevent or interrupt AF, while others (I_{k1} and $I_{K,Ach}$) seem to enhance the arrhythmia. Interestingly, intravenous administration of adenosine has been shown to accelerate drivers of human AF. [15] Finally, structural remodeling has been shown to modify rotor

behavior, e.g. fibrosis in chronic heart failure has been shown to affect a stable rotor and lead to multiple unstable rotors and wave breaks.[15]

The parasympathetic system seems to play an important role in AF promotion. Vagal stimulation decreases the action potential duration of atrial myocytes and produces hyperpolarization of atrial action potentials by inducing an acetylcholine-dependent K^+ current, I_{KACh}. In a recent study,[16] vagal stimulation proved to be more effective than rapid atrial pacing in promoting AF maintenance. Both interventions have been reported to enhance inwardly rectifying K^+ currents, i.e. the muscarinic receptor-activated I_{KACh} in the case of vagal nerve stimulation, and the I_{K1} and $I_{KACh,c}$ currents in the case of atrial pacing. The main difference between the effects of vagal stimulation effects and atrial pacing is I_{CaL} downregulation, which plays a main role in atrial pacing but is not produced by vagal nerve stimulation. The cardiac autonomic nervous system forms a complex neural network and converges at the ganglionated plexi (GP), embedded within epicardial fat pads, which modulate cardiac electrophysiology. Recent data indicate that activity of the intrinsic autonomic nervous system, particularly parasympathetic activation, may be critical for the initiation and maintenance of AF; it appears that focal firing from the pulmonary veins is effected via activation of the GPs adjacent to these veins.[2] According to this proposal, it is the GPs associated with the pulmonary veins and not the pulmonary veins themselves that are important in the initiation of AF and that the interruption of axons from these hyperactive GPs to pulmonary veins may have mainly contributed to the procedural success of PVI.

Recent data have also provided evidence that GP hyperactivity is responsible for CFAEs.[4] Moreover, CFAEs can be provoked by acetylcholine-induced activation of the autonomic nervous system and thus may have an autonomic neural basis. Studies have indicated that the CFAEs are generally located at sites of the distribution of GPs. Thus, ablation of CFAEs and/or GPs can both be considered cardiac autonomic denervation. Adjunctive ablation of CFAEs and/or GPs has been proposed as strategies to increase the rate of AF cure. In a recent meta-analysis, PVI followed by CFAE/GP ablation was suggested as more effective in the maintenance of sinus rhythm compared with PVI alone.[4] The working hypothesis is that AF triggers emanate from the pulmonary veins, while atrial substrate regions are mainly the presumed anatomic areas of CFAEs and GPs. Thus, PVI alone only eliminates the triggers of AF but when combined with CFAE/GP ablation, the atrial substrate is also modified. Nevertheless, CFAE/GP ablation alone was not superior to PVI alone after a single procedure, especially in patients with paroxysmal AF. In paroxysmal AF patients, the trigger mechanism appears more responsible for the development of AF. Thus, PVI can eliminate triggers of AF and CFAE/GP ablation mainly changes the maintenance mechanism. PVI ablation is preferable in paroxysmal AF, while the combination therapy would be desirable in patients with persistent or chronic AF. Another form of autonomic denervation, renal artery denervation via radiofrequency ablation, has recently been clinically applied, mainly for refractory hypertensive patients, but this has also preliminarily been tested in patients with AF, as well. In a recent study, among 27 patients, 14 were randomized to PVI only, and 13 to PVI with renal artery denervation. At 12 months, significant reductions in systolic and diastolic blood pressure were recorded only in patients treated with PVI with renal denervation, but 9 of the 13 patients (69%) treated with PVI with renal denervation were AF-free versus 4 (29%) of 14 patients in the PVI-only group ($p = 0.033$). [17]

Current working hypotheses give emphasis on the sources (of automatic, triggered or reentrant mechanisms) that are identified in the pulmonary veins as initiating the arrhythmia, and mechanism(s) of arrhythmia maintenance within the atria, the source of which has remained elusive. Achieving a precise localization of the source(s) responsible for AF maintenance would lead to finally solving the puzzle of the AF mechanism with an integrated approach to therapy or even prevention of this most common cardiac arrhythmia. The role of rotors and focal sources as a mechanism of AF perpetuation has recently been demonstrated by acute AF termination by brief FIRM ablation alone. This novel, practical and effective technique of AF ablation changes our conceptual model for AF and opens the possibility for patient-tailored approach. Of course, this needs validation in larger populations, by other investigators, and in randomized trials, before being finally adopted.

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Development of Transcatheter Aortic Valve Implantation and its Clinical Implications

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In the early 1990s the concept of transcatheter aortic valve implantation (TAVI) appeared challenging and totally unrealistic. It was a true "resurrection" for Cribier and his whole team[1] performing the first TAVI in an inoperable patient in 2002, using a transeptal antegrade approach and balloon-expandable aortic valve prosthesis. Since then TAVI has been performed in more than 50000 patients worldwide. TAVI is currently indicated in patients with severe symptomatic aortic stenosis (AS) and acceptable life expectancy who are not suitable for aortic valve replacement (AVR) (indication class IB) or as an alternative to aortic valve replacement (AVR) in selected high-risk operable patients (class IIB), according to the "Heart Team" assessment.[2]

The TAVI Heart Team comprised of clinical cardiologists, interventionalists, surgeons, anaesthetists and imaging specialists with expertise in the treatment of valve disease, selects patients suitable for TAVI taking into account advantages and disadvantages of both AVR and TAVI. A logistic EuroSCORE ≥20% (logistic EuroSCORE I tends to overestimate observed mortality risk by a factor of 2 to 3 and a newly updated logistic EuroSCORE II is currently available in clinical practice) or a Society of Thoracic Surgeons (STS) score >10% are suggested as indications for TAVI therapy.[3] Recent publications have identified a number of baseline variables independently associated with mortality or poor outcome in patients undergoing TAVI (low body mass, functional status, left ventricular dysfunction, NT-proBNP, prior stroke, diabetes, chronic kidney disease, anemia, severe tricuspid and mitral regurgitation, porcelain aorta or history of chest radiation) which could be integrated into new scoring systems to quantify and predict the prognosis of TAVI both in the immediate and in the long term (Table 1).[4] Apart from certain absolute and relative contraindications for TAVI (Table 2)[2] a number of subgroups require more precise evaluation, for example transcatheter 'valve in a valve' appears as an attractive alternative in bioprosthesis failure with more than 100 successful TAV-in-surgical aortic valve procedures already been performed.[5,6] Several successful case reports document stenotic bicuspid aortic valves been treated with TAVI and according to a German