J. A. B. Zaman, M.D., M.A.

S. M. Narayan, M.D., Ph.D.

ABLATING ATRIAL FIBRILLATION: CUSTOMIZING LESION SETS GUIDED BY ROTOR MAPPING

Junaid A. B. Zaman, M.D., M.A.[a,b]; Sanjiv M. Narayan, M.D., Ph.D.[a]

[a]*Stanford University, Palo Alto, California;* [b]*Imperial College London, London, United Kingdom*

Abstract

Ablation occupies an increasing role in the contemporary management of atrial fibrillation (AF), but results are suboptimal, particularly for persistent AF. While an anatomic approach to ablation is a highly efficacious and safe method to isolate pulmonary vein (PV) triggers, recurrence of AF is not always associated with PV reconnection, and there is compelling evidence that non-PV sites sustain AF after it is triggered. Recent developments in wide-area mapping and signal processing now identify rotors in the vast majority of AF patients that sustain AF and whose elimination improves long-term freedom from AF in multicenter studies. Investigators have now demonstrated rotor and focal sources for AF that show many analogous properties between approaches: they lie in spatially reproducible regions temporally over hours to days, and they are amenable to targeted ablation. This review outlines the rationale and technical developments supporting this mechanistic paradigm for human AF, and discusses how rotor mapping may be implemented for individual patient customization of lesion sets. Mechanistic studies are required to explain why rotor elimination (or other ablation approaches) producing long-term elimination of AF may not always terminate AF acutely, how AF correlates with structural changes on magnetic resonance imaging, and how these findings can be integrated clinically with current ablation strategies to improve patient outcomes.

Introduction

Ablation is a mechanistically focused therapy. Historically, the field developed on the foundations of targeting accessory pathways as mechanisms for atrioventricular reentry, the slow AV nodal pathway as a mechanism for atrioventricular nodal reentry, and the cavotriscupid isthmus as the mechanism of slow conduction for typical atrial flutter.[1] Conversely, in atrial fibrillation (AF), for which ablation is an increasingly widespread and accepted therapy,[2] it is unclear what mechanisms should be targeted and increasingly debated how ablation works when it is successful. Seminal observations that triggers from the pulmonary veins (PV) can initiate AF[3] laid the foundation for the procedure of PV isolation (PVI). However, as our understanding advances, this approach leaves key observations unaccounted for.

Substantial data show that PVI-centered ablation exhibits an efficacy "ceiling" of 80% in paroxysmal AF, 60% in persistent AF with multiple procedures, and 40% to 50% with single procedures. While superior to medical therapy, the success of ablation for AF is thus lower than for other arrhythmias.[2] Notably, many patients after successful ablation have reconnected PVs,[4] while patients with recurrent AF often have isolated PVs.[2] In the absence of a mechanistic paradigm to explain these observations, ablation has focused on a similar anatomically based lesion set between patients, recognizing that better mechanistic targeting of ablation lesions in individual patients may be of benefit.

In this review we outline the rationale behind current lesion sets and how novel methods to map rotors and focal sources in the human atrium offer an alternative, individually-tailored ablation strategy for patients with AF.

Catheter Ablation of Atrial Fibrillation

Real-world data suggest that there is room for improvement in AF ablation,[5] with success rates even of extensive ablation being lower than reported in clinical trials and meta-analyses.[6] Paradoxically, cases have been reported in which a single ablation lesion[7] or even localized pressure in a single reproducible location[8] can terminate AF. Although it is difficult to reconcile these apparently contradictory scenarios, a mechanistic umbrella that explains such observations is likely to be a strong foundation for future advances in AF ablation.

Anatomical vs Functional Approaches

Two ablation approaches can be identified *a priori*. The first is anatomical, in which a consistent lesion set is applied, given interpatient variability, as exemplified by PVI. The second is functional, which requires identifying critical arrhythmogenic areas of the atrium.

It is reasonable to hypothesize that consistent regions of the atria may cause AF. Putative mechanisms may include fibrosis,[9] regions of ganglionic plexus innervation,[10] and preferential patterns of conduction slowing[11] that facilitate reentry, wavebreak, and AF. On the other hand, structural abnormalities are often unrelated to clinical AF.[12] Moreover, other than typical atrial flutter (ablated in the cavotricuspid isthmus), few arrhythmias lie at stereotypical locations. Variations exist in the precise ablation site for atrioventricular nodal reentry, and variation is more dramatic for atypical atrial flutters, accessory pathways, and atrial and ventricular tachycardias. The suboptimal results of stereotypical lesions sets for AF (e.g., PVI[6] or empirical lines[13])

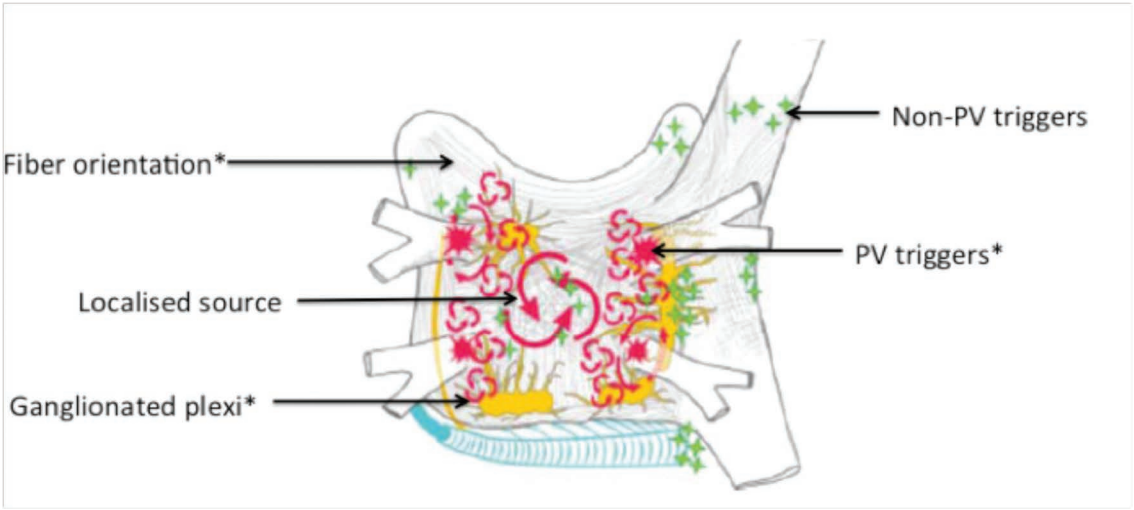

Figure 1. Atrial fibrillation likely results from an interaction among triggers, transitional mechanisms, and sustaining mechanisms, each of which are functional but may show anatomical consistency. Triggers (red asterisk in pulmonary vein [PV] and green stars for non-PV) are annotated, with substrate in the form of fiber angles and ganglionated plexi enabling the formation of localized sources in the form of rotors. Factors that provide anatomically conserved ablation lesion sets are depicted with an asterisk.[2]

accentuates the need to identify patient-specific functional targets for ablation.

Tailoring Lesion Sets to AF Mechanisms

Figure 1 summarizes important relationships between potential mechanisms and anatomic locations targeted by ablation lesions. It is increasingly recognized that triggers exist both within and outside the PV, with the suboptimal ablation results of these areas suggesting that arrhythmia-maintaining substrates may lie away from these sites.

One unifying paradigm for ablation is to consider that AF is a dynamic process involving a trigger, a susceptible milieu (transitional mechanism), and sustaining mechanisms. Triggers may include any arrhythmia, including ectopic beats originating in the PVs or from widespread regions of the atria. At the cellular level, ectopy inside or outside the PV may result from delayed afterdepolarizations (DADs) due to intracellular calcium overload,[14] which may also contribute to the functional milieu for AF by promoting reentry. As a final pathway, recent studies show that ectopy from many sites may produce conduction slowing at stereotypical locations in each patient, resulting in block, reentry, and AF initiation.[15]

Anatomically, considerations such as fiber angle (see Figure 1) or the presence of scar may determine how a small focus (a "source") can depolarize a large body of myocardium (a "sink") and explain why certain triggering sites promote AF whereas others produce only premature atrial contractions. The stochastic distribution of these regions may explain why "anatomic" strategies such as the maze procedure, roof lines, or appendage isolation may prevent AF recurrence after ablation.[2]

Sustaining Mechanisms in AF

Once AF has been triggered, what mechanisms are responsible for sustaining the arrhythmia for minutes, hours, or longer? Two main theories (Figure 2) have been the subject of intense debate for more than a century.[16] The first proposes a nonhierarchical mechanism (Figure 2 A[17]), with AF driven by self-sustaining, widely distributed, multiwavelet reentry as shown in computational modeling, experimental studies in animals, and epicardial mapping during cardiac surgery.[18] This theory is linked to the "critical mass" hypothesis of AF, whereby a certain atrial size is required to sustain enough wavelets for the arrhythmia.[19] The second is the localized source model (Figures 2 B, 2 C, and 3)[17,20–23] in which macro-organization in the form of spiral wave reentry (rotors) or focal sources cause secondary disorganization. This hypothesis is also based on recent computational modeling, animal studies using optical mapping to directly visualize action potential propagation, and basket catheter recordings in patients.[24]

This debate has been invigorated by the advent of novel clinical mapping, which has recently revealed stable rotors and focal sources[25] that appear to sustain AF and where localized ablation can eliminate AF on long-term follow-up. Other groups have reported similar results with different techniques.[26,27] Localized sources reconcile clinical observations that are difficult to explain by nonhierarchical mechanisms, such as how localized treatment can eliminate persistent AF, stable gradients in AF dominant frequency,[28] and reproducible vectors of activation in AF.[29] The success of the Maze procedure supports the multiple wavelet reentry, but recent clinical results of this surgery vary,[30] and both extensive lesions and Maze could also modulate localized sources and increase the likelihood of encountering a barrier and terminating.

Rotor Mapping in AF

Elegant studies in animal models demonstrated organized spiral waves that drive AF but used approaches that are difficult to replicate in humans. From a recording perspective, this included a wide field of view and use of action potentials that indicate local activation more accurately than clinical electrograms. From a processing perspective, this included phase mapping—which detects zones, called "phase singularities" or "rotor cores," where activation is sufficiently rapid to meet repolarization ("head meets tail")—and techniques to increase signal-to-noise ratio.[16]

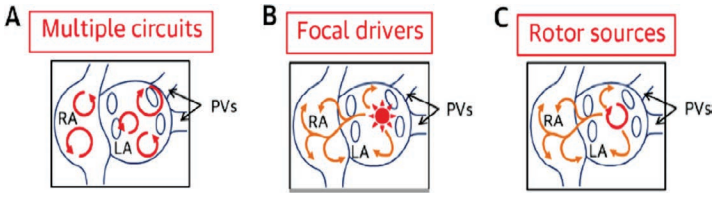

Figure 2. Proposed mechanisms for the maintenance of atrial fibrillation. (A) Multiple wavelet reentry, with nonhierarchical wavelets giving rise to fibrillatory conduction. (B) Focal drivers either inside or outside of the pulmonary veins. (C) Rotor sources, or spiral wave reentry giving rise to a localized source, stable gradients of activation, and fibrillatory conduction in the rest of the atrium. B and C may be considered together as localized whereas A is based on widely distributed substrates.[17]

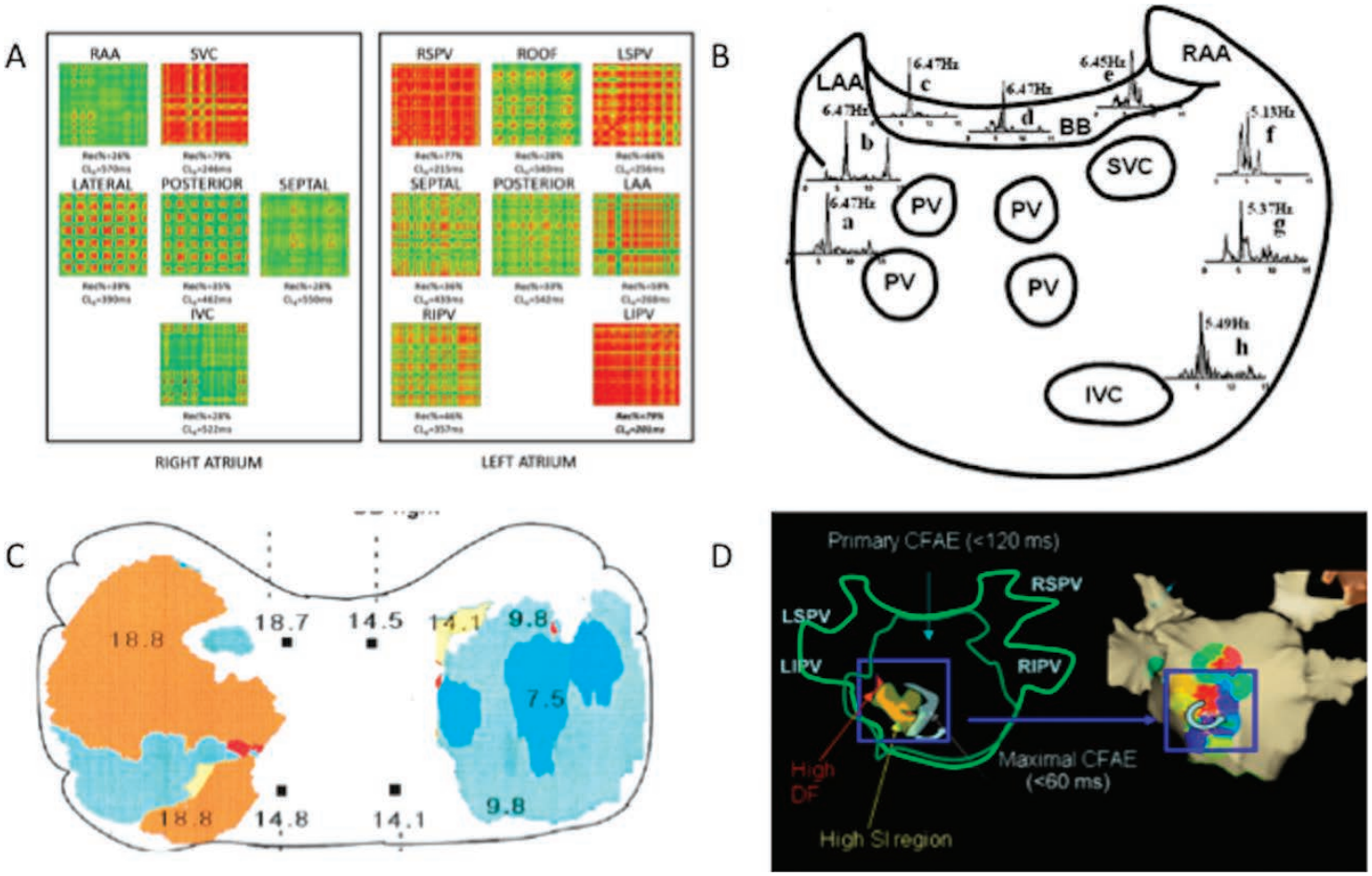

Figure 3. Indirect clinical evidence for localized sources. (A) Recurrent electrogram patterns in specific zones identify areas in the left inferior pulmonary vein (LIPV) and superior vena cava (SVC) that are not random nor disorganized and may drive atrial fibrillation (AF).[20] (B) Epicardial mapping at time of mitral valve surgery shows conserved distribution of dominant frequencies in a patient with AF for longer than 10 years.[21] (C) Dominant frequency left-right gradients revealed by optical mapping are preserved in an ovine model of AF.[22] (D) Rotational activity from endocardial recordings in a patient with persistent AF adjacent to sites of high electrogram complexity.[23]

Focal impulse and rotor modulation (FIRM) mapping was developed to translate these principles to humans, using basket catheters to widely record AF and signal processing based on human atrial physiology to identify rotor cores by phase mapping.[31] The signal processing algorithms filter unipolar electrograms, using the previously described rate-dependence of bi-atrial action potential duration and conduction velocity, to reveal the primary components of activation at each electrode that are subjected to phase mapping (Figure 4). Rotors and focal sources identified by this approach are spatially constrained, temporally conserved, and drive AF based on maps of propagation and the ability of localized ablation at these sites to eliminate AF.[32] These findings have been confirmed in multicenter studies.[33]

Several clinical trials of AF source ablation have now been reported. In the CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial, freedom from AF from a single procedure, measured using implantable loop recorders in most patients, was significantly greater (82.4%) in patients undergoing source-guided (FIRM) ablation with standard ablation versus those receiving standard ablation alone (44.9%).[34] These results have been supported by multicenter studies.[35]

Several other approaches have reported rotors and focal sources in human AF that share many similarities with those recorded by FIRM.[36] One emerging approach is body surface mapping using the inverse solution.[33] This approach describes sources as unstable, although they do show temporospatial stability in that they remain in reproducible regions of the atria for days between mapping and are targeted by limited ablation.[33] It is not clear whether differences in AF source stability between mapping approaches reflects basket coverage, movement of the heart relative to the torso, amplification of rotor meander when projected to the body surface,[37] or other factors. Thus, many studies now support the presence of AF sources whose elimination by limited ablation can improve clinical outcome (Figure 2).

Customizing Lesions to Rotor Sites

Current approaches to rotor-based ablation[32] target these regions prior to PVI, empirical lines, or other lesion sets to maximize signal fidelity during rotor mapping and to enable empiric lesion sets to pass through identified rotor sites. In FIRM, ablation covers approximately 2 to 3 cm^2 areas of AF sources, while body surface-based mapping appears to target larger areas.[33,34]

The proximity of rotor sites to some anatomic lesion sets suggests that empiric lesion sets may work by inadvertently targeting rotors.[32] This is an alternative to the explanation that ablation reduces atrial mass, which is unlikely since endocardial ablation typically covers far less than the ~100 cm^2 area of the

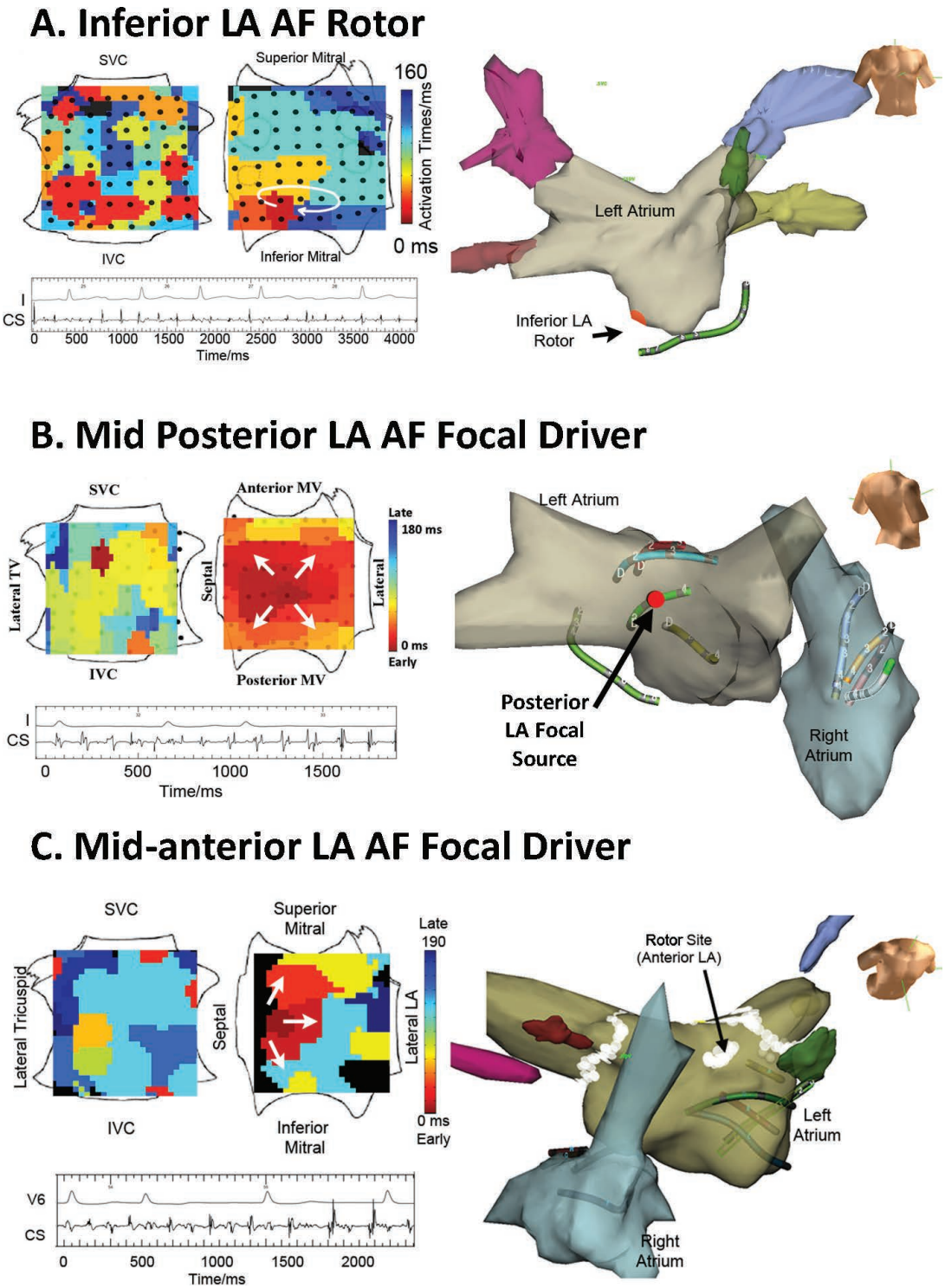

Figure 4. Focal impulse and rotor modulation (FIRM) mapping reveals rotors and focal sources in human atrial fibrillation (AF). Biatrial baskets show activation patterns. Rotors in (A) inferior left atrium, (B) posterior left atrium, and (C) left atrial anterior wall. White lesions indicate ablation lesions.[32]

left atrium alone from recent magnetic resonance imaging (MRI) studies. The 30% prevalence of right atrial rotors may contribute to the observed 30% to 40% recurrence of AF after conventional left atrial ablation procedures.

Do Localized Sources Explain Efficacy of Current Lesion Sets?

Figure 4 shows examples of rotors and focal sources in human AF and their proximity to existing lesion sets. This supports the hypothesis that PVI may work by means other than electrical isolation of the veins. The use of balloons and extensive PV antral ablation (to avoid PV stenosis) may inadvertently target substrates in the posterior left atrial roof and other areas. For example, wide PVI lesion sets may overlap sites of ganglionated plexi (autonomic innervation) or sites of rotor anchoring.

In most PVI trials, additional ablation was required to achieve the reported high success rates, and when a second procedure was required, it was the norm to add empiric treatment beyond PVI.[38] Thus, PVI-based strategies often ablate beyond PVI, and an important question is whether it modifies sources or organizes

disorganized wavelets. If benefits are due to constraining multiple wavelets, then more extensive empirical ablation should have better outcomes. Paradoxically, some studies suggest the opposite, that outcomes are better in patients requiring *less* ablation.[39] Early results from the STAR-AF II study suggest that lesions targeting empirical lines or complex fractionated atrial electrograms offer little efficacy beyond PVI alone in persistent AF.[13] One interpretation is that localized mechanisms are missed by empirical non-map-guided lines, which should be tested prospectively in studies targeting patient-specific AF rotors and focal sources.

Electrogram Surrogates of Drivers

Complex fractionated atrial electrograms (CFAEs) have been used as patient-specific ablation targets, but initial promising data have been difficult to reproduce. This may be because CFAEs represent diverse mechanisms or because AF is temporally unstable.[40] Beyond the electrogram, studies have demonstrated prolonged conduction time prior to AF initiation at sites where rotors form.[11] Conduction velocity mapping in the human atrium is challenging, but it integrates a wealth of information hidden within the substrate and may also reflect structural abnormalities such as fibrosis. Additional studies in this area, in combination with MRI detection of atrial structural abnormalities, are underway.

Conclusions

Rotor mapping offers a novel method for customizing lesion sets to target sources that sustain AF in individual patients after it is triggered. In multicenter nonrandomized studies, FIRM-guided ablation shows superior early and late results compared to conventional ablation alone. The validity of rotor mapping is further strengthened by studies showing that conventional lesion sets such as PVI may inadvertently ablate rotors as well as by early data on FIRM-only ablation. Future studies will determine if mechanistically tailored, patient-specific ablation can challenge the stereotypical anatomic approach to ablate AF.

Conflict of Interest Disclosure: This work was supported by grants to Dr Narayan from NIH (HL 83359, HL103800). Dr. Narayan is coauthor of intellectual property owned by the University of California Regents and licensed to Topera, Inc. Dr. Narayan has received honoraria from Abbott Electrophysiology, Medtronic, Inc., St. Jude Medical, and BIOTRONIK.
Keywords: surgical ablation, atrial fibrillation, complex fractionated atrial electrograms, rotor mapping, focal impulse and rotor modulation mapping, FIRM mapping

References

1. Wellens HJ. Forty years of invasive clinical electrophysiology: 1967-2007. Circ Arrhythm Electrophysiol. 2008 Apr;1(1):49-53.
2. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012 Apr;14(4):528-605.
3. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998 Sep 3;339(10):659-66.
4. Jiang RH, Po SS, Tung R, et al. Incidence of pulmonary vein conduction recovery in patients without clinical recurrence after ablation of paroxysmal atrial fibrillation: mechanistic implications. Heart Rhythm. 2014 Jun;11(6):969-76.
5. Arbelo E, Brugada J, Hindricks G, et al. The atrial fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. Eur Heart J. 2014 Jun 7;35(22):1466-78.
6. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc. 2013 Mar 18;2(2):e004549.
7. Herweg B, Kowalski M, Steinberg JS. Termination of persistent atrial fibrillation resistant to cardioversion by a single radiofrequency application. Pacing Clin Electrophysiol. 2003 Jun;26(6):1420-3.
8. Tzou WS, Sághy L, Lin D. Termination of persistent atrial fibrillation during left atrial mapping. J Cardiovasc Electrophysiol. 2011 Oct;22(10):1171-3.
9. Kottkamp H. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. Eur Heart J. 2013 Sep;34(35):2731-8.
10. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res. 2014 Apr 25;114(9):1500-15.
11. Lalani GG, Schricker A, Gibson M, Rostamian A, Krummen DE, Narayan SM. Atrial conduction slows immediately before the onset of human atrial fibrillation: a bi-atrial contact mapping study of transitions to atrial fibrillation. J Am Coll Cardiol. 2012 Feb 7;59(6):595-606.
12. Kistler PM, Sanders P, Fynn SP, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. J Am Coll Cardiol. 2004 Jul 7;44(1):109-16.
13. Verma A, Jiang CY, Betts T et al. Approaches to catheter ablation for persistent atrial fibrillation. N Eng J Med. 2015 May 7; 372(19): 1812-22.
14. Patterson E, Lazzara R, Szabo B, et al. Sodium-calcium exchange initiated by the Ca2+ transient: an arrhythmia trigger within pulmonary veins. J Am Coll Cardiol. Mar 21;47(6):1196-206.
15. Schricker AA, Lalani GG, Krummen DE, Rappel W-J, Narayan SM. Human atrial fibrillation initiates via organized rather than disorganized mechanisms. Circ Arrhythm Electrophysiol. 2014 Oct;7(5):816-24.
16. Narayan SM, Jalife J. CrossTalk proposal: Rotors have been demonstrated to drive human atrial fibrillation. J Physiol. 2014 Aug 1;592(Pt 15):3163-6.
17. Nishida K, Datino T, Macle L, Nattel S. Atrial fibrillation ablation: translating basic mechanistic insights to the patinet. J Am Coll Cardiol. 2014 Aug 26;64(8):823-31.
18. Allessie M, de Groot N. CrossTalk opposing view: Rotors have not been demonstrated to be the drivers of atrial fibrillation. J Physiol. 2014 Aug 1;592(Pt 15):3167-70.
19. Rensma PL, Allessie MA, Lammers WJ, Bonke FI, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res. 1988;62(2):395-410.
20. Ng J, Gordon D, Passman RS, Knight BP, Arora R, Goldberger JJ. Electrogram morphology recurrence patterns during atrial fibrillation. Heart Rhythm. 2014 Nov;11(11):2027-34.
21. Sahadevan J, Ryu K, Peltz L, et al. Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. Circulation. 2004 Nov 23;110(21):3293-9.
22. Mansour M, Mandapati R, Berenfeld O, Chen J, Samie FH, Jalife J. Left-to-right gradient of atrial frequencies during

acute atrial fibrillation in the isolated sheep heart. Circulation. 2001;103(21):2631-6.
23. Lin YJ, Lo MT, Lin C, et al. Prevalence, characteristics, mapping, and catheter ablation of potential rotors in nonparoxysmal atrial fibrillation. Circ Arrhythm Electrophysiol. 2013 Oct;6(5):851-8.
24. Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation. Circ Res/ 2013;112(5):849-62.
25. Narayan SM, Krummen DE, Enyeart MW, Rappel WJ. Computational mapping identifies localized mechanisms for ablation of atrial fibrillation. PLoS One. 2012;7(9):e46034.
26. Lin T, Kuck KH, Ouyang F, Tilz RR. First in-human robotic rotor ablation for atrial fibrillation. Eur Heart J. 2014 Jun 7;35(22):1432.
27. Miller JM, Kowal RC, Swarup V, et al. Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: multicenter FIRM registry. J Cardiovasc Electrophysiol. 2014 Sep;25(9):921-9.
28. Martins RP, Kaur K, Hwang E, et al. Dominant frequency increase rate predicts transition from paroxysmal to long-term persistent atrial fibrillation. Circulation. 2014 Apr 8;129(14):1472-82.
29. Gerstenfeld EP, Sahakian AV Swiryn S. Evidence for transient linking of atrial excitation during atrial fibrillation in humans. Circulation. 1992;86(2):375-82.
30. Weimar T, Bailey MS, Watanabe Y, et al. The Cox-maze IV procedure for lone atrial fibrillation: a single center experience in 100 consecutive patients. J Interv Card Electrophysiol. 2011 Jun;31(1):47-54.
31. Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol. 2012 May;23(5):447-54.
32. Narayan SM, Krummen DE, Clopton P, Shivkumar K, Miller JM. Direct or coincidental elimination of stable rotors or focal sources may explain successful atrial fibrillation ablation: on-treatment analysis of the CONFIRM (Conventional ablation for AF with or without focal impulse and rotor modulation). J Am Coll Cardiol. 2013 Jul 9;62(2):138-47.
33. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation. 2014 Aug 12;130(7):530-8.
34. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial. J Am Coll Cardiol. 2012 Aug 14;60(7):628-36.
35. Narayan SM, Baykaner T, Clopton P, et al. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared to trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). J Am Coll Cardiol. 2014 May 6;63(17):1761-8.
36. Swarup V, Baykaner T, Rostamian A, et al. Stability of rotors and focal sources for human atrial fibrillation : Focal Impulse and Rotor Mapping (FIRM) of AF sources and fibrillatory conduction. J Cardiovasc Electrophysiol. 2014 Dec;25(12):1284-92.
37. Rodrigo M, Guillem MS, Climent AM, et al. Body surface localization of left and right atrial high-frequency rotors in atrial fibrillation patients: A clinical-computational study. Heart Rhythm. 2014 Sep;11(9):1584-91.
38. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA. 2014 Feb 19;311(7):692-700.
39. Forclaz A, Narayan SM, Scherr D, et al. Early temporal and spatial regularization of persistent atrial fibrillation predicts termination and arrhythmia-free outcome. Heart Rhythm. 2011 Sep;8(9):1374-82.
40. Berenfeld O, Jalife J. Complex fractionated atrial electrograms: is this the beast to tame in AF? Circ Arrhythm Electrophysiol. 2011 Aug 1;4(4):426-8.