



REVIEW ARTICLE

## The continuous challenge of AF ablation: From foci to rotational activity



Sanjiv M. Narayan\*, Mohan N. Vishwanathan, Christopher A.B. Kowalewski, Tina Baykaner, Miguel Rodrigo, Junaid A.B. Zaman, Paul J. Wang

Stanford University, Palo Alto, CA, United States

### KEYWORDS

Atrial fibrillation;  
Ablation;  
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Computer;  
Mapping

**Abstract** Pulmonary vein isolation (PVI) is central to ablation approaches for atrial fibrillation (AF), yet many patients still have arrhythmia recurrence after one or more procedures despite the latest technology for PVI. Ablation of rotational or focal sources for AF, which lie outside the pulmonary veins in many patients, is a practical approach that has been shown to improve success by many groups. Localized sources lie in atrial regions shown mechanistically to sustain AF in optical mapping and clinical studies of human AF, as well as computational and animal studies. Because they arise in localized atrial regions, AF sources may explain central paradoxes in clinical practice – such as how limited ablation in patient specific sites can terminate persistent AF yet extensive anatomical ablation at stereotypical locations, which should extinguish disordered waves, does not improve success in clinical trials. Ongoing studies may help to resolve many controversies in the field of rotational sources for AF. Studies now verify rotational activation by multiple mapping approaches in the same patients, at sites where ablation terminates persistent AF. However, these studies also show that certain mapping methods are less effective for detecting AF sources than others. It is also recognized that the success of AF source ablation is technique dependent. This review article provides a mechanistic and clinical rationale to ablate localized sources (rotational and focal), and describes successful techniques for their ablation as well as pitfalls to avoid. We hope that this review will serve as a platform for future improvements in the patient-tailored ablation for complex arrhythmias.

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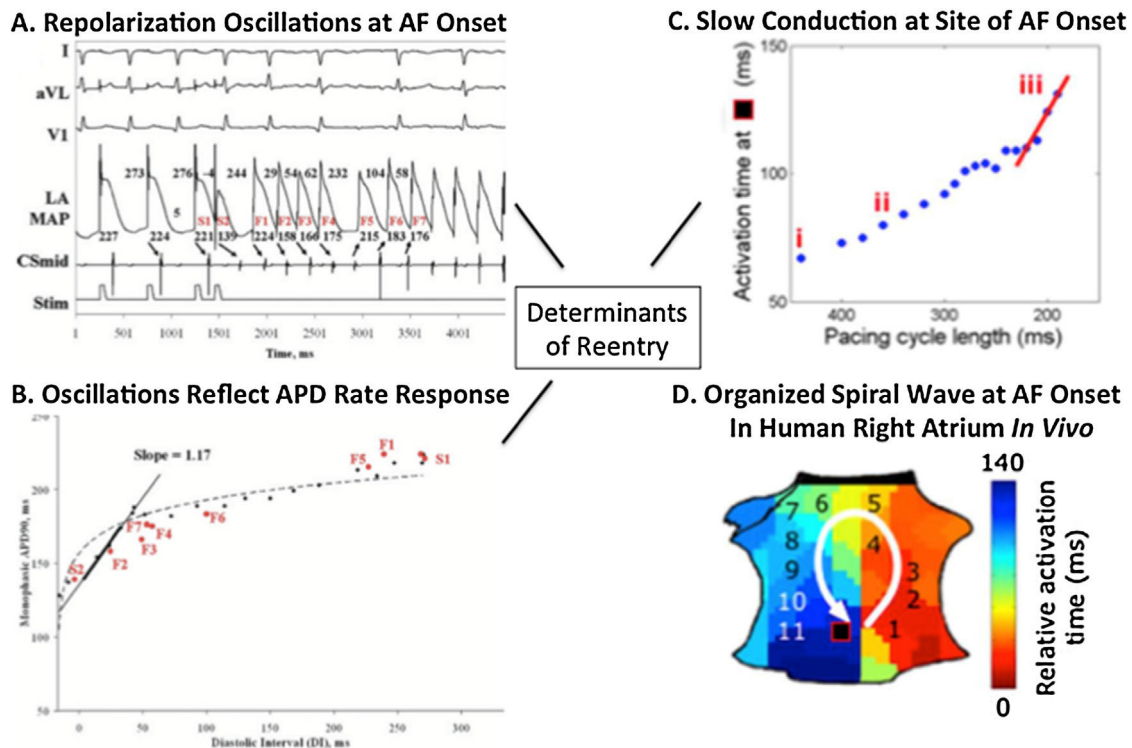
### Introduction

Ablation is increasingly used to treat atrial fibrillation (AF), yet the 1-2 year success rate of pulmonary vein isolation (PVI) remains 40-50% for persistent AF<sup>1,2</sup> and 50-65% for

paroxysmal AF.<sup>3-5</sup> Studies of the often extensive ablation of lines, empiric electrogram targets and particularly the posterior left atrium often have not improved success versus PVI alone in multicenter trials.<sup>1,2,6</sup>

Targeting AF sources has gained much attention in recent years. In the source model, AF is sustained by rotational (rotor) or focal sources in localized patient-specific regions of either atria. This model is now supported by wide evidence in many patients ranging from optical mapping of

\* Corresponding author.  
E-mail address: [sanjiv1@stanford.edu](mailto:sanjiv1@stanford.edu) (S.M. Narayan).



**Figure 1** Initiating mechanisms for human atrial fibrillation. (A) Electrograms of ectopy (S2) initiating AF. (B) Steep relationship of atrial repolarization to preceding interbeat interval (APD vs DI) enables S2 to produce repolarization oscillations. (C) Conduction also shows drastic slowing immediately preceding AF onset (iii, red slope). (D) Conduction slowing and dispersion of repolarization cause formation of a counter-clockwise spiral on the atrial shell, that initiated AF and was conserved for multiple AF initiations and diverse triggers in this patient.

human AF,<sup>7</sup> multicenter (non-randomized) clinical trials of AF rotor ablation,<sup>8–13</sup> optical mapping of animal AF,<sup>14</sup> and mathematical analyses.<sup>15</sup> Moreover, this model can reconcile the paradox that limited ablation can terminate persistent AF in some patients,<sup>8,16,17</sup> while extensive (untargeted) ablation of left atrial regions can be ineffective in others.<sup>1,2,18</sup>

The source model may contradict the multiwavelet hypothesis, in which AF is caused by disordered waves alone,<sup>19,20</sup> although ongoing studies on the interaction between organized sources and disordered waves may reconcile this. A central tenet of the ‘pure’ disordered model is that extensive ablation limits the critical mass for wave propagation and will increase success, yet this is contradicted by multicenter trials<sup>1,2,6</sup> with suboptimal results even in some surgical studies<sup>21</sup> compared to original reports.

This review provides an overview of the science for localized drivers of human AF, and technical factors explaining why they may be revealed by some but not all mapping approaches. In particular, we focus on potential explanations for why some clinical ablation studies have been disappointing despite promising results at many independent centers. We hope to provide a mechanistic/clinical foundation to help reconcile debates in this field.

## Initiation of human atrial fibrillation

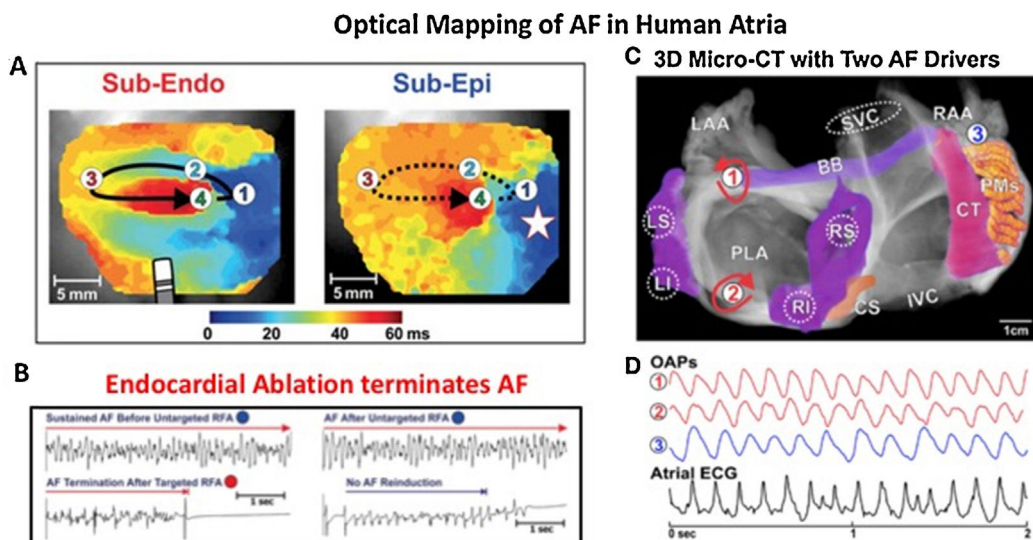
Human arrhythmias have dynamic and static mechanisms.<sup>22</sup> In AF, triggers such as ectopic beats,<sup>23</sup> bursts of atrial

tachycardia<sup>24</sup> or varying autonomic balance<sup>25,26</sup> may on occasion initiate AF as a dynamic process, despite a relatively static atrial architecture and fibrosis.<sup>27</sup>

Dynamics in the physiology of atrial repolarization and conduction can explain how triggers initiate AF. In Figure 1A, an ectopic beat produces dramatic oscillations of human left atrial action potential duration (APD),<sup>24,28,29</sup> because the graph relating APD to diastolic interval (DI, time between beats; Figure 1B)<sup>30</sup> is steep, so that an early beat (short DI) drastically shortens APD, lengthening subsequent DI, producing APD alternans and wavebreak. Figure 1C shows that triggers, such as from the PVs, may also abruptly slow human atrial conduction to facilitate reentry and AF (Figure 1D).<sup>31</sup> These dynamics likely interact with atrial anatomy<sup>32</sup> and/or fibrosis,<sup>33</sup> explaining why sites of spiral wave reentry may initiate at spatially conserved sites for diverse triggers.

## Mechanisms that sustain human atrial fibrillation after it has been triggered

Once AF is initiated by triggers from pulmonary veins<sup>23</sup> or other sites, two central hypotheses may explain how disorganized wavefronts in AF sustain. In the multi-wavelet hypothesis,<sup>19</sup> disorganized activity generates new wavelets in a stochastic fashion, where no specific atrial region plays a crucial role in the AF maintenance. This hypothesis therefore precludes ‘‘special’’ regions of the atria, such that structural elements e.g. fibrosis distribution are not critical



**Figure 2** Human atrial fibrillation sustained by stable rotational sources on optical mapping.<sup>7,34</sup> (A) Rotational AF source in right atrium, stable on endocardium yet transient on epicardium. (B) Ablation at AF source terminates AF.<sup>7</sup> (C) Concurrent AF sources near and remote from PVs, anchored to micro-fibrosis and fiber architecture. (D) Electrograms in AF, unlike regular optical potentials, comprise noise including far-field signals.<sup>34</sup>

to the maintenance of AF. A second, alternative, mechanism is that “special” regions of the atria do indeed exist and act as functional sources, manifest electrically in the form of spiral waves or focal activation patterns. These organized sources generate wavefronts that break down (“fibrillatory conduction”) to explain the disorder of AF.

Some of the most important evidence for localized drivers of human AF comes from optical mapping. **Figure 2** shows results from the gold standard of optical mapping of human AF.<sup>7,34</sup> Rotational drivers are seen (**Figure 2A**) where ablation terminated AF to sinus rhythm (**Figure 2B**) and, in another specimen, 2 concurrent AF sources are seen in left atrium (**Figure 2C**). Sources hence lay in either atrium in these diseased atria, stabilized by micro-reentry around fibrotic and slowly conducting regions, which are less reported in animal models. One important methodological issue arising from this work, that we will revisit later, is that action potentials in AF may be quite regular (**Figure 2D**), yet traditional electrograms show additional deflections in AF (“noise”, “far-field activation”) which will reduce accuracy for mapping.

### Reconciling differences between mapping studies of AF rotational drivers

Despite data in favor of rotational or focal drivers for human AF,<sup>8,10</sup> there is an active debate on this issue. First, historical AF mapping shows only disorganized waves with no driving regions,<sup>35</sup> albeit in patients rarely referred for ablation (with permanent AF at non-arrhythmia surgery). Second, organized drivers by frequency analysis<sup>36</sup> may be unstable by activation<sup>37</sup> or phase<sup>38–40</sup> maps. This may reflect mapping of the epicardium in these studies, where drivers are less stable on optical maps.<sup>7,34</sup> Third, AF-driver ablation outcomes are disappointing at some centers<sup>41–43</sup> (**Table 1** summarizes PVI and driver ablation studies). Mapping dif-

ferences will alter reported AF mechanisms, and Rudy et al. show that combined activation with phase may be optimal in AF.<sup>44</sup> The method used by our group, Focal Impulse and Rotor Modulation (FIRM), uses such a combined activation and phase approach.<sup>45,46</sup> However, it is unresolved to what extent conflicting studies reflect mapping methods, patient selection, species specificities or other differences.

Since long-term ablation success varies dramatically between centers even for PVI,<sup>47</sup> reconciling differences in AF mapping requires other study designs. On the basis that sites where ablation terminates persistent AF may have mechanistic relevance, we are systematically comparing maps created by different techniques for analyzing the same raw electrographic data in cases of clear termination of persistent AF by ablation in the ongoing COMPARE-AF study.

**Figure 3** shows a patient in whom ablation outside the PVs before PVI terminated persistent AF to sinus rhythm. In panels C–E, detailed analysis of raw AF electrograms prior to ablation revealed sustained rotational activation by 3 methods.<sup>48</sup> Of these methods, traditional activation maps of AF electrograms may be confused by spurious deflections, perhaps reflecting far field (e.g. **Figure 2**, compared to optical maps), and often showed only disorder at AF termination sites where phase and combined phase/activation maps showed rotations.

We reported an early series of such patients,<sup>48</sup> which was the inspiration for the international COMPARE-AF study (NCT02997254) from which mapping data and code are being made available online to accelerate developments in AF mapping.

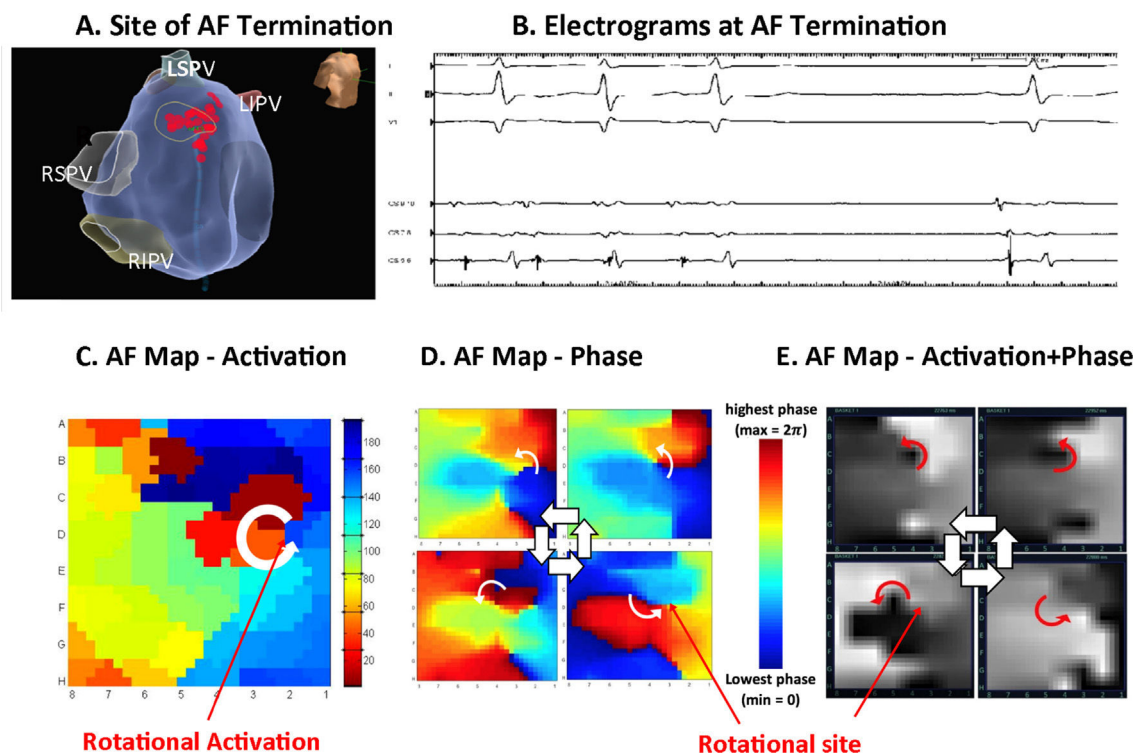
### Reconciling heterogeneity in the success of source-guided ablation

Initial reports of mapping-guided ablation of AF drivers were positive, using endocardial mapping by FIRM in

**Table 1** Single procedure success of AF source plus PVI ablation. Average results weighted by number of patients per study.

Year	Authors	N	Persistent AF (N)	Source mapping method	Automatic map read software?	Endpoint	Estimated cases/operator	1-Proc AF Free All (%)	1-Proc AF/AT Free Persist AF (%)
2012	Narayan <sup>8</sup>	107	76	FIRM	No	Termination, AF slowing	50	82	70
2014	Haissaguerre <sup>10</sup>	103	103	ECGI	No	Termination, AF slowing	30	85	n/a
2015	Sommer <sup>54</sup>	20	18	FIRM	Yes	Elimination on remap	20	85	80
2015	Tomassoni <sup>12</sup>	80	60	FIRM	Yes	Elimination on remap	80	95	70
2015	Rashid <sup>11</sup>	56	43	FIRM	Yes	Elimination on remap	56	82	77
2015	Hoummse <sup>62</sup>	22	15	FIRM	Yes	Elimination on remap	11	73	60
2015	Foreman <sup>63</sup>	125	72	FIRM	Yes	Elimination on remap	30	69	63
2016	Buch <sup>42</sup>	43	19	FIRM	No (<20%; pre 2013)	Termination, AF slowing	6	37	25
2016	Gianni, OASIS <sup>41</sup> Mohanty, OASIS RETRACTED	42	42	FIRM	Yes	Remap; AT Not ablated	7	n/a	52
2016	Steinberg <sup>43</sup>	47	35	FIRM	No (pre 2013)	Termination, AF slowing	10	12	n/a
2016	Lin, Shih-Ann Chen <sup>64</sup>	68	68	Novel Pentarray	No	Elimination	30	75	n/a
2017	Tilz <sup>61</sup>	25	15	FIRM	Yes	Elimination on remap	12	76	52
2017	Spitzer <sup>65</sup>	53	53	FIRM	Yes	Elimination on remap	26	n/a	79
2017	Seitz <sup>51</sup>	105	81	Novel Pentarray	Yes	Termination	50	n/a	62*
2017	Miller <sup>13</sup>	170	106	FIRM	Yes (>80% of cases)	Elimination on remap	55	74	62
Total	15 studies	1066	806				Average	74.6%	64.9%

\* With no PVI performed.



**Figure 3** Rotational drivers for AF by multiple mapping methods. In a 67 year old woman, ablation (A) at the left atrial roof prior to PVI (B) terminates persistent AF to sinus rhythm. (C) Traditional activation mapping, (D) phase mapping using published methods<sup>38</sup> and (E) Focal Impulse and Rotor Mapping (FIRM) each confirmed sustained rotations at the site where ablation terminated AF. Modified from references <sup>66</sup> and <sup>48</sup>.

2011-12,<sup>8,49</sup> body-surface mapping,<sup>10</sup> novel mapping by Shih-Ann Chen et al.,<sup>50</sup> Seitz et al.<sup>51</sup> and other centers<sup>52,53</sup> (Table 1). However, while independent centers continue to report positive results,<sup>11,12,54,55</sup> outcomes are disappointing by some operators<sup>41-43</sup> (Table 1).

Table 1 details the heterogeneity in outcomes from map-guided AF source ablation across centers. Notably, this does not appear to stratify by patient comorbidity or disease severity. For instance, Sommer, Hindricks et al.<sup>54</sup> and Miller et al.<sup>9,13</sup> reported 70-80% maintenance of sinus rhythm by FIRM-ablation in populations that included challenging patients with prior failed procedures and long-standing persistent AF; as did Tomassoni,<sup>12</sup> Rashid<sup>11</sup> and others. Conversely, Buch, Shivkumar et al.<sup>42</sup> report 21% success and Steinberg et al. report 12% success<sup>43</sup> in patients even with paroxysmal AF despite also performing PVI. It is difficult to reconcile these results based primarily on disease severity.

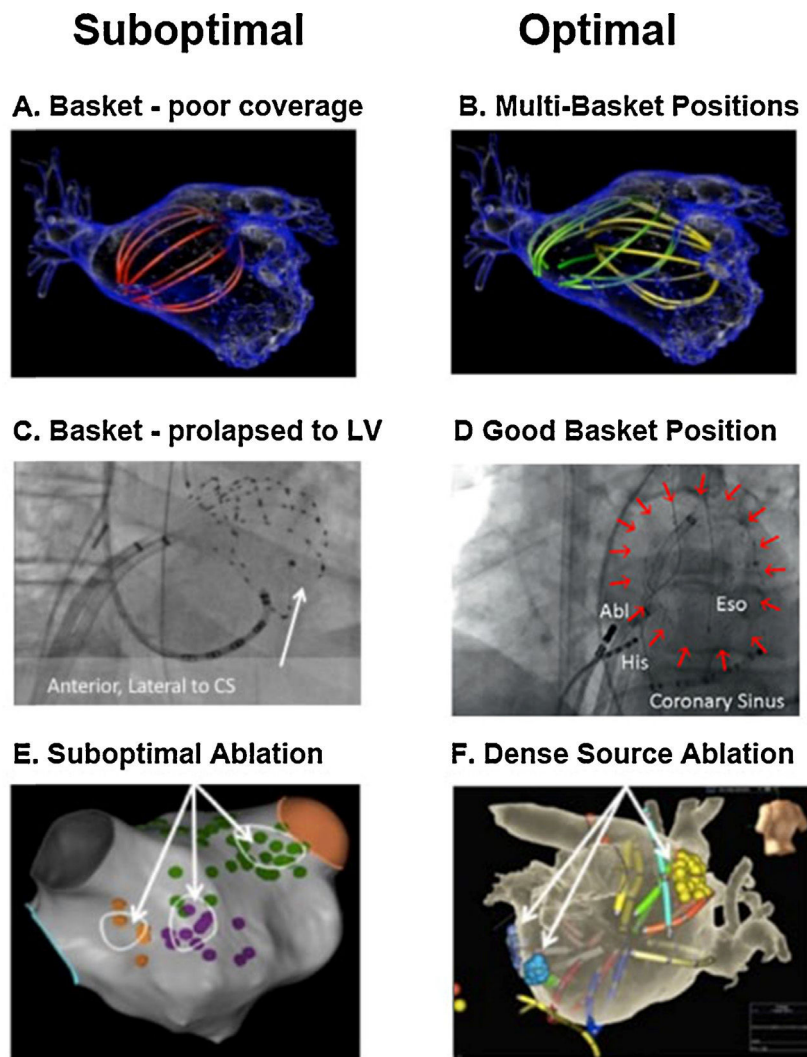
Much of the heterogeneity in results between centers may thus reflect technical differences. It is noted that reading AF rotational/focal source maps and/or guiding ablation accordingly are novel skills and not learned as part of traditional PVI. Indeed, in Table 1 lower success was seen at centers with fewer cases per operator, and in patients studied early (pre-2013) when no automatic tools were available to interpret maps to assist the operator. Although follow-up duration is typically a confounder, positive studies in Table 1 are reported at 1-2 years, 2 years<sup>12</sup> and 3 years<sup>49</sup> by separate groups.

### Areas for technical improvement in source-guided ablation of AF

Three core components are required for effective source-guided ablation: effective broad-area mapping of both atria, precise identification of sources to target, and ensuring full elimination of target areas. Each of these components also requires urgent technical improvement, since they may explain much of the heterogeneity in outcomes between centers.

Our approach to widely map the atria is to use multipolar basket catheters to analyze many wavefronts at the same time.<sup>45</sup> Figure 4 shows optimal and suboptimal basket placement. Various basket sizes and types are available from an increasing number of vendors. We select the most appropriate basket size based on atrial size from intracardiac echocardiography or computed tomography. Since the atrium is not a spherical structure, the basket may have to be moved sequentially for optimal mapping. Figure 4A shows a single suboptimal left atrial basket position, which does not contact the walls (noted by its spherical shape). Figure 4B shows successive repositioning in this case to cover most of the atria in 2-3 epochs, showing spline deformation i.e. good contact. Figure 4C shows that suboptimal basket positioning may not be recognized.<sup>56</sup> Figure 4D shows careful basket positioning at a high-volume center in a recent large series.<sup>57</sup>

Theoretically, baskets can resolve 1-2 cm diameter reentry circuits in human AF as predicted by Allessie et al.<sup>58</sup>



**Figure 4** Reported pearls and pitfalls in AF source ablation. (A) Suboptimal basket position in left atrium. (B) Multi-Position Basket Mapping, the method of choice in large atria. (C) Suboptimal basket in a disappointing report, consistent with inadvertent LV prolapse – conical shape, anterolateral to coronary sinus, ventricular electrograms<sup>56</sup>; (D) good basket position covering atrium well; (E) sparse lesions over source area in disappointing series<sup>41,67</sup>; (F) dense source area lesions in a more successful series.<sup>54</sup>

and confirmed in human optical maps (Figure 2A).<sup>7</sup> Conversely, if electrodes are too closely spaced, calculated wave propagation may fall within measurement error. For instance, for atrial conduction velocity in AF patients of 40 cm/sec,<sup>31,59</sup> reported errors in assigning onset time in AF ( $\approx 5\text{-}10$  ms) translate to a distance of 2-4 mm ( $=40 \times 0.005$  to  $40 \times 0.010$ ). Closer electrode separation than this will be attempting to identify circuits within measurement noise, and will have less confidence. A related issue is that closely-spaced electrode arrays typically cover small distances simultaneously, which may also miss the 1-2 cm diameter circuits in human AF noted in optical maps.<sup>7,34</sup>

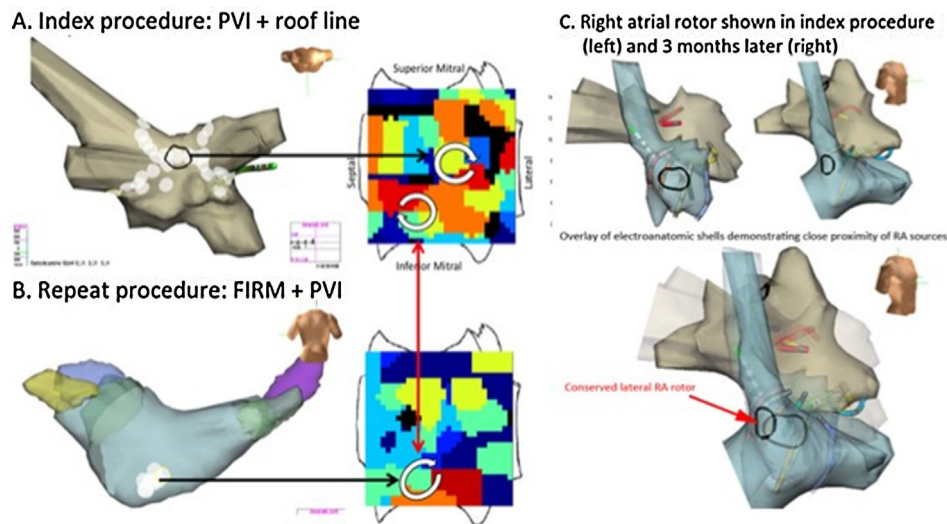
Successful source ablation should fully cover the affected source areas, and contact force sensing catheters may help in this regard. Incomplete coverage may explain lower success rates in some source ablation studies. For instance, Figure 4E (Gianni et al.<sup>41</sup> in patients from OASIS) shows sparse lesions that may not have eliminated sources in the

long-term even if AF terminates acutely. Conversely, in the successful series in Figure 4F, ablation lesions densely cover the affected atrial regions.

As shown in Figure 5, incompletely eliminated source regions may cause recurrent post-ablation AF or AT. Thus, it is critical to ablate the entire affected region, although the science on how much atrium to ablate has yet to be fully established.

Finally, source-guided ablation does not appear to increase complication rates over traditional ablation alone,<sup>8,9,54,60</sup> and is likely not pro-arrhythmic.<sup>11,12,42,54,55,57,61</sup>

In summary, the endpoint of AF source ablation is the elimination of sustained rotational or focal activity that lie in conserved spatial locations. This endpoint is achievable in most patients, and may be superior to historical endpoints of AF termination. Lack of AF termination may reflect many mechanisms including residual AF sources, but clinical results have been promising even in such patients if sources are eliminated.



**Figure 5** Rotors may drive recurrent AF if not fully eliminated.<sup>68</sup> Temporospacial conservation of rotational AF sites in the inferior LA in a man with longstanding persistent AF. (A) At index procedure, anatomic roof line bisected a roof rotor; wide area PVI was also performed. The inferior LA rotor was not prospectively treated by FIRM ablation. (B) During recurrent AF 5 months later, the inferior LA rotor was still present but the previously ablated roof rotor was absent. (C) Right atrial rotor shown in index procedure (left) and 3 months later (right).

## Conclusions

Evidence continues to mount that human AF is maintained by rotational and focal sources, and that targeting these areas may improve outcomes over PVI alone. We have outlined the scientific rationale for source ablation, and practical strategies for ablation associated with promising outcomes in multicenter studies. Analysis of smaller less promising studies suggests that suboptimal basket placement, resulting in greater difficulty in reading maps and in targeting ablation may explain at least some of these discrepancies. Future improvements in AF source ablation may be facilitated by better computational interpretation of AF maps, comparative studies between potentially complementary mapping approaches, and improvements in basket design. Combined mechanistic and imaging studies may enable better and functional classification of AF that may enable better patient tailoring of AF ablation. Ultimately a better mechanistic and clinical understanding of AF may pave the way for novel drug discovery or regenerative therapies for AF. This is an exciting prospect.

## Disclosures

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## References

1. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372:1812–22.
2. Wong KC, Paisey JR, Sopher M, et al. No benefit of complex fractionated atrial electrogram (CFAE) ablation in addition to circumferential pulmonary vein ablation and linear ablation: Boca study. *Circ Arrhythm Electrophysiol*. 2015;1316–24.
3. Calkins H. Demonstrating the value of contact force sensing: more difficult than meets the eye. *Circulation*. 2015;132:901–3.
4. Dukkipati SR, Cuoco F, Kutinsky I, et al. Pulmonary vein isolation using the visually guided laser balloon: a prospective, multicenter, and randomized comparison to standard radiofrequency ablation. *J Am Coll Cardiol*. 2015;66:1350–60.
5. Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2016;74:2235–45.
6. Vogler J, Willems S, Sultan A, et al. Pulmonary vein isolation versus defragmentation: the CHASE-AF clinical trial. *J Am Coll Cardiol*. 2015;66:2743–52.
7. Hansen BJ, Zhao J, Csepe TA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial sub-endocardial optical mapping in explanted human hearts. *Eur Heart J*. 2015;36:2390–401.
8. Narayan SM, Krummen DE, Shivkumar K, et al. Treatment of atrial fibrillation by the ablation of localized sources: the conventional ablation for atrial fibrillation with or without focal

- impulse and rotor modulation: CONFIRM trial. *J Am Coll Cardiol*. 2012;60:628–36.
9. 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;25:921–9.
  10. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. *Circulation*. 2014;130:530–8.
  11. Rashid H, Sweeney A. Approaches for focal impulse and rotor mapping in complex patients: a US private practice perspective. *J Innov Cardiac Rhythm Manage*. 2015;6:2193–8.
  12. Tomassoni G, Duggal S, Muir M, et al. Long-term follow-up of firm-guided ablation of atrial fibrillation: a single-center experience. *J Innov Cardiac Rhythm Manage*. 2015;6:2145–51.
  13. Miller JM, Das MK, Jain R, et al. Single-center experience with rotor mapping and ablation for treatment of atrial fibrillation in 170 patients (abstract). *Heart Rhythm*. 2016.
  14. Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation. *Circ Res*. 2013;112:849–62.
  15. Rappel WJ, Zaman JA, Narayan SM. Mechanisms for the termination of atrial fibrillation by localized ablation: computational and clinical studies. *Circ Arrhythm Electrophysiol*. 2015;8:1325–33.
  16. Herweg B, Kowalski M, Steinberg JS. Termination of persistent atrial fibrillation resistant to cardioversion by a single radiofrequency application. *Pacing Clin Electrophysiol*. 2003;26:1420–3.
  17. Shivkumar K, Ellenbogen KA, Hummel JD, et al. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: first multicenter experience of focal impulse and rotor modulation (firm) ablation. *J Cardiovasc Electrophysiol*. 2012;23:1277–85.
  18. Haissaguerre M, Hocini M, Sanders P, et al. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol*. 2005;16:1138–47.
  19. Moe GK, Rheinboldt W, Abildskov J. A computer model of atrial fibrillation. *Am Heart J*. 1964;67:200–20.
  20. de Groot NM, Houben RP, Smeets JL, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation*. 2010;122:1674–82.
  21. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014.
  22. Weiss JN, Garfinkel A, Karagueuzian HS, et al. Perspective: a dynamics-based classification of ventricular arrhythmias. *J Mol Cell Cardiol*. 2015;82:136–52.
  23. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659–66.
  24. Narayan SM, Bode F, Karasik PL, et al. Alternans of atrial action potentials as a precursor of atrial fibrillation. *Circulation*. 2002;106:1968–73.
  25. Patterson E, Po SS, Scherlag BJ, et al. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. *Heart Rhythm*. 2005;2:624–31.
  26. Katriotis DG, Giatzoglou E, Zografos T, et al. Rapid pulmonary vein isolation combined with autonomic ganglia modification: a randomized study. *Heart Rhythm*. 2011;8:672–8.
  27. Engelman ZJ, Trew ML, Smaill BH. Structural heterogeneity alone is a sufficient substrate for dynamic instability and altered restitution. *Circ Arrhythm Electrophysiol*. 2010;3:195–203.
  28. Narayan SM, Kazi D, Krummen DE, et al. Repolarization and activation restitution near human pulmonary veins and atrial fibrillation initiation: a mechanism for the initiation of atrial fibrillation by premature beats. *J Am Coll Cardiol*. 2008;52:1222–30.
  29. Narayan SM, Franz MR, Clopton P, et al. Repolarization alternans reveals vulnerability to human atrial fibrillation. *Circulation*. 2011;123:2922–30.
  30. Franz MR, Swerdlow CD, Liem LB, et al. Cycle length dependence of human action potential duration in vivo. Effects of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady-state frequencies. *J Clin Invest*. 1988;82:972–9.
  31. Schricke A, Rostamian A, Lalani G, et al. Human atrial fibrillation initiates by organized not disorganized mechanisms. *Circ Arrhythm Electrophysiol*. 2014;7:816–24.
  32. Gonzales MJ, Vincent KP, Rappel W-J, et al. Structural contributions to fibrillatory rotors in a patient-derived computational model of the atria. *Europace*. 2014;16, iv3–iv10.
  33. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA*. 2014;311:498–506.
  34. Zhao J, Hansen BJ, Csepe TA, et al. Integration of high-resolution optical mapping and 3-dimensional micro-computed tomographic imaging to resolve the structural basis of atrial conduction in the human heart. *Circ Arrhythm Electrophysiol*. 2015;8:1514–7.
  35. Allesie MA, de Groot NM, Houben RP, et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol*. 2010;3:606–15.
  36. Atienza F, Almendral J, Ormaetxe JM, et al. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a noninferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol*. 2014;64:2455–67.
  37. Lee S, Sahadevan J, Khrestian CM, et al. Simultaneous bi-atrial high density (510-512 electrodes) epicardial mapping of persistent and long-standing persistent atrial fibrillation in patients: new insights into the mechanism of its maintenance. *Circulation*. 2015;132:2108–17.
  38. Kuklik P, Zeemering S, Maesen B, et al. Reconstruction of instantaneous phase of unipolar atrial contact electrogram using a concept of sinusoidal recombination and Hilbert transform. *IEEE Trans Biomed Eng*. 2015;62:296–302.
  39. Kuklik P, Lau DH, Ganesan AN, et al. High-density mapping of atrial fibrillation in a chronic substrate: evidence for distinct modes of repetitive wavefront propagation. *Int J Cardiol*. 2015;199:407–14.
  40. Kuklik P, Zeemering S, van Hunnik A, et al. Identification of rotors during human atrial fibrillation using contact mapping and phase singularity detection: technical considerations. *IEEE Trans Biomed Eng*. 2016.
  41. Gianni C, Di Biase L, Deneke T, et al. Acute and short-term outcomes in persistent and long-standing persistent patients undergoing rotors only ablation (abstract). *Heart Rhythm*. 2015;12:PO01–58.
  42. Buch E, Share M, Tung R, et al. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: a multi-center experience. *Heart Rhythm*. 2016;13:636–41.
  43. Steinberg JS, Shah Y, Bhatt A, et al. Focal impulse and rotor modulation: acute procedural observations and extended clinical follow-up. *Heart Rhythm*. 2016.
  44. Vijayakumar R, Vasireddi SK, Cuculich PS, et al. Methodology considerations in phase mapping of human cardiac arrhythmias. *Circ Arrhythm Electrophysiol*. 2016;9.
  45. Narayan SM, Krummen DE, Rappel W-J, et al. Clinical mapping approach to identify rotors and focal beats in human atrial fibrillation. *J Cardiovasc Electrophysiol*. 2012;23:447–54.



46. Narayan SM, Krummen DE, Enyeart MW, et al. Computational mapping approach identifies stable and long-lived electrical rotors and focal sources in human atrial fibrillation. *PLoS ONE*. 2012;7:e46034.
47. 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;2:e004549.
48. Alhousseini M, Vidmar D, Meckler GL, et al. Two independent mapping techniques identify rotational activity patterns at sites of local termination during persistent atrial fibrillation. *J Cardiovasc Electrophysiol*. 2017;28:615–22.
49. 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 followup of the confirm (conventional ablation with or without focal impulse and rotor modulation) trial. *J Am Coll Cardiol*. 2014;63:1761–8.
50. 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;6:851–8.
51. Seitz J, Bars C, Theodore G, et al. AF ablation guided by spatiotemporal electrogram dispersion without pulmonary vein isolation: a wholly patient-tailored approach. *J Am Coll Cardiol*. 2017;69:303–21.
52. Ghoraani B, Dalvi R, Gizurarson S, et al. Localized rotational activation in the left atrium during human atrial fibrillation: relationship to complex fractionated atrial electrograms and low-voltage zones. *Heart Rhythm*. 2013;10:1830–8.
53. Ng J, Gordon D, Passman RS, et al. Electrogram morphology recurrence patterns during atrial fibrillation. *Heart Rhythm*. 2014;11:2027–34.
54. Sommer P, Kircher S, Rolf S, et al. Successful repeat catheter ablation of recurrent longstanding persistent atrial fibrillation with rotor elimination as the procedural endpoint: a case series. *J Cardiovasc Electrophysiol*. 2016;27:274–80.
55. Spitzer SG, Karolyi L, Rammler C, et al. Treatment of recurrent non-paroxysmal atrial fibrillation using focal impulse and rotor mapping (firm)-guided rotor ablation: early recurrence and long-term outcomes. *J Cardiovasc Electrophysiol*. 2017;28:31–8.
56. Benharash P, Buch E, Frank P, et al. Quantitative analysis of localized sources identified by focal impulse and rotor modulation mapping in atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2015;8:554–61.
57. Miller JM, Das MK, Jain R, et al. Clinical benefit of ablating localized sources for human atrial fibrillation: the Indiana university firm registry. *J Am Coll Cardiol*. 2017;69:1247–56.
58. Allesie MA, Bonke FIM, Schopman FJG. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The “leading circle” concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. *Circ Res*. 1977;41:9–18.
59. Lalani G, Schricker A, Gibson M, et al. 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;59:595–606.
60. Krummen DE, Baykaner T, Swarup V, et al. Multicenter procedural safety of firm ablation (abstract). *Europace*. 2016.
61. Tilz RR, Lin T, Rillig A, et al. Focal impulse and rotor modulation for the treatment of atrial fibrillation: locations and one year outcomes of human rotors identified using a 64-electrode basket catheter. *J Cardiovasc Electrophysiol*. 2016.
62. Houmsse M, Hummel JD, Hamam I, et al. Long term outcome of firm guided rotor ablation for atrial fibrillation (abstract). *Heart Rhythm*. 2015;18:PO03–120.
63. Foreman JR, Padanilam BJ, Olson JA, et al. Single center experience with firm ablation: a case series of 125 patients. *Heart Rhythm*. 2015;PO01–56.
64. Lin Y-J, Lo M-T, Chang S-L, et al. Benefits of atrial substrate modification guided by electrogram similarity and phase mapping techniques to eliminate rotors and focal sources versus conventional defragmentation in persistent atrial fibrillation. *JACC Clin Electrophysiol*. 2016;2:667–78.
65. Spitzer S, Karolyi L, Raemmler C, et al. Rotor-mapping/-ablation of redo-cases of persistent atrial fibrillation-procedural and follow-up data (abstract). *J Cardiovasc Electrophysiol*. 2016;27:648.
66. Zaman JAB, Baykaner T, Swarup V, et al. Recurrent post ablation paroxysmal atrial fibrillation shares substrates with persistent atrial fibrillation: an 11 center study. *JACC Clin Electrophysiol*. 2016;3:393–402.
67. Gianni C, Mohanty S, Di Biase L, et al. Acute and early outcomes of firm-guided rotors-only ablation in patients with non-paroxysmal atrial fibrillation. *Heart Rhythm*. 2016;13:830–5.
68. Lalani GG, Coysh T, Baykaner T, et al. Organized sources are spatially conserved in recurrent compared to pre-ablation atrial fibrillation: further evidence for non-random electrical substrates. *J Cardiovasc Electrophysiol*. 2016;27:661–9.