Atrial fibrillation (AF) ablation remains suboptimal—despite spectacular results in individual patients—for both persistent and paroxysmal AF using contemporary catheters.1 The benefits of pulmonary vein isolation (PVI) likely extend beyond isolating triggers because ablation may be more successful if wide areas are ablated by radiofrequency or cryoballoons,2 and patients without AF may have reconnected pulmonary veins.3 Hence, it seems intuitive that additional lesion sets should improve outcomes.

However, several meta-analyses have suggested that commonly applied ablation sets beyond PVI provide inconsistent benefit.4 This was illustrated vividly by the Substrate and Flutters and had longer procedural and ablation times. Patients in the CFAE limb experienced more atrial arrhythmias at 12 months. Patients in the CFAE limb had no advantage over the control arm, with similar single (46.2% versus 56.9%, P=0.67) and linear (80% versus 80%, P=1.0) freedom from atrial arrhythmias at 12 months. Patients in the CFAE limb had no advantage over the control arm, with similar freedom from atrial arrhythmias at 12 months. Patients in the CFAE limb had no advantage over the control arm, with similar freedom from atrial arrhythmias at 12 months. Patients in the CFAE limb had no advantage over the control arm, with similar freedom from atrial arrhythmias at 12 months.

The authors should be commended on designing and executing this important trial. Their success compares favorably with STAR-AF2, particularly given that many patients had LV systolic dysfunction, elevated body mass index, and long-standing persistent AF. Limitations include the facts that follow-up using ambulatory ECGs only at 12 months could easily miss asymptomatic recurrences, that block across PVI and lines was not verified with adenosine, and that contact force sensing was not used. However, these factors should influence both limbs similarly. Taken in context, results from the BOCA and STAR-AF2 trials suggest that PVI produces at least equivalent success with less ablation than PVI+lines, PVI+CFAE, or PVI+lines+CFAE in persistent AF. The overwhelming message that less is more for AF ablation gives us pause to reflect on which AF mechanisms are ablated by current lesion targeting.

**Possible Mechanisms by Which Lines/CFAE May Not Improve PVI**

If AF is caused by disordered wavelets that self-sustain, as hypothesized by Moe from computer models,2 then lines and additional lesions should reduce the tissue available for these wavelets and should thus improve outcomes.

Figure shows a conceptual schematic of AF driven by 2 fundamental mechanisms: (1) preferred regional mechanisms (sources) driving disorganized waves or (2) disorganized wavelets that self-sustain, that is, without preferred regional sources, such as the multiple-wavelet or endo-epi dissociation hypotheses. Ablation lesions are shown in gray shading and may operate by hitting sources (Figure A) or by constraining disordered wavelets (Figure B) as shown in the table.

It has been questioned whether self-sustaining disorder (Figure B) drives AF. Reports of AF caused simply by complexity4 are inconsistent with data that activation shows consistent patterns in AF7 or that localized ablation can terminate persistent AF,10 plus these studies examined <10% of atrial area without mechanistic interventions.8 Because successful therapy for self-sustaining disordered AF must compartmentalize the atrium, its strongest support has come from the need for extensive ablation.11 One could thus argue that lines applied in BOCA and STAR-AF2 were insufficient to limit atrial mass, although this does not explain the success of targeted ablation,10 or how in the Bordeaux stepwise approach11 the first steps may be successful while patients with the longest ablation times often had the worst acute and long-term outcomes—all of which argue against this mechanism.

Conversely, an alternative mechanism is that disorganized activity in AF is maintained by spatially preferred mechanisms (sources) which, in the majority of optical mapping studies, take the form of localized rotors that produce disorder. In recent human optical mapping studies, AF was sustained by
stable endocardial micro-reentrant sources anchored to muscle bundles that produced unstable breakthroughs and rotations on the epicardium abolished by endocardial ablation. These optical data support results from wide-area-contact basket mapping and may reconcile the instability of sources on ECG imaging of the epicardium. If AF Is Due to Localized Sources, Should Not Lines Hit Some of Them? Although this has yet to be proven prospectively, in the CONFIRM trial stereotypical lines sometime hit sources, but also often missed sources that lay in patient-specific locations with small areas of 1 to 2 cm² on endocardial optical and basket maps (Figure A). Because studies increasingly show that persistent AF is a biatrial disease, with a third of sources occurring in the right atrium on endocardial or epicardial mapping, ablation lines intersected only 40% to 60% of sources, and such patients had substantially higher success than those in whom sources were missed. Notably, other methods show similar AF source distributions. Should Not CFAE Ablation Hit Some Sources, and Are Widespread Lesions Pro-Arrhythmic? CFAE are increasingly felt to be mechanistically nonspecific because electrograms in AF may poorly reflect local activation and because CFAE algorithms vary. CFAE ablation is often patchy and scattered, and although its impact on clinical rotors is unclear, in animal models, such lesions destabilize rotors possibly by creating additional attractors. This adds to the concern that widespread ablation is proarrhythmic, also shown by the high incidence of atrial tachycardia after CFAE ablation in BOCA and STAR-AF2. The Path Forward: Patient-Specific Mapping of AF Given ample evidence that less is more in AF ablation, is there a way to improve the current 50% to 60% success? A nihilistic view—that outcomes cannot be improved—is at odds with abundant anecdotes of success when ablating AF outside the pulmonary veins. To solidify these anecdotes into personalized ablation, a promising approach is to target ablation to mapped AF mechanisms in each patient. Of course, such mechanisms remain debated. Nevertheless, wide-area basket mapping shows that AF is often maintained by stable rotors and focal sources, with similarities to recent human optical mapping studies, whose ablation is promising in multicenter nonrandomized studies. Although AF sources have been questioned, many studies had issues, such as atrial cycle lengths of 250–500 ms (dominant frequencies 2–4 Hz), in patients ostensibly with AF and analysis of unipolar signals using indices designed for bipolar signals (Shannon’s entropy) or mapping small areas. Recent data showing how localized ablation can eliminate AF rotors, by interacting with nonuniformities in remodeled atria, explain and thus strengthen the results of AF source ablation. At the other end of the spectrum, it has been proposed that debulking should be further extended, such as by posterior LA wall ablation. Limitations of this approach include the fact that success is currently still suboptimal and that targeting right atrial sources will require essentially biatrial obliteration and a risk of sequelae, including but not limited to stiff left atrial syndrome. Conclusions The BOCA trial shows that nontargeted debulking of atrial tissue, based on early assumptions that AF is a random process, fails to improve patient outcomes. This and other recent trials further support the mounting evidence that human AF is sustained by localized sources in both atria. Accordingly, a promising direction that must be tested is to personalize ablation guided by mapping mechanisms. It is time to better translate basic and translational science to the bedside to improve AF ablation. Sources of Funding Dr Zaman was supported by the Fulbright Commission and British Heart Foundation (FS/14/46/30907). Dr Narayan was supported in part by grants from the National Institutes of Health (R01 HL 83359 and K24 HL103800). Disclosures Dr Narayan reports being coinventor on intellectual property owned by the University of California and licensed to Topera Medical, Inc.
in which he has held equity. Dr Narayan reports having received consulting fees from the American College of Cardiology, Medtronic, St Jude Medical, UpToDate and Janssen Pharmaceuticals. Dr Zaman reports no conflicts.

References


Key Words: Editorial ▪ ablation ▪ atrial fibrillation ▪ catheter ablation ▪ electrophysiology ▪ fractionated electrograms ▪ pulmonary vein
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Junaid A.B. Zaman and Sanjiv M. Narayan

Circ Arrhythm Electrophysiol. 2015;8:1303-1305
doi: 10.1161/CIRCEP.115.003495
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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