Journal of Interventional Cardiac Electrophysiology (2024) 67:27–28
https://doi.org/10.1007/s10840-023-01639-0

COMMENTARY

Seeing the forest for the trees: the promise of electrogram-guided ablation of persistent atrial fibrillation

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Received: 30 August 2023 / Accepted: 1 September 2023 / Published online: 13 September 2023

Since catheter ablation of atrial fibrillation debuted over 20 years ago, it has rapidly become ubiquitous in clinical practice. With improved technology, first-time success rates have risen to approximately 80% freedom from symptomatic atrial fibrillation (at one year) and complication rates have dropped. Catheter ablation earned a Class IIa first-line indication for paroxysmal atrial fibrillation in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE consensus statement [1] with stronger recommendations in certain clinical scenarios. This procedure now represents the backbone of most clinical EP practices.

Against this backdrop of positive experience with catheter ablation in paroxysmal atrial fibrillation, successful ablation of persistent atrial fibrillation has proven more challenging. Early ablative strategies successfully targeted pulmonary vein (PV) foci as triggers of atrial fibrillation using pulmonary vein isolation (PVI) [2]. This remains the core of ablative therapy for atrial fibrillation but addresses only one aspect of the overall mechanism of arrhythmia. At least three decades ago, nonuniform anisotropy of atrial myocardium was described and noted to be prevalent in patients with atrial fibrillation [3]. This, along with atrial fibrosis and dispersion of refractoriness, plays key roles in sustaining atrial fibrillation. It remains uncertain whether persistent atrial fibrillation is dependent on focal drivers or whether focal or rotational activation on endocardial mapping is reflective of focal breakout of complex 3-dimensional activation [4]. A plethora of trials have attempted to characterize this substrate and modify it through ablation or interventions targeted at autonomic influence.

Most strategies that have shown initial promise have been disappointing in real-world application. Focal impulse and rotor modulation (FIRM) mapping did not appear to be effective in the REAFFIRM or more recent REDO-FIRM trials [5], complex fractionated atrial electrogram (CFAE) ablation does not appear to improve outcomes beyond PVI, and while small trials and meta-analyses have provided support for posterior wall isolation, no large RCT has yet demonstrated superiority for this strategy [6]. Some strategies have been shelved for safety reasons, such as left atrial appendage isolation due to risk of thrombotic complications [7]. Others have been limited by suboptimal ablative results; linear ablation and posterior "box" isolation are plagued by reconnection due to inability to achieve full thickness ablation. There is hope that pulsed field ablation (PFA) may permit effective transmural ablation with little risk of esophageal injury, and trials exploring PFA in persistent atrial fibrillation are ongoing. The major unanswered question in this space is whether our ablation strategies fail because we are unable to achieve the targeted lesion set or because the strategy itself is flawed.

It should be noted that persistent atrial fibrillation remains a heterogenous disease, constituting a common end-state for a variety of predisposing conditions and pathological processes. Clearly, a patient with extensive atrial fibrosis may benefit from a different strategy compared to those with normal left atrial voltage, yet both populations have been grouped in many trials. It is not clear whether these ablative strategies are truly broadly ineffective, or whether our growing understanding of the pathophysiology and genetic basis of atrial fibrillation will eventually identify discrete patient populations where specific strategies are beneficial. Additionally, the longstanding convention for defining procedural success (freedom from at least 30 s of atrial arrhythmia) is clearly less clinically meaningful than arrhythmia burden and other clinical endpoints, with secondary analysis of a recent PFA trial suggesting quality of life improvement in all persistent atrial fibrillation patients, even those with recurrent atrial fibrillation [8].

This comment refers to the article available at https://doi.org/10.1007/s10840-023-01594-w.

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In this issue of the *Journal of Interventional Cardiac Electrophysiology*, Dr. Mitrani et al. published an article entitled "Electrogram morphology recurrence guided catheter ablation for repeat ablation of persistent atrial fibrillation [9]." In this pilot study, they explored a novel method of leveraging high-density mapping to identify non-pulmonary vein targets for ablation in patients with persistent atrial fibrillation undergoing redo catheter ablation. At multiple mapping sites throughout the atria, they analyzed electrograms looking for the most frequent recurring electrogram morphology (EMR), the frequency of recurrence of that EMR (Rec%), and the cycle length (CLr) of each EMR, then targeted sites with the shortest CLr and a Rec% of > 80 for ablation. Their hope was to filter EGMs looking for the rapid repetitive activation patterns expected closest to drivers of atrial fibrillation and then selectively target those drivers. Of 10 patients enrolled, six underwent CLr-guided catheter ablation, one had no site meeting designated CLr criteria, and three were not ablated at the shortest CLr due to operator preference—in at least two cases due to the shortest CLr occurring in the LAA. COnfounding interpretation, nine of the patients were found to have PV reconnections, all of which were treated. Interestingly, AF termination was not observed in any patient undergoing CLr-guided ablation, a disappointing result if this technique targets drivers. On ambulatory monitoring of patients treated per protocol, one had recurrent persistent atrial fibrillation, one had paroxysmal atrial fibrillation, and two had atrial flutter, while all four patients treated without CLr-guided ablation had recurrent persistent atrial fibrillation. These results are likely confounded by the different mechanisms underlying persistent AF in patients with and without CLr sites. Furthermore, CLr sites at the LAA (which may reflect activation from epicardial sites in the vein of Marshall or Bachman's bundle) may be a marker for lack of response to typical ablation strategies.

The question of ideal atrial ablation strategy fundamentally comes down to "how much is just enough, but not too much," as we attempt to treat persistent atrial fibrillation and improve clinical outcomes for patients without exposing them to excessive risk or loss of left atrial compliance. CLr mapping is attractive in its potential to allow for more precise ablation in comparison with anatomic ablation strategies. Ultimately, this pilot study accomplished its goal, which was to demonstrate the technical feasibility of identifying, localizing, and ablating sites with frequently recurring electrogram morphologies. Any conclusions about clinical efficacy of this strategy are premature given the small sample size and application of CLr-guided ablation in only 60% of the population. However, as a mapping strategy, the technique seems promising.

Declarations

Conflict of interest Brian C. Pomerantz has no competing interests to declare. Travis D. Richardson has received research funding from Medtronic and Abbott and has served as a consultant for Medtronic and Johnson & Johnson.

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