EDITORIAL COMMENTARY

# Recurrent atrial fibrillation after pulmonary vein isolation: Box it or not?

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Selecting the optimal approach for patients undergoing repeat catheter ablation of atrial fibrillation (AF), especially those with persistent AF or significant atrial myopathy, remains a challenge. If 1 or more pulmonary veins (PVs) are reconnected, there is little debate that PV reisolation (PVRI) should be done. However, for patients with no PV reconnections, persistent AF, or AF associated with demonstrable atrial myopathy, PVRI alone has limited success and the preferred ablation strategy remains unclear. Many strategies have been proposed, including empiric isolation of potential AF trigger regions, ablation of non-PV triggers after isuprel infusion, isolation of low-voltage zones (LVZs), empiric linear ablation, and others.[1]

One approach chosen by many operators is empiric isolation of the left atrial posterior wall (LAPW).[2] The LAPW derives from the same embryonic tissue as the PV musculature, and AF triggers may originate from this region. In addition, complex fiber orientation at the LAPW can produce anisotropic conduction with low voltage and fragmentation of contact electrograms (EGMs), suggesting a possible role in AF perpetuation.[2] Most data regarding outcomes after LAPW isolation (LAPWI) are observational, though 6 randomized trials have been reported.[2] Conclusions from these studies have been mixed, with 3 reporting improved AF outcomes after LAPWI. A recent expert consensus statement on AF ablation gives PWI a IIb recommendation during initial or repeat ablation for all forms of AF.[1]

In this issue of *Heart Rhythm O*$^2$, Pothineni and colleagues[3] report a retrospective observational study of arrhythmia recurrence after a repeat ablation, comparing 103 patients who received LAPWI in addition to PVRI if needed (48% in the LAPWI group had no evident PV reconnection) to 93 patients with documented PV reconnection who received PVRI but no LAPWI. All patients underwent isuprel infusion with ablation of triggers followed by LAPWI at the operators' discretion; the decision to do LAPWI was not protocolized. About 20% of subjects in the LAPWI group had AF triggers from the LAPW prompting the decision to do LAPWI, and the remaining 80% had LAPWI done "empirically." The primary and secondary study endpoints were freedom from atrial arrhythmias at 1 year off antiarrhythmic drugs (AADs) and without regard to AAD use, respectively. The authors report no significant differences in arrhythmia recurrence between the 2 groups (LAPWI vs PVRI: 43.7% vs 69.9%, $P = .50$; and 66% vs 77.4%, $P = .36$). Of clinical interest, the authors describe that 35% of subjects undergoing LAPWI required focal ablation within the PW region to achieve isolation after delivery of intact linear "box" lesion sets, consistent with the existence of "epicardial" connections.

As is common to uncontrolled retrospective observational studies that compare unique therapies chosen at the discretion of operators based on clinical judgement, baseline characteristics of the comparative groups in this study appear to be quite different. Nearly half of the LAPWI group had recurrent AF despite no PV reconnections, implying that AF was due to some "extra-PV" pathophysiology, whereas all the PVRI patients had PV reconnections. Furthermore, the PWRI group had >3 times more non-LAPW triggers identified during isuprel challenge compared to the PVRI group and were more likely to be discharged on an AAD (73.7% vs 43%, $P < .001$), and the proportion of LAPWI subjects with persistent AF was much higher (53.4% vs 22.6%, $P < .001$). These findings are consistent with LAPWI subjects having more advanced forms of AF. Lastly, the LAPWI group was older and had significantly more hypertension that also portends poorer outcome after ablation. With this in mind, the finding that LAPWI patients did *not* do worse, overall, compared to the PVRI cohort could be interpreted to represent a benefit of LAPWI. Prior studies of AF patients with atrial myopathy manifest by endocardial LVZs that are then isolated as an adjunct to PVI report improved arrhythmia-free survival approaching that of patients without atrial myopathy treated with PVI alone; achieving such equivalence has been interpreted as evidence that LVZ isolation yields clinical benefit.[4] If, as seems likely for this study, the LAPWI cohort was selected for more advanced AF disease, the overall finding that there was no significant difference in outcome between the LAPWI and PVRI groups may in and of itself be informative and reveal a clinically relevant benefit of LAPWI.

The authors also report a subgroup analysis of only those with persistent AF (LAPWI n = 55, PVRI n = 21). The LAPWI group had *lower* freedom from atrial arrhythmias off AADs (36.4% vs 61.9%; $P = .05$), though there was no

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difference in the secondary endpoint of freedom from arrhythmia on or off AADs (56.4% vs 71.4%, $P = .33$). These results are more difficult to interpret owing to loss of power with subgroup analyses and the small number of subjects with persistent AF in the PVRI group. If the comparative groups were indeed similar with regard to baseline AF disease state, a significantly poorer outcome with LAPWI would imply proarrhythmia, yet the authors report no differences in overall organized atrial arrhythmia recurrences during follow-up with LAPWI vs PVRI (20% vs 26%, $P = .16$). While one cannot exclude an AF-specific proarrhythmic effect of LAPWI, this would not be consistent with prior studies. Accordingly, it seems most likely that this observation is due to enrollment bias and important baseline differences between the study cohorts.

An overarching question not directly addressed by the study of Pothenini and colleagues[3] has to do with whether adjunctive lesion sets during catheter ablation of AF should be delivered empirically or guided by patient-specific information such as that gleaned during endocardial mapping to identify regions of low voltage, EGM fractionation, or demonstrable AF triggers. The authors describe a hybrid approach where all subjects had activation map–guided focal ablation of isuprel-induced triggers, some of which were targeted at the LAPW in patients assigned to the PVRI group (which, too, could bias results against LAPWI). Kircher and colleagues[5] reported that map-guided isolation of LVZs regardless of location is superior to empiric LAPWI to improve arrhythmia-free survival of patients with persistent AF in a prospective single-center randomized study of 124 ablation-naïve subjects.[5] Other studies, including map-guided decision-making about whether to do LAPWI, corroborate an approach of targeting adjunctive ablation to patient-specific targets. It is possible that the empiric approach to LAPWI as reported by Pothenini and colleagues diminished power to identify a benefit of LAPWI.

Other important questions regarding PWI remain. There is evidence that reconnection rates as high as 40% can be seen after PWI when endocardial radiofrequency ablation is used to deliver a "box" lesion set.[6] This limitation makes studying the true effect of PWI difficult and may in part account for inconsistent outcomes of prior studies. Use of the cryoballoon to perform PWI has the theoretical advantage that contiguous PW ablation to eliminate EGMs may reduce the potential for reconnection, and was reported to improve outcomes in patients with persistent AF (74.5% vs 54.5% freedom from AF, $P = .028$).[7] It is also interesting to note that epicardial surgical ablation of the LAPW in the CONVERGE trial, which may be less prone to result in incomplete ablation and reconnection, resulted in lower recurrence rates of AF in patients with persistent AF.[8] Future technologies, such as pulsed field ablation, may allow creation of more durable PWI lesion sets with little or no risk to extracardiac structures like the esophagus and enhance benefits of LAPWI.

We are reaching the limits of knowledge using preliminary and hypothesis-generating retrospective observational studies of adjunctive lesion sets such as LAPWI to improve arrhythmia-free survival for patients with advanced forms of AF. Planned or ongoing randomized trials will examine the utility of PWI, including the PLEA AF trial (NCT04216667) examining various combinations of PVI, PWI, and isolation of the left atrial appendage isolation or coronary sinus in patients with persistent and long-standing persistent AF. At least 2 other trials will examine PVI vs PVI + PWI (NCT04405258, NCT03295422). It seems likely that there will also be an increasing role for patient-specific characterization of the AF substrate to guide ablation lesion sets beyond PVI. Carefully designed prospective randomized controlled trials and observational studies using well-matched control groups will be needed to further advance our knowledge about how best to treat advanced forms of AF that are relatively resistant to PVI-focused ablation strategies.

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## Authorship

All authors attest they meet the current ICMJE criteria for authorship.

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