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COMMENTARY

Pulmonary vein activity: a step towards personalizing atrial fibrillation ablation

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Freedom from atrial arrhythmias in patients with paroxysmal atrial fibrillation (AF) following pulmonary vein isolation (PVI) remains around 70% at 1 year and significantly decreases in the longer-term follow-up [1]. A substantial rate of pulmonary vein (PV) reconnection during follow-up has been postulated to explain AF recurrence in patients with paroxysmal AF; however, AF recurrence has been observed in 20% of those with documented durable PVI [2]. Therefore, identification of patients with paroxysmal AF in whom PVs play a crucial role in the mechanism of AF would be a step towards a more tailored ablation approach allowing identification of patients who can benefit from a PVI-only strategy and those who may require additional mapping and ablation to achieve long-term freedom from atrial arrhythmias.

Atrial sites with faster cycle length (CL) during AF have been suggested to have a mechanistic role as triggers and drivers of the fibrillatory conduction [3]. CL gradients between the left and right atria have been shown, to suggest that high-frequency periodic sources in the LA drive the fibrillatory conduction [4]. Moreover, in patients with paroxysmal AF, shorter AF CL inside the PVs highlight the influence of PVs in AF arrhythmogenesis and has been linked to catheter ablation outcomes [5, 6].

A wide range of manual and automated methods to measure CL in AF have been used, without a gold standard technique, due to challenges in annotating and interpreting continuously changing fibrillatory electrogram morphology, timing intervals and fractionation. A novel non-automated method to measure AF CL, proposed by Spera et al., relies on manually calculating the average of 10 successive "Fastest Atrial Repetitive Similar morphology signals" CL (FARS10-CL) within a 1-min observation period during AF [6]. This method has been demonstrated to effectively predict ablation results in patients with persistent AF undergoing a PVI-only ablation strategy; [6] however, its role in predicting responders to PVI-only ablation in paroxysmal AF patients has not previously been studied.

In this issue of the *Journal*, Bergonti et al. prospectively studied 104 paroxysmal AF patients undergoing first-time PVI with either point-by-point radiofrequency ablation or cryoballoon ablation in three European centers, to assess whether FARS10-CL measurement predicts responders to PVI-only ablation [7]. In patients presenting with sinus rhythm, AF was induced before ablation, and AF-CL was calculated using the FARS10-CL method. The authors found that patients with CL < 160 ms inside the PVs (indicating fast PV activity) had excellent results 1 year after a PVI-only approach compared to patients with PV CL ≥ 160 ms (indicating slow PV activity). Due to the low rate of AF recurrence after a PVI-only approach in paroxysmal AF patients with fast-PV CL, the authors advocate for an alternative mechanistic classification of AF as PV-driven and non-PV-driven. Notably, the authors show a correlation between PV activity and arrhythmia progression during follow-up: Among patients with slow PV activity, 12.9% progressed to persistent AF, while no similar progression was observed among patients with fast PV-CL.

This study by Bergonti et al. deserves commendation for providing further insights into the intricate and unresolved mechanistic interplay between PV activity and AF arrhythmogenesis. This is the first report demonstrating the ability of PV-CL, measured with the FARS10-CL method, to predict ablation outcomes after PVI in paroxysmal AF

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patients. If these findings are validated through larger studies, assessment of AF CL in the PVs may become a valuable predictor of outcome at the time of ablation, along with determination of those that might benefit for further assessment of electrical and anatomic substrates.

Prior studies evaluating the relationship between AF-CL in the PVs and ablation outcomes in persistent AF patients had conflicting results: Pascale et al. found that the ratio between the shortest PV-CL and left atrial appendage-CL was a good predictor of acute AF termination and long-term outcomes after a stepwise ablation approach that involves PVI [8]. Conversely, Prabhu et al. showed no association between the ratio of PV-CL to left atrial appendage-CL and AF ablation outcomes in patients undergoing PVI and posterior wall isolation [9]. These contradictory results may be partly explained by the varying methodologies used for AF-CL measurement and varying ablation lesion sets among these studies.

Some noteworthy limitations of this study warrant discussion. First, in the vast majority of patients (73%), antiarrhythmic medications were stopped on the day of the procedure. A residual effect of these medications may influence the atrial refractory period and reduce conduction velocity, affecting the PV-CL measurement and the proposed cutoff value of 160 ms. Second, although the FARS10-CL method has been shown to be reproducible by the authors, the manual identification of the 10 fastest CL with similar morphology and without significant fragmentation is based on visual inspection. The development and validation of a fully automated tool for PV-CL calculation would therefore improve the reliability and reproducibility of the PV-CL and provide a practical tool that could help predict responders to PVI and have the potential to direct selection of the ablation approach. Third, PV reconnection following catheter ablation may mask predictors of a PVI-only approach as patients are often not systematically brought back to the lab for assessment of PV isolation in follow-up. As the durability of PVI lesion sets improve with improving catheter ablation technologies, the assessment of the predictive ability of PV-CL in identifying responders of a PVI-only approach would be more accurate. Lastly, as acknowledged by the authors, a clear causal relationship between PV activity and AF arrhythmogenesis has not been demonstrated and could only be speculated based on PVI outcomes. Faster PV-CL may represent a marker of an underlying healthy atrial substrate, favoring faster conduction to the PVs; with slower PV-CL being a marker of advanced atrial substrate which may be associated with AF recurrence.

In summary, paroxysmal AF treatment remains challenging due to poor understanding of individualized disease mechanisms. The evaluation of PV activity using the novel FARS10-CL method has shown promise in predicting ablation outcomes following a PVI-only strategy. This approach can find applicability in clinical practice and might represent the initial step towards the future of personalized AF therapy.

Declarations

Conflict of interest Tina Baykaner, MD, MPH: Speaker and consultant fees from Biotronik, Abbott, Medtronic, and PaceMate unrelated to this work. National Institutes of Health grant K23 HL145017. Alvise Del Monte, MD: nothing to disclose.

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