Pulmonary Vein Isolation for Atrial Fibrillation
Forever Young*

Pasquale Santangeli, MD, Francis E. Marchlinski, MD

The efficacy of pulmonary vein isolation (PVI) as a treatment for drug-refractory atrial fibrillation (AF) has been established through more than 15 years of clinical studies, which have shown consistent, reproducible results worldwide. The PVI technique has evolved to include antral isolation to enhance safety and efficacy. However, the success rate with current PVI techniques remains suboptimal, with single-procedure efficacy ranging between 50% and 75% (1).

Patients with persistent AF experience the worst outcomes, leading to the hypothesis that additional ablation beyond the pulmonary veins (PVs) may be required to improve success in these patients. Additional targets have focused on putative mechanisms responsible for AF maintenance, such as empirical linear ablation (1) or ablation of AF focal sources or rotors identified using various computational mapping techniques (2,3). This hypothesis, although sound from a mechanistic perspective related to AF maintenance, is flawed by the fact that none of the studies comparing PVI alone with other non-PV ablation strategies (with or without PVI) ever achieved the desired goal of durable PVI: PV reconnection in patients experiencing post-ablation arrhythmia recurrence (4). In the presence of PV reconnection, AF recurrences should neither be used to claim ineffectiveness of PVI nor used to support the necessity of additional extra-PV ablation, although confusion in this sense may easily arise when facing data from published studies (Figure 1).

The results of the randomized RADAR-AF (Radio-frequency Ablation of Drivers of Atrial Fibrillation) trial published in this issue of the Journal should be viewed in this context (3). The RADAR-AF trial tested the hypothesis that localized high-frequency source ablation (HFSA) is noninferior to conventional antral PVI in patients with paroxysmal AF and that a hybrid strategy of PVI plus HFSA is superior to PVI alone in patients with persistent AF. High-frequency sources (HFS) have been implicated in the maintenance of human AF, and HFSA has achieved arrhythmia control in patients with drug-refractory AF in uncontrolled case series (5). However, no prior clinical study compared HFSA with conventional PVI as a treatment strategy for drug-refractory AF.

The primary endpoint of the RADAR-AF trial was freedom from AF off of antiarrhythmic drugs at 6 months. Secondary endpoints included freedom from AF at 1 year and procedural safety outcomes. In brief, the study failed to meet the primary endpoint; indeed, PVI only was superior to HFSA only at 6-month follow-up in patients with paroxysmal AF and was equivalent to PVI plus HFSA in patients with persistent AF. The study, however, did show that HFSA-only ablation reached the secondary endpoint of noninferiority at 1 year compared with PVI alone in patients with paroxysmal AF (79% vs. 81%) and trended toward higher procedure-related complications with PVI (14% vs. 5%).

To what extent can the findings of RADAR-AF be generalized to the reader’s patients? The main results appear valid; the trial was well conducted and...
adequately powered to address its primary endpoint. However, caution is necessary when interpreting the secondary endpoints, for which the study was not specifically designed and likely not powered. For instance, the higher rate of complications occurring in the PVI arm of the paroxysmal AF group (14%), which was driven by 4 pericardial effusions, appeared substantially higher than that occurring with the same procedure in patients with persistent AF (3%). Without sufficient power, it is hard to evaluate the effect of chance in the reported complications.

Overall, the main findings of the RADAR-AF trial provide additional evidence supporting the current recommendations for using PVI across the spectrum of patients with AF (1). Importantly, PV reconnection was confirmed as the leading mechanism of AF recurrence in both study groups. Even in patients who underwent HFSA only, PV isolation was used to eliminate HFS at most index procedures and, in those with AF recurrences, all of the PVs harboring AF-triggering HFS at repeat procedures had been isolated at the index procedure. These findings further support the notion that achieving permanent PVI should be the main goal of catheter-based approaches to treat AF, but it remains a big challenge. In this regard, generalization of the RADAR-AF results is still questionable, due to the variability in ablation techniques and approaches, which can affect PVI durability and, therefore, procedure efficacy. For example, for several years we have been implementing strategies to enhance catheter stability to increase the effectiveness of ablation lesions, decrease the chance of chronic PV reconnection, and ultimately improve the success rate (6). These strategies include general anesthesia with jet ventilation to minimize respiratory movement, steerable sheaths, periprocedural monitoring of tissue-catheter contact and lesion formation with intracardiac echocardiography, and the use of adenosine to confirm early persistence of PVI. None of these tools was used in the RADAR-AF trial, and their absence might have undervalued an even greater benefit of PVI when analyzing arrhythmia-free survival at longer follow-up (1 year).

There are a few other considerations regarding the protocol of this important study worth highlighting. The procedural endpoint adopted for PVI in the RADAR-AF study was entry block, and additional roof linear ablation (without mandatory achievement of conduction block) was performed but at the discretion of the operator. In our experience, demonstration of exit block in addition to entry block is clinically relevant, as unidirectional entry block (with exit conduction) can be observed in up to 20% of PVs (7). Also, no information was provided on whether any effort was made to elicit acute PV reconnection at the time of the index procedure with intravenous adenosine or high-dose isoproterenol. The latter could have increased the chance to elicit and appropriately target latent non-PV triggers for AF that seem clinically relevant in an important subgroup of patients. Previous studies suggest that non-PV locations with HFS are consistent with common AF trigger sites, and empirical ablation of such sites may have explained some of the benefit of HFSA.

Finally, the discretionary use of linear roof ablation might have diluted PVI effectiveness, as no conclusive data support the benefit of any left atrial linear ablation (especially in paroxysmal AF); in fact, evidence suggests that linear ablation may be proarrhythmic, particularly if performed without confirming block. Given the good outcome with PVI in both paroxysmal and persistent AF patients in the RADAR-AF trial, these additional technical modifications would only further support the primacy and outcome of antral PVI and non-PV trigger ablation.

In conclusion, the results of the RADAR-AF trial should be considered as more evidence favoring antral PVI in patients with either paroxysmal or persistent AF. Future research efforts should be directed toward the attainment and noninvasive confirmation of durable PVI. By achieving this goal, we can unequivocally identify the smaller group of patients who truly do not respond to effective PVI only and may require different ablation approaches and/or targets, including HFSA.
In 1974, after 8 years away from the stage, during which time he had become a father, Bob Dylan released his 14th studio album, *Planet Waves*. The album featured 2 versions of a song dedicated to his son, where he wished him to stay “Forever Young” (8). More than 15 years after its introduction, PVI has stood the test of time and, in the words of Bob Dylan, will likely stay “forever young” and consistently important when performing AF ablation procedures.

**REFERENCES**


**KEY WORDS** atrial fibrillation, catheter ablation, pulmonary vein isolation

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Francis E. Marchlinski, Hospital of the University of Pennsylvania, 9 Founders Pavilion–Cardiology, 3400 Spruce Street, Philadelphia, Pennsylvania 19104. E-mail: francis.marchlinski@uphs.upenn.edu