The role of the pulmonary veins (PVs) in initiating (1,2) and maintaining (3,4) paroxysms of atrial fibrillation (AF) has been well documented. The fact that the arrhythmia can be eliminated in  90% of patients undergoing antral PV isolation (5) also speaks to the critical role of the thoracic veins in patients with paroxysmal AF. However, these outcomes are attained at the expense of repeat procedures, most often for PV reconnection. Although these results are encouraging and can be realized with a low risk of complications at experienced centers, the potential for late recurrence years after the ablation procedure is sobering (6). In an effort to improve outcomes, several adjunctive targets have been promulgated, including complex, fractionated atrial electrograms (CFAEs) (7), left atrial (LA) linear lesions (8), non-PV ectopy, and the intrinsic cardiac autonomic nervous system (ANS) (9). Identification of driver as opposed to passive sites remains problematic with CFAE mapping (10), with the result that we probably end up ablating too much atrial tissue. Linear lesions are very effective in eliminating AF but at a cost of LA re-entry, which frequently requires repeat procedures (11). Patients who require ablation of non-PV foci may fare worse than those undergoing PV isolation (12).

The intrinsic cardiac ANS is composed of multiple ganglonated plexi (GP), which are located in the fat pads on the epicardial aspect of the atria. These include the anterior right GP located at the right superior PV-LA junction, the inferior right GP located in the vicinity of the right inferior PV, the superior left GP located near the left superior PV-LA junction, and the inferior left GP located near the left inferior PV-LA junction. The extrinsic cardiac ANS, made up of ganglia from the brain and spinal cord and their axons destined for the heart, modulates sinoatrial and atrioventricular nodal function and influences AF inducibility through the GPs (13). In animal models, stimulation of the GPs results in rapid, repetitive discharges from the PVs, and autonomic denervation suppresses this firing (14). It is hypothesized that AF may develop in humans on the basis of a “hyperactive” intrinsic cardiac ANS.

The initial clinical studies incorporating the GPs into conventional LA ablation showed very good outcomes (15). The GPs were identified by eliciting a parasympathetic response (bradycardia/hypotension) during high-frequency stimulation (HFS). However, studies using a GP-only approach were met with disappointment. In part, this was attributed to the suboptimal sensitivity of HFS in identifying the extent of GPs. Currently, an anatomic approach to GP ablation is preferred, i.e., one in which the atrial tissue subjacent to the general location of the GPs is targeted without the need for demonstrating bradycardia or hypotension with HFS (16).

In this issue of the Journal, Katritsis et al. (17) sought to determine the incremental benefit of GP ablation in patients undergoing PV isolation for paroxysmal AF. Patients were randomized to antral PV isolation or antral PV isolation combined with GP ablation. In addition, a GP-only group was also included. Only GPs that are likely to be encountered along the circumference of the antral lesion set were targeted to decrease the likelihood of gaps and pro-arrhythmia. There was no requirement for the demonstration of a parasympathetic response, but if it was encountered, the endpoint, in addition to voltage reduction, included its abolition. After a single procedure and a follow-up period of 2 years, 74% of patients in the PV+GP group remained arrhythmia-free compared with 56% of the patients in the PV-only group and 48% in the GP-only group. In one half of the study population, rhythm status was assessed by an implantable loop recorder. The mean radiofrequency duration in the PV+GP, PV-only, and GP-only groups was 67 min, 41 min, and 46 min, respectively. There were no complications attributable to GP ablation and the incidence of post-ablation atrial tachycardia, in contradistinction to a previous study (9), was not increased.

The investigators should be lauded for contributing a well-conceived randomized study to a discipline that has been guided by only a handful of such studies. Their endeavor further supports the role of the intrinsic cardiac ANS in the pathophysiology of paroxysmal AF. How might autonomic denervation lead to improved outcomes in patients undergoing PV isolation? Because GP ablation was anchored to the antral lesion set, it is possible that it results in more durable PV isolation. However, studies using a GP-only approach have noted that the PVs are rarely isolated (18). If one assumes that the rate of PV isolation (12).
reconnection is similar in the PV+GP and the PV-only groups, then the additional LA ablation in the former must be playing a role. It is possible that although the PVs may be connected and capable of focal firing, elimination of the adjacent GP by ablation may render the PV incapable of initiating AF. In an animal study, activation of the GP was required to convert PV firing into AF, and injection of lidocaine, a neuronal blocker, into the GP prevented AF induction (19). Further, in an experimental model of vagally mediated AF, ganglion-sparing PV ablation had no effect on AF maintenance, whereas epicardial ablation of both left- and right-sided GPs rendered AF noninducible (20). The antiarrhythmic effect of neural ablation may in part be due to its effect in preventing abbreviation and dispersion of atrial refractoriness—factors that favor re-entry—during vagal stimulation.

How well these experimental models relate to human AF is unknown. Given the paucity of mechanistic data in humans, we must rely on animal models in hopes of building a framework that helps us understand how GP ablation leads to salutary outcomes in patients. To this end, several critical questions may be raised. Because the GPs are epicardial structures, can we even be sure that endocardial ablation is sufficient in eliminating the neural activity in the epicardium? Is it possible that we are instead targeting driver sites in the form CFAEs or discrete sources (21) that happen to colocalize to endocardial areas underlying the GPs? How does the hyperactive GP hypothesis account for structural remodeling in patients with paroxysmal AF even in the absence of obvious heart disease (22)? Although a single procedure success rate of 74% is impressive, what about the remaining one-fourth of the patients? Might they benefit from right atrial GP ablation or a more definitive ablation of the ligament of Marshall, which also contains autonomic elements? Perhaps the mechanism in these patients is not related to the intrinsic cardiac ANS. What of the difficulty in achieving complete denervation, the possibility of reinnervation and end-organ hypersensitivity, and the long-term effects of neural imbalance (23)?

Apart from these far-reaching questions, several practical issues remain that also need to be sorted out before we can adopt GP ablation. Relatively high power settings (up to 35 W with an irrigated-tip catheter for as long as 40 s) were used in this study, presumably in an attempt to target the epicardial location of the GPs. Although no evidence of collateral damage was found in this study of 240 patients, there remains a concern for myocardial injury and perforation, esophageal injury (during ablation of the inferior GPs), injury to the phrenic nerve and atrial arteries (24) (during ablation of the anterior right GP), and gastric hypomotility (25). If all 4 GPs cannot be ablated because of safety concerns (e.g., unfavorable esophageal course), data from animal studies suggest that the resultant partial denervation may not only be inefficacious (20) but also proarrhythmic (26).

There is little doubt that the standard antral lesion set results in at least some modification of the intrinsic cardiac ANS. The appeal of formally adding GP ablation to our current approach is its simplicity and the fact that it does not require additional tools or technology. The potential downside is that we continue down the path of empiricism and more tissue destruction, albeit guided by the prospect of better outcomes. Recent studies have raised the possibility that sources of AF may be discrete and may be eliminated without extensive ablation (21). Until the age of mechanistic AF ablation arrives, we are left to decide on which adjunct, be it CFAEs, non-PV foci, contact force technologies, and now the GPs, might best prevent recurrence after PV isolation. At the very least, the excellent contribution by Katritsis et al. (17) should make us question our current practice and exhort us to pursue novel strategies in an effort to improve the lives of our patients with AF. And that’s a good thing.

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REFERENCES


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