Is all Hope Lost For the Plexus?

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Despite decades of progress, contemporary ablation approaches for atrial fibrillation (AF) have reached an efficacy 'ceiling' with reported single-procedure success beyond 3 years after percutaneous catheter ablation of 54% for paroxysmal AF (PAF) and 42% for persistent AF [PeAF] (1). Surgical approaches in experienced hands have reported better outcomes (AF-free survival 82% off anti-arrhythmic drugs [AAD] at 3.6 years), albeit with greater morbidity (2). There is agreement that incomplete efficacy is due to (i) inability to create transmural atrial lesions (during pulmonary vein isolation [PVI] or linear ablation), and (ii) imprecise definition of triggering and sustaining AF mechanisms beyond the axiomatic role of the PVs (3). As such, targets and methods for ablation vary, especially in PeAF (rotors, complex fractionated atrial electrograms, linear ablation, voltage-guided ablation, ganglionic plexus [GP] ablation), and it is unclear if targeting anything beyond the PVs is universally applicable, or of incremental benefit (4).

Elegant experimental studies and supporting clinical data have reinforced the critical role of the intrinsic cardiac autonomic nervous system in AF initiation and maintenance (5). This extensive, highly interconnected epicardial neural network consisting of multiple GPs, nerve axons, and interconnecting neurons cover the epicardial surface of both atria (especially the posterior left atrium [LA] and PV antra). The 4 major GPs that innervate the PVs are embedded within epicardial fat pads (except the ligament of Marshall) can be ablated via an anatomic ablation approach which is superior to an approach targeting sites that exhibit an “AV nodal” response with endocardial high-frequency stimulation [HFS (6)]. Some GPs are fortuitously located in areas that are
targeted by conventional percutaneous catheter ablation techniques; thus inadvertent injury to GP tissue and/or axonal interruption are thought to partly contribute to success (7). Indeed, some degree of autonomic denervation is common after PVI and is associated with a lower risk of AF recurrence (8); it may also explain the phenomenon of reduced PV firing after PVI (9). In randomized studies, adding GP ablation to percutaneous antral PVI reportedly increases ablation success by ~25% in PAF patients (10-12). Non-randomized surgical studies show incremental benefit of GP ablation when added to linear ablation amongst mixed AF substrates (2), (13).

The study by Driessen et al. (14), in this edition of the Journal is the first substantial randomized effort comparing outcomes of thoracoscopic ablation with PVI plus linear ablation with and without GP ablation. The 240-patient population comprised of those with drug-refractory PAF (41%) or PeAF (59%) who had enlarged LA, previously failed catheter ablation (23%), or those who preferred a surgical approach. Notably only 11% had PAF with normal atrial size and no prior ablation. Demonstration of PVI confirmed by entrance and exit block was mandatory as was bidirectional block across ablation lines. GPs were identified using anatomical landmarks and HFS but anatomic GP ablation was performed regardless of a HFS-evoked response. Absence of residual GP response was demonstrated in all GP ablation patients. AADs were discontinued at 3 months post ablation. AF recurrence was assessed by symptoms, ECG or Holter. There was no difference in 1-year AF recurrence with the addition of GP ablation to PVI+linear ablation over PVI + linear ablation alone in either PAF (80% vs. 75%) or PeAF patients (66% vs. 63%, respectively). Other notable findings were (i) a very high incidence of atrial tachyarrhythmias (AT) in both groups, but greater with GP
vs. linear ablation (78% vs. 51%); (ii) higher procedural complications with GP ablation driven by major bleeding events (19% vs. 8%) and symptomatic sinus node dysfunction (10% vs. 3%) necessitating pacemaker implantation (5% vs. 0%); (iii) recovery of mean heart rate (a marker of denervation) during the follow up period.

There are clear strengths to this study, which is the first randomized surgical study of GP ablation, including a large sample size from an experienced surgical center, use of acute electrophysiologic endpoints that include confirmation of PVI, linear block and elimination of HFS-evoked response in the GP group, and institution of a combined anatomic and HFS-guided GP ablation. Some argue the benefit of endocardial GP ablation with percutaneous catheter ablation may be due to more extensive LA ablation, which may result in more durable PVI or critical endocardial atrial debulking. It is unclear if endocardial energy delivery even reaches the epicardial fat pads. Thus thoracoscopic visualization and ablation of the epicardial fat pads where the GPs reside, as performed in the present study, more directly measures the incremental benefit of GP denervation in the setting of a relatively durable lesion set.

Given the obvious problems of a heterogeneous patient population with varying underlying AF mechanisms (PAF and PeAF patients), inclusion of patients with prior ablation, intermittent arrhythmia monitoring and short follow up, the neutral result of this study is perhaps not surprising. However prior percutaneous catheter ablation studies have suggested that anatomical GP ablation may be less efficacious in PeAF substrates (15), or that its effects may be delayed as one study found modest superiority of PVI + GP (49% vs. 34%), over PVI + linear ablation at 3 years, but not 1 year follow up
respectively (16). It is plausible that results of the present study may show important differences with longer follow up.

The lack of benefit of GP ablation in this high-risk group of patients may also be explained on a mechanistic basis. Autonomic neural activity may explain AF sustenance in the very early stages (the first few hours) (17), by virtue of GP parasympathetic action on shortening PV action potential duration and GP sympathetic effect on increasing calcium loading creating early after-depolarizations and triggered PV firing (18). However, the role of autonomic remodeling in electrically, structurally, and autonomically remodeled atria of patients with PeAF remains incompletely defined. It is plausible that autonomic influence may play a stronger role early in the disease process while its importance may diminish with progression of the disease to more advance stages and the development of atrial remodeling and fibrosis (5). Also, differential effects of neural remodeling may contribute to varying successes of GP ablation in discrete AF substrates. One animal study showed that neither PVI nor GP ablation altered atrial remodeling and AF vulnerability related to congestive heart failure, whereas GP ablation alone altered tachycardia-related atrial remodeling and AF vulnerability (19).

The recovery of parasympathetic denervation in this study is consistent with prior studies showing reversibility of denervation attributed to atrial neural re-sprouting, hyper-re-innervation (20), with the potential for future heightened sensitivity to remaining neural stimulation and increased vulnerability to AF (21). Indeed parasympathetic denervation has been shown to recover after GP ablation in humans (6), much like the present study. This may have contributed to lack of success of GP ablation.
The notably high incidence of AT in both groups suggests lesion recovery (PVI and/or lines), which is fundamentally acknowledged as a reason for AF-recurrence after catheter or surgical ablation techniques, and may be the likely major contributing factor of failure in both groups. Moreover, the increased incidence of AT in the GP group may also suggest some inadvertent myocardial damage during GP ablation. Likewise some GPs may have been suffered collateral damage during linear ablation, although the fact that 87% still had a persistent HFS-evoked response in the linear group suggests otherwise. The loss of HFS is specific, but not sensitive and some argue that loss of HFS-evoked responses may be an unreliable electrophysiologic endpoint (5). The reason for higher complication rates in the GP group is not immediately apparent. Sinus node dysfunction may be a reflection of right inferior GP ablation that has a final common pathway to the sinus node. The high rate of bleeding may be due to more extensive surgical fat pad dissection necessary to eliminate GP.

So why did GP ablation have a beneficial effect in patients undergoing catheter but not surgical ablation? Beyond differences in patient populations, perhaps patients undergoing surgical ablation have more durable PVI, which mitigates the autonomic effects of GP innervation. Nevertheless, the study by Driessen et al. (14) highlights an emerging theme: we do not know what to do beyond a durable PVI, particularly for patients with PeAF (4,22). More studies are needed to sort out the incremental benefits of GP ablation as catheter ablation techniques produce more durable PVI, but as a surgical adjunct, hope seems lost.
References


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