GP or No GP, Is That the Question?

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It has long been recognized, on the basis of numerous experimental and clinical studies, that the autonomic nervous system has a significant role in the pathogenesis of atrial fibrillation (AF). More recent studies have focused on the ganglionated plexi (GP), which are part of an interconnected structural and functional atrial neural network constituting the intrinsic cardiac autonomic nervous system.\(^1\) The procedure known presently as pulmonary vein isolation (PVI) has undergone substantial changes from ablation of ectopic firing within the pulmonary veins\(^2\) to segmental ostial ablation\(^3\) to circumferential PVI (CPVI).\(^7\) Similarly, targeting the GP has also shown a progression of changes in this procedure. Initially, the GP were identified by high-frequency electric stimulation, which caused a marked slowing of the ventricular response during AF.\(^9\) Further studies found that efficacy of GP ablation could be enhanced by a combination of CPVI and GP ablation.\(^11\) Still others chose to ablate GP using an anatomic approach, which they found to be more effective than using high-frequency electric stimulation to identify and ablate GP and thereby terminate AF.

Follow-up Results of Catheter Ablation for AF

More than a decade of catheter ablation for AF using the myocardial approach (CPVI) with additional linear lesions has resulted in outcomes ranging from 29% to 61%.\(^11\)-\(^17\) Follow-up periods have been as long as 6 years. Success rates have been consistently better in paroxysmal AF, particularly in those patients without structural heart disease and lowest in those with long-standing persistent AF, particularly in patients with comorbidities. In any event, the long-term success rates for catheter ablation for all forms of AF fall far short of those achieved with catheter ablation in patients with the Wolff–Parkinson–White syndrome, AV junctional re-entrant tachycardia, and atrial flutter. The general impression has formed that isolation of the pulmonary veins alone may not be sufficient to achieve optimal success.\(^18\) Others have surmised that differences in outcomes are likely related to a more complex atrial substrate in patients with persistent AF and the fact that the mechanisms responsible for maintenance of persistent AF more often reside outside the pulmonary veins.\(^19\) The same could be said for GP ablation with or without CPVI. A very recent randomized study for catheter ablation in patients with persistent/long-standing persistent AF\(^20\) compared CPVI and additional linear lesions with GP ablation plus CPVI. Although the 3-year follow-up showed a superior result for a single procedure, in the latter group, the best outcome was 49%.

In the present issue of Circulation: Arrhythmia and Electrophysiology, Malcom-Lawes et al\(^21\) studied autonomic modification in patients with paroxysmal and persistent AF. Using continuous high-frequency stimulation, applied endocardially subtending GP sites, they showed that AV block could be induced until the inferior right GP was ablated, thereby confirming previous experimental\(^3\) and clinical observations.\(^12\) More importantly, although the emphasis, by many investigators, has been directed to the GP, they called attention to the atrial neural network. That is, the interconnected part of the intrinsic cardiac autonomic nervous system consisting of axons and smaller collections of GP scattered throughout the atria and the ventricles.\(^22\) An earlier experimental study demonstrated that there was a gradient of atrial refractoriness and AF inducibility that proceeded from the GP at the PV–atrial junction toward the atrial appendages. The AF inducibility increased progressively toward the GP, and the refractoriness also shortened progressively toward the GP. Stimulation of the GP at progressively increasing levels of activation but without atrial excitation exacerbated the bidirectional gradient insofar as the decrease in the atrial refractory periods and enhancement of AF inducibility. Thus, hyperactivity of the GP leads to hyperactivity of the neural network extending into the PV and toward the atrial appendage. In this regard, Malcom-Lawes et al\(^23\) used electric stimulation at atrial sites with synchronized high-frequency stimulation during the atrial refractory period to excite local nerves without atrial excitation. They demonstrated that applying synchronized high-frequency stimulation at atrial sites outside the GP induced PV ectopy. These authors suggest that “ablation of all sites initiating [PV] ectopy may be a potential strategy to prevent paroxysmal AF...and possibly overcome the problem of PV reconnection” (by myocardial and neural conduction?). Extension of autonomic hyperactivity diffusely to the atria may well explain, in part, the progression of paroxysmal to persistent/long-standing persistent AF and the ablation of larger areas of the atria that are required in the latter forms of AF. Indeed, recent studies\(^24\) have identified peripheral trigger sites in the left atrial appendage, particularly in a large number of patients with nonparoxysmal AF after catheter ablation of CPVI and complex fractionated atrial electrograms in the right and left atria and the coronary sinus. Additional lesions were applied to isolate the left atrial appendage, the location of these under-recognized trigger sites. In a recent experimental study,\(^24\) we ablated all the major GP in the dog...
heart and demonstrated that the atrial neural network was a readily responsive area for inducing AF. Moreover, the larger the area involved, the longer the duration of induced AF.

The ability to achieve long-term success with catheter ablation in patients with persistent/long-standing persistent AF remains a significant challenge. This situation has been analogized to metastatic cancer, “It is more difficult to treat, with lower success rates and is much more challenging than localized, more benign disease.” Perhaps, new drugs or combinations of well-known agents may prove effective for AF control. Also alternative therapies may become part of the treatment regimen as recently described.

Disclosures

None.

References


