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Cardiac regulation by the autonomic nervous system: A fine balance

Anna Pfenniger, MD PhD, Rishi Arora, MD

Feinberg Cardiovascular Research and Renal Institute, Northwestern University-Feinberg School of Medicine, Chicago, Illinois

The autonomic nervous system abundantly innervates the myocardium and is composed of extrinsic and intrinsic ganglion cells. The extrinsic autonomic nervous system includes parasympathetic (vagal nerve) fibers and sympathetic fibers (superior cervical ganglion, middle cervical ganglion, cervicothoracic (stellate) ganglion, and thoracic ganglia). The intrinsic nervous system is mostly found in the atria and is composed of ganglionated plexi (GPs) and the ligament of Marshall. The intrinsic nervous system predominantly contains parasympathetic fibers, but about 30% of ganglion cells express a dual adrenergic phenotype.

In the last decade, the autonomic nervous system was shown to play a critical role in the initiation and maintenance of atrial fibrillation (AF), with both sympathetic and parasympathetic innervation being proarrhythmic in the atria.¹ These discoveries led to attempts at modulation of the autonomic nervous system to treat AF. As a proof of concept, the extrinsic autonomic innervation of the heart was ablated in the animal models of AF by targeting both stellate ganglia and vagus nerves.² This led to a reduction in atrial ectopic activity and delay in onset of sustained AF but did not completely prevent the development of AF. Choi et al³ showed that intrinsic autonomic nervous system activity invariably preceded the episodes of atrial arrhythmias in an animal model of AF, suggesting GPs as a promising target for AF treatment.

The catheter or surgical pulmonary vein isolation (PVI) is one of the most important strategies for treating AF. Surgical GP ablation was attempted in addition to minimally invasive surgery for AF, as reviewed by La Meir et al⁴ Initial studies were small, but did not appear to provide a significant increase in surgical success. A subsequent randomized control trial in patients with advanced AF also did not reveal any benefit from surgical GP ablation in addition to PVI.⁵ Of note, most patients enrolled in this study suffered from persistent AF or had received a prior ablation with recurrence, and had relatively large atria.

Due to the proximity of GPs to the pulmonary veins, circumferential catheter-based PVI is expected to affect GP function as well. Inadvertent autonomic denervation has been

Correspondence Rishi Arora, MD, Feinberg Cardiovascular Research and Renal Institute, Northwestern University-Feinberg School of Medicine Northwestern Memorial Hospital, 251 East Huron St, Feinberg 8-503, Chicago, IL 60611. r-arora@northwestern.edu.

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proposed as a critical element in the therapeutic effect of catheter-based PVI in patients with AF. In two randomized clinical trials, Katritsis et al^{6,7} showed superior freedom from AF recurrence in patients who received GP ablation in addition to PVI when compared with PVI alone or GP ablation alone. A recent meta-analysis by Kampaktsis et al⁸ also confirmed better clinical outcomes with a combination of catheter-based PVI and GP ablation for patients with paroxysmal AF, with a less clear effect in patients with persistent AF. However, the overall safety of GP ablation in other clinical contexts remains to be demonstrated. Specifically, the effect of GP ablation on electrophysiological properties of the ventricles is not known.

The ventricles are innervated both by intrinsic and extrinsic autonomic nerve fibers, with the participation of sympathetic and parasympathetic fibers. Zhou et al⁹ have demonstrated that after myocardial infarction (MI), local nerve growth factor (NGF) secretion by the myocardium causes global sympathetic hyperinnervation after retrograde transfer of NGF to the left stellate ganglion. This sympathetic hyperinnervation promotes life-threatening ventricular arrhythmias. Conversely, and as opposed to the effect seen in the atria, the parasympathetic nervous system has an overall protective effect against ventricular arrhythmias.¹⁰

In this Journal, Wu et al¹¹ examined the important question of GP ablation safety, in particular, focusing on the risk of ventricular arrhythmias in the setting of MI. They carefully assessed the effect of surgical GP ablation in a canine model of MI induced by mid left anterior descending (LAD) ligation. They showed that whereas an MI caused ERP prolongation and dispersion, GP ablation led to a more pronounced effect when compared with the sham procedure. This also correlated with increased QTc interval and dispersion. In addition, animals subjected to GP ablation were also more susceptible to ventricular tachycardia or ventricular fibrillation induction after programmed stimulation with ventricular extrastimuli.

They correlated these electrophysiological findings with the increased density of sympathetic innervation in the peri-infarct zone in animals subjected to GP ablation. Interestingly, these animals also displayed the higher levels of NGF in that area, pointing towards a potential mechanism for sympathetic hyperinnervation.

In addition to the sympathetic hyperinnervation demonstrated by Wu et al,¹¹ GP ablation is also expected to cause relative parasympathetic denervation. Given the known protective effect of the parasympathetic nervous system against ventricular arrhythmias, this by itself could also partially explain the electrophysiological consequences of GP ablation illustrated in this study. Jungen et al¹² recently showed that parasympathetic blockade in isolated murine hearts, either pharmacologically or with partial atrial denervation, caused increased susceptibility to ventricular arrhythmias. Interestingly, this effect was associated with shortening of ventricular ERP. This difference may be attributed to the difference in model (murine vs canine, isolated heart vs in vivo, intact heart vs post-MI), possibly due to subtle differences in the fine balance of parasympathetic to sympathetic activity.

The precise mechanism by which GP ablation leads to sympathetic hyperinnervation after an MI remains to be elucidated. The authors discovered the concomitant upregulation of NGF in the peri-infarct area, which could lead to increased sympathetic innervation as previously demonstrated by Zhou et al,⁹ However, the pathway leading to NGF secretion remains unknown. Alternatively, the loss of parasympathetic innervation may also lead to increased sympathetic activity by disrupting homeostatic antagonism. It is for instance known that muscarinic receptors on sympathetic nerve terminals attenuate norepinephrine release,¹³ which participates in a phenomenon called accentuated antagonism.¹⁴

The findings detailed by Wu et al¹¹ in this journal argue for a careful patient selection for performing GP ablation, given the potential for harm in some clinical situations, such as after an MI. It also highlights the need for a more targeted strategy for atrial parasympathetic inhibition that would not disrupt ventricular innervation. Such a refined method has not been established so far and merits further investigation.

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