Another Piece to the Puzzle
Linking the Cardiac Nervous System to Atrial Fibrillation in Pulmonary Arterial Hypertension

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See related article, pp 1042–1049

Pulmonary arterial hypertension (PAH) is a rare, debilitating disease characterized by an occlusive pulmonary vasculopathy, resulting in elevated pulmonary vascular resistance and subsequently death from right ventricular (RV) failure. Current therapeutic options in PAH are limited to pulmonary vasodilator therapy, which have improved clinical outcomes but only target part of the underlying pathology. Because of the persistent high mortality of this disease process, there is a need and an interest to develop novel therapeutic targets for PAH.

Sympathetic and parasympathetic abnormalities are well identified in PAH. Downregulation and desensitization of adrenoceptors have been observed in RV myocytes. In patients with PAH, decreased RV β-adrenoreceptor density is associated with increased incidence of RV failure. Although there are increased circulating catecholamine levels in patients with RV failure from PAH, the RV is less responsive to β-agonists.

These findings represent an adrenergic remodeling manifesting as an inability to augment RV function with catecholamine stimulation and demonstrate a potential need to develop interventions that can target sympathetic nervous abnormalities in the RV in PAH.

It is provocative to think what the effects of a therapeutic intervention that targets both sympathetic overactivity and atrial arrhythmias could have on clinical outcomes in PAH. In this current issue of Hypertension, Huang et al demonstrate the utility of anterior right ganglionated plexus ablation in the sensitivity of the right atrium to atrial fibrillation and atrial flutter in patients with PAH.

The authors measured the atrial effective refractory period and atrial fibrillation and atrial flutter inducibility before and after anterior right ganglionated plexus ablation with sympathetic stimulation by left stellate ganglion or left renal sympathetic nerve in a canine model of PAH. Histological analysis identified the cellular substrate of increased β1-adrenergic receptors, as well as an increased heterogeneity of non-phosphorylated connexin 43 expression in the PAH canine group, thus, creating the perfect storm for an increased atrial tachyarrhythmia susceptibility in a sea of elevated sympathetic neurohormones. The combination of electrophysiological cellular remodeling and anterior right ganglionated plexus and left stellate ganglion stimulation increased vulnerability to atrial fibrillation and atrial flutter in canines with PAH. With ablation of the anterior right ganglionated plexus, the authors demonstrated a suppression of atrial arrhythmias in response to sympathetic stimulation. This showed that both intrinsic cardiac nerves, especially right atrial, as well as extrinsic nerves, contribute to atrial fibrillation and atrial flutter sensitivity in this PAH model. As a result, modulation of both the parasympathetic and sympathetic inputs of the cardiac nervous system can reduce the susceptibility to atrial tachyarrhythmias that occurs with PAH. The work presented here by Huang et al suggests that in addition to the current standard of care for atrial fibrillation, renal denervation and ganglionated plexi ablation may have a particular benefit for improving the outcomes of atrial tachyarrhythmias in the PAH population.

This study is limited by being performed in a single animal model of PAH. There are considerable differences between species in terms of innervation of the pulmonary vasculature. In dogs and humans, sympathetic noradrenergic axons innervate small arteries down to 50 μm in diameter, whereas in rats and mice, noradrenergic innervation ceases soon after the hilum of the lung. Therefore, how applicable these findings are to human pulmonary blood vessels is unclear because this interspecies variation could impact the response to ablation therapy or changes to sympathetic tone.

Pulmonary artery and renal artery denervation have been studied as methods of modifying sympathetic tone in PAH. In a small study by Chen et al, pulmonary artery denervation produced a sustained decrease in mean pulmonary arterial pressure of >10 mm Hg at 3-month follow-up in addition to an improvement in 6-minute walk distance.

In a canine model of PAH, animals with PAH that underwent renal sympathetic denervation had significantly lower pulmonary artery pressures, as well as less vascular remodeling and RV fibrosis on pathology. Renal sympathetic denervation decreases central sympathetic activation, and this study suggested that renal sympathetic denervation might attenuate the pulmonary vasculopathy that characterizes PAH, although the utility of this procedure in humans is yet to be examined. These studies highlighted the possibility of procedural...
denervation as a treatment of PAH; however, the durability of the results and the long-term complications is yet to be seen.

Pharmacological adrenergic modification with β-blockade has been a topic of recent research as a method to decrease systemic sympathetic tone in patients with PAH. Bisoprolol and carvedilol have both been studied in rodent models of PAH and demonstrate improved RV function, decreased RV fibrosis, and less maladaptive remodeling.12,13 Nebivolol has also been studied in a rodent model of PAH and was shown to improve endothelial dysfunction, pulmonary vascular remodeling, and right heart function.14 Nebivolol is particularly intriguing because of the potential to combine sympathomimetic effects, as well as vasodilator effects, from altering nitric oxide signaling. These studies have demonstrated that β-blockers may have potential therapeutic impact in PAH.

The work by Huang et al in this issue of Hypertension serves to improve our understanding of the sympathetic nervous system and modifications thereof in PAH. Increased sympathetic tone has been established in left ventricular systolic heart failure, and modification of the autonomic nervous system with β-blockade has proven to be a durable and effective therapy. Currently, the optimal management of increased sympathetic tone in patients with PAH is yet to be determined. In addition to establishing possible therapies for atrial arrhythmias in PAH, these authors reaffirm the presence of increased sympathetic tone and highlight modification of the vagal and adrenergic nervous system in a PAH patient as an emerging therapeutic target (Figure).

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**Disclosures**

None.

**References**


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