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EDITORIAL COMMENT

Vagal Nerve Stimulation for Pulmonary Hypertension

Some Promise, Some Skepticism*

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Pulmonary hypertension (PH) or elevated blood pressure in the pulmonary vasculature is a serious disease entity in its own right and a grave complication of other disorders. PH is divided into 5 classes by the World Health Organization. Class 1, or pulmonary artery hypertension (PAH), includes PH due to idiopathic, heritable, and genetic causes, as well as drugs, toxins, and some connective tissue diseases and infections. Unfortunately, PAH is lethal, with one-half of all patients dying within 7 years of their initial diagnosis (1). The pathophysiology of PH is complex, with an intricate interplay among diverse cell types, including smooth muscle cells, endothelial cells, fibroblasts, inflammatory cells, and neurons (2–6). Undoubtedly, this complexity contributes to the difficulty in devising therapies to substantially improve the clinical course of patients with PAH.

Neurohumoral input modulates the behavior of many of these implicated cell types, and autonomic dysregulation (enhanced sympathetic activity and parasympathetic withdrawal) characterizes many cardiovascular diseases, including heart failure with reduced ejection fraction (HFrEF) and PAH (7–9). Beta-adrenergic blockers are standard of care for patients with HFrEF and increase survival in this setting; however, the use of beta-adrenergic blockers for PAH remains controversial (10). The renin-angiotensin-aldosterone system (RAAS) is upregulated in PH (5). Indeed, elevated plasma levels of RAAS hormones (aldosterone in humans with PAH [11] and angiotensin II in a monocrotaline-induced dog model of PH [12]) have been reported. Mineralocorticoid antagonism in rodents attenuates experimental PH and pulmonary vascular remodeling (13), and renal sympathetic denervation in dogs suppresses RAAS activation and prevents monocrotaline-induced PH (12). Pulmonary artery denervation reduces pulmonary artery pressure in thromboxane A_2-induced PH in pigs (14) and was reported to improve clinical outcomes in patients with PH/PAH (15). However, controversy regarding methodological and ethical issues in the latter study has arisen (16).

In contrast to these efforts to inhibit sympathetic activity in PH, little is known regarding the therapeutic efficacy in PH of restoring autonomic balance by enhancement of parasympathetic activation. Pyridostigmine is an acetylcholinesterase inhibitor that augments parasympathetic activity, is widely used in myasthenia gravis, and improves autonomic and left ventricular function in HFrEF (17). Recently, in experimental PH induced in rats by SU5416 injection and then hypoxia exposure, daily pyridostigmine treatment normalized cardiovascular autonomic function and attenuated pulmonary vascular remodeling and inflammation, as well as right ventricular afterload and dysfunction (17). The authors postulate that in addition to enhancing parasympathetic activity, pyridostigmine may blunt sympathetic tone.

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With this background, the study by Yoshida et al. (18) investigating the role of direct vagal nerve stimulation (VNS) as a therapeutic strategy for PH in this issue of *JACC: Basic to Translational Science* is of high interest. Stimulation of the right cervical vagus nerve via electrodes from an implanted neurostimulator attenuated the increased pulmonary artery pressure, resistance, and vascular remodeling in rats exposed to SU5416 followed by 3 weeks of hypoxia.

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Furthermore, VNS stimulation dramatically improved survival of these rats. Inflammation is increasingly recognized as a key contributor to PH pathogenesis (4), and Yoshida et al. (18) found that the lungs of rats subjected to VNS have reduced inflammation, as indicated by reduced levels of the cytokines interleukin-1β, interleukin-6, and monocyte chemoattractant protein-1 and by accumulation of CD68-positive cells.

Although the results are compelling, this study (18) has important limitations and raises questions that should be addressed in future investigations. First, it remains to be delineated how much of the positive effects of VNS in the SU5416/hypoxia model of PAH is due to enhancing parasympathetic input directly to the right heart versus directly to the lung and its vasculature. Extending this point further, mechanisms linking autonomic dysregulation to worsened pulmonary vascular remodeling are not defined. Second, Yoshida et al. (18) astutely point out that as with all animal models of PAH, the pathology of the SU5416/hypoxia rat model substantially differs from that of human PAH, and thus, VNS should be assessed in multiple animal models. If the effects of VNS prove promising across diverse animal models, the safety and efficacy in humans then need to be evaluated in clinical trials. Indeed, VNS may interact with medications used by patients with PAH. Along these lines, some skepticism regarding whether the positive results will be translatable to humans is warranted as VNS has been shown to benefit animals in models of ischemic heart failure, but studies in humans with HFrEF report safety but not efficacy (19). Finally, mechanical failure of the VNS system in 11 rats in the current PAH study is concerning given the limited number of rats (n = 54) in the survival study. Taken together, the findings of this initial study are compelling and call for further investigations that will evaluate the efficacy, safety, and mechanisms of restoring autonomic system balance with VNS in the context of PH.

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