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EDITORIAL COMMENT

Do Not Lose Your Nerves

Autonomic Neuromodulation in Pulmonary Arterial Hypertension*

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Vital functions of the cardiovascular system, including heart rate and contractility or vascular tone, are unconsciously controlled by the autonomic branch of the peripheral nervous system and its 2 interacting components: the sympathetic and the parasympathetic nervous systems. Whereas neurotransmitters released from sympathetic neurons usually activate, parasympathetic signals downregulate or lower a given function, including blood pressure. It comes as no surprise that an imbalance of sympathetic and parasympathetic neuronal signals may contribute to organ dysfunction and disease, including arterial hypertension, chronic heart failure, and several others. Cardiac and other thoracic organ functions are controlled via the sympathetic trunk branching into lower cervical and upper thoracic ganglia, in parallel with parasympathetic signaling via the vagal ("wandering") nerve. Efferent vagal nerve fibers are located in the so-called cardiac plexus and the adventitia of major arteries and precapillary arterioles; afferent nerve fibers are the baroreceptors located at the carotid sinus or the aortic arch, transmitting information from stretch fibers to the solitary tract nucleus in the medulla.

Manual or mechanical stimulation of the vagal nerve by compression of the carotid artery was first described in the early 1880s for the abortive treatment of seizures, using quite drastic methods such as the so-called carotid fork.[1] More than a century later, electronic nerve-stimulating implants are widely used for several disease conditions, thanks to technical advancements and innovations in this area. Among others, device-based electrical stimulation of carotid baroreceptors to lower sympathetic activity is being explored as a therapeutic option in patients with resistant arterial hypertension.

Pulmonary arterial hypertension (PAH) is characterized by progressive small pulmonary artery remodeling that results in increased pulmonary vascular resistance and pulmonary artery pressure. The resulting hemodynamic changes lead to right heart remodeling and ultimately dysfunction, and the severity of heart failure determines the patients' prognosis. Endothelial dysfunction, smooth muscle cell proliferation, and inflammation have been established as key events in the pathophysiology of this cardiopulmonary disease.[2] Sympathetic and parasympathetic nerves are also abundant in the adventitia of the pulmonary artery, and reduced parasympathetic nervous system activity, reported in patients with PAH, may contribute to right ventricular (RV) dysfunction.[3] However, and although pharmacologic inhibition of adrenergic receptors has proved to be successful in preventing pulmonary vascular remodeling and RV dysfunction in experimental models of PAH, β-blockers are not recommended in patients with PAH because HEART rate is needed to compensate for the systolic dysfunction and cardiac output reduction in this condition. For this reason, nonpharmacologic approaches to target sympathetic overactivation in the pulmonary circulation, such as interventional pulmonary artery denervation or cervical sympathetic trunk transection, have been considered as potential therapeutic strategies.

In this issue of *JACC: Basic to Translational Science*, Wang et al[4] use an experimental PAH model in rats to

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test the effects of carotid baroreceptor stimulation (CBS), achieved by delivering periodic electrical impulses to nerve bundles at the right common carotid artery near the carotid sinus. After an observation period of 4 weeks, CBS improved pulmonary hemodynamics and mitigated RV hypertrophy, stiffening, and dysfunction. Histologic analyses confirmed less cardiac fibrosis, and Western blot analysis reduced MMP2 and MMP9 protein expression. At the end of the 70-day observation period, the survival rate of CBS-treated PAH rats was higher than that in rats implanted with CBS without stimulus delivery. Systemic systolic and diastolic blood pressure levels also normalized in CBS-treated PAH rats, although reductions in systolic blood pressure may, at least in part, also have developed as a consequence of the chosen device settings. Thus, the present study is 1 of the first to show that device-based autonomic neuromodulation is effective for combating hypertension in the pulmonary artery and its sequelae affecting the heart.

Moreover, what makes this study particularly interesting are the findings from the RNA sequencing analysis of material explanted from the intralobar pulmonary artery: GO enrichment analyses discovered 79 differentially expressed genes in rats in which sympathetic overactivation was inhibited by CBS, and protein-protein interaction network construction of 10 hub genes revealed altered expression signatures of genes related to inflammatory immune signaling pathways. These findings suggest that CBS device treatment exerted, at least in part, its beneficial effects on cardiopulmonary remodeling and RV function in PAH by modulating immune cell activation and inflammation.

That signals derived from neurons act on immune cells and may induce their activation and the release of cytokines has been discovered earlier. In particular, signals from cholinergic neurons were found to inhibit acute inflammation and to promote an anti-inflammatory response in real time, just as they control heart and respiratory rate and other vital functions. The bidirectional communication of neuron and immune cells is possible because of the expression of adrenergic receptors on cells of the innate immune system, in particular macrophages, which enables them to respond to neurotransmitters. Since the discovery of this new biological pathway, termed the inflammatory reflex,[5] the possibility to manipulate the neuroimmune axis has been explored as a novel therapeutic strategy for treating inflammatory disease.[6] Being spatially localized and restricted to cells expressing cholinergic receptors, the anti-inflammatory circuit by neuronal acetylcholine offers several advantages compared with systemic, diffusible, and less specific anti-inflammatory mediators such as glucocorticoids. Of note, as with all biological systems, a careful balance between activating and inhibiting signals is crucial, inasmuch as the immune system is also involved in tissue healing and repair.

Looking at the specific candidates identified in the current study: Besides elevated levels of the "usual suspects" of proinflammatory cytokine mediators, such as TNF-α and IL-6, or genes associated with their activities, such as TRAF3 interacting protein 3 (Traf3ip3) or immunoglobulin superfamily member 6 (Igsf6), several novel potential mediators were found to be differentially expressed in CBS-treated PAH rats, many of which were not previously associated with PAH, such as protein tyrosine phosphatase, receptor type C (Ptprc), but also genes whose function in disease has yet to be established, such as membrane spanning 4-domains A7 (*Ms4a7*) or interleukin-21 receptor (*Il-21r*). For others, such as toll-like receptor-7, a role as potential inducer of an autoimmune vasculopathy in PAH was recently shown in a rat model of Sugen 5416-induced pulmonary endothelial injury.[7] More such studies will be needed to validate the role of specific factors in the pathophysiology of PAH or in mediating the beneficial effects of CBS. This is of particular importance, given that gene expression changes were observed in material obtained after 4 weeks of CBS treatment; thus, causality needs to be established in future studies.

When interpreting the data, one needs to keep in mind that a single intraperitoneal injection of monocrotaline, a pyrrolizidine alkaloid present in plants, was used to induce the clinical and hemodynamic characteristics of PAH in rats. Monocrotaline acts by inducing an inflammatory response and organ toxicity, including lung fibrosis, and the findings in this experimental model therefore cannot be directly extrapolated to patients with the disease. In this regard, validation of potential candidates in patients' biomaterial would have helped to rule out effects related to this specific model and also added to the translational potential of the study. How CBS affects different vascular cell types involved in the pathophysiology of PAH, and whether the observed changes in gene expression also explain the inhibitory effect of CBS on smooth muscle cell proliferation, also were not examined in more detail.

Nonpharmacologic approaches to treat hypertension and other diseases are on the rise, and a new field of bioelectronic medicine is developing that uses electricity to regulate the biological processes underlying various diseases. In PAH, current treatment

options and drugs approved by the US Food and Drug Administration that target the prostacyclin, nitric oxide, and endothelin pathways exert their effects mainly by counteracting vasoconstriction and vascular proliferation. Although the presence of inflammation and immune dysregulation in the pathophysiology of PAH have been known for some time, specific anti-inflammatory therapy is not part of the standard therapy of PAH, and increased levels of factors not targeted by those pharmacotherapies may explain why there is still a need for approaches that improve patients' prognosis. Electrical stimulation of the parasympathetic anti-inflammatory response may be an option to fill this gap. Of note, the study by Wang et al[4] did not test pharmacologic therapy as a control; such a comparison, or combined treatment, would have been helpful to disentangle the contribution of nervous system imbalance from those of other signaling pathways.

In conclusion, the present work adds to our understanding of the pathomechanisms of PAH and underscores the contribution of autonomous nervous system dysregulation and immune system activation. Moving forward from here, demonstrating its safety and effectiveness in humans will be necessary to determine the usefulness of harnessing the neuroimmune axis in this disease.

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