EDITORIAL COMMENT

Targeting Neurohormonal Activation in Pulmonary Arterial Hypertension

Putting the Puzzle Together*

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Pulmonary artery hypertension (PAH) is an angioproliferative disorder of the lung circulation that results in a heart failure syndrome with a grim prognosis [1]. Similar to other forms of left ventricular failure, right ventricular failure (RVF) is progressive and largely incurable unless the primary cause can be eliminated (i.e., lung transplantation for PAH). Although pressure overload is a key factor in RVF due to PAH, pressure overload alone does not explain the progression of the disease [1]. Indeed, similarly to what has been described for left ventricular failure, neurohormonal activation affects the progression of RVF.

The renal body fluid regulating system plays a central role in neurohormonal activation in heart failure, regulating volemia, cardiac contractility, venous return, and arterial tone [2]. As an attempt to permanently modulate the renal body fluid regulating system, investigators have postulated the use of renal denervation [2]. Efferent sympathetic nerves accompany the renal arteries up to glomerular arterioles, the juxtaglomerular apparatus and renal tubules, which upon activation increase the secretion of renin by the juxtaglomerular cells [3]. Renal denervation is being studied for the treatment of resistant systemic hypertension and for left ventricular failure, and arrhythmias such as atrial fibrillation and ventricular tachycardia [2]. In addition to reducing left ventricular afterload, renal denervation appears to improve left ventricular function in a load-independent manner [2], likely by reducing the maladaptive effects of neurohormonal activation on the heart and vasculature.

The role of neurohormonal activation in the pathobiology of both RVF and PAH is less defined, but it is likely to affect not only the systemic but also the pulmonary vasculature. Lung tissue samples from animal models and humans with PAH exhibit an increased expression and activity of the angiotensin converting enzyme, as well as up-regulation expression of the angiotensin II type 1 receptor [4,5]. The

angiotensin receptor blockade, losartan, reduces pulmonary vascular resistance in monocrotaline-treated rats [5]. Following this line of thought, Da Silva Gonçalves Bos et al. [6] report in this issue of *JACC: Basic to Translational Science* that renal artery denervation reduces pulmonary vascular remodeling and right ventricular (RV) diastolic stiffness in experimental PAH through modulation of the neurohormonal system, thus expanding the previously postulated link [5] between the renal body fluid regulating system, neurohormonal activation, and pulmonary vascular remodeling. In this elegant study, the investigators used 2 independent models of PAH and severe RVF in the rat, including the 1 induced by the combination of a vascular endothelial growth factor receptor blocker and chronic

hypoxia that closely resembles PAH in humans (7). Renal artery denervation was achieved surgically by removing nerve bundles and chemically by using a 10% phenol-ethanol solution. The efficacy was validated by measuring norepinephrine content in renal tissue and physiologically by a reduction in systemic arterial pressures. Renal denervation resulted in a reduction of muscularized and obliterated arterial vessels in the lung vasculature, a subsequent reduction in pulmonary vascular resistance, and an improvement of arterial elastance. Perhaps 1 of the strongest features of the study is the assessment of ventricular-arterial coupling and diastolic stiffness by pressure-volume loops, showing an improvement of RV-arterial coupling. In addition, renal denervation resulted in a reduction of RV fibrosis, which was associated with an improvement in RV diastolic stiffness despite having no significant effects in RV end-diastolic diameter, tricuspid annular plane systolic excursion or cardiac output. Lastly, the authors demonstrated a significant increase in the expression of angiotensin II type 1 receptor and mineralocorticoid receptor in the arterioles of animals with experimental PAH, which decreased after renal artery denervation.

Neurohormonal modulation via renal artery denervation has been shown to improve systemic arterial hemodynamics and cardiac hypertrophy in preclinical animal models of both RV and LV failure (2), thus the results from the present study between renal artery denervation, reduced neurohormonal activation, and improved pulmonary vascular remodeling are sound. Other researchers have previously reported a similar improvement in pulmonary vascular resistance and RV fibrosis after preventive renal artery denervation in 7 dogs with PAH, a change that was associated with a reduction in circulating plasma levels of aldosterone (8).

However, despite the high quality of the experimental work (6), the mechanism(s) explaining the cardiovascular improvements are largely unexplored and not entirely explained by the available data. To what extent the changes seen in lung vascular remodeling after renal denervation depended on the hemodynamic unloading of the lung circulation remains unclear. This question is particularly interesting because other mechanical—nonpharmacological—approaches to improve RV-arterial coupling have been described. Denervation of the pulmonary artery has demonstrated beneficial effects preclinically (9) as well as clinically in selected patients with severe PAH (10). Importantly, and in contrary to renal denervation, pulmonary artery denervation effectively decreases mean pulmonary arterial pressure (10).

The potential implications of the present study (6) are many. Although it is unlikely that renal artery denervation will be used as a treatment strategy for PAH in the near future, the concept of neurohormonal blockade to prevent or treat severe PAH continues to be a strategy worth exploring. Only few studies have evaluated the role of angiotensin converting enzyme inhibition in small cohorts of patients with idiopathic PAH (11) and congenital heart disease-associated PAH (12), setting the stage for further exploration.

One additional consideration should be given, however, to the limitations of animal studies, as well as the challenges of developing clinical translational programs. The rise and fall of the SYMPLICITY trials (13), which were designed to treat resistant hypertension with renal denervation, left many lessons that should be considered before translating the findings of this study. Indeed, despite the vast amount of pre-clinical data and evidence from pilot clinical trials, renal denervation proved insufficient to meet its goals when the method was rigorously tested (13). Moreover, renal artery denervation appears to be in no way curative in experimental PAH (6), and the reductions in pressure are modest at best, thus emphasizing that neurohormonal activation—at least through renal artery sensing—modulates but it is not an essential mechanism of disease in PAH. Nonetheless, the potential protective effects of renin-angiotensin-aldosterone blockade on the RV should not be overlooked, considering that RVF is a major prognostic indicator in PAH and that a strategy aimed at protecting the RV independent of reducing pulmonary artery pressure may be sufficient to prolong survival (1). In this regard, it will be interesting to compare and contrast renal nerve denervation with pharmacological intervention trials using neurohormonal antagonists to determine which strategy is more effective in terms of slowing RVF (6). Targeting imbalanced neurohormonal activation in pulmonary hypertension has been and continues to be a tough puzzle to put together. However, paraphrasing the American composer Stephen Sondheim, "the nice thing about doing a puzzle is that you know there is a solution."

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