



Pulmonary artery denervation: a novel treatment modality for pulmonary hypertension

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Pulmonary arterial hypertension (PAH) is a complex pulmonary vascular disease that leads to right ventricular (RV) failure and sudden cardiac death (1). PAH is associated with sympathetic nervous system (SNS) over-stimulation, renin-angiotensin-aldosterone system (RAAS) activation and cardiac arrhythmias. RAAS activation generates vasoactive compounds that result in pulmonary vasoconstriction and vascular remodeling, hallmarks of PAH (2). It is suggested that patients with PAH often have a low cardiac output and that RAAS and SNS over-activation are merely compensatory mechanisms for that decreased cardiac output (3).

Strategies aimed at reducing activation of SNS and RAAS by pharmacologic and direct invasive interventions have yielded mixed results. In a recent effort to directly target the over-activation of the sympathetic nerves in patients with left ventricular (LV) failure associated pulmonary hypertension (PH), Zhang and colleagues demonstrated that pulmonary artery denervation (PADN) is associated with significant improvements in hemodynamic and clinical outcomes in patients with combined pre- and post-capillary PH (4).

The effects of β -adrenergic receptor signaling in PAH development have been extensively studied in pre-clinical and clinical settings using different pharmacologic α/β -adrenergic receptor agonists/antagonists with mixed results. Multiple clinical trials have been conducted to assess the efficacy and safety of β -blockers in PAH. Smaller or escalating doses

of β -blockers seem to be beneficial and well-tolerated in PAH (5-11). In fact, Carvedilol resulted in improvement of RV ejection fraction in RV failure (12) without any discernable adverse events or clinical deterioration (5,6). In an exploratory study involving 18 PAH patients, Bisoprolol did not show improvement in RV function or 6-minute walk distance (6-MWD) (7). Although β -blockers have been effective in partially reversing RV remodeling associated with PAH (12,13), their negative chronotropic and inotropic effects may result in impairment of RV function and worsening of RV failure. This highlights the importance of the choice of β -blockers based on their receptor specificity.

Pharmacologic inhibition of RAAS in PAH has also been tested in both pre-clinical and clinical studies, as PAH is associated with an increase in circulating renin activity, angiotensin I and II levels (3,14,15). Eight-week treatment with losartan resulted in a significant decrease in mean pulmonary artery pressures, an increase in RV ejection fraction and improvement in functional capacity compared to baseline in thirty-three PH patients with different etiologies (15).

More recently, various invasive strategies aimed at modulating the autonomic nervous system have been tested for the treatment of PAH. These include sympathetic ganglion block (16), PADN (17-20) and catheter based renal denervation (21,22).

PADN is a novel, minimally invasive endovascular catheter-based interventional therapy using radiofrequency ablation to abolish the pulmonary arterial baroreceptors to pressure response aimed at decreasing sympathetic activation in PAH or PH secondary to LV failure (19). Chen *et al.* tested efficacy of PADN in 10 Mongolian dogs with balloon occlusion-induced acute PAH and found complete abolishment of pressure responses at the main bifurcation of the left pulmonary artery (19). Recently, Rothman and colleagues applied radiofrequency PADN in a swine model of PH caused by Thromboxane A2 agonist-mediated vasoconstriction, that resulted in reduced mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) and increased cardiac output. These changes correlated with the number of histological denervation lesions in the pulmonary arteries, highlighting the fact that location is critical to successful PADN (17). In the PADN-1 study, Chen and colleagues tested the safety and efficacy of PADN in patients with PAH (n=13) and found significant reduction of mPAP and PVR and significant improvement of 6-MWD, WHO class, and N-terminal brain natriuretic peptide levels at 3-month follow up (20). The phase II of this study was performed in a larger cohort of 66 patients with mixed PH etiologies who all underwent PADN. Interestingly, the beneficial effects of PADN treatment observed in phase I of the study at 3-month follow up were maintained at 6-months and 1-year follow-up (18).

In a recent prospective, randomized sham-controlled trial (PADN-5 trial) of 98 combined pre- and post-capillary pulmonary hypertension (CpcPH) secondary to left sided heart failure patients, Zhang *et al.* assessed the benefits of PADN versus Sildenafil plus sham PADN procedure (4). The authors defined CpcPH as mean pulmonary arterial pressure ≥ 25 mmHg, pulmonary capillary wedge pressure >15 mmHg, and PVR >3.0 Woods Units. At 6-month time point, 6MWD was significantly higher and PVR was significantly lower in PADN group *vs.* Sildenafil group. Clinical worsening was also significantly less frequent in the PADN group (4). Compared to the previous clinical studies, this was a much-improved study as it was a larger, multicenter, randomized study with a sham PADN-treated control group. On the other hand, patients in this control group received Sildenafil plus standard medical therapies, that have not been shown to have any proven beneficial effects in CpcPH patients. Furthermore, the precise mechanisms by which PADN improves cardiac function are yet to be fully elucidated.

Nevertheless, the study by Zhang *et al.* opens the door

to more focused studies in the near future. Their data demonstrated that within both treatment groups there were extreme responders, mild responders, and non-responders. And while the PADN arm had a greater proportion of responders *vs.* non-responders, dramatic improvement was not limited to this group. The greatest challenge may be to discern which treatment best fits an individual patient. Finally, PADN is an irreversible and tissue destroying procedure; less altering interventions such as spinal cord stimulation may one day allow more nuanced modulation of pulmonary sympathetic outflow.

In conclusion, the evidence for SNS and RAAS activation in various forms of PH is convincing and could serve as a common therapeutic target. Direct, targeted, and minimally invasive procedure such as PADN offers a novel therapeutic option for the treatment of PH. Whether these procedures are superior to the standard of care pharmacologic therapies for PH is still debatable. The efficacy and safety of such procedures remains to be established in the long term.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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