AsiaIntervention
2026;12:14-16
DOI: 10.4244/AIJ-D-26-00006

EDITORIAL

Flipping the focus – treating post-capillary pulmonary hypertension with pulmonary artery denervation

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Heart failure (HF) is a worldwide health issue. Many HF cases involve patients with preserved ejection fraction (HFpEF). HFpEF results in elevated morbidity and mortality. Long-term pulmonary venous congestion causes pulmonary hypertension (PH). PH driven by HF (PH-HF) includes isolated post-capillary PH (IpcPH) as well as combined pre- and post-capillary PH (CpcPH). While directed therapies for World Health Organization (WHO) Group I PH are not recommended for PH-HF, the presence of PH does worsen HF severity. Preclinical studies show promise for pulmonary artery denervation (PADN). The PADN-5 study (ClinicalTrials.gov: NCT02220335) demonstrated that PADN significantly improved outcomes in patients with CpcPH. However, the effects of PADN in HFpEF patients with IpcPH are still unknown.

In this issue of AsiaIntervention, the study by Jiang and colleagues from Nanjing Medical University aimed to evaluate the feasibility, safety, and efficacy of PADN in patients with HFpEF-induced IpcPH[1]. PADN is an emerging option in some subsets of HF patients[2]. Focusing on the impact of PADN to improve diastolic function is a conceptually promising avenue[3-5]. Diastolic function, active ventricular relaxation or compliance, is a historically overlooked component of overall cardiac function[6-10].

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This report is a single-centre, proof-of-principle cohort study conducted in China among adult patients with chronic ischaemic or non-ischaemic cardiomyopathy (≥6 months duration) and stage C HF[1]. Subjects with New York Heart Association (NYHA) Class III or ambulatory Class IV symptoms and who had received guideline-directed medical therapy (GDMT) for at least 3 months before enrolment were included in the analysis. PADN is approved for Group I PH in China. However, PADN remains unapproved for IpcPH; this work relied on a compassionate use framework. Right heart catheterisation (RHC) was performed via the femoral vein immediately before PADN. Pulmonary artery angiography was also performed. The PADN system consists of a radiofrequency generator, a control handle, and a PADN catheter. Three ablation sites were treated using a target temperature of ≥50°C, a maximum temperature of 60°C, and an ablation duration per site of 120 seconds. Binary data were analysed using Fisher's exact test. Haemodynamic changes were assessed at baseline and at 1, 3, 5, and 10 minutes post-PADN using SPSS Statistics (IBM).

Ten patients (mean age: 65.4 years) with IpcPH secondary to HFpEF were enrolled. All patients were NYHA Functional Class III at baseline. The PADN procedure was successfully performed in all patients without procedural complications. All were discharged the following day without complications. At 10 minutes post-PADN, systolic pulmonary arterial pressure (PAP) decreased from 38.9±4.6 mmHg to 32.3±6.4 mmHg (a 16.9% reduction), with mean PAP and pulmonary artery wedge pressure (PAWP) reductions of 16.9% and 22.9%, respectively. The authors noted no significant changes in cardiac output, right atrial pressure, or pulmonary vascular resistance (PVR). Mean PAP reduction was observed in all ten patients. Of the

ten patients, two experienced an increase in the minimum rate of change of ventricular pressure (dP/dt_{min}) at 10 minutes post-PADN, alongside a significant rise in cardiac output.

This study demonstrates the feasibility, safety, and potential clinical efficacy of PADN in patients with HFpEF and IpcPH. PADN achieved technical success in all cases, leading to improved haemodynamic and functional outcomes. In particular, left ventricular (LV) diastolic function significantly improved, as indicated by a marked fall in dP/dt_{min}. Since pulmonary vasodilators recommended for WHO Group I pulmonary arterial hypertension (PAH) are not approved for PH-HF, GDMT remains the standard of care for heart failure with reduced ejection fraction but not for HFpEF. Consequently, device-based therapies have emerged as promising alternatives for this high-risk population. HF subjects suffer autonomic dysfunction, marked by excess sympathetic activation and parasympathetic withdrawal. In the pulmonary circulation, excessive sympathetic activity contributes to increased PVR, PAP, and right ventricular (RV) dysfunction. PADN-5 demonstrated that PADN favourably impacts exercise capacity, cardiac function, and clinical outcomes in patients with CpcPH, irrespective of HF subgrouping (reduced ejection fraction [EF] vs preserved EF); its role in HFpEF-induced IpcPH has evolved slowly. High pulmonary artery pressures in IpcPH are due to passive backward transmission of left atrial pressure, without significant pulmonary vascular remodelling. In this study by Jiang et al[1], PADN resulted in a significant reduction in PAP, accompanied by a 16.9% reduction in PAWP. No patient developed an acute pulmonary oedema. PADN may have potential for treating LV diastolic dysfunction in HFpEF-induced IpcPH. As was noted in PADN-5, the present study reduced PAWP (–22.9%), correlating with improved LV relaxation[1]. HFpEF is primarily driven by impaired LV diastolic function or compliance, even in the presence of preserved LVEF (>40%). In cardiac physiology, the maximum rate of change of ventricular pressure (dP/dt_{max}) is an indicator of LV contractility, while dP/dt_{min} reflects LV relaxation. The work shows no significant change in dP/dt_{max} or maximum left ventricular end-systolic pressure over 10 minutes post-PADN. Also, the authors document a significant 20.5% reduction in dP/dt_{min}, mirroring the PAWP reduction and thus argue for improved LV compliance. Two patients with prior surgical valve replacement exhibited transient increases in dP/dt_{min} and cardiac output post-PADN, which then subsequently normalised. This observation suggests that cardiac output fluctuations may transiently affect dP/dt_{min}.

Unsurprisingly, this novel work has several limitations: a limited sample size and a non-normal data distribution limit generalisability. A larger, multicentre study is needed. The short follow-up duration (10 minutes post-PADN) in this work precludes the assessment of long-term clinical effects. Neurohormonal biomarkers (renin-angiotensin-aldosterone system, noradrenaline) were not measured since this study primarily aimed to evaluate PADN's feasibility and its impact on LV relaxation.

Jiang et al present further preliminary evidence favouring PADN for HFpEF-induced IpcPH. PADN was associated with significant improvements in LV relaxation and a subsequent reduction in PAWP, highlighting its potential as a novel device-based treatment for HFpEF with IpcPH[1]. HFpEF patients comprise a critical subgroup of heart failure patients. IpcPH in HFpEF represents an advanced disease state, with progressive PH and impaired LV relaxation. HFpEF treatment options are limited to diuretics and sodium-glucose cotransporter-2 inhibitors; no approved PAH therapies have demonstrated efficacy in IpcPH. PADN has shown efficacy in CpcPH but has not been studied in HFpEF-induced IpcPH until now. This feasibility study suggests that PADN leads to significant reductions in pulmonary arterial pressure and PAWP. PAWP treatment appears to improve diastolic function, as evidenced by significant reductions in dP/dt_{min}. Further randomised trials are warranted to assess PADN's long-term clinical benefits in HFpEF, in particular within the IpcPH subgroup.

The PADN-5 trial included patients with CpcPH, specifically those with severe heart failure, who were on maximal medications but still symptomatic (WHO Class III), requiring a mean pulmonary artery pressure ≥25 mmHg and meeting other criteria. The current study suggests that abnormal sympathetic activity in the pulmonary circulation, independent of inflow to the left ventricle, can moderate diastolic dysfunction in HFpEF, as measured by dP/dt[1]. This is an incremental addition to the data from PADN-5 and should prompt a further clinical trial of PADN as an adjunct to guideline-based therapy for IpcPH.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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