To the editor,

Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance (PVR) and right ventricular (RV) dysfunction with normal left-sided cardiac filling pressures.\(^1\) Heart failure with preserved ejection fraction (HFpEF) can be accompanied by pulmonary hypertension (PH) with normal PVR (post-capillary) or with elevated PVR (combined pre- and post-capillary) and comprises an increasing proportion of PH. An elevated pulmonary artery wedge pressure characterizes PH-HFpEF, as increased left ventricular afterload is a key manifestation, whereas increased RV afterload is key in PAH. We hypothesized that patients with PAH and PH-HFpEF would have distinct systemic arterial properties.

Assessment of pulsatile proximal aortic hemodynamics characterizes arterial load and left ventricular (LV)–arterial interactions.\(^2,3\) As the LV ejects blood into the aorta, the change in pressure relative to the change in aortic flow depends on the aortic root characteristic impedance (Zc). The pressure wave propagates forward in the arterial system and, when it encounters sites of impedance mismatch (such as bifurcations), a portion of the wave is reflected backward. If wave reflections arrive back at the heart while still in systole, they increase LV workload, as seen with aging and systemic hypertension.\(^4\) For this reason, arterial stiffness and pulsatile arterial load measurements including total arterial compliance and aortic Zc are independent predictors of cardiovascular risk in the general population.\(^5\) However, systemic arterial properties have not been extensively studied in PH-HFpEF and PAH, and whether differences exist between these patients is unknown.

We conducted a small cross-sectional pilot study to assess systemic arterial properties in patients with PAH and PH-HFpEF and to assess the relationship between RV and LV structure/function with key systemic arterial measures. We enrolled 10 patients with PAH (mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg in the absence of other causes of PH) and 10 patients with PH-HFpEF (mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure >15 mmHg with left ventricular ejection fraction >50%). We excluded patients with heart rate <55 beats/min, atrial fibrillation, or other cardiac arrhythmias. Two-dimensional echocardiography and carotid-arterial applanation tonometry were performed simultaneously. A tonometer probe was applied to the carotid artery to obtain high-fidelity central pressure waveforms.\(^5\) Transthoracic echocardiograms were performed.\(^6\) All assessments were performed by a technician who was blinded to the PH case status. The carotid and LV outflow Doppler waveforms were digitized and utilized for wave intensity analysis.\(^3,7\) The main parameters of interest were total arterial compliance, and proximal aortic Zc (both of which relate to large artery stiffness) as assessed by pressure-flow analyses, and the area under the dominant wavefronts characterized via wave intensity analysis (i.e. the forward compression and forward expansion waves, both of which relate to the LV-arterial crosstalk). Cohen’s d was used to estimate effect sizes of continuous variables between PAH and PH-HFpEF patients. Pearson correlation coefficients of systemic arterial properties and RV and LV parameters including longitudinal strain and tricuspid annular plane systolic excursion (TAPSE) were assessed.

Patients in both groups were similar in age (median age 57 years for PAH and 61 years for PH-HFpEF). All patients with PAH were female, whereas only 60% of

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PH-HFpEF were female. Compared to patients with PAH, patients with PH-HFpEF had larger waist and hip circumference (124.0 cm and 125.0 cm for PH-HFpEF vs. 82.3 cm and 94.2 cm for PAH, respectively) and higher body mass index (40.1 kg/m² for PH-HFpEF vs. 24.1 kg/m² for PAH). Patients with PAH were more likely to have moderate-to-severe right atrial dilation, RV dilation, and RV dysfunction (100%, 90%, and 70% for PAH vs. 44%, 43%, and 20% for PH-HFpEF, respectively). There was no difference in Zc between patients with PAH and those with PH-HFpEF (0.12 dynes.s/cm⁵ (IQR 0.10–0.14) for PAH vs. 0.10 dynes.s/cm⁵ (IQR 0.08–0.16) for PH-HFpEF). However, patients with PAH had a smaller forward compression wave area as compared to patients with PH-HFpEF (48.7 (IQR 36.3–61.8) vs. 72.7 (IQR 53.4–86.5), respectively) and lower total arterial compliance indexed to body surface area (0.96 vs. 1.34 mL/mmHg/m², respectively).

In the combined population, Zc was directly correlated with RV longitudinal strain ($r = +0.65$), indicating greater Zc was associated with worse RV function (negative strain) (Fig. 1). Zc also correlated with LV wall thickness ($r = +0.62$), whereas total arterial compliance was inversely correlated with RV longitudinal strain ($r = -0.62$) and LV wall thickness ($r = -0.67$). The forward compression wave and the forward expansion wave areas directly correlated with TAPSE ($r = +0.55$ and $+0.68$, respectively).

We found that patients with PAH and PH-HFpEF manifested different systemic arterial properties. Patients with PAH had greater RV size and worse function, along with a dampened aortic forward compression wave and lower total arterial compliance. In a small study comparing idiopathic PAH patients to hypertensive patients and healthy controls, patients with PAH had lower carotid-femoral pulse wave velocity than hypertensive patients but higher than controls, and despite age matching, PAH patients had abnormal arterial stiffness even with normal range systemic blood pressure. In another small study of patients with PAH compared to controls, PAH patients had higher carotid-femoral pulse wave velocity (increased stiffness) which correlated with lower diffusion capacity for carbon monoxide, shorter 6-minute walk distance, and worse functional class. As expected, Zc and total arterial compliance were associated with LV wall thickness. Higher Zc increases the pulsatile afterload of the LV which eventually leads to LV hypertrophy. We found correlations between systemic arterial properties and measures of the RV function which probably reflect abnormal interventricular interaction, highlighting the importance of the ventricular interdependence. While exercise limitation in PAH is primarily attributed to RV dysfunction, our findings suggest that systemic arterial properties and LV function could also play a role in these patients. Using phase-contrast magnetic resonance imaging during exercise, PAH patients had reduced peak systolic flow and reduced aortic relative area change compared to age-matched controls also suggesting abnormal interventricular interaction.

The primary limitation of this pilot study is the small sample size. Due to technical difficulties with applanation tonometry in patients with large body habitus, some of the
waveforms were uninterpretable. However, we did observe differences between these two PH populations and these results should be considered hypothesis generating.

In conclusion, applanation tonometry is feasible for estimation of central systemic arterial properties of patients with PH. Systemic arterial properties may explain some of the disease manifestations and ventricular effects in PAH and PH-HFpEF. These results should be validated in larger cohorts and considered for studies of morbidity and mortality in PAH and PH-HFpEF.

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Authors’ contribution
NAN, SMK, and JAC conceived the conception and design of the work. RG contributed to the data curation. NAN and RG performed the data analysis. NAN supervised the study. RG, JAC, and NAN drafted the article. RG, JAC, B.K, JAM, KAS, HIP, JSF, SP, SMK, and NAN reviewed and edited the article.

Conflict of interest
The author(s) declare that there is no conflict of interest.

Ethical approval
This study was approved by the University of Pennsylvania Institutional Review Board (#827531).

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