Integrating haemodynamics identifies an extreme pulmonary hypertension phenotype

To the Editor:

Pulmonary hypertension (PH) is a highly morbid disease defined foremost by elevated mean pulmonary artery pressure (mPAP) measured during right heart catheterisation (RHC) at rest. Patients are classified further into one of three PH haemodynamic subgroups based on specific pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR) thresholds: pre-capillary PH (PAWP ≤15 mmHg+PVR ≥3.0 Wood units (WU)), isolated post-capillary PH (PAWP >15 mmHg+PVR <3.0 WU) and combined pre-/post-capillary PH (PAWP >15 mmHg+PVR ≥3.0 WU) [1].

Achieving an accurate haemodynamic diagnosis is essential to ensure the appropriate clinical management of PH patients [2]. However, a binary approach to haemodynamic interpretation may overgeneralise risk assessment for individual patients [3]. Prior studies have focused largely on differences in individual haemodynamic parameters for prognostication [4], even though point-of-care assessment in PH hinges on integrating data collected during RHC [5]. Furthermore, little is established on the association between PAWP and mortality despite the importance of PH to cardiovascular morbidity in left heart disease [6].

To address these dilemmas, we analysed RHC and outcome data from the Veterans Affairs Clinical Assessment Reporting and Tracking Program (2008–2016). The methods for assembling the study cohort have been reported [7]. We focused our analysis on patients with mPAP ≥19 mmHg, which is independently associated with increased mortality in this study population [4], with ≥1 year follow-up (median 1153 days, interquartile range (IQR) 570–1971 days). A Cox proportional hazards model incorporating age, sex, race and 19 other covariates was used to assess the association between PAWP and all-cause mortality [7]. The Colorado Multiple Institutional Review Board approved this study with a waiver of informed consent.

From a study population of 32725 patients (97% male; median (IQR) age 66 (61–74) years; body mass index 30.1 (26.1–35.0) kg·m$^{-2}$), a history of left heart disease or congestive heart failure (CHF) was observed in 26255 (80.2%) patients, and 29352 (89.7%) patients had systemic hypertension [7]. We observed a bimodal (i.e. U-shaped) distribution in PAWP relative to all-cause mortality (figure 1). Among all PAWP 1 mmHg bins, the absolute mortality rate and adjusted hazard for mortality were lowest for patients with PAWP 12 mmHg, which was selected as the reference point for further analyses involving PAWP. From this approach, PAWP 15 mmHg was the minimal PAWP bin above 12 mmHg at which the mortality hazard was ≥1.0. Similarly, PAWP 11 mmHg was the minimal PAWP bin below 12 mmHg at which the mortality hazard was ≥1.0.

Indeed, the association between PAWP and adjusted mortality spanned three general ranges: <12 mmHg, 12–15 mmHg and >15 mmHg, representing 14.6% (n=4793), 22.2% (n=7280) and 63.1% (n=20652) of the study population, respectively. There was no meaningful difference in age across these patient subgroups (66.7 (61.3–66.9) years versus 66.9 (61.7–74.0) years versus 66.5 (51.2–73.5) years, p=0.009); however, a step-wise increase was observed in the prevalence of CHF (46.4% versus 50.4% versus 71.5%, p<0.001), atrial flutter (19.1% versus 24.5% versus 36.6%, p<0.001), chronic kidney disease (24.9% versus 27.9% versus 37.4%, p<0.001) and obstructive sleep apnoea (11.4% versus 13.1% versus 15.5%, p<0.001). By contrast, connective tissue disease (4.8% versus 3.6% versus 2.6%, p<0.001) and COPD

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These data illustrate the risk continuum based on multiple right heart catheterisation measurements when modelled together, but also identify pulmonary artery wedge pressure >15 mmHg and <12 mmHg as particularly high risk https://bit.ly/3whDEOV

(41.15% versus 34.6% versus 35.0%, p<0.001) were more common in the PAWP <12 mmHg subgroup compared to the 12–15 mmHg and >15 mmHg subgroups.

The haemodynamic profile (median (interquartile range)) for patients in the PAWP <12 mmHg, 12–15 mmHg and >15 mmHg ranges was right atrial pressure (RAP) 6 (4–8) mmHg versus 8 (6–10) mmHg versus 12 (9–16) mmHg (p<0.001); mPAP 22 (20–27) mmHg versus 24 (21–28) mmHg versus 34 (28–41) mmHg (p<0.001); PVR 2.6 (2.0–3.8) WU versus 2.0 (1.5–2.9) WU versus 2.1 (1.3–3.2) WU (p<0.001); cardiac output 5.2 (4.3–6.2) L·min⁻¹ versus 5.3 (4.4–6.3) L·min⁻¹ versus 4.9 (4.0–6.1) L·min⁻¹ (p<0.001); transpulmonary gradient 14 (11–18) mmHg versus 10 (8–14) mmHg versus 10 (7–15) mmHg (p<0.001); and RAP/PAWP ratio 0.64 (0.45–0.82) versus 0.58 (0.43–0.75) versus 0.54 (0.41–0.68) (p<0.001).

Compared to patients with PAWP 12–15 mmHg, the adjusted hazard ratio (HR) for mortality was increased significantly in patients with PAWP <12 mmHg (HR 1.17, 95% CI 1.11–1.25; Chi-squared 27.0, p<0.001) and PAWP >15 mmHg (HR 1.19, 95% CI 1.14–1.24; Chi-squared 54.4, p<0.001). Compared to PAWP 12 mmHg, patients with PAWP 15 mmHg had higher mPAP (23 (21–27) mmHg versus 25 (22–29) mmHg, p<0.001) and lower PVR (2.1 (1.6–2.9) WU versus 1.9 (1.3–2.8) WU, p<0.001), but similar cardiac output (5.3 (4.4–6.3) L·min⁻¹ versus 5.3 (4.4–6.3) L·min⁻¹, p=0.828).

We identify an extreme PH haemodynamic profile among patients with PAWP <12 mmHg that is characterised by elevated PVR, transpulmonary gradient and RAP/PAWP ratio. These data suggest that there is opportunity to prognosticate PH patients with low PAWP even in the absence of cor pulmonale, as the median cardiac output (5.2 L·min⁻¹) was above the range independently associated with mortality in
this population and the follow-up period in this study is beyond longevity expectations when frank end-stage right heart failure is diagnosed at the time of RHC [7–9]. This subgroup was enriched with lung disease PH, but may also include some patients with combined pre-/post-capillary PH on diuretic therapy and a small number of pulmonary arterial hypertension patients. In addition, our data provide the first comprehensive information on the association between elevated PAWP and mortality hazard in PH. In the PAWP >15 mmHg subgroup, RAP was also elevated, but the RAP/PAWP ratio was decreased relative PAWP <12 and 12–15 mmHg patients, indicative of biventricular heart failure. These findings reinforce the importance of elevated left heart filling pressure to prognosis in post-capillary PH. The adjusted mortality risk was unchanged between PAWP 12–15 mmHg. We have shown previously that in this study population, there is a continuous relationship between mPAP and mortality hazard [4], suggesting that mPAP may be particularly useful for risk stratification of patients in this haemodynamic zone between pre- and post-capillary PH.

Importantly, reference PAWP levels alternative to 12 mmHg as well as other statistical approaches could have been used to define the elevated versus low PAWP subgroups. The retrospective design and inaccessibility to comprehensive patient-level data are important methodological limitations that prevent this study from identifying an optimal haemodynamic profile among patients with elevated mPAP, which is likely to vary by clinical and comorbidity profile. Rather, these data lay the framework for an evidence-based approach to delineating PAWP ranges that separate pre- and post-capillary PH subgroups. The study population was largely male, which may limit the generalisability of our findings to females or other sex-balanced cohorts. Prospective studies are therefore needed to validate our data, as over-representation of males and referral bias are important considerations when interpreting our findings.

To the best of our knowledge, this study provides the first comprehensive analysis involving multiple haemodynamic parameters modelled simultaneously and linked to clinical outcome in patients with PH. Applying this approach to a large RHC referral population inclusive of patients with elevated mPAP and highly enriched with cardiopulmonary comorbidities identified a bimodal distribution in mortality. This included a particularly high-risk haemodynamic profile defined by low PAWP, elevated PVR and widened transpulmonary gradient. Although elevated PAWP is known to associate with adverse clinical events in left heart failure [10], the current data expand on this concept by illustrating an important risk continuum associated with PAWP in post-capillary PH. Overall, our findings support integrating RHC variables as a key step toward improving PH classification, and suggest that PAWP <12 mmHg and >15 mmHg may be reasonable thresholds delineating pre- and post-capillary PH. Additional data are needed to clarify the relevance of mPAP and other variables for prognosticating patients across a haemodynamic transition zone between pre- and post-capillary PH that emerged in this study.

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Data availability: The data from the study cohort that support the findings of this study are available from the corresponding author on reasonable request, although they will be subject to the stringent data privacy rules of the Veterans Affairs Healthcare System and the US Government.

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References


