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Hemodynamics Should Be the Primary Approach to Diagnosing, Following, and Managing Pulmonary Arterial Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a highly morbid cardiopulmonary disease characterized by plexogenic pulmonary arteriole remodeling. Importantly, PAH severity correlates inversely with cardiac output and directly with pulmonary vascular resistance and right atrial pressure, illustrating the importance of accurately measured hemodynamics to defining the clinical profile of patients. Currently available non-invasive technology offers only hemodynamic *estimates*. By contrast, right heart catheterization is the principle diagnostic procedure in PAH and is *required* to i) definitively exclude alternative pulmonary vascular diseases, and ii) quantify hemodynamics at baseline, following vasoreactivity testing, or in response to therapy in order to prognosticate outcome and guide therapeutic escalation.

Introduction

Evolving technology and the repurposing of existing imaging methods has generated a range of novel approaches by which to acquire hemodynamic correlates non-invasively. This, in turn, has raised speculation that such methodologies are well positioned to supplant right heart catheterization (RHC) for the diagnosis and management of pulmonary vascular disease, including PAH.¹ Although forward thinking and useful, these methods generate hemodynamic *estimates*; are unable to provide the totality of hemodynamic data required to manage patients in clinical practice; and, remain by and large untested or unvalidated in routine clinical care. By contrast, RHC in PAH is safe and remains the sole evidence-based strategy for diagnosis, risk stratification, therapy selection, and monitoring treatment responsiveness in patients afflicted with this highly morbid disease.

Invasive hemodynamic assessment is necessary for PAH diagnosis

The 2013 expert consensus definition of PAH is unchanged from previous iterations by retaining the following three critical hemodynamic criteria assessed invasively to achieve the appropriate diagnosis: mean pulmonary artery pressure (mPAP) >25 mmHg and

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pulmonary vascular resistance (PVR) >3.0 Wood units in the setting of a pulmonary artery occlusion pressure (PAOP) 15 mmHg.² Importantly, the *collective* assessment of these and other relevant hemodynamic indices, such as intracardiac shunt, is critical, since any single measurement recorded (or assumed) in isolation characterizes pulmonary vascular disease pathophysiology or severity insufficiently, and may be misleading. For example, mPAP is contingent, in part, on RV systolic function and may therefore be either elevated or low in PAH if RV contractility is preserved or impaired, respectively. Likewise, an increase in transpulmonary gradient (mPAP-PAOP) >12 mmHg (or diastolic PA gradient >5 mmHg) often distinguishes pre-capillary- from post-capillary pulmonary hypertension. In the absence of PVR or cardiac output data, however, characterizing PAH subtype, disease severity, or patient prognosis is not possible.³

Indeed, higher likelihood of misdiagnosis and inappropriate treatment in PAH are linked to incomplete RHC assessment. In one study characterizing the diagnostic strategies for evaluating pulmonary vascular disease in a community-based cohort of at-risk patients (N=340), appropriate RHC testing was performed in a minority of the study population (N=122, 36%) despite clinical evidence suggesting the possibility of severe pulmonary hypertension.⁴ In turn, the adverse consequences of under utilizing RHC in the evaluation of PAH has also been established. Deaño and colleagues performed a multi-center cross-sectional analysis to assess the diagnostic accuracy of PAH in a referral cohort of 140 patients evaluated at a PAH specialty center. Among 38 referred patients undergoing RHC at the specialty center for the first time, a change in diagnosis occurred in 37% (N=14). Similarly, among 21 referred patients undergoing first time right and left heart catheterization, 52% (N=11) received a different diagnosis. In the overall study cohort, 57% (N=42) of referred patients receiving PAH medications had been prescribed these therapies inappropriately.⁵

Invasive hemodynamic measurements collected at baseline, in response to vasodilator challenge, or modified by treatment predict outcome in PAH

In a meta-analysis of 54 studies, Swiston and colleagues reported that mean right atrial pressure (mRAP), mPAP, cardiac index, PVR, and mixed venous partial pressure of oxygen recorded invasively were among only 10 clinical variables of 107 assessed that predicted mortality in 4 published studies. By contrast, pericardial effusion severity was the single variable in the group of 10 that requires non-invasive imaging for evaluation.⁶ From the French Network on Pulmonary Hypertension registry, which prospectively assessed outcome (2002–2005) in 354 incident or prevalent PAH cases (including congenital heart disease), survival correlated inversely with mRAP (HR 1.06; 95% CI, 1.016–1.107, $P<0.01$), and directly with cardiac output (HR 0.746; 95% CI, 0.591–0.942, $P<0.01$).⁷ Interestingly, while analyses derived from data in the REVEAL[†] registry affirmed these earlier findings by suggesting, for example, that mRAP >20 mmHg in PAH was associated with increased risk of death within 12 months (HR=1.79, $P=0.043$),⁸ a subgroup analysis (N=1825) demonstrated an incremental decrease in 2-year unadjusted survival corresponding to

[†]The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) PAH database is funded by Actelion Pharmaceuticals US, Inc

increasing PAOP, particularly for patients with PAOP ≥ 16 mmHg ($P < 0.001$ vs. PAOP ≤ 15 mmHg), while risk of death was exaggerated further among patients achieving PAOP ≥ 19 mmHg.⁹

Estimation of PAOP using lung ultrasound, echocardiography, and physical examination is semi-quantitative, corresponds only modestly with invasive estimates, has poor discriminative power to detect subtle changes in levels, and/or are untested in PAH.¹⁰ On the other hand, diminished transpulmonary gradient following confrontational volume challenge testing has been linked to unmasked left atrial hypertension in approximately one of four patients with a hemodynamic profile otherwise suggestive of PAH at the time of RHC.¹¹ Collectively, these data and findings from REVEAL analyses affirm the importance of right-sided and left-sided hemodynamics precision to PAH diagnosis, and also illuminate their relevance to crystalizing pathophysiology and mortality risk.

The importance of assessing hemodynamic *trajectory* in PAH is likewise supported by various clinical studies that link functional class improvement or survival with favorable changes to PVR or cardiac output following treatment with prostacyclin analogues,¹² endothelin receptor antagonists,¹³ or the soluble guanylyl cyclase stimulator riociguat,¹⁴ among others. To quantify this relationship, Tiede and colleagues¹⁵ analyzed retrospectively hemodynamic data from 122 PAH patients (mPAP 55.1 ± 14.6 mmHg; CO 3.9 ± 1.3 L/min; PVR 13.8 ± 7.0 Wood units) treated with various PAH-specific drug treatments. They identified that transplant-free survival was greater (absolute difference +23.3%) in patients for whom PAH pharmacotherapy decreased PVR > 2.2 Wood units ($P = 0.044$), which paralleled the survival benefit observed for patients demonstrating increased cardiac output > 0.22 L/min ($P = 0.015$) to treatment (Figure 1).

Along these lines, RHC pulmonary vasoreactivity testing in patients with selected forms of PAH is a Class I recommendation by the European Society of Cardiology,¹⁶ and described as “mandatory” to identify calcium channel antagonist (CCA)-responsive PAH patients by other international consensus statements on this topic.¹⁷ Among CCA-responsive patients during RHC, high dose therapy with nifedipine or diltiazem is associated with significant cardiopulmonary hemodynamic and survival benefits.¹⁷ Moreover, preserved vasoreactivity, even when not supportive of CCA use, has important prognostic value in PAH: in one analysis of 80 PAH patients, a 30% reduction in PVR following administration of inhaled nitric oxide or 90% inspired oxygen was associated with an attendant 53% lower relative risk of mortality at 5 years (Cox HR 0.47; 95% CI, 0.23–0.99, $P = 0.047$) (Figure 2). This relationship was also preserved in patients with collagen vascular disease (CVD)-associated PAH ($N = 24$), a particularly high-risk PAH sub-phenotype. From 24 CVD-PAH patients in that study, PVR responsiveness was reported in 45.8% ($N = 11$) and, when present, was associated with a substantial reduction in 5-year mortality risk (HR 0.11; 95% CI, 0.01–0.097, $P = 0.047$).¹⁸

Invasive hemodynamic data measured after PAH diagnosis

Recommendations defining RHC appropriateness during follow-up care of PAH patients are not available, nor are clinical data demonstrating superiority of non-invasive imaging over RHC for this purpose. Nevertheless, it is reasonable that invasive hemodynamic assessment

be considered in PAH patients for whom the mechanism of clinical decline is unclear. For example, RHC is useful for elucidating pathophysiological changes in PAH treatment under-responders, such as quantifying (or diagnosing new) right-to-left intracardiac shunt. This may be of relevance in the setting of severe pulmonary hypertension and co-morbid lung disease,¹⁹ in which measurement of oxyhemoglobin saturation levels in right- and left-sided vascular compartments, including pulmonary veins, is useful for distinguishing impaired lung oxygenation from intracardiac shunt as the etiology of progressive dyspnea or systemic hypoxemia.

Coupling hemodynamic deterioration with severe symptom burden, such as in patients with World Health Organization (WHO) functional class III or IV symptoms, may also inform clinical decision-making in PAH. For example, randomized clinical trial data^{20,21} in support of a survival benefit from continuous parenteral prostacyclin replacement therapy in PAH is derived primarily from WHO class III patients (76%^[20] and 75%^[21] of the study cohorts) with increased PVR (mean 16 ± 1 Wood units^[20] and 14.2 ± 7.1 Wood units^[21]) and markedly decreased cardiac index (2.0 ± 0.6 L/min/m²^[20] and 1.9 ± 0.6 L/min/m²^[21]). In turn, it was demonstrated recently that the oral endothelin receptor antagonist macitentan (10 mg daily) decreased mortality in PAH patients with WHO class III symptoms (47.9% of the study cohort) expressing comparably less severe pulmonary hypertension (mean PVR=11.3, [range 3.17–34.73] Wood units) and right ventricular dysfunction (cardiac index=2.63 [range 1.20 – 6.24] L/min/m²).²² Taken together, commitment to parenteral prostacyclin replacement therapy in WHO class III patients may be best suited for those with lower cardiac index levels measured invasively, such as below ~ 2.3 L/min/m², whereas initiation or escalation of oral PAH therapy is reasonable for otherwise similar patients with a higher measured cardiac index.

Invasive hemodynamic assessment by RHC is safe

The safety profile of right heart catheterization in patients with pulmonary vascular disease is well documented: from the largest dataset (N=7,218) analyzing complications in association with RHC studies, the procedural fatality rate was 0.055% (N=4; 95% CI, 0.01% – 0.99%) and serious adverse event rate was 1.1% (N=76; 95% CI, 0.7 – 1.9%), which, aside from the fatalities, were generally mild to moderate in severity and largely confined to localized hematoma at the vascular access site.²³ Importantly, this procedural risk profile, which is well within RHC complication rates reported in patients with LV dysfunction, was observed despite substantial pulmonary hypertension in the study cohort (mPAP 47 ± 15 mmHg; cardiac index, 2.7 ± 1.9 L/min/m²; PVR 9.3 ± 6.3 Wood units) and application of vasoreactivity testing in the majority of patients (73%, N=5,267).

Non-invasive strategies estimate but do not measure cardiopulmonary hemodynamics

Despite the effectiveness and favorable safety profile of RHC, the possibility that invasive hemodynamic testing may be obviated in PAH by contemporary imaging modalities and sophisticated diagnostic algorithms has been introduced recently. Opatowsky and colleagues²⁴ described a clever echocardiographic prediction rule (“Echo score”) based on the following metric: left atrial (LA) anterior-posterior dimension >4.2 cm or <3.2 cm was -1 or $+1$ point, respectively; PA outflow tract Doppler morphology “notch” or PA

acceleration time <80ms was +1, and lateral mitral annular relaxation velocity ($E:e'$) >10 was -1. In that retrospective study of 108 patients referred to a pulmonary hypertension specialty clinic, the sensitivity and positive predictive value of a composite score ≥ 0 for pulmonary vascular disease, defined by PAOP ≥ 15 mmHg and PVR >3.0 Wood units, was 100% and 63%, respectively, and through the application of mathematical modeling involving the same metrics, RHC-measured PVR was observed to correlate strongly ($r=0.8$) with echocardiographic estimates.²⁵ However, it is noteworthy that in this study the echocardiogram and RHC tests occurred at a median of 22.5 days apart, and were analyzed retrospectively at a single center. Additionally, a PVR >3 Wood units was observed in 42% of patients with a score ≤ 0 and 73% of the overall study population, thereby raising speculation that selection bias may have influenced the study findings. Overall, the Echo score data demonstrate that detecting a hemodynamic profile compatible with PAH non-invasively is plausible, although the accuracy and merit of this strategy requires further investigation prior to routine use in general practice.

By leveraging three-dimensional spatial resolution measurements, others have used cardiac magnetic resonance (CMR)-derived left atrial volume and PA phase contrast imaging as surrogates for PAOP and cardiac output, respectively, and interventricular septal angle and LV mass to calculate mPAP.²⁶ Akin to the Echo score method, using this technique to identify patients with PVR >3.0 Wood units appeared possible, but evidence in support of these applications to routine clinical practice is less defined. As an example, it has been reported that PVR calculated by CMR using the following equation:

$$19.38 - [4.62 \times \ln \text{PA average velocity (in cm/s)}] - [0.08 \times \text{RV ejection fraction (in \%)}]$$
correlates strongly with invasively measured PVR in patients with pulmonary hypertension from mixed etiologies ($N=20$; $r=+0.84$, $P<0.001$).²⁷ However, a difference in PVR values between CMR and RHC methods of $>30\%$ was observed in 45% of patients in that study, which is consistent with accuracy rates reported from other similarly designed CMR studies.²⁸ Furthermore, the use of impedance cardiography, pulse contour analysis, and inert gas rebreathing systems to calculate cardiac output, stroke volume, or maximal volume of oxygen consumption non-invasively has been proposed and studied in selected small subpopulations of pulmonary vascular disease patients,²⁹ but the empirical experience to support their routine use in patients with PAH for diagnosis or clinical management remains insufficient.

Non-invasive hemodynamic assessment strategies are secondary to RHC in PAH

There are numerous reasons for which the aforementioned methods are secondary to RHC for the diagnosis, prognosis, and management of PAH. First, non-invasive single variable assessments of pulmonary hypertension severity are notoriously inaccurate. Farber and colleagues³⁰ demonstrated definitively that in PAH there is unacceptable discordance between RHC- and echocardiographically-assessed PASP ($N=1360$, Spearman correlation coefficient = +0.56, $P<0.001$) and mRAP ($N=721$, Spearman correlation = +0.36, $P<0.001$), even when procedures are conducted on the same day ([PASP] $N=98$, Spearman correlation = +0.57, $P<0.001$; [mRAP] $N=35$, Spearman correlation = +0.40, $P=0.18$), and, as discussed earlier, this is not subverted by the use of advanced imaging modalities including CMR. Prediction rule methods, which coordinate data from numerous variables within a single

diagnostic test, are proven effective only for the broad characterization of hemodynamic profiles (e.g., PVR >3 Wood units), but cannot be used to calculate specific PVR (or mRAP) levels *per se*. In turn, the strength of data derived from these methods relative to RHC for achieving the diagnosis of PAH, determining disease prognosis and severity, or as a metric to follow treatment (in)efficacy is not known.

Secondly, a composite analysis of PAOP, PVR, and cardiac output, which is critical to the management of PAH patients, is not clinically feasible using non-invasive methods. While each method may produce estimates of one or more of the component variables, none can provide equivalent or better reproducibility compared with RHC. For example, while CMR provides excellent estimates of pulmonary blood flow, estimates of PA pressure based on secondary modeling and assessment of LA pressure are even more limited. The ramifications of this are of particular relevance to pulmonary vasoreactivity testing-eligible patients, PAH treatment un(der)responders, or if the contribution of left heart disease to disease pathophysiology is unclear. In these circumstances, the role of RHC is incontrovertible and supported by numerous guideline statements, clinical studies, and practice patterns reported by PAH experts.^{2,16,31–33}

Third, the appropriateness of any of the proposed non-invasive hemodynamic assessment modalities for routine use has not been validated in multiple samples and populations (if at all), especially in unselected patients. To the contrary, increasing evidence suggests that the penetration of predictive rules into widespread “real world” clinical practice may be impractical due, in part, to the acquisition of numerous variables required for accurately estimating hemodynamics. For example, in one large cohort analysis of patients with multiple pulmonary vascular disease risk factors and increased PASP (≥ 60 mmHg) measured echocardiographically, full diastology assessment, including E/e’ calculation for echocardiography-estimated PVR, could only be performed in 43% of the study sample due to co-morbidities or technical factors limiting appropriate image acquisition.⁴ In the case of inert rebreathing technologies, the capability of this strategy to determine cardiac output relative to RHC in the setting of comorbidities common to pulmonary vascular disease patients, such as pulmonary shunt or parenchymal lung disease, is incompletely characterized.³⁴ Even among patients for whom predictive modeling accurately confirms the presence of pulmonary vascular disease (i.e., increased PVR), the mechanism underpinning disease expression is not resolved by this technique. In these patients, clinching a diagnosis of PAH to confirm that PAH-specific therapies are indicated and safe ultimately requires data collected invasively.

Conclusions

Hemodynamic assessment with RHC is safe and remains the diagnostic standard for PAH. Specifically, RHC is required for the coordinated analysis of 4 variables critical to the clinical profile of PAH patients: mRAP, PVR, cardiac output, and PAOP. In selected PAH subgroups, RHC is also required to assess vasoreactivity to predict CCA-responsiveness, which, when present, is linked to improved outcome and survival. Therefore, PAH diagnosis, intracardiac shunt measurement, and assessment of hemodynamic markers indicative of increased (or decreased) mortality may be accomplished using a single test

when performed by RHC. Although non-invasive methods are described for determining hemodynamic measurements, these are largely estimates based on surrogate markers that express low discriminative power for characterizing the full clinical profile of patients accurately, and remain untested in clinical practice.

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Figure 1. Improvement in pulmonary vascular resistance (PVR) mediated by pulmonary arterial hypertension (PAH)-specific pharmacotherapy predicts survival

The PVR change following therapy predicts survival in Cox plots of predicted transplant-free survival among 122 patients with PAH according to risk group assignment by change in pulmonary vascular resistance (PVR) after 16 weeks of therapy: group 1, less than $-176 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ (2.2 Wood units); group 2, change in PVR: more than $-176 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ (2.2 Wood units); $P = 0.044$. Adapted with permission from Ref. 15.

Figure 2. Cardiopulmonary hemodynamic response to vasoreactivity challenge during right heart catheterization predicts survival in pulmonary arterial hypertension (PAH)

Kaplan-Meier survival curves for PAH patients stratified by vasoreactivity, defined by at least a 30% decrease in pulmonary vascular resistance (PVR) with vasodilator challenge with nitric oxide and 90% oxygen. The Log-rank test shows reduced mortality in vasoreactive patients ($P=0.039$). *Reproduced with permission from Ref. 18.*