What Echocardiography Can Reliably Tell Us About Our Pulmonary Hypertension Patients

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Pulmonary hypertension (PH) is a complex, multi-organ system disease that is broadly defined by an elevation in pulmonary artery pressures. There are key biologic differences in the pathophysiology among the different PH subgroups that warrant a targeted approach to clinical care of these patients. The complex geometry of and wide array of clinical tools to assess the right heart in PH add another layer of complexity in patient care. Echocardiography can be used as a powerful tool to discriminate among the subgroups of PH, a critical first step in evaluating a new case of PH. In this article, we will explore novel approaches using echocardiography that go beyond simply estimating pulmonary pressures and provide a readily accessible means of adding diagnostic and prognostic accuracy in the clinical setting.

BACKGROUND
At the first World Symposium on Pulmonary Hypertension (WSPH) in 1973, pulmonary hypertension (PH) was defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg measured by right heart catheterization (RHC) at rest.\(^1\) At the sixth WSPH, which met in 2018, the aforementioned definition of PH was criticized for being too conservative and lacking specificity for identifying patients with pulmonary vascular disease (PVD) or precapillary PH.

In a systematic review of over 130 studies, Kovacs et al. showed that mPAP in the supine position at rest in healthy individuals was 14.0 ± 3.3 mm Hg and rarely exceeded 20 mm Hg.\(^2\) Therefore, the prior definition of PH (mPAP ≥ 25 mm Hg) was greater than 2 standard deviations higher than what is observed in healthy individuals and could miss patients with true PH. For this reason, the latest WSPH changed the definition of PH to ≥ 20 mm Hg. Another major limitation of the previous definition was its lack of ability to distinguish between patients with precapillary and postcapillary disease. For example, an elevated mPAP would identify both a patient with underlying chronic obstructive pulmonary disease who has evidence of PVD and a patient with PH due to heart failure with preserved left ventricular ejection fraction (LVEF), but we know that these patients have very different physiologic pathways at play and thus are managed quite differently from a PH perspective.

Finally, in the previous classification of PH subgroups, only Group 1 or pulmonary arterial hypertension (PAH) included pulmonary vascular resistance (PVR ≥ 3 Wood units [WU; mm Hg/L/min]) despite the fact that almost all subgroups can exhibit a precapillary phenotype characterized by an elevated PVR.

This led to the proposal by the sixth WSPH to include PVR ≥ 3 WU in the definition for all forms of precapillary PH.\(^3\)

There are several important clinical implications for the changes proposed by the sixth WSPH. The lowering of the mPAP criterion to define PH could potentially increase the number of PH patients referred for PH evaluation. In order to respond to a larger volume of patients being referred for PH evaluation, there must be readily accessible and validated tools to initially assess patients with suspected PH. Further, while RHC remains the “gold standard” for diagnosis, it is not always a practical tool for immediate accessibility and repeated measurements which are necessary in managing PH over time and in response to therapy. For this reason, novel echocardiographic measures that recapitulate invasive hemodynamics and even predict outcomes in PH represent a powerful tool in a clinician’s arsenal. While we acknowledge that echocardiography can be technically difficult due to the unique shape and geometry of the right heart, we sought to highlight echocardiographic measurements that are easy to perform and can accurately phenotype PH subgroups. Recognizing that there are multiple clinical factors that contribute to a patient’s presentation and ultimate prognosis, this review will focus on how echocardiography can be used to comprehensively assess patients with PH.

ESTIMATING HEMODYNAMICS
PVD is defined by the presence of PVR > 3 WU and normal to low left heart filling pressures. While RHC is required to make the diagnosis of PVD, it has...
Figure 1: Examples of the 3 distinct patterns appreciated in the flow velocity envelope obtained from pulsed-wave Doppler interrogation from the right ventricular outflow tract (FVE$_{RVOT}$). (1a) and (1b) show representative Doppler tracings without evidence of Doppler notching (no notch group); note the envelope may be (a) parabolic or (b) somewhat triangular in shape. (2a) and (2b) show examples in the mid-systolic notch group, characterized by a distinct notch or nadir in its mid portion, dividing the flow profile into 2 distinct peaks. (3a) and (3b) show Doppler tracings with a late systolic notch, characterized by transient notching on the terminal aspect of the Doppler signal without 2 distinct peaks. Arrows indicate the location of the notch in the Doppler signal. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Arkles JS, Opotowsky AR, Ojeda J, et al. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. Am J Respir Crit Care Med. 2011;183(2):268–276. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

several noteworthy limitations. It is an invasive procedure with nontrivial risks to the patient, including complications related to bleeding, vascular, lung, or cardiac injury. In fact, a large prospective study across 54 centers in the United States, the REVEAL registry, observed that the average duration between symptom onset and diagnostic catheterization was 2.8 years in patients with World Health Organization (WHO) Group 1 PAH. Further, common technical errors observed with RHC are often amplified in patients with underlying cardiopulmonary disease and, hence, several subgroups of PH. Wide variations across the respiratory cycle lead to underestimated end-expiratory values, and enlarged and dilated distal pulmonary artery branches in PVD make it difficult to obtain a fully occluded pulmonary capillary wedge pressure (PCWP), which can overestimate PCWP. RHC is often reserved only for patients in whom PVD is suspected, leaving a large population of PH patients where hemodynamic profiles are unknown and potentially misclassified. For this reason, novel approaches using echocardiography have emerged as a noninvasive and readily accessible alternative to hemodynamic assessment by catheterization.

Benza et al. performed a comprehensive evaluation of 2635 patients with PAH and observed that those who were initiated on therapy within 6 months of diagnosis had significantly improved long-term survival. Therefore, accurate identification of elevated PVR by echocardiography could reduce time to diagnosis of PVD and, more importantly, time to initiation of lifesaving PH therapies. Doppler echocardiography (DE)-derived estimates of PVR, such as the ratio of peak tricuspid regurgitation velocity to right ventricular outflow velocity-time integral (VTI$_{RVOT}$) have shown excellent correlation with invasive PVR across several studies; however, this correlation was not observed in patients with PVR > 8 WU. Thus, patients with the most severe degree of PVD, and therefore the most clinically vulnerable and urgent, are excluded from accurate utility of this tool. Others have used DE to estimate variables included in the calculation of PVR such as pulmonary artery pressures and cardiac output; however, this approach is time intensive and less useful for clinical practice. Arkles et al. demonstrated that easily observable differences in the shape of the right ventricular outflow tract (RVOT) Doppler signal could rapidly and accurately distinguish between patients with or without elevated PVR. Specifically, the presence of “notching,” either midsystolic or late systolic notching, of the right ventricular (RV) Doppler envelope was strongly associated with a PVR > 3 WU (odds ratio = 29.4, 95% confidence interval [CI] = 9.9, 87.2; Figure 1).

Similarly, Opotowsky et al. explored several models incorporating readily measurable echocardiographic parameters to estimate PVR. The model (Equation 1) that correlated best with invasive PVR (correlation coefficient $r$ = 0.80) also exhibited excellent discriminatory power across a range of PVR values (area under curve [AUC] = 0.946 for PVR > 3 WU).

$$PVR = \frac{PASP}{VTI_{RVOT}} + 3 \text{ if notch present} \quad (1)$$

where PASP is pulmonary artery systolic pressure.

Further work done by Opotowsky et al. demonstrated that a simple prediction score based on a few easy-to-perform echocardiographic measurements (left atrial size, $E/e'$ transmittal and tissue Doppler, and RVOT Doppler notch or acceleration time) had a positive likelihood ratio of 2.4 and a negative likelihood ratio of 0. A score > 2 was highly suggestive of PVD, whereas a negative score, in the presence of normal RV function (tricuspid annular plane systolic excursion or TAPSE > 1.8 cm), ruled out an elevated PVR (Figure 2).

Some studies have suggested that there are measurable changes in the pulmonary vasculature that precede an elevation in PVR. Bhattacharya et al. defined pulmonary arterial compliance (PAC) as the ratio of VTI$_{RVOT}$ over PASP. In this particular study, 156 patients from the University of Penn-
syltiana were included only if they had a preserved ejection fraction (HFpEF). By including patients without reduced LVEF, the investigators of the study were able to demonstrate that PAC, measured by VTI_RVOT/PASP, can readily withstand gastrointestinal side effects. Invasive hemodynamics: mPAP = 40 mm Hg, PAWP = 10 mm Hg, PVR = 2.0 mm Hg/L/min. Column B demonstrates normal LA size, normal E/e', and abnormal RVOT Doppler profile (score = +2). Invasive hemodynamics: mPAP = 45 mm Hg, PAWP = 10 mm Hg, PVR = 8.8 mm Hg/L/min. AccT = right ventricular outflow tract acceleration time; LA = left atrial; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; RVOT = right ventricular outflow tract. Reproduced with permission from Opotowsky AR, Ojeda J, Rogers F, et al. A simple echocardiographic prediction rule for hemodynamics in pulmonary hypertension. Circ Cardiovasc Imaging. 2012;5(6):765-775. See https://www.ahajournals.org/journal/circimaging. Published by the American Heart Association.

RV Function

TAPSE: The presence of RV dysfunction has been widely recognized as an independent predictor of poor outcomes in PH. In a study of 110 patients with PAH, 25% of patients who experienced an improvement in PVR after medical therapy continued to have worsening RV function and ultimately had the worst outcomes, suggesting that RV dysfunction may be specific for severe or refractory disease. Similar to RHC, cardiac magnetic resonance imaging, which is the “gold standard” imaging modality to assess RV function, is limited by cost, accessibility, and patient-related factors such as claustrophobia and inability to lay supine. In normal right hearts, longitudinal shortening accounts for up to 80% of overall RV function. For this reason, systolic displacement of the tricuspid annulus toward the RV apex or TAPSE is frequently investigated as an echocardiographic surrogate of RV function. Compared to other echocardiographic measurements of RV function, TAPSE offers several advantages in that it is highly reproducible, independent of geometric assumptions, and does not require RV endocardial tracing which is prone to error and technical difficulty. In a prospective study of a heterogeneous population of PH, with approximately 75% in WHO Group 1, TAPSE < 1.8 cm was associated with a fourfold increased risk of death. Follow-up TAPSE measurements, and not baseline, after initiation of PAH therapy predicted survival in a cohort of PAH patients. Specifically, follow-up TAPSE

**ASSESSMENT OF THE RIGHT HEART**

**RV Morphology**

Because there are many factors that contribute to RV function (right heart preload, afterload, intrinsic contractile function, and right atrial function), it is not surprising that echocardiographic parameters of RV function lack specificity to discriminate among different clinical forms of PH. Raza et al. explored whether there are specific profiles of RV shape or morphology that can be used to identify and distinguish among 3 PH subtypes: PVD; pulmonary venous hypertension, or PVH (such as PH due to left heart disease); and those with a mixed phenotype (PVD and PVH). The authors of this study showed the RV base and apex dimensions were nearly the same in the PVD group, while the RV apex dimension was approximately half of that of the base in patients with PVH (Figure 3). Specifically, RV base and apex of similar dimensions (sRV_b/a < 1.5) were associated with a 17 times increased odds of having a PVR > 3 WU. sRV_b/a (AUC = 0.873) outperformed parameters which measure RV function, namely TAPSE (AUC = 0.563) and fractional area change (AUC = 0.700), suggesting that the RV undergoes morphological changes prior to a reduction in function. Finally, a low sRV_b/a and presence of dilated left atrium (>40 mm) correctly identified patients with mixed-physiology PH with a mean PVR of 18.0 ± 5.4 mmHg.13

**Figure 2:** Representative echocardiographic images of LA size, transmitral flow, tissue Doppler of the lateral mitral annulus, and RVOT Doppler showing score calculation for 2 patients. Column A (top to bottom) shows LA enlargement, ‘E/e’ and normal RVOT Doppler profile (score = -2). Invasive hemodynamics: mPAP = 40 mm Hg, PAWP = 20 mm Hg, PVR = 2.0 mm Hg/L/min. Column B demonstrates normal LA size, normal E/e’, and abnormal RVOT Doppler profile (score = +2). Invasive hemodynamics: mPAP = 45 mm Hg, PAWP = 10 mm Hg, PVR = 8.8 mm Hg/L/min. AccT = right ventricular outflow tract acceleration time; LA = left atrial; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; RVOT = right ventricular outflow tract. Reproduced with permission from Opotowsky AR, Ojeda J, Rogers F, et al. A simple echocardiographic prediction rule for hemodynamics in pulmonary hypertension. Circ Cardiovasc Imaging. 2012;5(6):765-775. See https://www.ahajournals.org/journal/circimaging. Published by the American Heart Association.
≥ 2 cm was associated with a decrease in all-cause mortality (hazard ratio = 0.21, 95% CI = 0.08, 0.60) and improved WHO functional class and 6-minute walk distance.18

Prior to a study published by Sivak et al., it was unclear how much right atrial function contributed to RV function. Because total RV function is largely due to longitudinal shortening, Sivak et al. hypothesized that the increased distance between RV base and apex that occurs during right atrial systole is an important contributor to overall RV function. They compared 37 patients with PAH to 35 healthy controls and showed that RA systolic function accounted for 51% of TAPSE compared to only 32% in controls.19 This has important clinical implications in that maintenance of sinus rhythm in PAH is essential for preserving RV function.

Several studies have highlighted the significance of nonlongitudinal shortening of the RV, particularly in the context of underlying cardiopulmonary disease. It was initially observed that TAPSE values were lower in cardiac surgery patients, but overall RV function appeared to be preserved. This led to a study by Vaidya et al., who compared RV contractile patterns in patients who underwent cardiac surgery with controls. They found that, in the surgical cohort, there was a dramatic decrease in longitudinal shortening, but overall RV function was normal due to a gain in transverse shortening.20 In this patient population, a lower value of TAPSE could be misleading; therefore, careful examination for special cases of RV contractile patterns, such as postcardiothoracic surgery patients, should be part of routine RV functional assessment.

Limitations of PASP Estimation: In a single-center prospective analysis of PH patients who underwent RHC and had DE performed 1 hour later, pulmonary artery pressures derived from DE differed significantly from those measured invasively (48% > ±10 mm Hg of the invasive measurement). In the case of underestimated measurements, the Doppler jet across the tricuspid valve was of poor quality, a significant limitation in DE. Approximately half of the cases that had overestimated PASP had overestimated right atrial pressures. Therefore, known physiologic variations in inferior vena cava collapsibility can cause variability in right atrial pressures and is also a source of error in PASP estimation. In patients with underlying lung disease, it is technically more difficult to obtain optimal window views of the tricuspid regurgitant jet, which leads to inaccurate estimation of PASP.21

CONCLUSIONS

- Echocardiography allows clinicians to simultaneously investigate the interplay between pathologic remodeling of the pulmonary vasculature in PH and the right heart’s adaption to it, thus providing a powerful means for comprehensive assessment.
- Novel echocardiographic measures and scoring tools can enable clinicians to confidently predict a patient’s predominant hemodynamic profile across several subtypes and severity of PH.
- Careful echocardiography interpretation should be used in conjunction with RHC, including serially, in the context of disease progression and response to therapy.

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Figure 3: Representative echocardiographic apical 4-chamber view of 3 different groups of pulmonary hypertension (PH). (A) PH_PVD = pulmonary vascular disease, (B) PVH = pulmonary venous hypertension, (C) PH_MIXED = PH mixed physiology. Endocardium is marked with orange-colored broken line, red lines mark RV basal diameter (above tricuspid annulus) and RV apical diameter (level of moderator band). RV = right ventricle; LV = left ventricle; RA = right atrium; LA = left atrium. Reproduced from Raza F, Dillane C, Mirza A, et al. Differences in right ventricular morphology, not function, indicate the nature of increased afterload in pulmonary hypertensive subjects with normal left ventricular function. Echocardiography. 2017;34(11):1584–1592, with permission from John Wiley & Sons, Inc.
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