REGULAR ARTICLE

COUNTERPOINT: Pulmonary Vascular Resistance 2.0—Shedding Light or Casting Shadows?

Robert P. Frantz, MD
Mayo Clinic
Department of Cardiovascular Medicine
200 First St SW
Rochester, MN 55905

The recent revision of the European Society of Cardiology/European Respiratory Society pulmonary hypertension (PH) guidelines, which lower the threshold for pulmonary vascular resistance (PVR) deemed to be abnormal to >2 Wood units (160 dynes·cm^{-5}), is based on sound evidence.[1] This includes expanding knowledge about the range of pulmonary artery pressure and PVR at rest and with exercise in healthy adults.[2,3] Although the PVR in healthy adults drifts up with age, it is consistently 2 Wood units or less. Additional information derives from analysis of a large database of subjects undergoing right heart catheterization, with the finding that PVR ≥2.2 was associated with worse outcome than lower PVR values.[4] This value was derived from a large cohort, and the findings were validated in a separate cohort. However, the derivation cohort is from the US Veterans Affairs Health Care System and reflects the nature of that population. On closer inspection it is quite remarkable to realize that the derivation cohort was 97% male, 88% had systemic hypertension, and 58% had coronary heart disease. In the validation cohort, about half were male and around 80% had systemic hypertension while over half had coronary heart disease. Precapillary PH, of particular interest to readers of *Advances in Pulmonary Hypertension*, carried greater risk than postcapillary PH, perhaps reflecting relatively robust treatment approaches for left heart disease. Of those with precapillary PH, 42% had chronic obstructive pulmonary disease (COPD), while less than 1% had interstitial lung disease. Presence of PH in patients with COPD is known to be associated with increased risk, but no PH-directed therapy has been found that has positive impact on outcome in PH due to COPD. Whether the PH in such patients mediates outcome or is just a marker of more advanced disease is also unknown. The only actions based on knowledge of mild PH in COPD are to redouble efforts to prevent hypoxemia (which should be done anyway) and to consider timing of lung transplant referral (which should be done anyway based on other COPD prognostic information and patient eligibility). Accordingly, there does not seem to be any point in chasing down presence of mild PH in COPD unless relevant to lung allocation score calculation in patients being considered for lung transplantation.

To be diagnosed with mildly elevated PVR, it is necessary to have undergone a right heart catheterization. Presumably the majority of the patients who underwent right heart catheterization in the cohorts described above and were found to have mildly elevated PVR were having the right heart catheterization not with a goal of detecting that condition, but for some other purpose likely associated with adverse prognosis (eg, severe COPD undergoing lung transplant evaluation, evaluation of left heart failure or valvular heart disease). Therefore, it is not known whether patients with undiagnosed mildly elevated PVR have as adverse a prognosis as those who have undergone right heart catheterization and had the diagnosis established. Furthermore, since we remain uncertain of the role for treatment of mildly elevated PVR, perhaps there is no great role for finding it. This may be part of the reason that there was not a decision in the latest PH guidelines to change the echo tricuspid regurgitation velocity worthy of further pursuing for PH. Another reason may reflect concern about reducing the specificity of echocardiographically suspected PH for presence of PH worth pursuing with right heart catheterization.

THE CONUNDRUM OF MILD PRECAPILLARY PH: MEAN PULMONARY ARTERY PRESSURE 19 TO 24, PULMONARY CAPILLARY WEDGE <15, AND PVR 2.2 TO 2.9

Recently this writer cared for a patient with a mean pulmonary artery pressure (mPAP) of 19 to 24, pulmonary capillary wedge pressure <15, and PVR of 2.2 to 2.9, thus meeting the criteria for mild precapillary PH. She had googled "pulmonary hypertension" and came to the visit following her right heart catheterization extremely worried about her condition. She had great questions for me. When I told her that we were not going to treat her PH with vasodilators, she became even more concerned. This is the ugly underbelly of the concept

Key Words—mild pulmonary hypertension, guidelines, right heart catheterization, exercise, prognosis
Correspondence: Frantz.robert@mayo.edu
Disclosure: Dr. Frantz reports consulting relationships with Aerovate, Acceleron, Altavant Sciences, Bayer, Gossamer Bio, Insmed, Janssen, Shouti, Tenax Pharmaceuticals, and UptoDate and stock ownership of Tenax pharmaceuticals.

of mild PH, and is where harm can be done. "Doctor, you mean you are just going to watch it get worse and do nothing? How does that make any sense? Tell me I have a condition that worsens my prognosis and do nothing but get me more worried? Can you even tell me why I have pulmonary hypertension? How quickly is it going to get worse? What should we do to keep track of it? *What can I do to improve my outcome?*" For the busy practitioner with the clock ticking until the next patient is ready, navigating this discussion in a compassionate fashion that provides clear information, when even the experienced practitioner may not be sure of what is driving the mild PH, requires a lexicon and approach that is in its infancy. No matter the debate about the pros and cons of the concept of mild PH, it is here to stay. In the spirit of providing an approach to the patient with mild PH that has been detected on right heart catheterization, consider the following:

- Consider the context of why the patient underwent a right heart catheterization.
- Strongly consider referral to a PH expert center.
- Strive to be a master clinician.
    - Take a thorough history, considering all possible causes of PH.
    - Follow the clues in the history, exam, labs, electrocardiogram, echocardiogram, and lung function tests.
    - Collate patient risk factors for heart failure with preserved ejection fraction.[5]
    - Always do overnight oximetry, and consider a formal polysomnogram.
    - If pulmonary function tests are abnormal and/or diffusing capacity of the lungs for carbon monoxide (DLCO) is low, always do thin-section chest computed tomography.
    - Always do an exercise test (6-minute walk, also cardiopulmonary exercise test if available).
    - Strongly consider ventilation/perfusion lung scan.
    - Strongly consider invasive exercise hemodynamics if the patient is symptomatic.
- Maximize information obtained at time of right heart catheterization.
    - Examine nitric oxide vasodilator challenge for those with wedge pressure ≤15 mm Hg.
    - Obtain exercise hemodynamics if available.
    - Perform 500-mL saline fluid challenge if wedge values are 12 to 18 mm Hg and exercise is not feasible.

Nitric Oxide Vasodilator Challenge: Rationale

Some patients with precapillary PH and PVR values of 2.2 to <3 Wood units will normalize PVR with inhaled nitric oxide (R.P.F., unpublished data). The prognostic implications of this finding are unknown, but may suggest less pulmonary vascular remodeling, may provide some rationale for using calcium channel blockers if the patient requires antihypertensive therapy anyway, and careful collection of this information may in the future be analyzed to better understand implications of such a finding.

Exercise Hemodynamics or Fluid Challenge: Rationale

Patients with PVR values of 2.2 to 3 Wood units and wedge values <15 mm Hg, or even up to 18 mm Hg, may have exercise hemodynamic or volume challenge tests that are very informative.

Scenario 1: Occult Heart Failure With Preserved Ejection Fraction

- Patients with occult heart failure with preserved ejection fraction (HFpEF) may already be on diuretics so may have a wedge pressure <15 mm Hg, which may rise with exercise or fluid challenge in a fashion that is diagnostic of exercise-induced HFpEF.
- Patients with wedge pressure of up to 18 mm Hg but with elevated PVR of 2.2 to <3 form a group of diagnostic uncertainty. Fluid challenge or exercise hemodynamics may be clarifying. This scenario, particularly when combined with other clinical features to support the diagnosis, can allow the practitioner to consider HFpEF treatment options and/or referral for clinical trials for HFpEF. This approach may be considered in patients with wedge pressure of up to 18 mm Hg, to help further define extent of pre- and postcapillary disease. If the wedge pressure does not rise much further but there is major rise in pulmonary arterial (PA) pressure, this may identify a phenotype where the precapillary PH is not merely secondary to the left heart disease. An example could be an elderly patient with scleroderma and history of systemic hypertension who has precapillary pulmonary vascular disease related to their scleroderma, but also has a comorbidity of mild left heart disease.

Scenario 2: Mild Precapillary PH That Worsens With Exercise, With Wedge Staying Normal

- Patients with mild precapillary PH may have significant pulmonary vascular remodeling and be unable to recruit sufficient additional pulmonary vasculature during exercise to avoid further substantial rise in PA pressure with exercise.
- Mean PA pressure to cardiac output slope >3 mm Hg/L/min is abnormal.[6]
- Pulmonary artery wedge pressure to cardiac output slope of <2 mm Hg/L/min suggests precapillary PH, while values >2 mm Hg/L/min suggest postcapillary PH.[6]

Exercising such patients may reveal limitation in exercise capacity that in turn may explain symptoms of dyspnea based upon limited cardiac output response, abnormal rise in PA pressure and occasionally right atrial pressure, and further confirm abnormalities of the precapillary pulmonary vasculature. This may be particularly informative in patients with risk factors for PAH, such as connective tissue disease, methamphetamine use, family history of PAH, HIV infection. Measurement of gas exchange parameters with a metabolic cart can allow assessment of ventilatory inefficiency (eg, the ratio of minute ventilation to carbon dioxide; VE/VCO_2 slope and na-

dir), detect exercise-related desaturation, and assess adequacy of cardiac output response.

Doctor, What Are We Going to Do? Context Is Everything

With these thoughts in mind, it is worth stepping back and putting the patient at the center of the conversation. Why are they being seen? If the patient is being seen for unexplained dyspnea, the following approach can be taken.

- Exclude chronic thromboembolic PH with nuclear medicine ventilation/perfusion lung scan, and additional evaluation if needed. Chronic thromboembolic PH or chronic thromboembolic pulmonary disease can cause significant exertional dyspnea, sometimes in the absence of PVR of >3 Wood units.[7] It can be treated with surgical thromboendarterectomy, balloon pulmonary angioplasty, or vasodilators such as riociguat. The best approach requires evaluation at a comprehensive chronic thromboembolic PH center.
- When mildly elevated PVR is found in a patient with unexplained dyspnea, invasive cardiopulmonary exercise testing at the time of diagnostic right heart catheterization is recommended if available.
- If only resting right heart catheterization was performed, then additional noninvasive testing in an effort to establish a clinical phenotype that explains the dyspnea is warranted.
- If the noninvasive testing fails to establish sufficient phenotypic information, then referral to a center that can perform invasive hemodynamic exercise testing is suggested.

Risk Factors for PAH Sufficient to Screen for PAH

Connective Tissue Disease

- Patients with scleroderma should be screened for PAH. In scleroderma, the DETECT algorithm can be utilized to guide utilization of echocardiography and right heart catheterization.[8] An approach to mild PH in scleroderma is shown in Figure 1.

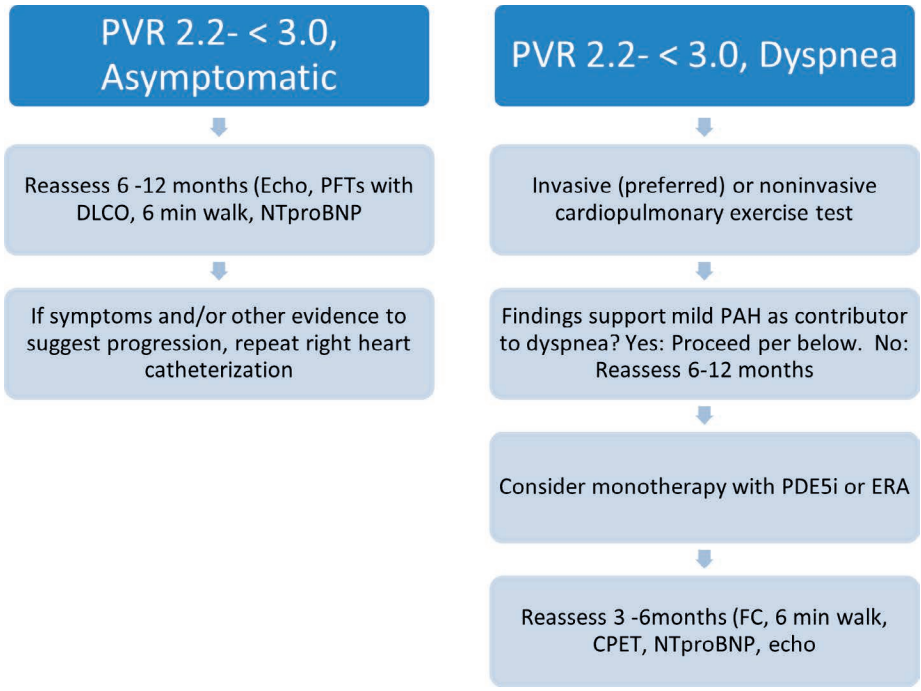

Figure 1: Approach to mild pulmonary hypertension in scleroderma.

If mild precapillary PH (mPAP 21 to 24, or >25 but PVR 2 to <3) is present, what is known? For those with DLCO <60% predicted and mPAP 21 to 24, there is about a 25% 5-year risk of developing mPAP >25 mm Hg.[9] These patients with scleroderma and PVR of 2 to < 3.0 fall into 3 categories: (1) asymptomatic; (2) asymptomatic but with objective exercise testing limitations; (3) symptomatic (eg, exertional dyspnea). If they are asymptomatic, then the presence of the mild PH needs to be explained to the patient. The following steps form a reasonable approach to this discussion:

1. The PH is mild and knowledge about role of treatment is limited.
2. Reassessment in 6 months to 1 year with repeat echocardiography, 6-minute walk test, pulmonary function tests with DLCO, and NTproBNP or BNP is appropriate.
3. If at reassessment there is concern for progression of PH, a repeat right heart catheterization should be performed.
4. Subsequent reassessment at 6- to 12-month intervals should be performed, or sooner if symptoms of dyspnea develop.
5. Those patients who are asymptomatic but with objective exercise limitation should be followed at 6-month intervals.
6. For symptomatic patients with PVR of 2.0 to <3 Wood units, there are some data to support treatment but the evidence base remains limited.[10 11]

Family History of PAH

For patients with a family history of PAH, a finding of PVR 2.2 to <3.0 raises concern that the patient may have an early stage of heritable PAH. Recommendations in this situation include the following:

1. Discuss genetic testing if it has not already been done.
2. Determine whether affected family members have genotyping results available; if so test specifically for that gene. If not, do full-panel testing.
3. If positive and asymptomatic, reassess in 6 months.
4. If positive and symptomatic, consider monotherapy (phosphodies-

terase type 5 inhibitors or endothelin receptor antagonist); reassess in 6 months.
5. If negative but other affected family members have not been genotyped or were negative, there may be an unrecognized mutation. Reassess in 6 months; if symptomatic consider monotherapy.

Idiopathic PH

1. Take a careful history (including drug use, especially methamphetamine).
2. Perform a perfusion lung scan to look for chronic thromboembolic disease.
3. If asymptomatic, recheck in 6 to 12 months.
4. If symptomatic with objective exercise limitation, Consider monotherapy with PDE5i or ERA.
5. Assess treatment response in 3 months.

Liver Disease

1. If asymptomatic, reassess in 6 months.
2. If symptomatic, it can be difficult to separate symptoms possibly attributable to PAH from those related to the liver disease such as due to anemia.
3. Perform exercise testing.
4. Reassess in 6 months.

HIV With Dyspnea

1. Perform exercise testing.
2. If there is an objective limitation, consider monotherapy but always consult with HIV pharmacist about drug interactions, which can be major.

SUMMARY

Proper diagnosis of PH is challenging even in situations where the PVR is >3 Wood units. Understanding the pathophysiology and causes of PH with PVR 2.0 to <3.0 Wood units is even more challenging, but noting these challenges is not going to make them go away. There is significant risk of creating confusion and psychological distress for the patient. There is significant financial cost for the patient as well, related to testing, time away from work, and travel to the medical center. In the worst-case scenario, an incorrect diagnosis is made, useless or harmful and expensive therapies are prescribed, and there is significant disruption of the patient's wellbeing. Providers who are evaluating and caring for patients with mild PH must be thorough, expert, compassionate, and able to acknowledge potential for misdiagnosis. Provisional diagnosis demands careful follow-up and a willingness to modify an approach based upon subsequent developments in patient symptoms and findings. In the best-case scenario, identification of mild PH allows detection of associated conditions for which appropriate treatment may be available, results in earlier diagnosis of disease that could lead to improved outcomes, and provides an opportunity for participation in research.

FUTURE DIRECTIONS

It is incumbent upon the PH community to facilitate research pertinent to mild PH. This includes funding, as well as careful design and conduct of prospective longitudinal registries to further our understanding of the natural history of mild PH. To be meaningful, such registries will require highly detailed patient characterization. Innovative study design regarding treatment of mild PH is also warranted. This is particularly challenging since the phenotypic variation in the mild PH population raises potential for differing and poorly understood pathophysiologies to be inadvertently lumped together. In addition, demonstration of an impact of a therapeutic approach in mild disease will demand very long-term follow-up, innovative study endpoints, or both. When patients with mild PH are identified, they should be offered the opportunity to participate in research pertinent to advancing understanding of the significance, natural history, and possible treatment of mild PH and, accordingly, referral to a PH center of excellence that is conducting such research is recommended. In this fashion, in the future we will hopefully not need to debate the pros and cons of identifying mild PH, because we will have developed better understanding of approaches to its evaluation and management.

References

1. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731.
2. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009;34(4):888-894.
3. Kovacs G, Olschewski A, Berghold A, Olschewski H. Pulmonary vascular resistances during exercise in normal subjects: a systematic review. *Eur Respir J*. 2012;39(2):319-328.
4. Maron BA, Brittain EL, Hess E, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med*. 2020;8(9):873-884.
5. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;138(9):861-870.
6. Zeder K, Banfi C, Steinrisser-Allex G, et al. Diagnostic, prognostic and differential-diagnostic relevance of pulmonary haemodynamic parameters during exercise: a systematic review. *Eur Respir J*. 2022;60(4):2103181.
7. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2021;57(6):2002828.
8. Coghlan JG, Denton CP, Grünig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis*. 2014;73(7):1340-1349.
9. Visovatti SH, Distler O, Coghlan JG, et al. Borderline pulmonary arterial pressure in systemic sclerosis patients: a post-hoc analysis of the DETECT study. *Arthritis Res Ther*. 2014;16(6):493.
10. Pan Z, Marra AM, Benjamin N, et al. Early treatment with ambrisentan of mildly elevated mean pulmonary arterial pressure associated with systemic sclerosis: a randomized, controlled, double-blind, parallel group study (EDITA study). *Arthritis Res Ther*. 2019;21(1):217.
11. Ratwatte S, Anderson J, Strange G, et al. Pulmonary arterial hypertension with below threshold pulmonary vascular resistance. *Eur Respir J*. 2020;56(1):1901654.