REGULAR ARTICLE

Heart Failure With Preserved Ejection Fraction and the Diagnosis of Pulmonary Hypertension

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Heart failure with preserved ejection fraction (HFpEF) is now the most common cause of pulmonary hypertension (PH), and the diagnosis of HFpEF should be considered in any patient with a preserved left ventricular systolic function being evaluated for PH. Accurately diagnosing HFpEF as compared with pulmonary arterial hypertension has critical treatment implications, given the vastly different treatment options available, and can be accurately guided using exercise right heart catheterization. In this review, the diagnostic approach and treatment implications of PH in patients at risk for HFpEF will be discussed.

INTRODUCTION

Elevated pulmonary artery (PA) pressure can arise from multiple different disease states. One of the most common causes of pulmonary hypertension (PH) worldwide is left-sided heart failure.[1,2] Coupled with the obesity epidemic,[3] the epidemiology of heart failure has gradually shifted over the last few decades to where heart failure with preserved ejection fraction (HFpEF) is now the most common cause of heart failure and thereby the most common cause of PH.

CURRENT DIAGNOSIS OF HFpEF AND PH

The diagnosis of PH relies on measurement of an elevated mean PA pressure. Based on normative values from population studies and thresholds of risk, the diagnostic threshold for PH has been progressively lowered from a mean PA pressure of ≥25 mm Hg to now ≥20 mm Hg.[4] Importantly, the threshold for diagnosing left heart disease at rest has not changed, where a mean pulmonary capillary wedge pressure (PCWP) ≥15 mm Hg is considered diagnostic of left heart disease. The margin of error for diagnosis of HFpEF compared with precapillary pulmonary arterial hypertension (PAH) is therefore now smaller and requires meticulous performance of right heart catheterization to accurately classify patients with mild PH at rest.

MEASURING PRESSURES AT END EXPIRATION DURING RIGHT HEART CATHETERIZATION

Pressures are measured during right heart catheterization by means of a fluid filled catheter connected to a pressure transducer system. This allows measurement of relative pressure changes over time, but pressure changes must be referenced to an external zero reference point, which is set by convention to atmospheric pressure with the pressure transducer leveled at the midchest. Since pressures are measured relative to atmospheric pressure, it is important to measure pressures manually at end expiration, when the lung is at its functional residual capacity and intrathoracic pressure is closest to atmospheric pressure (the chosen zero reference point). During inspiration, a drop in intrathoracic and pleural pressure normally occurs, which results in a decrease in all pressures in the chest (including the pressure recorded by the catheter in the heart), but no true change in intracardiac pressures as assessed by the transmural pressure (intracardiac pressure – pleural pressure).[5] Therefore, relying on computer-generated mean pressures throughout the respiratory cycle will include false declines in intracardiac pressure during inspiration and thereby underestimate the true PCWP. Due to the competing effects of increased venous return and right-sided stroke volume during inspiration (which tends to increase PA pressure) and decreased intrathoracic pressure (which tends to decrease PA pressure), the error-inducing effect of inspiration on PA pressure is smaller than its effect on the PCWP since the PCWP generally demonstrates greater respiratory variation. Therefore, failing to measure pressures at end expiration will generally underestimate the contribution of left heart disease to the PH and may result in misdiagnosis as precapillary PAH as opposed to the true diagnosis of HFpEF (Figure 1).

WEDGE PRESSURE OR LEFT VENTRICULAR END DIASTOLIC PRESSURE?

It is also important to use the PCWP and not the left ventricular (LV) end diastolic pressure (LVEDP) when trying to diagnose HFpEF and determine the precapillary contribution to PH.[6] The PCWP allows measurement of left atrial (LA) pressure throughout systole and diastole and therefore allows understanding of whether large V waves are present in the LA from atrial noncompliance during atrial filling. Large V waves impart a late systolic load to the right ventricle and contribute to PH and pulmonary arterial stiffness from

Key Words—heart failure with preserved ejection fraction, hemodynamics, pulmonary hypertension
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Disclosure: The authors have no relevant personal financial relationships to disclose.

 DOI:10.21693/1933-088X-22.3.130

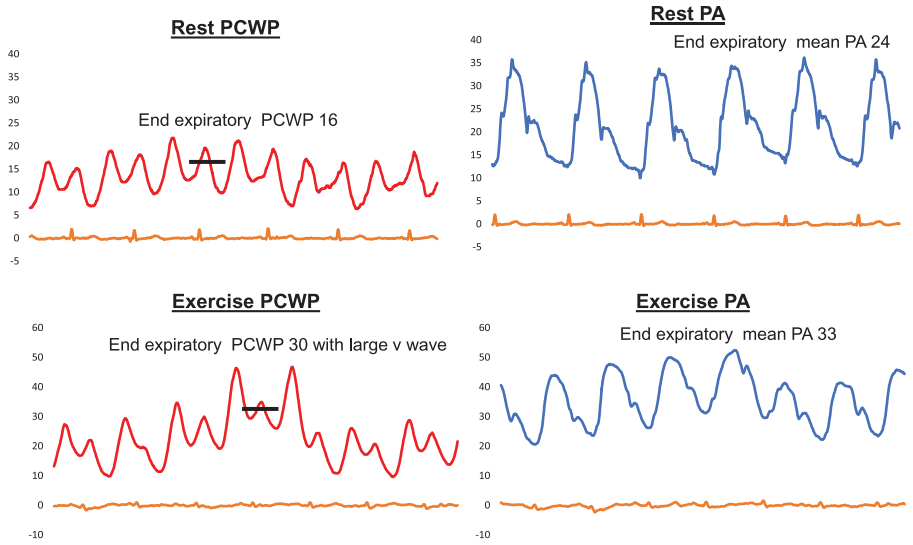

Figure 1: Value of end expiratory exercise hemodynamics to differentiate HFpEF from pulmonary arterial hypertension.

postcapillary mechanisms in HFpEF.[7,8] In contrast, the LVEDP reflects only a static measurement at end diastole, and although helpful in identifying LV pathology in HFpEF, the LVEDP does not allow assessment of LA myopathy and compliance, which is ultimately the critical determinant of pulmonary venous pressures and the degree to which the left heart is contributing to PH. Increasing atrial fibrillation burden with symptoms is generally associated with worse underlying LA myopathy with HFpEF[7], and even the mere presence of atrial fibrillation in a symptomatic patient with a preserved LV ejection fraction (EF) serves as a highly specific biomarker for underlying HFpEF.[9] The presence of atrial fibrillation in particular is uncommon in true Group 1 PAH and raises the pretest probability that HFpEF is the correct diagnosis and cause of PH. Therefore, when trying to understand if HFpEF is the cause of PH and to allow quantification of the burden of pulmonary vascular disease by calculation of pulmonary vascular resistance (PVR), it is important to use the PCWP and not the LVEDP.

PH IN HFpEF—NOT UNIVERSAL AT REST

Further complicating the evaluation for HFpEF in a patient with suspected PH is the dynamic nature of hemodynamic abnormalities in patients with HFpEF. Many patients with HFpEF and PH may have relatively normal left-sided filling pressures at rest that may increase with provocation or mild changes in volume status.[10] Exercise right heart catheterization is therefore the gold standard diagnostic test to either exclude or diagnose HFpEF based on the exercise PCWP measured during occurrence of exertional symptoms. Given the inaccuracies of resting right heart catheterization to diagnose HFpEF (a sensitivity of only 56%),[10] consideration of clinical characteristics is important to quantify the pretest probability of HFpEF and guide use of exercise catheterization so that the correct diagnosis is established in the presence of resting PH. We developed and validated the H_2FPEF score, to estimate this pretest probability more quantitatively. HFpEF is increasingly likely when patients have obesity, atrial fibrillation, hypertension, and are older.[10,11] When borderline resting hemodynamics with PH occurs with an intermediate to high H_2FPEF score, exercise right heart catheterization can therefore be helpful in clarifying the diagnosis and guide treatment (Table 1).

The presence of hypoxia during exercise is generally associated with PH and abnormal PVR in patients with HFpEF.[12] Patients with combined precapillary and postcapillary PH HFpEF have the greatest hypoxemia and ventilatory abnormalities coupled with greater hemodynamic derangements.[13] Isolated postcapillary PH in HFpEF is rarely associated with severe hypoxemia[14] despite dynamic occurrence of pulmonary edema during exercise.[15] Therefore, the presence of clinical hypoxemia should raise consideration for pulmonary vascular disease that can be seen either in precapillary PAH or combined precapillary and postcapillary PH due to HFpEF.

SPECTRUM OF PH PHENOTYPES IN HFpEF

Based on resting and exercise hemodynamics in a patient with PH at rest (mean PA ≥ 20 mm Hg), 3 hemodynamic profiles in a patient at risk for HFpEF are generally possible:

(1) isolated postcapillary PH HFpEF with mean PA ≥ 20, exercise PCWP ≥ 25 mm Hg, and normal PVR at rest (<2 Wood units);
(2) combined precapillary and postcapillary PH HFpEF with mean PA ≥ 20, PVR > 2 Wood units, and exercise PCWP ≥ 25 mm Hg; or
(3) precapillary PAH without HFpEF with mean PA ≥ 20, PVR > 2 Wood units, and exercise PCWP < 25 mm Hg.

In clinical practice, patients whose hemodynamics may be borderline or lie outside the boundaries of these categorical definitions may require consideration of pretest probability based on clinical profile and risk factors to help guide therapeutic decision making. Although some have advocated for use of PA pressure or PCWP indexed to change in cardiac output to define precapillary versus postcapillary PH, the use of flow-adjusted pressure measurements may not add incremental diagnostic value for most patients, at least during supine exercise. In a multicenter study, use of PCWP indexed to cardiac output appeared to misclassify patients without incremental diagnostic value.[11] Given the added complexity of using flow-adjusted PA and PCWP measurements with uncertain diagnostic value, use of absolute pressures is preferred for diagnostic purposes, with the cardiac output response providing independent physiological information with prognostic value.[16]

Table 1. Steps in Performance of Exercise Right Heart Catheterization for Evaluation of Borderline Hemodynamics at Rest

1	Jugular venous access with 9 French venous sheath to allow continuous monitoring of right atrial pressure throughout exercise from the side arm of the venous sheath
2	Right heart catheterization with end hole single lumen catheter with high fidelity micromanometer to avoid whip and ringing artifact which improves fidelity for accurate measurement of end expiratory hemodynamics
3	Arterial line placement to obtain accurate arterial saturations which may be unreliable with exercise using noninvasive oximetry
4	Measurement of PA saturation and SVC saturation with simultaneous VO_2 measurement using a metabolic cart to calculate cardiac output and rule out a left to right shunt
5	Measurement of PCWP saturation to confirm an appropriate PCWP position before exercise with a wedge saturation >90%. Without this confirmation, we risk that the PCWP tracing is a damped or partial PA tracing from incomplete occlusion of the PA segment with the inflated balloon volume
6	Exercise in 2 min ramped stages with measurement of PA and PCWP and cardiac output at each stage
7	Absolute PCWP during early and peak exercise at end expiration helps rule in (≥25 mm Hg) or rule out HFpEF (<25 mm Hg)
8	Relative changes in PA to PCWP during rest and exercise help determine the relative precapillary versus postcapillary component along with pretest probability
9	Relative changes in RA to PCWP ratio help determine the contribution of relative pericardial restraint to intracardiac hemodynamics

Abbreviations: HFpEF, heart failure with preserved ejection fraction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrium; SVC, superior vena cava.

THE CLINICAL CHALLENGE OF ATYPICAL PAH WITH RISK FACTORS FOR HFpEF BUT RESTING HEMODYNAMICS SUGGESTIVE OF PAH

Since patients with both PAH and HFpEF present with a preserved LV EF and symptoms, this can lead to diagnostic challenges in hemodynamic evaluation in patients with risk factors for HFpEF, as described above. When patients with risk factors for HFpEF (obesity, atrial fibrillation, hypertension) appear to have hemodynamics at rest consistent with PAH, they do not respond as well to pulmonary vasodilator therapy.[17,18] More aggressive pulmonary vasodilator therapy, in particular, did not appear to be associated with improved outcomes or symptoms in such patients with atypical PAH whose hemodynamics support PAH, but the risk factor profile and pretest probability suggest the possibility of undiagnosed HFpEF.[18] Since HFpEF cannot be ruled out with resting right heart catheterization and clinical profile alone, the diagnosis of HFpEF remains a probabilistic diagnosis based on standard resting clinical measures. This suggests that our current hemodynamic measures at rest may not provide sufficient diagnostic clarity in patients with atypical PAH. These patients likely represent a heterogenous cohort with (i) true precapillary PAH, (ii) combined precapillary and postcapillary PH HFpEF that has been missed by resting right heart catheterization, or (iii) passive isolated postcapillary PH with measurement error due to inaccurate PCWP or cardiac output measurements. The use of exercise hemodynamics may therefore enhance diagnosis and selection of patients with atypical PAH for appropriate therapies.[19] With the emergence of effective therapies for HFpEF, particularly with the sodium glucose cotransporter (SGLT)-2 inhibitors,[20] making an accurate diagnosis of HFpEF as compared with PAH has very important therapeutic implications, for which HFpEF requires treatment with SGLT2 inhibitors and PAH would require pulmonary vasodilator therapy.

SUMMARY

HFpEF is now the most common cause of PH, and the diagnosis of HFpEF should be considered in any patient with a preserved EF being evaluated for PH. Accurately diagnosing HFpEF as compared with PAH has critical treatment implications, given the vastly different treatment options available, and can be accurately guided using exercise right heart catheterization.

Hemodynamics obtained from a 70-year-old female with hypertension and unexplained dyspnea, using pressures averaged through the respiratory cycle, showed the mean PA pressure was 23, mean PCWP was 12, with a PVR of 2 Wood units, which would be consistent with precapillary PH. Using end-expiratory measures would measure the true PCWP, which is higher and consistent with HFpEF. End-expiratory mean PA pressures can be calculated using the Chemla regression equation using end-expiratory PA systolic pressure as (0.6 × PA systolic pressure) + 2. With exercise, end-expiratory wedge pressure increased to 30 with large V waves to 44 with associated PH and normal pulmonary vascular response with a decline in PVR during exercise. The patient symptoms are therefore consistent with HFpEF and not atypical PAH

Acknowledgments: YNR is supported by National Heart, Lung, And Blood Institute of the National Institutes of Health (NHLBI) Award No. K23HL164901, grants from Sleep Number, Bayer, United Pharmaceuticals, and the Earl Wood Career Development Award from Mayo Clinic.

References

1. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. *Lancet Respir Med.* 2016;4(4):306–322. https://doi.org/10.1016/S2213-2600(15)00543-3
2. Reddy YNV, Borlaug BA. Pulmonary hypertension in left heart disease. *Clin Chest Med.* 2021;42(1):39–58. https://doi.org/10.1016/j.ccm.2020.11.002

3. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med.* 2019;381(25):2440–2450. https://doi.org/10.1056/NEJMsa1909301
4. 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. https://doi.org/10.1093/eurheartj/ehac237
5. Smiseth OA, Thompson CR, Ling H, Robinson M, Miyagishima RT. Juxtacardiac pleural pressure during positive end-expiratory pressure ventilation: an intraoperative study in patients with open pericardium. *J Am Coll Cardiol.* 1994;23(3):753–758. https://doi.org/10.1016/0735-1097(94)90764-1
6. Reddy YNV, El-Sabbagh A, Nishimura RA. Comparing pulmonary arterial wedge pressure and left ventricular end diastolic pressure for assessment of left-sided filling pressures. *JAMA Cardiol.* 2018;3(6):453–454. https://doi.org/10.1001/jamacardio.2018.0318
7. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol.* 2020;76(9):1051–1064. https://doi.org/10.1016/j.jacc.2020.07.009
8. Reddy YNV, El Sabbagh A, Packer D, Nishimura RA. Evaluation of shortness of breath after atrial fibrillation ablation-Is there a stiff left atrium? *Heart Rhythm.* 2018;15(6):930–935. https://doi.org/10.1016/j.hrthm.2018.01.029
9. Reddy YNV, Obokata M, Gersh BJ, Borlaug BA. High prevalence of occult heart failure with preserved ejection fraction among patients with atrial fibrillation and dyspnea. *Circulation.* 2018;137(5):534–535. https://doi.org/10.1161/CIRCULATIONAHA.117.030093
10. 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. https://doi.org/10.1161/CIRCULATIONAHA.118.034646
11. Reddy YNV, Kaye DM, Handoko ML, et al. Diagnosis of heart failure with preserved ejection fraction among patients with unexplained dyspnea. *JAMA Cardiol.* 2022;7(9):891–899. https://doi.org/10.1001/jamacardio.2022.1916
12. Omar M, Omote K, Sorimachi H, et al. Hypoxaemia in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail.* 2023. https://doi.org/10.1002/ejhf.2930
13. Omote K, Sorimachi H, Obokata M, et al. Pulmonary vascular disease in pulmonary hypertension due to left heart disease: pathophysiologic implications. *Eur Heart J.* 2022;43(36):3417–3431. https://doi.org/10.1093/eurheartj/ehac184
14. Hardin KM, Giverts I, Campain J, et al. Systemic arterial oxygen levels differentiate pre- and post-capillary predominant hemodynamic abnormalities during exercise in undifferentiated dyspnea on exertion. *J Card Fail.* 2023:S1071-9164(23)00244-0. https://doi.org/10.1016/j.cardfail.2023.05.023
15. Reddy YNV, Obokata M, Wiley B, et al. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. *Eur Heart J.* 2019;40(45):3721–3730. https://doi.org/10.1093/eurheartj/ehz713
16. Omote K, Verbrugge FH, Sorimachi H, et al. Central haemodynamic abnormalities and outcome in patients with unexplained dyspnoea. *Eur J Heart Fail.* 2023;25(2):185–196. https://doi.org/10.1002/ejhf.2747
17. Opitz CF, Hoeper MM, Gibbs JS, et al. Pre-capillary, combined, and post-capillary pulmonary hypertension: a pathophysiological continuum. *J Am Coll Cardiol.* 2016;68(4):368–378. https://doi.org/10.1016/j.jacc.2016.05.047
18. McLaughlin VV, Vachiery JL, Oudiz RJ, et al. Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: Results from the AMBITION trial. *J Heart Lung Transplant.* 2019;38(12):1286–1295. https://doi.org/10.1016/j.healun.2019.09.010
19. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail.* 2010;3(5):588–595. https://doi.org/10.1161/CIRCHEARTFAILURE.109.930701
20. Borlaug BA, Reddy YNV, Braun A, et al. Cardiac and metabolic effects of dapagliflozin in heart failure with preserved ejection fraction: the CAMEO-DAPA trial. *Circulation.* 2023. https://doi.org/10.1161/CIRCULATIONAHA.123.065134