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RESEARCH LETTER

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Hemodynamic markers independent of pulmonary capillary wedge pressure can discriminate between pre and postcapillary exercise-induced pulmonary hypertension

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Abstract

The discrimination between pre and postcapillary exercise-induced pulmonary hypertension relies on accurate measurement of pulmonary capillary wedge pressure, which can be unreliable. We found that exercise pulmonary artery compliance and right atrial pressure (AUC 0.88, 0.89, respectively) can differentiate subtypes of exercise-induced pulmonary hypertension in the absence of wedge pressure.

KEYWORDS
exercise, heart failure, hemodynamics, pulmonary hypertension

Exercise-induced pulmonary hypertension (EIPH), defined by a multipoint exercise mean pulmonary artery pressure (mPAP)/cardiac output (CO) slope >3 mmHg/L/min, is an early manifestation of latent pulmonary vascular disease (PVD) or left heart disease (LHD).[1] EIPH is being increasingly recognized as a distinct clinical entity predictive of poor outcomes in patients with normal resting hemodynamics and in those with borderline pulmonary hypertension (mPAP 21–24 mmHg).[2–4] The discrimination between pre and postcapillary etiologies of EIPH relies on accurate measurement of pulmonary capillary wedge pressure (PCWP) to estimate left-sided cardiac filling pressures and calculate pulmonary vascular resistance [PVR = (mPAP−PCWP)/CO].[1] The measurement of PCWP during exercise, however, can be unreliable due to motion artifact, catheter ringing, incomplete PA balloon occlusion during increased flow, and respiratory variation.[5,6] Given these challenges, we aimed to investigate the ability of alternative hemodynamic markers to discriminate between pre (exercise-induced pulmonary arterial hypertension or EiPAH) and post-capillary (exercise-induced heart failure with preserved ejection fraction or EiHFpEF) disease in EIPH.

We retrospectively studied 25 consecutive participants diagnosed with EIPH after undergoing invasive exercise right heart catheterization for evaluation of exertional dyspnea at a single institution from 2012 to 2023. EIPH was defined as an exercise mPAP/CO slope of

>3 mmHg/L/min in patients despite normal resting hemodynamics (mPAP < 20 mmHg and PCWP < 15 mmHg).[1] Patients with known PAH or HFpEF were excluded. Hemodynamics were measured at end-expiration at rest and after passive leg raise (PLR), and automatically-derived and averaged across the respiratory cycle at the end of each 2-min graded exercise stage (beginning at 15 W and increasing in 10 W increments until symptom limitation). PCWP was also measured at end-expiration with exercise. EiHFpEF was defined by an end-expiratory PCWP ≥ 25 mmHg at any exercise stage.[7] Otherwise, EiPAH was diagnosed. Hemodynamic waveforms were independently reviewed by two physicians (S.H. and M.M).

Differences between groups were first compared using unpaired t-tests or Mann-Whitney tests where appropriate. A mixed-effect model for repeated measures was applied to determine the effects of group, exercise stage, and their interaction on hemodynamic variables of interest. A significant interaction term suggested a different trend across exercise between groups. Logistic regression with receiver operator characteristic (ROC) analyses were used to evaluate the diagnostic performance of selected peak exercise variables. Bootstrap resampling with 1000 replications was employed for internal validation. Optimal cut-off thresholds were determined using Youden's index. Values are reported as mean ± SD or median (25%, 75%), as appropriate. Area under ROC (AUC) values and likelihood ratios (LR) are reported with 95% confidence intervals. All statistical analyses were performed using Stata 18.0 and Prism 9.0. All primary data supporting the analysis are available upon reasonable request to the corresponding author.

We identified 14 patients with EiHFpEF (56%) and 11 with EiPAH (44%). EiHFpEF and EiPAH patients were similar in regard to age (65 ± 13 vs. 60 ± 10 years, $p = 0.28$), female sex (21% vs. 27%, $p = 0.73$), and body surface area (1.92 ± 0.33 vs. 1.87 ± 0.33 m^2, $p = 0.74$). Pulmonary artery systolic, diastolic, mPAP, and pulse (PAPP) pressures, right atrial pressure (RAP), PCWP, CO, heart rate (HR), and stroke volume (SV) were similar between groups at rest. Resting PVR was significantly higher in EiPAH (2.1 ± 0.8 vs. 1.3 ± 0.4 WU, $p = 0.005$). Pulmonary arterial compliance [PAC = SV/PAPP] was similar in EiPAH (3.8 ± 1.2 mL/mmHg) and EiHFpEF (4.3 ± 0.8 mL/mmHg, $p = 0.2$) at rest.

Both groups achieved a similar peak exercise workload. Exercise mPAP/CO slopes were similar between groups (3.9[3.3,5.4] vs. 3.7[3.3,5.1] mmHg/L/min in EiHFpEF vs. EiPAH, $p = 0.57$). Figure 1 illustrates exercise-induced hemodynamic changes in each cohort. Pulmonary pressures increased similarly with exercise in both groups. As expected, end-expiratory PCWP increased to a greater extent with exercise in EiHFpEF (31 ± 4 vs. 18 ± 5 mmHg, $p = <0.001$ at peak; interaction p = <0.001). Multipoint exercise PCWP/CO slope was similarly higher in EiHFpEF (2.5[2.2, 4.6] vs. 1.5[0.78, 1.7] mmHg/L/min, $p = 0.001$).

RAP similarly increased to a greater extent in EiHFpEF (11 ± 4 vs. 6 ± 2 mmHg, $p = 0.004$ at peak; interaction $p = 0.002$). PVR did not significantly vary with exercise in either group, remaining higher in EiPAH at peak exercise (2.4 ± 0.7 vs. 1.3 ± 0.6 WU, p = <0.001). Exercise PAC, while declining in both groups, declined to a greater extent in EiPAH (2.1 ± 0.4 vs. 3.3 ± 1 mL/mmHg, $p = 0.001$ at peak; interaction $p = 0.03$). Reduced exercise PAC in EiPAH was driven by both higher PAPP (35 ± 10 vs. 27 ± 7 mmHg, $p = 0.03$) and HR (136 ± 28 vs. 114 ± 18 bpm, $p = 0.03$) at peak exercise. The latter is likely reflective of previously described chronotropic incompetence in HFpEF patients.[8] SV and CO were similar between groups at peak exercise (73 ± 18 vs. 86 ± 23 mL, $p = 0.12$ and 9.7 ± 2.4 vs. 9.7 ± 2.6 L/min, $p = 0.99$ in EiPAH vs. EiHFpEF, respectively).

Area under ROC analyses revealed exercise PAC and RAP to be the best discriminators of EiPAH versus EiHFpEF, with AUCs of 0.88 (0.73–1) and 0.89 (0.75–1), respectively. Optimism-adjusted bootstrapped AUCs were 0.88 (0.77–1) and 0.90 (0.81–1) suggesting good internal validity with minimal overfitting. At peak exercise, PAC < 2.5 mL/mmHg and RAP < 8 mmHg predicted EiPAH with 82% sensitivity and 85% specificity (LR+ 5.7[1.3–21.3] and LR− 0.21[0.06–0.8]), and 89% sensitivity and 77% specificity (LR+ 3.9[1.4–10.1] and LR − 0.14[0.02–0.9]), respectively.

EIPH is being increasingly recognized an important clinical entity associated with poor outcomes including increased hospitalizations and mortality. Justifiably, it has been recently re-introduced into formal guidelines.[1,2] While recognition of EIPH offers an opportunity for early detection of latent PVD and LHD, the discrimination between these etiologies is crucial, with obvious diagnostic, prognostic, and therapeutic implications. In this work, we find significant differences in exercise PAC and RAP between pre- and post-capillary EIPH patients which may offer an important clinical tool allowing for successful discrimination between these cohorts in the absence of reliable PCWP measurement.

Although the presence of PVD is classically defined by an elevated PVR, a reduction in PAC is a more sensitive predictor of PVD in PAH.[9] Loss of PAC, a surrogate for increased arterial stiffness, occurs early in the development of PVD, leading to increased pulmonary artery pressure and pulsatility, enhanced right ventricular (RV) pulsatile afterload, and incitation of further vascular remodeling.[9] PVR and PAC exhibit a well-described inverse hyperbolic relationship with a product (RC time = PAC·PVR) that is

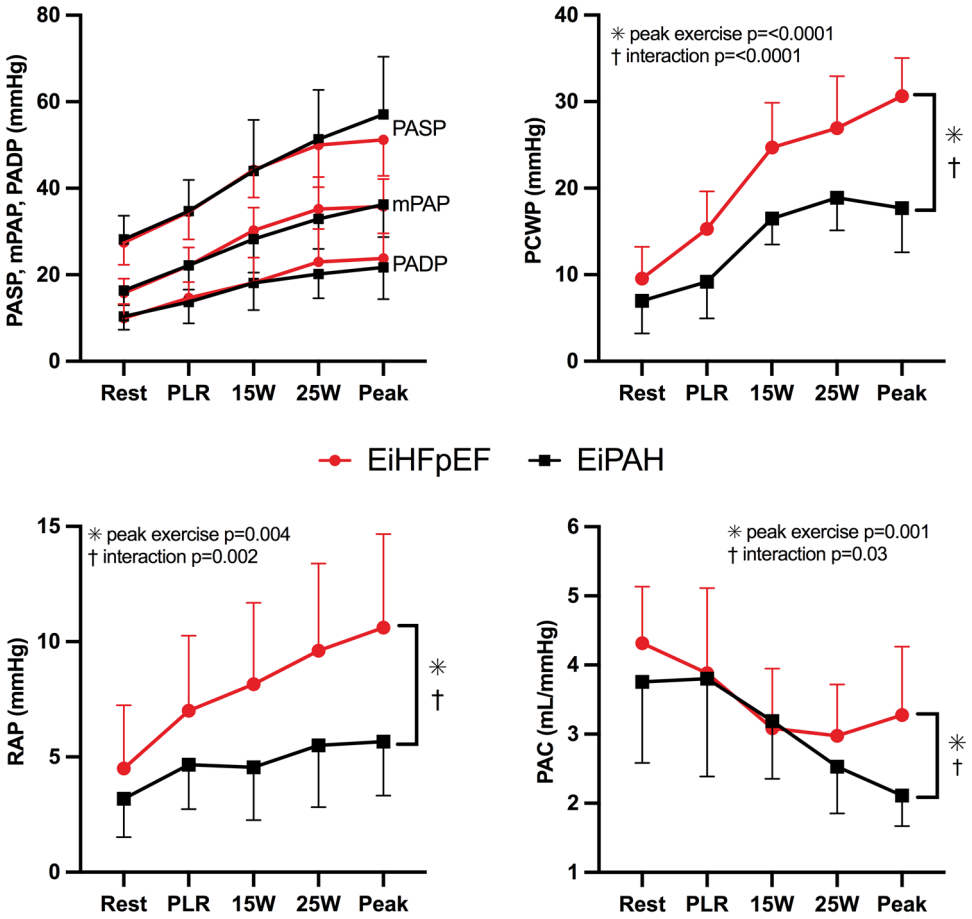

FIGURE 1 Data graphically depicted as mean ± SD. During exercise, EiHFpEF patients demonstrate disproportionate elevations in both PCWP and RAP, while EiPAH patients demonstrate significant reductions in PAC. * denotes $p < 0.05$ at peak exercise; † denotes interaction $p < 0.05$ suggesting a different trend between groups across all exercise stages.

constant across a variety of disease states.[9,10] The shape of their inverse hyperbolic relationship suggests that substantial reductions in PAC are associated with only minimal elevations in PVR in early PVD.[9] Previous studies have indeed shown that patients with early PVD demonstrate reductions in PAC despite normal pulmonary arterial pressures and minimal elevations in PVR.[11–14] Elevations in PCWP notably augment the relationship between PAC and PVR by decreasing RC Time thus reducing PAC at any given PVR.[10] As seen in Figure 1, PAC markedly declined during PLR and submaximal exercise in EiHFpEF, mirroring rapid elevations in PCWP, but plateaued thereafter. In EiPAH, however, PAC steadily declined with exercise. This illustrates that greater exercise-induced PAC reductions in EiPAH are driven by worsening PVD, as opposed to PCWP elevation. By taking advantage of this key physiologic difference between EiPAH and EiHFpEF, we can use PAC as a reliable way to distinguish the two when confronted with poor PCWP measurements. Importantly, our PAC measures were based on automated PA pressure measurements averaged over the respiratory cycle, removing subjectivity in their interpretations.

We also found that exercise-induced elevations in RAP occur in tandem with PCWP rise in occult LHD and are thus more predictive of EiHFpEF. Exercise-induced RAP elevations in HFpEF have been described and linked to increased stressed blood volume, obesity, impaired venous capacitance, RV dysfunction, and enhanced interventricular interactions and pericardial constraint. These highlight how myocardial dysfunction in HFpEF is a biventricular rather than univentricular process.[15–19] Our work confirms the results of previous studies demonstrating greater RAP elevations in isolated post-capillary PH as compared to PAH in a cohort of EIPH patients.[18,19]

Limitations of our study include its retrospective, single-centered nature, small sample size, and lack of an external validation cohort. While further work is needed to validate our findings in a larger cohort of patients, our results suggest that exercise PAC and RAP may have a

role in the discrimination between occult PVD and LHD in EIPH. This observation may offer an important clinical tool in the diagnosis of EIPH when PCWP is unavailable.

AUTHOR CONTRIBUTIONS

The authors have nothing to report.

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CONFLICT OF INTEREST STATEMENT

Dr. Tedford reports no conflicts related to this manuscript. Dr. Tedford is the cochair of the PH due to left heart disease task force for 7th World Symposium on Pulmonary Hypertension and Deputy Editor for the *Journal of Heart and Lung Transplantation*. He reports general disclosures to include consulting relationships with and receiving honorarium from Abbott, Acorai, Aria CV Inc., Acceleron/Merck, Alleviant, Boston Scientific, Cytokinetics, Edwards LifeSciences, Endotronix, Gradient, Medtronic, Morphic Therapeutics, Restore Medical, and United Therapeutics. Dr. Tedford serves on steering committee for Abbott, Edwards, Endotronix, and Merck as well as a research advisory board for Abiomed. He also does hemodynamic core lab work for Merck. All other authors have no relevant financial disclosures.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors have nothing to report.

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REFERENCES

1. Humbert M, Kovacs G, Hoeper MM. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). Eur Heart J. 2022;43(38):3618–731.
2. Ho JE, Zern EK, Lau ES, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Farrell R, Sbarbaro JA, Schoenike MW, Houstis NE, Baggish AL, Shah RV, Nayor M, Malhotra R, Lewis GD. Exercise pulmonary hypertension predicts clinical outcomes in patients with dyspnea on effort. J Am Coll Cardiol. 2020;75(1):17–26.
3. Douschan P, Avian A, Foris V, Sassmann T, Bachmaier G, Rosenstock P, Zeder K, Olschewski H, Kovacs G. Prognostic value of exercise as compared to resting pulmonary hemodynamics in patients with normal or mildly elevated pulmonary arterial pressure. Am J Respir Crit Care Med. 2022;206(11):1418–23.
4. Lau EMT, Godinas L, Sitbon O, Montani D, Savale L, Jaïs X, Lador F, Gunther S, Celermajer DS, Simonneau G, Humbert M, Chemla D, Herve P. Resting pulmonary artery pressure of 21–24 mmHg predicts abnormal exercise haemodynamics. Eur Respir J. 2016;47(5):1436–44.
5. Jain CC, Borlaug BA. Performance and interpretation of invasive hemodynamic exercise testing. Chest. 2020;158(5):2119–29.
6. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. how to handle the problems of zero leveling and respiratory swings. Am J Respir Crit Care Med. 2014;190(3):252–7.
7. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Failure. 2010;3(5):588–95.
8. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation. 2006;114(20):2138–47.
9. Thenappan T, Prins KW, Pritzker MR, Scandurra J, Volmers K, Weir EK. The critical role of pulmonary arterial compliance in pulmonary hypertension. Ann Am Thorac Soc. 2016;Feb 13(2):276–84.
10. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, Cingolani OH, Mudd JO, Borlaug BA, Redfield MM, Lederer DJ, Kass DA. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation. 2012;125(2):289–97.
11. Sanz J, Kariisa M, Dellegrottaglie S, Prat-González S, Garcia MJ, Fuster V, Rajagopalan S. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. JACC Cardiovasc imaging. 2009;2(3):286–95.
12. Mullin CJTR, Damico RL, Kolb TM. Resting compliance and stroke volume is associated with abnormal pulmonary vascular response to exercise in systemic sclerosis. Am J Respir Crit Care Med. 2015;191:A4790.
13. Lau EMT, Chemla D, Godinas L, Zhu K, Sitbon O, Savale L, Montani D, Jaïs X, Celermajer DS, Simonneau G, Humbert M, Hervé P. Loss of vascular distensibility during exercise is an early hemodynamic marker of pulmonary vascular disease. Chest. 2016;Feb 1 149(2):353–61.
14. Singh I, Oliveira RKF, Naeije R, Rahaghi FN, Oldham WM, Systrom DM, Waxman AB. Pulmonary vascular distensibility and early pulmonary vascular remodeling in pulmonary hypertension. Chest. 2019;156(4):724–32.
15. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure with preserved ejection Fraction. J Am Coll Cardiol. 2023;81(18):1810–34.

16. Lichtblau M, Bader PR, Saxer S, Berlier C, Schwarz EI, Hasler ED, Furian M, Grünig E, Bloch KE, Ulrich S. Right atrial pressure during exercise predicts survival in patients with pulmonary hypertension. J Am Heart Assoc. 2020; 9(22):e018123.
17. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J. 2016;37(43):3293–302.
18. van Wezenbeek J, Kianzad A, van de Bovenkamp A, Wessels J, Mouratoglou SA, Braams NJ, Jansen SMA, Meulblok E, Meijboom LJ, Marcus JT, Vonk Noordegraaf A, José Goumans M, Jan Bogaard H, Handoko ML, de Man FS. Right ventricular and right atrial function are less compromised in pulmonary hypertension secondary to heart failure with preserved ejection fraction: a comparison with pulmonary arterial hypertension with similar pressure overload. Circ Heart Failure. 2022;15(2):e008726.
19. Baratto C, Caravita S, Dewachter C, Faini A, Perego B, Bondue A, Senni M, Muraru D, Badano LP, Parati G, Vachiéry JL. Right heart adaptation to exercise in pulmonary hypertension: an invasive hemodynamic study. J Card Failure. 2023;29(9):1261–72.

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