

Chapter 6

Normal resting pulmonary artery wedge pressure:
a diagnostic trap for heart failure with preserved ejection fraction.

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**Normal resting pulmonary artery wedge pressure:
a diagnostic trap for heart failure with preserved ejection fraction.**

by

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INTRODUCTION

The diagnosis of heart failure with preserved ejection fraction (HFPEF) remains challenging. A correct diagnosis requires the presence of signs or symptoms of congestion, normal LV systolic function, and evidence of diastolic LV dysfunction.¹ Failure to establish the diagnosis of HFPEF correctly can be related to omission of evidence of diastolic LV dysfunction,² to exclusive reliance on elevated natriuretic peptides,³ which are only modestly raised in HFPEF,⁴ and to the fortuitous presence of a hypovolaemic status at the time of diagnostic evaluation,⁵ which necessitates a repeat assessment during exercise⁶ or saline infusion.⁷ The latter was convincingly demonstrated in the current issue of the journal by the study of Maor et al., who performed a limited upper body exercise stress test mimicking daily living activities during right heart catheterization in patients with pulmonary hypertension (PHT) [mean pulmonary artery pressure (mPAP) >25 mmHg] and normal resting pulmonary artery wedge pressure (PAWP <15 mmHg).⁸ Despite attaining a rise in heart rate of 10%, which was only 62% of the age-predicted maximal heart rate, one-third of the patients had a substantial rise of PAWP from 11.4 ± 3.3 to 28.0 ± 6.5 mmHg. Without exercise stress testing, their HFPEF-induced post-capillary (group 2) PHT would have remained unnoticed and these patients would have been erroneously classified as pre-capillary (group 1) PHT in accordance with the Dana Point PHT criteria.⁹ Significant predictors of an exercise-induced rise in PAWP were a borderline resting PAWP ($12 < \text{PAWP} < 15$ mmHg), a high body mass index (BMI), presence of obesity, and a dilated left atrium.

THE PAWP 'GREY ZONE'

The use of the E/e' (the ratio of early transmitral diastolic flow velocity to tissue Doppler early mitral annular diastolic velocity) as Doppler echocardiographic evidence of diastolic LV dysfunction in HFPEF has been discredited by the presence of a wide 'grey zone' ranging from $8 < E/e' < 15$. Only when E/e' exceeds 15 does it provide stand-alone diagnostic evidence of diastolic LV dysfunction.¹ When $8 < E/e' < 15$, secondary evidence of diastolic LV dysfunction is required, which can consist of transmitral diastolic flow velocities, combined transmitral and pulmonary flow velocities, left atrial size, LV hypertrophy, AF, or raised natriuretic peptides.¹ The presence of this wide 'grey zone' is considered to be a major

methodological shortcoming of Doppler echocardiographic imaging for the diagnosis of diastolic LV dysfunction. The study by Maor *et al.* in this issue sheds further light on this 'grey zone' as it suggests a similar 'grey zone' for a normal resting PAWP, which ranges from 12 to 15 mmHg.⁸ In their study, 62% of patients, who had a substantial rise in exercise PAWP, had a resting PAWP in the range of 12–15 mmHg, and a resting PAWP within this range made it 4.5 times more likely to be in the highest tertile of exercise PAWP. The upper cut-off value of this range corresponds to the upper limit of normal resting PAWP proposed by the Dana Point PHT consensus classification,⁹ whereas the lower cut-off value corresponds to the upper limit of normal resting PAWP proposed by the European HFPEF consensus document.¹ Hence, the study by Maor *et al.* and side by side comparison of the upper limits of normal resting PAWP proposed in both consensus documents suggest a 'grey zone' of normal resting PAWP ranging from 12 to 15mmHg similar to the $8 < E/e' < 15$ 'grey zone' of the Doppler evaluation of diastolic LV dysfunction. As patients with a resting PAWP in the range of 12–15mmHg are 4.5 times more likely to have HFPEF-induced post-capillary (group 2) PHT, a PAWP equalling 12mmHg is to be preferred as the upper cut-off value of a normal resting PAWP.¹

Both the $8 < E/e' < 15$ and $12 < \text{PAWP} < 15 \text{ mmHg}$ 'grey zones' are reflections of the physiological variability of volume status and not methodological shortcomings. The response of PAWP to shifts in volume status was recently compared between control subjects and HFPEF patients.⁷ Plots of PAWP (mmHg) vs. indexed volume of a rapid saline infusion (L/m^2) were constructed, and the slope of the relationship was twice as steep in HFPEF patients ($25 \pm 12 \text{ mmHg}/\text{L}/\text{m}^2$) than in both young and old control groups ($12 \pm 3 \text{ mmHg}/\text{L}/\text{m}^2$; $14 \pm \text{ mmHg}/\text{L}/\text{m}^2$). Based on these relationships, HFPEF patients appear to be exquisitely sensitive to volume status, with a small 0.6 L volume load already eliciting a 10mmHg PAWP rise. It is therefore no surprise that limited salt intake or use of a diuretic will cause many HFPEF patients to present with a low resting PAWP, as obvious from the study of Maor *et al.*, which reported a resting PAWP of $11.4 \pm 3.3 \text{ mmHg}$ in the PHT patient group reclassified as HFPEF following invasive exercise stress testing. The exquisite sensitivity of PAWP to volume shifts was also evident in this patient group from the impressive 18mmHg mean PAWP rise elicited by limited upper body exercise.

CHARACTERISTICS OF THE MISCLASSIFIED PULMONARY HYPERTENSION PATIENTS

In the study by Maor *et al.*, the PHT patients erroneously classified as group 1 PHT based on the Dana Point criteria and reclassified as HFPEF-induced group 2 PHT following exercise stress testing presented with interesting clinical, echocardiographic, and haemodynamic features.⁸ Specific clinical features were high BMI ($P = 0.023$) and obesity ($P = 0.035$). A relationship was established between BMI and exercise-induced rise in PAWP, with each 5 kg/m^2 increase in BMI causing a $2.5 \pm 1.0 \text{ mmHg}$ increase in exercise PAWP. The prominent role for obesity fits into a recently proposed paradigm whereby metabolic co-morbidities drive LV remodelling and dysfunction in HFPEF¹⁰ and into earlier observations that metabolic syndrome reinforces pulmonary venous hypertension.¹¹ The former was explained by deficient myocardial microvascular nitric oxide (NO)/cGMP signalling,¹² and the latter by excessive pulmonary venous endothelin-1-mediated vasoconstrictor tone.¹³ Both derive from a deranged Yin–Yang between endothelial NO and endothelin-1 in metabolic disturbances.¹⁴ The clinical characteristics of the misclassified PHT provide the readers of the journal with an important ‘take-home’ message, namely that overweight/obese patients with PHT and normal PAWP need to undergo invasive exercise testing or a volume infusion challenge before they can be classified as pre-capillary PHT group 1 patients.

The echocardiographic and haemodynamic features of the misclassified PHT patients are equally intriguing. Specific echocardiographic and haemodynamic features of the misclassified patients were higher resting mean PAWP ($11.4 \pm 3.3 \text{ mmHg}$) ($P = 0.007$), a large left atrial volume index (LAVI) ($P = 0.029$), and a tall E wave ($P = 0.030$). The higher resting mean PAWP is no surprise. In PHT group 1 patients, right ventricular dysfunction reduces filling of the left heart chambers and lowers intrinsically normal left-sided diastolic pressures. In the misclassified PHT patients, a fortuitous volume shift also reduces filling of the left heart chambers but lowers intrinsically elevated left-sided diastolic pressures because of high diastolic LV stiffness

In the misclassified PHT patients, the large LAVI ($57 \pm 22 \text{ mL/m}^2$) was an important tip off for HFPEF-induced group 2 PHT. The observed LAVI by far exceeded the previously proposed cut-off values for the diagnosis of HFPEF (40 mL/m^2).¹ The large LAVI observed in the misclassified PHT patients provides another important message for the practising clinician, namely that patients with

PHT, normal PAWP, and a dilated left atrium need to undergo invasive exercise stress testing or a volume challenge before they can be classified as pre-capillary group 1 PHT patients. The tall E wave indicative of restrictive LV filling is of interest because it implies that raised end-diastolic stiffness is obligatory for HFPEF development and that slow LV relaxation is not sufficient. This was also evident from a previous study looking at the response to a volume challenge in young and old controls and in HFPEF patients.⁷ Despite the slow LV relaxation in the old controls, their rise in PAWP was similar to that of the young controls and inferior to that of the HFPEF patients.

CONCLUSIONS

Patients with HFPEF are exquisitely sensitive to volume shifts, with a small 0.6 L saline infusion already eliciting a 10mmHg PAWP increase. A fortuitous reduction in fluid intake at the time of invasive testing can therefore lead to a normal PAWP and, as illustrated by the study of Maor *et al.*,⁸ to the incorrect diagnosis of group 1 PHT instead of HFPEF-induced group 2 PHT. Exercise stress testing or a volume challenge at the time of invasive measurements unmask the erroneously reduced PAWP. These additional tests are definitely indicated for patients presenting with PHT and normal PAWP, who are obese or who have a dilated LA.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, Keulenaer GD, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539–2550.
2. Persson H, Lonn E, Edner M, Baruch L, Lang CC, Morton JJ, Ostergren J, McKelvie RS. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol* 2007;49:687–694.
3. Shuai X-X, Chen Y-Y, Lu Y-X, Su G-H, Wang Y-H, Zhao H-L, Han J. Diagnosis of heart failure with preserved ejection fraction: which parameters and diagnostic strategies are more valuable? *Eur J Heart Fail* 2011;13:737–745.
4. Stahrenberg R, Edelmann F, Mende M, Kockskämper A, Düngen HD, Lüers C, Binder L, Herrmann-Lingen C, Gelbrich G, Hasenfuss G, Pieske B, Wachter R. The novel biomarker growth differentiation factor 15 in heart failure with normal ejection fraction. *Eur J Heart Fail* 2010;12:1309–1316.
5. 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;3:588–595.
6. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle R-P, Pieske B, Neumann FJ. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J* 2014;35:3103–3112.
7. Fujimoto N, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS, Carrick-Ranson G, Levine BD. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. *Circulation* 2013;127:55–62.
8. Maor E, Grossman E, Gingy Balmor R, Segel M, Fefer P, Ben-Zekry S, Buber J, DiSegni E, Guetta V, Ben-Dov I, Segev A. Exercise haemodynamics may unmask the diagnosis of diastolic dysfunction among patients with pulmonary hypertension. *Eur J Heart Fail* 2015;17:151–158.
9. Simonneau G, Gatzoulis M a, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H,

- Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34–D41.
10. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;62:263–271.
11. Robbins IM, Newman JH, Johnson RF, Hemnes RA, Fremont RD, Piana RN, Zhao DX, Byrne DW. Association of the metabolic syndrome with pulmonary venous hypertension. *Chest* 2009;136:31–36.
12. Van Heerebeek L, Hamdani N, Falcão-Pires I, Leite-Moreira AF, Begieneman MPV, Bronzwaer JGF, Velden, J van der, Stienen GJM, Laarman GJ, Somsen A, Verheugt FWA, Niessen HWM, Paulus WJ. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. *Circulation* 2012;126:830–839.
13. Rocha NG, Templeton DL, Greiner JJ, Staufer BL, De Souza CA. Metabolic syndrome and endothelin-1 mediated vasoconstrictor tone in overweight/obese adults. *Metabolism* 2014;63:951–956.
14. Eringa EC, Serne EH, Meijer RI, Schalkwijk CG, Houben AJHM, Stehouwer CDA, Smulders YM, van Hinsbergh VWM. Endothelial dysfunction in (pre)diabetes: characteristics, causative mechanisms and pathogenic role in type 2 diabetes. *Rev Endocr Metab Disord* 2013;14:39–48.