Mildly increased pulmonary arterial pressure: a new disease entity or just a marker of poor prognosis?

Gabor Kovacs1,2, Philipp Douschan1,2, Bradley A. Maron3, Robin Condliffe4, and Horst Olschewski1,2*

1Medical University of Graz, Graz, Austria; 2Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria; 3Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA; and 4Royal Hallamshire Hospital, Sheffield Pulmonary Vascular Disease Unit, Sheffield, UK

Introduction

In healthy subjects, mean pulmonary arterial pressure (mPAP) is 14.0 ± 3.3 mmHg1 with an upper limit of normal 20 mmHg.2 However, the initial World Health Organization conference on pulmonary hypertension (PH) in 1973 established that the diagnostic mPAP threshold for PH was 25 mmHg, which was based mainly on consensus opinion.3 Since that decision, most studies on PH epidemiology, diagnosis and therapy have used this ‘classical’ definition of mPAP > 25 mmHg, but the main focus of these efforts was on patients with advanced stage pulmonary vascular disease (PVD).4 On the other hand, some earlier studies suggested that even a mild increase in mPAP may be clinically important.5,6 More recent robust epidemiological data from numerous populations worldwide have clearly demonstrated that mPAP exceeding 19 mmHg is prognostically relevant.7–11 Modifying the approach to capturing PH patients early has important implications on risk stratification, clinical trial design, and the management of patients. This recognition also led to lowering the mPAP threshold in the suggested haemodynamic definition of PH according to the Proceedings of the 6th World Symposium on Pulmonary Hypertension.12 In this new definition, pre-capillary PH is defined by a mPAP > 20 mmHg, a pulmonary arterial wedge pressure (PAWP) of ≤ 15 mmHg and a pulmonary vascular resistance of ≥ 3 Wood Units (WU), while post-capillary PH is defined by mPAP > 20 mmHg and PAWP > 15 mmHg. These changes in the haemodynamic definitions of PH have raised several questions regarding the causes, the clinical relevance and the optimal management of mildly elevated mPAP. In this viewpoint we aim to discuss established knowledge, major controversies, evidence gaps and open questions requiring further research in this field.

What is ‘mild mean pulmonary arterial pressure elevation’?

Definitions used in the literature to characterize mildly elevated mPAP have been inconsistent. In some studies, for example, the median mPAP of the cohort under investigation was used to divide patients into two groups when doing so corresponded to differences in clinical outcome.5,6 Published mPAP thresholds derived using this approach (e.g. 17 mmHg), have, in turn, been proposed as relevant to prognosis.

Another approach used a pre-defined mPAP threshold set at the upper limit of normal (20 mmHg) and analysed if study subjects above this threshold, but < 25 mmHg, differed by clinical profile and prognosis compared with the mPAP ≤ 20 mmHg subgroup.9–11,15,16 A third method aimed to utilise unbiased methodologies for determining mPAP thresholds indicating worse prognosis.7,10 In one such study, a branch-chain logic algorithm was used to determine that mPAP ≥ 17 mmHg at rest corresponded to poor prognosis in patients with exercise dyspnoea or risk for PH, although this association was dependent on age and co-morbidities.10 In another study involving a national cohort of veterans referred for right heart catheterization (> 21 000), investigators leveraged sufficient statistical power to model mPAP as a continuous variable. From this analysis, an association between mortality and mPAP emerged beginning at 19 mmHg, and increased continuously until mPAP ~60 mmHg, suggesting that there is probably no single optimal cutoff but a gradually increasing risk relative to pulmonary arterial pressure.7

Based on these collective data, probably the best threshold to indicate a clinically relevant, age-independent mPAP elevation is around 19–20 mmHg.

*Corresponding author. Medical University of Graz, Auenbruggerplatz 20, 8036 Graz, Austria. Tel: +43 316 385-12183, Fax: +43 316 385-13930, Email: horst.olschewski@medunigraz.at
†These authors contributed equally.

© 2019 The Authors. European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
The clinical relevance of mild pulmonary arterial pressure increase

A mild increase in mPAP is clinically relevant due to several reasons. First, this haemodynamic profile is an independent risk factor for clinical symptoms, such as exercise dyspnoea, indicating its subjective importance for patients. This is consistent with a converging line of data showing that mildly elevated mPAP correlates strongly with an abnormal haemodynamic response to exercise, as well as right ventricular dysfunction assessed echocardiographically.

Second, a mild elevation in mPAP is associated with important clinical outcome events including diminished exercise capacity and time to hospitalization. These parameters are often used as endpoints in clinical trials and are widely considered to be relevant to prognosis in PH patients.

Third, subjects with risk factors for PH referred for right heart catheterization and a mild elevation in mPAP tend to present with increasing mPAP values and haemodynamic deterioration during follow-up compared to similar patients with normal mPAP.

Fourth, and most importantly, a mild elevation of mPAP is associated with mortality.

It is equally important to note, however, that despite the reproducible association between mildly elevated mPAP and symptom or disease burden, proof of a causal relationship between pressure elevation and such clinical events is lacking currently. In fact, it may rather be the underlying pathology that leads to both increased mPAP and poor clinical outcome.

Reasons for mild pulmonary arterial pressure increase

There are probably four major reasons, which alone or in combination, explain a mild mPAP increase in most subjects (Figure 1). The differentiation of these causes is important at point of care, as each implicates different management and therapeutic approaches. Their short description is provided in Table 1.

First, the most likely cause of a mild mPAP increase is left heart disease. This may be frequently observed in elderly subjects suffering from heart failure with preserved or reduced ejection fraction.

Second, a mild mPAP increase can often be observed in patients with lung diseases such as chronic obstructive pulmonary disease and lung fibrosis.

Third, early PVD, defined here as pulmonary vascular remodelling with haemodynamic consequences occurring in the absence of left heart or lung disease, may present with a mild elevation in mPAP and pulmonary vascular resistance. Patients with early PVD are of specific interest since even in the contemporary era, patients with pulmonary arterial hypertension (PAH) are frequently recognized in a late stage, although early diagnosis of the disease may lead to earlier initiation of specific therapy and better outcome.

Fourth, from a statistical point of view, assuming a Gaussian distribution of mPAP, around 2.5% of all healthy subjects will have mPAP values > 20 mmHg. Most of these individuals will not be clinically assessed, but they may be encountered incidentally for other reasons.

Exercise haemodynamics

A recent European Respiratory Society Expert Statement suggested that an abnormal pulmonary haemodynamic response to exercise (exercise PH) may be defined as an increase in mPAP to > 30 mmHg and total pulmonary resistance to > 3 WU at maximal exercise. A mild mPAP increase at rest appears to be closely related with exercise PH: in recent studies, 86% of patients with resting mPAP 21–24 mmHg and 75% of patients with chronic thromboembolic disease had exercise PH, while only 47% of patients with resting mPAP ≤ 20 mmHg fulfilled the criteria of exercise PH.

As shown in Table 1, exercise PH is not specific for early PVD; the pattern of pulmonary haemodynamics during exercise may depend on the underlying condition, which also leads to a mild mPAP elevation at rest. In theory, cardiac, pulmonary, or pulmonary vascular limitations to exercise may be distinguished, but in reality, specific haemodynamic patterns corresponding to each of these causes of exercise intolerance are often difficult to recognize and, of course, combinations of these conditions may occur.
Management of patients with mild pulmonary arterial pressure increase

As a mild increase in mPAP may be caused by different factors including left heart and lung diseases, the most important step is the recognition and optimal treatment of the underlying disease. In order to obtain reliable haemodynamic data, the importance of technically solid measurements cannot be overemphasized. The timely recognition of patients with early PVD is of great importance but not easy. As there are no published randomized controlled trials for the specific treatment of these subjects with PAH medications, currently no such treatment is generally recommended or approved. Close follow-up and, if possible, inclusion into clinical trials has been suggested. In specific subgroups, such as symptomatic patients with systemic sclerosis, PAH therapy may be initiated on an individual basis. Similarly, in patients with chronic thromboembolic disease and severe symptoms, pulmonary thromboendarterectomy, medical treatment or balloon angioplasty may be treatment options after careful consideration using an individualized care plan at an expert center.

### Research needs

In order to improve clinical management of early PVD, we would highlight four areas where further research is needed. First, non-invasive methods should be optimized, so that patients with mildly elevated mPAP and early PVD can be recognized timely and effectively. Specific screening tools, including exercise testing, may be especially useful in patient groups at risk for the development of PVD, such as systemic sclerosis and patients with a familial predisposition to PAH. Second, prospective randomized controlled studies should be performed with current PAH drugs in patients with early PVD in order to assess whether haemodynamic deterioration can be prevented and clinical improvement achieved by drug therapy in this patient population. Such trials would also provide prospective data on the natural course of early PVD. Third, molecular mechanisms defining early PVD and a better understanding of progression towards more severe disease are needed to identify treatment targets that are specific to early-stage disease. Finally, investigating pulmonary vascular and right ventricular function including compliance and ventriculo–arterial coupling in early PVD may help understand the clinical deterioration of patients.

### Conclusion

Mild elevation of mPAP in the range between 20–25 mmHg is associated with increased mortality. A subgroup of these patients presents with early PVD and increased pulmonary vascular resistance and is associated with progressive haemodynamic deterioration. Currently, there are no approved drugs for this indication and randomized controlled trials are warranted before such therapy can be generally recommended.

**Conflict of interest:** G.K. reports personal fees and non-financial support from Actelion, Bayer, GSK, MSD, Boehringer Ingelheim, Novartis, Chiesi and Vitalaire, outside the submitted work. P.D. reports personal fees and non-financial support from Actelion, non-financial support from Astra Zeneca, Bayer, GSK, m MSD,

---

**Table 1: Major causes of mild pulmonary arterial pressure elevation and their clinical relevance**

| Reason of mild PAP elevation | Main specific haemodynamic characteristics at rest and during exercise | Main clinical relevance |
|------------------------------|------------------------------------------------------------------------|-------------------------|
| Left heart disease           | • PAWP may be high-normal or mildly elevated at rest <br> • Steep increase of PAP and PAWP (and PAP/CO, PAWP/CO slope) during exercise <br> • Significant PAWP increase during fluid challenge | • PAP elevation is an important prognostic marker irrespective of left ventricular systolic function |
| Lung disease                 | • Increased intrathoracic pressure may contribute to PAP elevation, this is exaggerated at exercise and can be recognized by a concomitant increase in RAP <br> • Mild elevation of PVR at rest <br> • Steep increase of PAP (and PAP/CO slope) during exercise, PAWP and RAP remain usually low | • In COPD and lung fibrosis elevated PAP is associated with poor prognosis |
| Pulmonary vascular disease   | • Mild PAP elevation is an important prognostic marker irrespective of left ventricular systolic function | • Mild PAP elevation may predict haemodynamic deterioration in SSc associated PVD |
| No known underlying pathology| • Based on statistical considerations, healthy subjects may present with mildly elevated PAP | • SSc associated early PVD and CTED may represent a treatment indication on an individual basis in expert centres |

CO, cardiac output; COPD, chronic obstructive pulmonary disease; CTED, chronic thromboembolic disease; PAH, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SSc, systemic sclerosis; WU, Wood Units.

Of note, based on the available data, the normal value of PVR in the supine position is 0.9–1.2 WU with a standard deviation of 0.4–0.5 WU. Therefore the upper limit of normal PVR, if calculated as mean ± 2-times standard deviation, is ~2 WU.

© 2019 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.
Novartis, Teva, Boehringer Ingelheim, Vifor and Menarini, outside the submitted work. R.C. reports personal fees from Actelion, Bayer and MSD, outside the submitted work. H.O. reports grants from Actelion, Roche, Boehringer, and Inventiva, personal fees and non-financial support from Astra Zeneca, Bayer, BMS, Boehringer, Chiesi, GSK, Menarini, MSD, Novartis, and Pfizer, outside the submitted work. B.A.M. has nothing to disclose.

References

1. 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;34:888–894.

2. Giolli N, Hoeger MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Bocchiatti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Pacock A, Rubin L, Zellweger M, Simonneau G, Vahanian A, Auricchio A, Bakx J, Ceconi C, Dean V, Filippatos G, Funcun-Brentano C, Hobbs R, Kearney P, McDonagh T, McGregor K, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widdows P, Al Attar N, Andreotti F, Aschermann M, Asteggiano R, Benza R, Berger R, Bonnet D, Delcroix M, Howard L, Kissiou AN, Lang I, Mazzoni A, Nielsen-Kudsk JE, Park M, Perrone-Filardi P, Price S, Domenech MT, Vonk-Noordegraaf A, Zamorano JL. Guidelines for the diagnosis and treatment of pulmonary hypertension: 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 of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–2537.

3. Hatazo S, Strasser T. Primary Pulmonary Hypertension: Report on a WHO Meeting, Geneva, 15–17 October 1973. Geneva: WHO; 1975.

4. Kovacs G, Avian A, Douschan P, Foris V, Olschewski A, Olschewski H. Patients with pulmonary arterial hypertension less represented in clinical trials – who are they and how are they? Am J Respir Crit Care Med 2016;193:A3979 (abstract).

5. Kessler R, Faller M, Fourgout G, Menncieier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:158–164.

6. Hamada K, Nagi S, Tanaka S, Handa T, Shigematsu M, Nago T, Mishima K, Kitaichi M, Izumi T. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticators in patients with idiopathic pulmonary fibrosis. Chest 2007;131:650–656.

7. Maron BA, Hess E, Maddox TM, Opatowski AR, Tedford RJ, Lahm T, Jaynt KE, Kass DJ, Stephens T, Stanislavski MA, Swanen ER, Goldstein RH, Leopold JA, Zamarni RT, Elfwing J, Plomondon ME, Grunwald GK, Baron AE, Rumsfeld JS, Choudhary G. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the Veterans Affairs clinical assessment, reporting, and tracking program. Circulation 2016;133:1240–1248.

8. Assad TR, Maron BA, Robbins IM, Xu M, Huang S, Harrell FE, Farber-Eger EH, Wells QS, Choudhary G, Henness AR, Brittain EL. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. JAMA Cardiol 2017;2:1361–1368.

9. Heresi GA, Minai OA, Tonelli AR, Hammel JP, Farha S, Parambil JG, Dweik RA. Clinical characterization and survival of patients with borderline elevation in pulmonary artery pressure. Pulm Circ 2013;3:916–925.

10. Douschan P, Kovacs G, Avian A, Foris V, Gruber F, Olschewski A, Olschewski H. Mild elevation of pulmonary arterial pressure as a predictor of mortality. Am J Respir Crit Care Med 2018;197:509–516.

11. Valenzo CJ, Schreiber BE, Handler CE, Denton CP, Coghlan JG. Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. Arthritis Rheum 2013;65:1074–1084.

12. van der Bruggen CE, Nossent SJ, Grunberg K, Bogard HJ, Venk NA. The real face of borderline pulmonary hypertension in connective tissue disease. Ann Am Thorac Soc 2016;13:1428–1430.

13. Kolte D, Lakshmanan S, Jankowich MD, Brittain EL, Maron BA, Choudhary G. Mild pulmonary hypertension is associated with increased mortality: a systematic review and meta-analysis. J Am Heart Assoc 2018;7:e009729.

14. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:18001913.
arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011;63:3522–3530.

38. Kovacs G, Herve P, Barbera JA, Chouat A, Chemla D, Condille R, Garcia G, Grunig E, Howard L, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkrantz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A, Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. Eur Respir J 2017;50:1700578.

39. Guth S, Wiedenroth CB, Rieth A, Richter MJ, Gruenig E, Ghofrani HA, Arlt M, Liebetrau C, Pruffer D, Rolf A, Hamm CW, Mayer E. Exercise right heart catheterization before and after pulmonary endarterectomy in patients with chronic thromboembolic disease. Eur Respir J 2018;52:1800458.

40. Hoffmann-Vold AM, Fretheim H, Midvedt O, Kilian K, Angelshaug M, Chaudhary A, Gunnarsson R, Brunborg C, Garen T, Andreassen AK, Gude E, Molberg O. Frequencies of borderline pulmonary hypertension before and after the DETECT algorithm: results from a prospective systemic sclerosis cohort. Rheumatology 2018;57:480–487.

41. Kovacs G, Dumitrescu D, Barner A, Greiner S, Grunig E, Hager A, Kohler T, Kozlik-Feldmann R, Kruck I, Lammers AE, Mereles D, Meyer A, Meyer J, Pabst S, Seyfarth HJ, Sinning C, Sorichter S, Stahler G, Wilkens H, Held M. Definition, clinical classification and initial diagnosis of pulmonary hypertension: updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol 2018;272S:11–19.

42. Reiber JH, Alaiti A, Bezerra HG, De Sutter J, Schoenhagen P, Stillman AE, Van de Veire NR. Cardiovascular imaging 2017 in the International Journal of Cardiovascular Imaging. Int J Cardiovasc Imaging 2018;34:833–848.