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The revised definition of pulmonary hypertension: exploring the impact on patient management

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At the 6th World Symposium on Pulmonary Hypertension (PH), it was proposed that the mean pulmonary arterial pressure (mPAP) threshold used to define PH should be lowered from ≥25 mmHg to >20 mmHg. The rationale for this change is that the ≥25 mmHg threshold is arbitrary, whereas the revised threshold is based on scientific evidence. For the definition of all forms of pre-capillary PH, the inclusion of a pulmonary vascular resistance (PVR) ≥3 Wood Units was also proposed, placing greater emphasis on an elevated PVR to identify pulmonary vascular disease. Here, we discuss the possible impact of the revised definition of PH on future clinical management. This change may facilitate earlier PH detection, particularly in at-risk patient groups that are already undergoing screening programmes, e.g. those with systemic sclerosis or mutations associated with PH. As an mPAP above the upper limit of normal (>20 mmHg) but <25 mmHg is associated with increased risk of morbidity and mortality compared with a normal mPAP, early identification of patients in this group is important to enable close monitoring and timely treatment initiation once clinically indicated. Treatments currently approved for PH are not necessarily suitable for patients with an mPAP 21–24 mmHg, as the management of this group has not been widely examined. The revised definition may facilitate inclusion of these patients in prospective trials, allowing the evaluation of appropriate management strategies.

Introduction

A revised definition of pulmonary hypertension (PH) was proposed in 2018 by a task force at the 6th World Symposium on Pulmonary Hypertension, stating that the mean pulmonary arterial pressure (mPAP) threshold by which PH is defined during right heart catheterization (RHC) should be lowered from ≥25 mmHg at rest to >20 mmHg at rest[1] (*Table 1*). This proposed change recognizes that the >25 mmHg threshold defined at the 1st World Symposium on Pulmonary Hypertension in 1973, and updated to ≥25 mmHg in 2009,[4] was an arbitrary threshold,[5] conservatively chosen to prevent overdiagnosis and overtreatment.[1] In contrast, the >20 mmHg threshold is supported by scientific evidence. A systematic review of all available data from RHC studies in healthy individuals defined a normal mPAP (mean ± SD) at rest as 14.0 ± 3.3 mmHg.[6] If the upper limit of normal is regarded as the mean value +2 SDs, an mPAP >20 mmHg should be considered to be above normal.[6] PH is classified into five groups, according to similar clinical characteristics, underlying causes and treatment strategies,[2,3] and the revision to the mPAP threshold is proposed for all clinical groups of PH.

The revised definition incorporates inclusion of pulmonary vascular resistance (PVR) ≥3 Wood units (WU) in the definition of all forms of pre-capillary PH (Groups 1, 3, 4, and 5) (*Table 1*).[1] Despite a lack of definitive proof that PVR is a marker of pulmonary vascular disease, the revised definition

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Table 1 Haemodynamic definitions of PH

	Clinical groups[a]	Definition at rest	
		Previous[2,3]	Revised[1]
Pre-capillary PH	1, 3, 4 and 5	mPAP ≥25 mmHg	mPAP >20 mmHg
		PAWP ≤15 mmHg[b]	PAWP ≤15 mmHg
			PVR ≥3 WU
Isolated post-capillary PH (IpcPH)	2 and 5	mPAP ≥25 mmHg	mPAP >20 mmHg
		PAWP >15 mmHg	PAWP >15 mmHg
		DPG <7 mmHg and/or PVR ≤3 WU	PVR <3 WU
Combined post-capillary and pre-capillary PH (CpcPH)	2 and 5	mPAP ≥25 mmHg	mPAP >20 mmHg
		PAWP >15 mmHg	PAWP >15 mmHg
		DPG ≥7 mmHg and/or PVR >3 WU	PVR ≥3 WU

DPG, diastolic pressure gradient; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.
[a]Group 1: PAH; Group 2: PH due to left heart disease; Group 3: PH due to lung diseases and/or hypoxia; Group 4: PH due to pulmonary artery obstructions; Group 5: PH with unclear and/or multifactorial mechanisms.
[b]PVR >3 WU was included in the previous definition for Group 1 PH (PAH) only.[2,3]

acknowledges that to attribute an mPAP >20 mmHg to pulmonary vascular disease, and to differentiate pre-capillary PH from post-capillary PH, PVR in combination with pulmonary arterial wedge pressure is the best criterion available.[1]

The pros and cons of the proposed revision to the definition of PH have been debated in the literature.[7,8] In our opinion, the proposed threshold of an mPAP of >20 mmHg is the correct threshold to use for defining PH, and the greater emphasis given to elevated PVR for detecting pulmonary vascular disease is a necessary paradigm shift. The clinical justification for the suggested change has been described in detail elsewhere,[1,7] yet as the proposal is relatively recent and has not yet been adopted in clinical practice, there are limited data on how it will affect clinical management. Therefore, in this article, we will discuss the potential effect of this revised definition on patient management, based on our clinical experience.

The impact of the revised definition of pulmonary hypertension on patient management

We predict that the main impact of the new PH definition on patient management will be earlier identification of PH. If patients with abnormal elevation in mPAP (>20 mmHg) are identified when they have an mPAP within the range of 21–24 mmHg, i.e. at an earlier stage of disease than patients with an mPAP ≥25 mmHg, they can be closely monitored and recommended treatment can begin as soon as clinically indicated. There is accumulating evidence that an abnormal mPAP that is elevated but below 25 mmHg is associated with increased risk of morbidity, mortality and progression to symptomatic PH[9–11] compared with a normal mPAP. An elevated mPAP of 21–24 mmHg has been identified in several patient groups at risk of developing PH, such as those with lung disease, left heart disease, or connective tissue disease[12] and is predictive of progression to an mPAP of ≥25 mmHg in patients with systemic sclerosis.[13,14]

Group 1 pulmonary hypertension [pulmonary arterial hypertension]

As the initial symptoms of PH are non-specific, diagnosis is often only confirmed when the disease is already advanced.[15] Therefore, earlier diagnosis of PH, when mPAP is within the 21–24 mmHg range, is only likely to be feasible in patient populations known to be at high risk of PH who can be closely monitored in screening programmes for early signs of PH development.[2,3] In practice, this is likely to apply predominantly to patients with pulmonary arterial hypertension (PAH) (Group 1 of the clinical classification of PH), for example systemic sclerosis patients and subjects with mutations associated with PAH. As systematic screening programmes are already in use to identify patients at risk of developing PAH among these populations, these screening programmes may allow identification of patients with an elevated mPAP of 21–24 mmHg.[16] For example, for systemic sclerosis patients, the DETECT screening algorithm uses six widely available assessments to determine the need for echocardiography referral, and subsequently two echocardiographic variables to determine the need for RHC to identify PAH.[17] When applying the DETECT algorithm in a single centre in Norway, 31% of systemic sclerosis patients undergoing RHC to diagnose suspected PAH had an elevated mPAP of 20–24 mmHg. In contrast, before DETECT was introduced, only 17% of patients undergoing RHC had an mPAP of 20–24 mmHg.[16]

Patients who are carriers of mutations associated with PAH, such as the *BMPR2* gene mutations, are another

population at high risk of developing PAH.[18] At the time of their diagnosis, patients with PAH who have *BMPR2* mutations tend to be younger, with more severe disease and a greater risk of death than those without *BMPR2* mutations.[19] Screening of patients with a familial PAH-causing genetic mutation is recommended by the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines,[2,3] and asymptomatic carriers of *BMPR2* mutations are already offered inclusion in clinical screening programmes in some centres.[18] Research is underway to determine the optimal screening strategies to identify development of PAH in patients with *BMPR2* mutations.[20]

Although we anticipate that the revised definition will enable earlier diagnosis for some PAH patients, this does not imply that treatments currently approved for PAH are also appropriate for these patients. While it is accepted that early treatment is beneficial in PAH patients with an mPAP $\geq$25 mmHg,[21] the management of patients with an mPAP of 21–24 mmHg has not been widely examined.[2,3] Based on the previous definition of PAH, the inclusion criteria for clinical trials investigating PH therapies typically stipulated that only patients with an mPAP $\geq$25 mmHg are included. To date, only two small studies investigating PH therapies in patients with a resting mPAP $<$25 mmHg have been completed, both in the setting of systemic sclerosis[22,23] and only a small number of ongoing studies are enrolling patients with an mPAP of 21–24 mmHg.[24,25] Greater inclusion of patients with an mPAP of 21–24 mmHg in prospective trials of PAH therapies is required to gain further insight into their natural history and to determine the potential benefits of different management options. The proposed revision to the definition of PAH could address this need, enabling enrolment of this population in a greater number of clinical trials by bringing them within the standard PAH definition.

Other pulmonary hypertension groups

Looking beyond patients with PAH (Group 1 of the clinical classification of PH), the revised definition is not expected to have an immediate impact on patient management for other PH groups. In the case of PAH, clinical trials can be performed to confirm whether the PH-targeted treatment options available for patients with mPAP $\geq$25 mmHg are also effective in patients with mPAP 21–24 mmHg. In contrast, for patients with PH due to left heart disease or lung disease (Groups 2 and 3, respectively), such studies cannot be performed as there are currently no recommended treatment options available for these conditions.[2,3] For patients with Group 4 PH [chronic thromboembolic PH (CTEPH)], the lower mPAP threshold in the revised definition may lead to some patients who are classified based on the previous definition as having chronic thromboembolic disease without PH (CTED) being reclassified as having CTEPH.[26,27] As pulmonary endarterectomy—the gold-standard treatment recommended for operable CTEPH[2,3]—is also a beneficial treatment for operable CTED patients,[27,28] the revised definition is not expected to change the management of these patients.

Future perspectives

As discussed, we expect that the main impact of a lower mPAP threshold in the revised definition of PH will be the detection of PAH at an earlier disease stage in some patient groups, such as systemic sclerosis patients and patients with PAH-causing genetic mutations. Elsewhere in this series of review articles, Kiely *et al.*[15] discuss that several new screening approaches are currently being evaluated in PH, including non-invasive approaches such as imaging, cardiopulmonary function testing, and clinical biomarkers.[15] In the future, we anticipate that combining a lower mPAP threshold with improvements in screening methods, and the development of novel screening techniques for use in patients at risk of PH, will aid earlier disease identification. If evidence is generated to support the use of PH-targeted therapies in patients with mPAP 21–24 mmHg, earlier treatment can be initiated with the aim of improving outcomes. An open question requiring future study is whether or not the pulmonary arterial wedge pressure and PVR thresholds used to define pre-capillary PH also warrant revision. These were not amended in the revised definition of PH, remaining at their previous values (PVR $\geq$3 WU and pulmonary arterial wedge pressure $\leq$15 mmHg),[1–3] however, there is ongoing discussion around whether these thresholds could be lowered.[1,8]

Summary

Based on the available evidence, we believe that an mPAP of $>$20 mmHg is the correct threshold to use for defining PH. This threshold should be considered as a biomarker of an abnormal state of the pulmonary circulation (i.e. PH) rather than used to characterize a disease. An mPAP of $>$20 mmHg requires further haemodynamic characterization to identify the cause of the elevated mPAP and thus the type of PH, e.g. measurement of pulmonary arterial wedge pressure and PVR to distinguish between pre-capillary and post-capillary PH. The revised PH definition includes PVR in the diagnosis of all forms of pre-capillary PH, rather than just for PAH as per the previous definition, and thus emphasizes the importance of PVR for detecting pulmonary vascular disease (*Table 1*).

In terms of patient management, we anticipate that the main impact of the updated definition of PH will be to allow the identification of PH at earlier disease stages, particularly in patients at risk of PH who are already closely monitored in screening programmes, e.g. those with systemic sclerosis or PAH-causing genetic mutations. If PH is identified at an early stage, patients can be closely observed so that recommended treatment can begin as soon as it is clinically indicated.

To date, patients with an mPAP of 21–24 mmHg have generally been excluded from clinical trials and consequently there is little information on whether PH therapies are appropriate for use in these patients or on how best to manage their disease. We predict that the revised definition of PH will likely lead to a greater number of clinical trials

enrolling patients with an mPAP in the 21–24 mmHg range, thereby providing valuable insight into appropriate management strategies in this population and improved characterization of the natural history and epidemiology of this patient group. We hope that clinical studies in patients with an mPAP of 21–24 mmHg will eventually lead to evidence-based treatment recommendations and, ultimately, an improved outlook for this understudied group of patients.

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References

1. 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**:1801913.
2. Galiè N, Humbert M, Vachiéry JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015;**46**:903–975.
3. Galiè N, Humbert M, Vachiéry JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint 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: association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;**37**:67–119.
4. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;**54**:S55–S66.
5. Hatano S, Strasser R. *Primary Pulmonary Hypertension*. Geneva: WHO; 1975.
6. 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.
7. Hoeper MM, Humbert M. The new haemodynamic definition of pulmonary hypertension: evidence prevails, finally! *Eur Respir J* 2019;**53**:1900038.
8. Gibbs JSR, Torbicki A. Proposed new pulmonary hypertension definition: is 4 mm(Hg) worth re-writing medical textbooks? *Eur Respir J* 2019;**53**:1900197.
9. Assad TR, Maron BA, Robbins IM, Xu M, Huang S, Harrell FE, Farber-Eger EH, Wells QS, Choudhary G, Hemnes AR, Brittain EL. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. *JAMA Cardiol* 2017;**2**:1361–1368.
10. Kovacs G, Avian A, Tscherner M, Foris V, Bachmaier G, Olschewski A, Olschewski H. Characterization of patients with borderline pulmonary arterial pressure. *Chest* 2014;**146**:1486–1493.
11. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stanislawski MA, Swenson ER, Goldstein RH, Leopold JA, Zamanian RT, Elwing JM, 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.
12. 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.
13. Valerio 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.
14. Coghlan JG, Wolf M, Distler O, Denton CP, Doelberg M, Harutyunova S, Marra AM, Benjamin N, Fischer C, Grünig E. Incidence of pulmonary hypertension and determining factors in patients with systemic sclerosis. *Eur Respir J* 2018;**51**:1701197.
15. Kiely DG, Lawrie A, Humbert M. Screening strategies for pulmonary arterial hypertension. *Eur Heart J Suppl* 2019;**21**:K9–K20.
16. Hoffmann-Vold AM, Fretheim H, Midtvedt 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.
17. Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, Muller-Ladner U, Pope JE, Vonk MC, Doelberg M, Chadha-Boreham H, Heinzl H, Rosenberg DM, McLaughlin VV, Seibold JR. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2014;**73**:1340–1349.
18. Girerd B, Montani D, Jaïs X, Eyries M, Yaici A, Sztrymf B, Savale L, Parent F, Coulet F, Godinas L, Lau EM, Tamura Y, Sitbon O, Soubrier F, Simonneau G, Humbert M. Genetic counselling in a national referral centre for pulmonary hypertension. *Eur Respir J* 2016;**47**:541–552.
19. Evans JD, Girerd B, Montani D, Wang XJ, Galiè N, Austin ED, Elliott G, Asano K, Grunig E, Yan Y, Jing ZC, Manes A, Palazzini M, Wheeler LA, Nakayama I, Satoh T, Eichstaedt C, Hinderhofer K, Wolf M, Rosenzweig EB, Chung WK, Soubrier F, Simonneau G, Sitbon O, Graf S, Kaptoge S, Di Angelantonio E, Humbert M, Morrell NW. BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis. *Lancet Respir Med* 2016;**4**:129–137.
20. NCT01600898; DELPHI-2: www.clinicaltrials.gov (10 June 2019).
21. Galiè N, Rubin L, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;**371**:2093–2100.
22. Kawaguchi Y, Takagi K, Tochimoto A, Higuchi T, Yamanaka H. SAT0481 early detection and treatment for borderline pulmonary arterial hypertension in patients with systemic sclerosis in Japan. *Ann Rheum Dis* 2015;**74**:834.
23. Kovacs G, Maier R, Aberer E, Brodmann M, Graninger W, Kqiku X, Scheidl S, Troster N, Hesse C, Rubin L, Olschewski H. Pulmonary arterial hypertension therapy may be safe and effective in patients with systemic sclerosis and borderline pulmonary artery pressure. *Arthritis Rheum* 2012;**64**:1257–1262.
24. NCT02290613; EDITA: www.clinicaltrials.gov (10 June 2019).
25. NCT01725763; CMR-PH: www.clinicaltrials.gov (10 June 2019).
26. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani H-A, Jenkins DP. Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019;**53**:1801915.

27. Swietlik EM, Ruggiero A, Fletcher AJ, Taboada D, Knightbridge E, Harlow L, Harvey I, Screaton N, Cannon JE, Sheares KKK, Ng C, Jenkins DP, Pepke-Zaba J, Toshner MR. Limitations of resting haemodynamics in chronic thromboembolic disease without pulmonary hypertension. *Eur Respir J* 2019;**53**:1801787.

28. Taboada D, Pepke-Zaba J, Jenkins DP, Berman M, Treacy CM, Cannon JE, Toshner M, Dunning JJ, Ng C, Tsui SS, Sheares KK. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. *Eur Respir J* 2014;**44**:1635–1645.