



Proposed new pulmonary hypertension definition: is 4 mm(Hg) worth re-writing medical textbooks?

J. Simon R. Gibbs ^{1,3} and Adam Torbicki ^{2,3}

Affiliations: ¹National Heart and Lung Institute, Imperial College London and Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK. ²Dept of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Center for Postgraduate Medical Education at ECZ-Otwock, Otwock, Poland. ³Contributed equally to the manuscript.

Correspondence: Adam Torbicki, Medical Centre for Postgraduate Education, Pulmonary Circulation, ECZ-Otwock, ul.Borowa 14/18, Otwock, Mazowsze, 05-400, Poland. E-mail: adam.torbicki@ecz-otwock.pl

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With risks of overdiagnosis, unclear treatment implications and additional psychological burden placed on patients, a new definition of PH based on reduction of the mean PAP threshold to >20 mmHg is premature <http://ow.ly/8eB730nIdEk>

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Last year's 6th edition of the World Symposium on Pulmonary Hypertension held in Nice, France, erupted with the suggestion of a new definition of pulmonary hypertension (PH). It came as a surprise to the audience during the presentation of the task force on definitions and classifications and generated a vivid and long-lasting discussion, which we now join, driven by recently published highlights from the Nice meeting [1].

The definition of a disease, describing what that disease is, provides the medical lingua franca by which we communicate with each other. When a continuous haemodynamic measurement defines the disease, the value of that measurement at which the disease is present or absent is necessarily arbitrary and should finally be decided by its clinical significance.

The concerns regarding the definition of PH based on mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at right heart catheterisation, as introduced by the World Health Organization (WHO) Meeting in Geneva in 1973 [2], are not new. Indeed, normal values in healthy people seem lower than 25 mmHg [3], and a recent retrospective database based on 21 727 right heart catheterisations showed increased mortality in patients with mPAP > 19 mmHg [4] and the authors defined "borderline" PH as mPAP of 19–24 mmHg [5]. Increased risk at mPAP > 19 mmHg was shown in 16 482 patients in a systematic review and meta-analysis [6], and a further retrospective and prospective study found that mPAP values 20–25 mmHg represent an independent predictor of poor survival [7]. On such data rests the case for redefining PH but is unclear from these studies whether the "borderline" cases in the range 20–25 mmHg have a poor outcome as a result of PH or whether PH is simply a biomarker of poor outcome [5]. Until this is resolved, these findings do not in themselves justify any change in the definition of PH.

Of clinical relevance is whether cases of "borderline" PH have been shown to progress to the current definition of pulmonary arterial hypertension (PAH) (mPAP ≥ 25 mmHg, pulmonary artery wedge

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pressure (PAWP) ≤ 15 mmHg, pulmonary vascular resistance (PVR) ≥ 3 Wood units). The evidence for progression of pulmonary haemodynamics from a mPAP at baseline of 21–24 mmHg to mPAP ≥ 25 mmHg has been examined in two studies in scleroderma patients with a diffusing capacity of the lung for carbon monoxide $< 60\%$ [8, 9]. In the first study, 23 of 76 patients developed PAH over 3 years and 13 of these PAH cases followed a benign course. In the second study, three of 71 patients developed PAH after 3 years [1]. In view of these small numbers, this observation of progression to PAH in just 26 patients with a particularly strong risk factor such as scleroderma and from a single centre requires further study before it is used to drive a change of definition of PH.

Indeed, our objections are related to the details and practical consequences of such sudden change in PH definition at this particular moment, rather than to the fact that an mPAP value somewhere around 20 mmHg is more appropriate than 25 mmHg in separating “normal” from “abnormal” pulmonary haemodynamics in humans.

Interestingly, a “soft” proposal embracing patients with mPAP between 20 and 25 mmHg was already made 10 years ago at the World Symposium on Pulmonary Hypertension held at Dana Point in 2008. It was suggested that the term “borderline PH” was introduced to describe this population excluded from the WHO definition [10]. At that time this term was not agreed and continued to be criticised until very recently by several key opinion leaders as likely to lead to misdiagnoses and overtreatment with PH targeted therapies.

In a recent issue of the *European Respiratory Journal*, SIMONNEAU *et al.* [1] argue that in defining PH, the threshold for mPAP of 25 mmHg was an arbitrary choice and that lowering it to > 20 mmHg, two standard deviations above the mPAP for the population [3], assures a scientific approach. This rigour is not consistent with the PAWP, itself part of the haemodynamic definition of pre-capillary PH, which would remain at an upper limit of 15 mmHg despite the upper limit of two standard deviations being 12 mmHg [11]. In addition, requiring a PVR of ≥ 3 Wood units for the diagnosis of pre-capillary PH is unfortunately also arbitrary, especially since the authors acknowledge that a PVR > 2 Wood units may be abnormal. If such incongruences are allowed to pass now, the definition of PH may require a further redefinition in the next decade, something that is undesirable and confusing for patients and non-specialist physicians.

As far as members of the PH community are concerned, we have accepted the existing gap between “normal” values defined by two standard deviations and those defining PAH, which as already mentioned are present in all three components of its definition, namely mPAP, PVR and PAWP. This gap has been considered as a kind of buffer zone, protecting patients, albeit a small number (table 1), from premature diagnosis of PAH, a diagnosis which for a patient and their family has an immediate and dramatic psychological impact.

Now, we suspect, leaving the PVR and PAWP thresholds unaltered will serve exactly the same purpose as the existing buffer zone against overdiagnosis or misclassification of PH due to measurement errors. This would, after liberating the cut-off value of mPAP, require ever more precision in the assessment of PVR and PAWP. Unfortunately, PVR is a complex index requiring measurement of mean pressures in the pulmonary artery and in the left atrium, as well as mean pulmonary arterial flow for 1 min, the latter serving as denominator. Complex indices inevitably magnify the errors of their components, particularly when they are multiplied or divided by each other. Moreover, left atrial pressure is estimated from PAWP,

TABLE 1 Proportion of patients who would be included in the proposed definition of pre-capillary pulmonary hypertension (PH) at the authors’ institutions, based on existing referral criteria

PH centre	All patients submitted to RHC	Patients with mPAP 21–24 mmHg	Patients with mPAP 21–24 mmHg and PAWP ≤ 15 mmHg	Patients with mPAP 21–24 mmHg and PAWP ≤ 15 mmHg and PVR ≥ 3 Wood units
Medical Center for Postgraduate Education, ECZ-Otwock, Otwock, Poland	1242	152 (12.2%)	135 (10.8%)	29 (2.3%)
Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK	2111	133 (6.3%)	101 (4.8%)	23 (1.1%)

Note that the referral patterns might change if the new definition of PH is adopted. mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance.

one of the trickiest measurements in clinical haemodynamics. To complicate matters even more, underestimation of PAWP not only increases PVR but may also result in misclassification of a patient as having pre-capillary PH, potentially leading to an erroneous diagnosis of PAH.

Recommendations regarding optimal assessment of PAWP, as presented at the World Symposium on Pulmonary Hypertension by the task force on PH in left heart disease, include visually averaging multiple measurements directly from a calibrated pressure tracing at relaxed end-expiration and at precisely identified end-diastole [11]. This is because computer-derived mean values may under- or overestimate the PAWP compared to this standard. The risk of error is particularly significant in patients with comorbidities leading to increased intrathoracic pressure shifts. It would be interesting to know how many haemodynamic laboratories respect these recommendations, rather than rely on immediately available computer-averaged values. Finally, it is well known that there is variability in the measurement of pulmonary flow by thermodilution and Fick methods, and often it is necessary to perform multiple saline injections during thermodilution measurement to decide which three consecutive measurements are representative.

Regardless of the potential technical problems encountered, particularly in diagnosing pre-capillary PH, extending the definition of PH just by decreasing mPAP threshold will provide an illusion of clarity where there is still uncertainty. As ASHER [12] observed, this gives the condition a tangibility which makes it seem more likely to be overcome, even before we can find evidence that patients who were not previously included in the definition will benefit from specialist treatment.

Holding back a change of the definition of PH will not deprive patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) of evidence-based PH targeted drug treatments, since these only have an evidence base for a mPAP ≥ 25 mmHg. Neither will this present a barrier for clinical trials focused on patients with a mPAP between 20 and 25 mmHg. For patients with CTEPH, pulmonary endarterectomy has already been shown to be successful in selected patients with a lower mPAP who are referred to as having chronic thromboembolic disease rather than CTEPH [13]. The argument that some patients with mPAP between 21 and 24 mmHg need close monitoring still stands and does not require a change in the definition of PH for this practice to continue, akin to systemic blood pressure monitoring in at-risk individuals.

On the other hand, labelling a patient with pre-capillary PH and mPAP 21–24 mmHg as PAH does create a problem. The diagnosis is “life-threatening”, but no validated or approved treatment can be prescribed on the basis of evidence, as yet. It will be very difficult to resist the natural pressure from patients and their families to start off-label treatment immediately. Such off-label treatment may be declared a therapeutic success if, at follow-up, the patient remains in the borderline mPAP zone or even has fully normalised haemodynamics; this in turn may become a reason to continue chronic PH targeted therapy with all its implications. And what if without such therapy the outcome were to be the same?

Therefore, before deciding on a new definition, the PH community should collect data from all available high-volume PH centre registries to ascertain the clinical characteristics, haemodynamic trends and outcomes of “borderline” PH. This will help to determine the optimal minimum threshold values of mPAP and PVR across a wide spectrum of PH clinical practice. Further research needs to be undertaken to show what criteria should be used for a definition of exercise PH, and whether patients with a mPAP between 20 and 25 mmHg and PVR >3 Wood units (or whatever limits are finally deemed optimal) with PAH or CTEPH benefit from PH targeted therapies. Finally, we need to know how best to identify patients at high or moderate risk of PH according to a new definition using echocardiography to identify patients for right heart catheterisation. Without validation work, concern about missing patients newly included by the changed definition may result in an increased number of catheterisations that turn out to be unnecessary.

It is timely to consider a redefinition of PH but it is certainly not overdue. At this point in time, with the uncertainty about how to grade the probability of newly defined PH, unclear treatment implications, the additional psychological burden which will be placed on patients who were previously excluded, and the huge challenges of the differential diagnosis of PH in the ageing population, a new definition of PH based on reduction of the mPAP threshold down to >20 mmHg is premature. What is the hurry for a revolutionary change when there needs to be much wider debate about what threshold values should be used, a careful evaluation of the gaps in the evidence, and appropriate research undertaken and reported to address these gaps, to inform the optimal definition for the next 50 years? Without these considerations the PH community risks making a precipitous decision without due diligence.

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