Did the World Symposium on Pulmonary Hypertension Get It Right in Redefining Abnormal Pulmonary Arterial Pressure? Yes

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When Walt Whitman wrote down the words “The truth is simple. If it was complicated, everyone would understand it” in the 19th century, he may not have expected how helpful his observation could be in some scientific debates. The ongoing discussion of the hemodynamic definition of pulmonary hypertension (PH) within the PH community over the last 50 years may belong to these debates.

The proceedings of the first World Health Organization meeting on PH provided a basis for the hemodynamic diagnosis of PH, stating that (1) the mean pulmonary arterial pressure (mPAP) is “little affected by age and never exceeds 20 mm Hg” and that (2) PH is “definitely present if the pressure exceeds 25 mm Hg.”

Admittedly, this definition of PH was based on expert opinion and reflects the intention to define a safety margin above the upper limit of normal mPAP. The following World Symposia on PH (WSPH) and clinical practice guidelines implemented some changes into the hemodynamic definition of PH; however, these mainly involved the definitions of precapillary PH, postcapillary PH, and pulmonary arterial hypertension. The main mPAP cutoff has not been changed significantly in 45 years (except for a minor adjustment at the 4th WSPH, which changed the cutoff from >25 mm Hg to ≥25 mm Hg).

This does not mean that the mPAP >25 mm Hg threshold has not been challenged at all. At the 4th WSPH in 2008, the results of a systematic literature search on pulmonary hemodynamics of almost 1,200 healthy subjects at rest and during exercise were presented. These data revealed that the average resting mPAP in healthy subjects is 14.0 mm Hg and that the upper limit of normal mPAP may be considered at 20.6 mm Hg. Although an upper limit of normal mPAP of >20 mm Hg had already been postulated at the first World Health Organization meeting on PH in 1973, since 2008, this has been accepted broadly because of a large published database. However, both the 4th and 5th WSPH (the latter in 2013) decided against changing the hemodynamic threshold for PH, mainly because of concerns of overdiagnosis and overtreatment of patients without significant pulmonary vascular disease.

Instead, further investigations were requested to better determine the prognostic impact of mPAP of <25 mm Hg.

In the following years, besides confirming previous findings, such investigations revealed further important details on the pulmonary circulation. One of the milestones was the study of Maron et al that described a continuum of increasing risk for death beginning from an mPAP of ≥19 mm Hg. Further studies confirmed the prognostic relevance of the mPAP of >19 to 20 mm Hg cutoff and showed that patients whose threshold was above this were at increased risk for the progression of pulmonary vascular disease, which means that for mPAP, both the upper limit of normal and the first threshold for increased mortality rate coincide at approximately 20 mm Hg and provides a perfect rationale for a hemodynamic cutoff for PH: an elegant outcome “à la Walt Whitman.”
Indeed, the 6th WSPH in 2018 suggested changing the hemodynamic definition of PH and lowered the mPAP threshold from ≥25 mm Hg to >20 mm Hg. The authors of the WSPH proceedings argued that, against the previous arbitrary threshold, this cutoff was based on a scientific approach. Potential overdiagnosis and overtreatment were not considered a major concern. In this regard, the necessity to confirm the diagnosis of PH by right heart catheterization was highlighted.

Two important clinical limitations of the new hemodynamic definition should be acknowledged. First, a clinical decision should never rely on a single parameter, but on the whole clinical context, which may be especially true in patients with mild increase in mPAP, who frequently experience cardiac or pulmonary comorbidities. Second, the evidence for the beneficial effects of pulmonary arterial hypertension therapies is based exclusively on therapeutic trials with pulmonary arterial hypertension (or nonoperable chronic thromboembolic PH) patients with mPAP ≥25 mm Hg; patients with mPAP <25 mm Hg should not be treated with such drugs outside of clinical studies.

Lowering the mPAP threshold for the diagnosis of PH has not been the only important change regarding the PH definitions at the 6th WSPH. Further, the pulmonary vascular resistance ≥3 Wood unit threshold was re-introduced for all forms of precapillary PH, which means that precapillary PH is now diagnosed when mPAP is >20 mm Hg, pulmonary arterial wedge pressure is ≤15 mm Hg, and pulmonary vascular resistance is ≥3 Wood units. A recent study confirmed that the hemodynamic and clinical profiles of patients with the "new precapillary PH" (hemodynamically characterized by mPAP of 21 to 24 mm Hg and pulmonary vascular resistance of ≥3 Wood units) are enriched by those with early forms of pulmonary vascular disease that supports the rationale of the decision of the 6th WSPH.

In conclusion, the 6th WSPH got it right in redefining PH. It is time to put an end of a 50-year long discussion and open the field for new clinical and scientific questions.

References