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Revising the hemodynamic criteria for pulmonary hypertension: A perspective from China

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At the 6th World Symposium on Pulmonary Hypertension (WSPH) in Nice, France, in 2018, the redefinition of the hemodynamic criteria for the diagnosis of pulmonary hypertension (PH) was proposed by a task force, suggesting a modification of the threshold value of the mean pulmonary arterial pressure (mPAP) for defining PH from ≥ 25 mmHg to > 20 mmHg. The proposed new hemodynamic criteria were published a year later in the proceedings of the 6th WSPH in *European Respiratory Journal*, which received considerable attention and sparked widespread controversy.[1]

China has the largest population, and thereby a potentially huge number of patients with PH, among whom the most common types are PH due to left heart disease and due to lung diseases and/or hypoxia. Pulmonary arterial hypertension (PAH) is relatively rare and often associated with congenital heart disease (CHD) in China.[2] Because of the lack of effective therapeutic options, PH used to gain scant attention from clinicians in China. However, the introduction of the targeted drugs for PH into China in 2006 turned the tide. Great improvements in the management and research of PH have been achieved since then. On this basis, we aim to provide some insights into the hemodynamic definition of PH from a Chinese perspective.

Since the 1st WSPH in Geneva, 1973, PH has long been defined by a resting mPAP above 25 mmHg via right heart catheterization (RHC) in the supine position. At that time, studies mainly focused on primary pulmonary hypertension (PPH) or idiopathic pulmonary arterial hypertension (IPAH), which is characterized by a significant increase in mPAP. The diagnostic threshold value was set primarily to better diagnose PPH and spare patients from the potential risks of overdiagnosis and overtreatment.

Though widely adopted by various guidelines, the current hemodynamic criterion for PH defined as mPAP ≥ 25mmHg was established empirically with little clinical evidence. It was reported in 1961 by the WHO expert committee on chronic cor pulmonale that normal mPAP measured by RHC at rest was lower than 15 mmHg, barely above 20 mmHg, and was independent of age.[3] According to the study conducted by Mao *et al.* in China in the 1970s, the range of mPAP was between 10 and 18 mmHg, with a mean value of 15.4 mmHg among 50 healthy Chinese individuals by RHC.[4]

In 2009, Kovacs *et al.* conducted a meta-analysis to study the hemodynamic data of 1187 healthy subjects from 47 studies, which unveiled a mean mPAP value of 14.0 ± 3.3 mmHg and was independent of sex and ethnicity and marginally associated with age and posture.[5] On this basis, the value of 20 mmHg, calculated from a mean value plus twice the standard deviations, was recognized as the upper limit of mPAP to discriminate PH patients from normal individuals better.

In 1993, Cheng Xiansheng suggested the diagnostic criteria for PH in China, defining

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PH as mPAP > 20 mmHg at rest or > 30 mmHg during exercise with reference to the pertinent studies, which had been embraced nationwide since the 1990s in China.[6] The definition remained unchanged until the publication of the 2009 European Society of Cardiology (ESC) guidelines for PH. From then on, the criterion of mPAP ≥ 25 mmHg was widely adopted in China for better collaboration with other PH research centers worldwide.[7]

The inconsistency in the cutoff value of mPAP for the physiological upper limit and diagnostic threshold of PH has resulted in patients with mPAP in the gap being missed. Therefore, the concept of "borderline PH" was put forth and discussed at 4th (2008) and 5th (2013) WSPH in an attempt to address the issue. It was also suggested that mPAP of 21 mmHg be considered the upper limit of the normal, and PH be defined as an abnormal hemodynamic condition with mPAP ≥ 25 mmHg while borderline PH as mPAP within the range of 21–24 mmHg on RHC. However, the category wasn't immediately adopted to avoid overdiagnosis and overtreatment, as little knowledge existed at that time concerning epidemiology, diagnosis, treatment, and prognosis of patients with borderline PH. Therefore, close follow-up remained the main and the only modality recommended for managing such patients in case of progression, especially for those with connective tissue disease (CTD) or a family history of IPAH.[8]

Recent clinical studies revealed that mPAP between 21 and 24 mmHg was associated with an increased risk of future PH and correlated with adverse prognosis compared to those with normal mPAP.[9–12] A meta-analysis study showed that individuals with a mildly elevated mPAP (20 mmHg < mPAP < 25 mmHg) were at higher risk of progression to PH and of increased mortality (HR = 2.48, 95% CI, 1.69–3.64) than those with a normal mPAP. The pooled 1-, 3-, 5-, 7-, and 9-year survival rates in the mildly elevated mPAP group were 97.0%, 89.4%, 77.0%, 64.5%, and 49.6%, respectively.[13] These accumulating findings added fuel to the promotion of revisiting the category of borderline PH, eventually leading to the proposal of reconsidering diagnostic criteria of PH at the 6th WSPH in 2018, in which a lower defining threshold was suggested for early identification, close monitoring, and timely treatment of PH.[1]

There has been concern about the application of the revised PH definition for risk of overdiagnosis. Though limited, the data available provide a valuable insight. A study included 1251 patients undergoing RHC in Fuwai Hospital, with 1069 having mPAP ≥ 25 mmHg. In the remaining 182, 33 (2.6%) were diagnosed as PH under the new definition, among whom only 7 (0.6%) satisfied the criteria of PAH with pulmonary artery wedge (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥ 3WU at the same time.[14] Jaafar *et al.* found in an SSc cohort that 137 out of 268 patients had mPAP ≥ 25 mmHg, and 7 (2.6%) in the other 131 were diagnosed as PAH or PH related to other etiologies under the new hemodynamic definition.[15] In a Polish study, 152 (12.2%) out of 1242 had mPAP between 21 and 24 mmHg, and only 29 (2.3%) were further confirmed as PAH.[16]A comparable study from Britain showed that 133 (6.3%) out of the 2111 patients had mPAP in the range, and 23 (1.1%) were diagnosed as PAH.[16] These studies suggested that individuals with mPAP between 21 and 24 mmHg comprise approximately 2.6%–12.2% of all patients undergoing RHC, among whom less than 2.3% were confirmed as PAH, indicating that patients missed under the current criteria for PH took up a very small proportion in the population with suspected PH.

Based on these findings, the redefinition of the criteria could be more controversial in the setting of PAH because few treatment options currently exist for patients with mPAP between 21 and 24 mmHg. The effect of targeted drugs for treating PAH is not clear in these patients, as the registered clinical trials of these drugs only enrolled patients with mPAP ≥ 25 mmHg following the published guidelines. Physicians may be confused about the application of medications in these patients for the lack of evidence-based guidelines.

Considering the current clinical practice and research in the PH field, a sudden change in the hemodynamic definition of PH may seem less advisable at present in daily practice. Once the revised diagnostic criteria are adopted into clinical practice, patients with mPAP between 21 and 24 mmHg that are currently excluded from the disease following the 2015 ESC/European Respiratory Society (ERS) guidelines will receive a confirmed diagnosis of PH. Labeling patients with a disease of high malignancy that requires long-term treatment will undoubtedly bring tremendous pressure to them and their families. In this regard, broader diagnostic criteria that include more patients may, in turn, diminish the positive effect of early identification in the overall population level, since the number of patients expected to benefit from the redefinition of PH is relatively small and limited, whereas examinations necessary to formulate the diagnosis could result in the irrational use of healthcare resources. There is an apparent gap in the study about patients with borderline PH in China. Also, data and evidence available are too limited to draw any conclusion with confidence in the issue. Therefore, it would be wiser and more practical at present to continue with the current hemodynamic criteria for PH.

Whatever the case, it is still of substantial clinical

significance to pay extra attention to patients with borderline PH. More emphasis should be placed on finding the causes, and careful examinations should be performed, especially for the detection of thrombotic disease, CTD, CHD, and other diseases or abnormal conditions that may elevate the pulmonary arterial pressure, as early interventions targeting these causes could allow for reversal and even a cure for the disease. Genetic testing and close monitoring are recommended for patients with both mPAP between 21 and 24 mmHg and a family history of PH. For those with borderline PH only, annual echocardiography is preferentially recommended. Furthermore, in order to gain a better appreciation of the clinical characteristics, hemodynamic features, prognosis, and the nature history of this condition as well as to further advance multicenter clinical research on these patients, the establishment of a database on abnormally increased mPAP within the range of 21–24 mmHg in China is urgently warranted.

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Conflict of Interest

None declared.

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