Insights From the Fifth World Health Organization Symposium Working Group: Definitions and Diagnosis of Pulmonary Hypertension

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During the Fifth World Symposium on Pulmonary Hypertension, the working group on diagnosis and assessment was charged with evaluating the definition of pulmonary arterial hypertension (PAH) as it was established at the Fourth World Symposium. The group also covered related topics such as "borderline PAH," exercise-induced PAH, and issues surrounding the measurement of pulmonary capillary wedge pressure (PCWP). The working group's discussion specifically addressed the following questions:

1. Should pulmonary hypertension (PH) continue to be defined by a resting mean pulmonary artery pressure (MPAP) ≥25 mm Hg, and should the term "borderline PH" be introduced?
2. Should exercise-induced PH be included as a subset of PH?
3. Should pulmonary vascular resistance (PVR) be reintroduced in the definition of PAH?
4. Is pulmonary artery wedge pressure (PAWP) of 15 mm Hg adequate to distinguish between pre- and post-capillary PH, and how should it be measured?
5. Should fluid or exercise challenge be used to distinguish patients with PAH from pulmonary venous hypertension (PVH)?
6. Should exercise hemodynamics be used to unmask left sided heart failure?

The task force met for 2 consecutive days to address these 6 questions. The group spent many hours reviewing research and communicating with experts in the specific fields, and was able to successfully provide evidence-based, expert opinion surrounding these issues. Specific recommendations for each of the 6 issues are summarized in this article.

The first question concerned the definition of PH. The controversial issue at hand is considering the value of 25 mm Hg of mean pulmonary artery pressure (MPAP) as the cutoff to define PH. A normal MPAP has been described as less than 20 mm Hg; however, the value 25 mm Hg has historically been used as the lowest pressure to define PH.[1] This value comes from data on 1187 healthy volunteers from 47 studies in 13 countries. The MPAP at rest was 14.0 ± 3.3 mm Hg, independent of gender and ethnicity. Age did not seem to change this value either (<30 years: 12.8 ± 3.1 mm Hg; 30-50 years: 12.9 ± 3.0 mm Hg; ≥50 years: 14.7 ± 4.0 mm Hg). All multicenter clinical trials have used 25 mm Hg as part of the definition to define PAH, and this pressure is now well established in the PH community. Furthermore, patients with significant PH generally have MPAP well above 25 mm Hg. The controversy involves those patients with MPAP 21-24 mm Hg who in fact have an elevated MPAP, but no "diagnosis." Thus, the committee considered use of the term "borderline PH" for this subset of patients. The group agreed that this population does have an abnormal MPAP, but had concerns regarding the implications of labeling it as PH.

There is some evidence showing that patients with scleroderma-spectrum PAH who have MPAP between 21 and 24 are at risk for developing PAH.[2] The PHAROS registry was a multicenter, prospective, longitudinal cohort of patients with scleroderma "at risk" for or recently diagnosed with resting PH on right heart catheterization. Using the PHAROS registry, out of 206 patients who underwent right heart catheterization, 28 patients were found to have borderline MPAP. Of the patients with borderline PH, 55% developed resting PAH in the following 25.7 months. Little is known about the implications of these pressures in other diseases associated with PH. One concern involves the group of patients with heart failure with preserved ejection fraction (HFpEF) who may be mistakenly classified as having PAH and then be exposed to medications that have shown no clear benefit. In the HFpEF population, the term "borderline PH" as discussed in the current context does not apply. Thus, after multiple discussions the group determined that the creation of this category would be a disservice to patients. The final recommendations

Key Words—exercise-induced pulmonary hypertension, HFpEF, pulmonary vascular resistance, right heart catheterization, scleroderma
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Disclosure: Fernando Torres has served as a Consultant/Advisory Board/Steering Committee member for Actelion Pharmaceuticals, Gilead Sciences, United Therapeutics Corporatuon, Novartis, SteadyMed, Pfizer, and Bayer HealthCare. He has also received Institutional Grant/Research Support from Ikaria Pharmaceuticals, Reata Pharmaceuticals, Medtronic, and Bayer HealthCare.

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were to continue close monitoring of patients at high risk of developing PH if they had MPAP 21-24 mm Hg, as they could progress to PAH.

The second question addressed by the work force related to the controversial term "exercise-induced PH." This term was introduced before the Fourth World Symposium. There are patients who develop a "significant" elevation of their MPAP with exercise—the definition of exercise-induced PH. This term has been used to describe an increase of the MPAP ≥30 mm Hg for patients during exercise. However, the workload level, type, or position of exercise has not been standardized. Furthermore, the MPAP seems to increase with age, especially in patients over age 50. During the review of the literature, subjects >50 years of age had MPAP 29.4 ± 8.4 mm Hg during exercise. This was statistically higher ($P<0.001$) than the younger patients, whose MPAP increased to 19.4 ± 4.8 mm Hg during exercise.[1] One of the purposes to define "exercise-induced PH" is the ability to determine prognostic values and therapeutic implications during exercise. Currently, we do not have definitive data on either of these measures. Active studies are being conducted among the patients with scleroderma-spectrum disease and exercise-induced PH.

During a 24-week study, patients exercised in a supine position on a lower extremity cycle ergometer. At baseline, they all had normal resting hemodynamics, but with exercise MPAP >30 mm Hg and transpulmonary gradient of >15 mm Hg. After 24 weeks of treatment with ambrisentan, there were improvements in MPAP: -4.1 mm Hg ($P=0.02$), PVR -1.0 Wood units ($P=0.003$), and cardiac output (CO) 1.4 L/min ($P=0.006$).[3] Tolle et al described the cardiopulmonary exercise test of patients with "exercise-induced PH," identifying 78 patients with the condition. These patients were compared to 15 resting PAH and 16 normal subjects. All subjects did the cardiopulmonary exercise test with a PA catheter in place. The VO2 max 55.8% ± 20.3% vs 66.5% ± 16.3% vs 91.7% ± 13.7% predicted was lowest in the resting PAH, "exercise-induced PH," and normal groups respectively. The MPAP at exercise was 48.4 ± 11.1 vs 36.6 ± 5.7 vs 27.4 ± 3.7 mm Hg respectively.[4] Studies on exercising patients, attempting to better define this population, are increasing in number. But despite the available data, the final recommendation was to not incorporate the term "exercise-induced PH" as part of the formal PH definition until further studies have been performed.

The third issue discussed was the need to add PVR to the definition of PH and/or PAH. Much of the conversation focused on ensuring that a right side catheterization was performed to make the diagnosis of PAH in conjunction with certain conditions that increase blood flow through the pulmonary capillary bed, which can cause an elevation of the MPAP without increasing the PVR. Thus, it was considered important for the definition of PH to remain without the requirement of a specific PVR during the 4th World Symposium meeting. When the current state of hemodynamic considerations were discussed in Nice, the strong opinion of the committee was to add PVR to the definition of PAH to ensure that patients will have a cardiac output measurement as well as a PAWP measurement at the time of diagnosis of PAH and, for patients with left heart disease and PH, to incorporate PVR along with PAWP to aide in discriminating the two entities. Though the upper limit of normal for PVR is 2 Wood units, keeping a PVR >3 Wood units is important since that value is used in hemodynamics in clinical trials, and patients with PAH rarely have a lower PVR. Standardization of the units of the PVR was also part of the discussion. The group agreed on the preference of using Wood units since this measurement does not necessitate using a factor of 80 to calculate $dyn{\cdot}s{\cdot}cm^{-5}$. The use of SI unit was not recommended as it is not used clinically.

The fourth subject addressed by the working group involved the use of the term PAWP rather than PCWP, and the value of keeping the definition of abnormal PAWP at >15 mm Hg. The term PCWP can be deceiving, as the pressure in the capillary bed may be different in the "occluded" vessel than in the "nonoccluded" areas. At the same time, the term "wedge" is very well established in the medical community, including countries that do not have English as their first language. Therefore, the group decided to recommend using the term pulmonary artery occlusion pressure (PAOP) or PAWP. Thus, PAWP will become the new official term for "wedge."

Following the consensus of the term PAWP, the group discussed the normal value of PAWP and how to measure it correctly—ultimately agreeing that the standard way to measure PAWP is at the end of expiration. It is concerning that digital equipment will sometimes underestimate PAWP, as it does not always account for the breathing pattern. Measuring PAWP at end of expiration, across all ages, normal PAWP should be 9 ± 2 mm Hg. The committee acknowledged that during a small study of healthy volunteers at ages >70, the normal level appeared to be higher, but not over 15 mm Hg. Also, Prasad et al had a small group of patients well characterized as having HFpEF in which hemodynamics were performed showing that normal PAWP increased with age slightly, but usually not greater than 15 mm Hg.[5] So, the group acknowledged that PAWP ≤15 mm Hg did not rule out the presence of HFpEF, therefore introducing the consideration of lowering the PAWP ≤12 mm Hg rather than the historical ≤15 mm Hg. Lowering the PAWP cutoff was favored in one regard, because it would decrease the chance of misclassifying HFpEF patients as having PAH. This was balanced with the increased sensitivity of keeping the PAWP ≤15 mm Hg and identifying more PAH patients. The committee recognized that there is no single PAWP that enables correct classification of all patients. Abraham et al implanted hemodynamic monitoring devices on 500 patients with left heart failure, and noticed that it is possible to at least temporarily lower the PAWP below 15 mm Hg with diuretics and medications for treatment of left heart failure.[6] Ultimately the group decided it was more important not to risk mistakenly missing presence of PAH by lowering the PAWP to 12 mm Hg, and recom-

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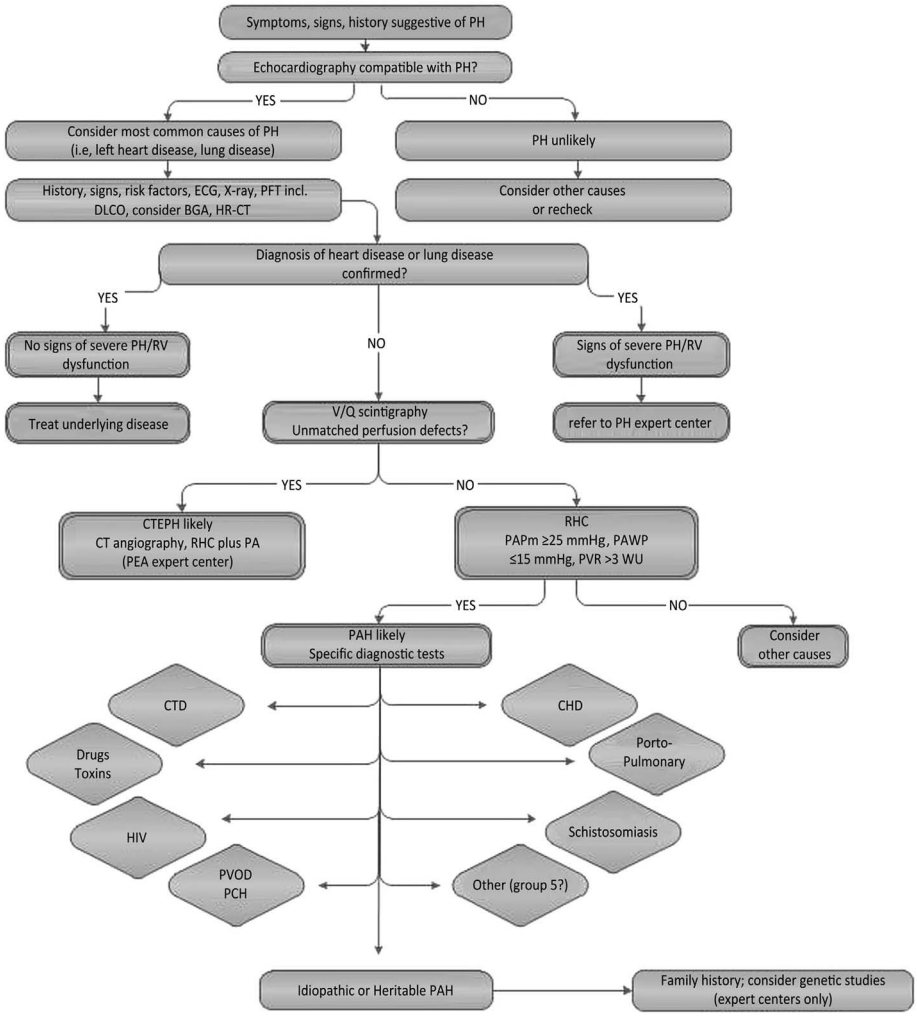

Figure 1: Diagnostic approach to pulmonary hypertension. Reprinted from Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013; 62 (25 Suppl): D42-D50. With permission from Elsevier.

mended the PAWP ≤15 mm Hg remain as the cutoff for the definition of PAH.

The fifth question of performing fluid challenges was very interesting, as it was evident that most of the group had been performing fluid challenges during right side catheterization to increase the sensitivity of identifying patients with HFpEF when their wedge is normal in patients with clinical scenario of HFpEF rather than PAH. Data from Bush et al were analyzed: in a small study, 6 patients used as control had an infusion of 1 L normal saline over 6-8 minutes. The subjects had an increase in PAWP by 3 mm Hg, but not above 11 mm Hg.[7] In another study by Fox et al of 107 patients at high risk of developing HFpEF, only 500 cc over 5 minutes was required to identify patients whose PAWP increased over 15 mm Hg. Furthermore, using this technique, 11 out of 53 patients were reclassified as having PVH rather than PAH.[8] Other data from Fujimoto et al described marked increase in PAWP in normal volunteers when a large volume of fluid was given. Infusion of 1 L normal saline at 100-200 cc/min to healthy volunteers increased the PAWP from 10 ± 2 to 16 ± 3 mm Hg and to 20 ± 3 mm Hg after 2 L of saline. In addition, females >50 years of age demonstrated a steeper increase in PAWP relative to the volume infused at 16 ± 4 mm Hg·L^{-1}·m^2. Subjects with HFpEF showed a greater increase in PAWP at 25 ± 12 mm Hg·L^{-1}·m^2.[9] Thus, the group determined that there is no optimal standardized fluid challenge procedure, and the response to fluid challenge may differ depending on gender and age. Furthermore, there were not enough safety data on patients with severe PH or HFpEF to determine definitively regarding fluid challenge testing. However, based on collective experience in the absence of formal guidelines, 500 cc over 5 to 10 minutes would be considered enough to distinguish PAH from HFpEF.

The last topic addressed by the committee related to the use of exercise hemodynamics to unmask left heart failure. This was a nonstarter early in the discussion. During exercise, the pleural pressures and airway pressures change, making it very difficult to assess PAWP. Further complicating the issue, there are multiple reports about normal volunteer athletes with PAWP over 20 mm Hg during exercise. It is understood that patients with presumed HFpEF and normal resting PAWP levels at rest would increase their PAWP >30 mm Hg with exercise. It is also known that

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patients with left heart disease have higher PAWP than PAH scleroderma patients. Thus, the committee acknowledged some value to the exercise hemodynamics. But, given the difficulty of doing the procedure during exercise, with no standardization and lack of normal values at different ages, the group could not endorse this practice until further studies are completed.

The committee recognized a need to reinforce some of the previous recommendations regarding right heart catheterizations, as inaccurately measuring hemodynamics could have significant consequences. Thus, the group discussed the necessity of measuring the right atrium (RA), right ventricle, MPAP, PAWP, CO, and mixed venous saturations on all right side catheterizations. The Fick method was deemed the gold standard test for measuring CO, but the group determined that its difficulty and limited availability are not enough to endorse it as the preferred method. The indirect Fick measure is considered too unreliable. Thus, the group feels that thermodilution CO is the preferred CO measurement during right catheterization. The committee was also careful to remind physicians of the importance of making the zero level of the pressure transducer at the RA level, and also discussed that pulmonary arteriogram (if it was to be performed) should be done after the full set of hemodynamics have been collected.

The committee remains concerned about the delay in diagnosis of this lethal disorder, and highlighted some of the advances and recommendations to improve early diagnosis of PAH. The group discussed the challenge of using genetic markers on patients with hereditary PAH (HPAH). In the sporadic cases of idiopathic PAH, 20% have a BMPR2 gene mutation, while 70% of HPAH have the mutation. The low penetrance of the mutation makes the genetic testing difficult to justify, as it will cause significant psychological distress on a patient who may never develop the disorder. Thus, it is still the recommendation that if genetic testing is ordered, expert counseling must be provided to the patient. Screening protocols on other at-risk populations have not changed, except for patients with the scleroderma spectrum of disease.

The DETECT (evidence-based detection of PAH in systemic sclerosis) study is a 2-step method to screen patients for PAH. The first step is to look for telangiectasia, anti-centromere antibodies, right axis deviation on ECG, and low diffusion lung capacity for carbon monoxide (DLCO) (<60%) and biomarkers. This gave a 97% sensitivity for PAH. Step 2 included doing an echocardiogram and then right side catheterization. The DETECT algorithm has not been validated for DLCO >60%. Finally, the committee made a diagnostic algorithm for PH (Figure 1) modified from the 2009 European guidelines.[10]

In summary, the working group reviewed new published data attempting to better understand PH. Significant advances have been made in the scleroderma-spectrum disease, clarifying hemodynamics in this population and making guidelines on how to screen for PAH in this population. But still more is needed in other types of PAH patients. The HFpEF population continues to present a challenge for the PH community, and progress is underway in identifying these patients and understanding their hemodynamics on exercise and with fluid challenges. Still, the correct use of right side catheterization to diagnose this disease—the most critical aspect in determining the presence, type, and severity of PH— is not at 100%, and the committee hopes that this article helps expand its use.

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