

Definitions and Diagnosis of Pulmonary Hypertension

Marius M. Hoeper, MD,* Harm Jan Bogaard, MD,† Robin Condliffe, MD,‡ Robert Frantz, MD,§ Dinesh Khanna, MD,|| Marcin Kurzyna, MD,¶ David Langleben, MD,# Alessandra Manes, MD,** Toru Satoh, MD,†† Fernando Torres, MD,‡‡ Martin R. Wilkins, MD,§§ David B. Badesch, MD||||
Hannover, Germany; Amsterdam, the Netherlands; Sheffield and London, United Kingdom; Rochester, Minnesota; Ann Arbor, Michigan; Warsaw, Poland; Montreal, Quebec, Canada; Bologna, Italy; Tokyo, Japan; Dallas, Texas; and Denver, Colorado

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure ≥ 25 mm Hg at rest, measured during right heart catheterization. There is still insufficient evidence to add an exercise criterion to this definition. The term pulmonary arterial hypertension (PAH) describes a subpopulation of patients with PH characterized hemodynamically by the presence of pre-capillary PH including an end-expiratory pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg and a pulmonary vascular resistance > 3 Wood units. Right heart catheterization remains essential for a diagnosis of PH or PAH. This procedure requires further standardization, including uniformity of the pressure transducer zero level at the midthoracic line, which is at the level of the left atrium. One of the most common problems in the diagnostic workup of patients with PH is the distinction between PAH and PH due to left heart failure with preserved ejection fraction (HFpEF). A normal PAWP does not rule out the presence of HFpEF. Volume or exercise challenge during right heart catheterization may be useful to unmask the presence of left heart disease, but both tools require further evaluation before their use in general practice can be recommended. Early diagnosis of PAH remains difficult, and screening programs in asymptomatic patients are feasible only in high-risk populations, particularly in patients with systemic sclerosis, for whom recent data suggest that a combination of clinical assessment and pulmonary function testing including diffusion capacity for carbon monoxide, biomarkers, and echocardiography has a higher predictive value than echocardiography alone. (J Am Coll Cardiol 2013;62:D42–50) © 2013 by the American College of Cardiology Foundation

Diagnosis and assessment of patients with pulmonary arterial hypertension (PAH) have been major topics at all previous world meetings on pulmonary hypertension (PH), with the last update coming from the 4th World Symposium

on Pulmonary Hypertension (WSPH) held in Dana Point, California (1). The recommendations from that conference were incorporated into the most recent international guidelines (2–4). During the 5th WSPH in 2013 in

From the *Department of Respiratory Medicine and German Center for Lung Research, Hannover Medical School, Hannover, Germany; †Department of Pulmonary Medicine, VU University Medical Center, Amsterdam, the Netherlands; ‡Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, United Kingdom; §College of Medicine, Mayo Clinic, Rochester, Minnesota; ||University of Michigan Scleroderma Program, Ann Arbor, Michigan; ¶Department of Pulmonary Circulation and Thromboembolic Diseases, Medical Centre of Postgraduate Medication, Warsaw, Poland; #Center for Pulmonary Vascular Disease, Division of Cardiology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; **Department of Experimental, Diagnostic and Specialty Medicine—DIMES, Bologna University Hospital, Bologna, Italy; ††Division of Cardiology, Kyorin University School of Medicine, Tokyo, Japan; ‡‡Pulmonary Hypertension Program, University of Texas Southwestern Medical Center, Dallas, Texas; §§Experimental Medicine, Imperial College London, London, United Kingdom; and the ||||Division of Pulmonary Sciences and Critical Care Medicine and Cardiology, University of Colorado, Denver, Colorado. Dr. Hoeper has received speaker and/or consulting fees from Actelion, Bayer, Gilead, GlaxoSmithKline, Eli Lilly, Lung Rx, Pfizer, and Novartis. Dr. Bogaard has received speaker fees from and served on advisory boards for Pfizer and United Therapeutics. Dr. Condliffe has received speaker and/or conference travel fees from and/or served on advisory boards for Actelion, Bayer, Pfizer, GlaxoSmithKline, and Eli Lilly. Dr. Frantz has received consulting fees from Pfizer; and has received research funding from United Therapeutics. Dr. Khanna has received speaker

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Nice, France, the working group on diagnosis and assessment did not attempt to fully revise previous recommendations but proposed changes only where strong new evidence has been generated to support new proposals.

Definitions, Limitations, Uncertainties, and Controversies

Some aspects of the definitions and recommendations derived from the 4th WSPH have remained controversial. Debates are still ongoing, especially regarding the following questions. 1) Should PH be defined by a resting mean pulmonary artery pressure (PAPm) ≥ 25 mm Hg as is currently the case or by a resting PAPm > 20 mm Hg and should the term “borderline PH” be introduced for patients with a PAPm between 21 and 24 mm Hg? 2) Should exercise-induced PH be reintroduced as part of the PH definition? 3) Should pulmonary vascular resistance (PVR) be included in the PH/PAH definition? 4) Is pulmonary artery wedge pressure (PAWP) of 15 mm Hg appropriate to distinguish between pre-capillary and post-capillary PH and how should PAWP be measured? 5) Should fluid or exercise challenge be used to distinguish patients with PAH from patients with PH due to left ventricular (LV) dysfunction? **Should PH be defined by a resting PAPm ≥ 25 mm Hg as is currently the case or by a resting PAPm > 20 mm Hg and should the term “borderline PH” be introduced for patients with a PAPm between 21 and 24 mm Hg?** A resting PAPm > 25 mm Hg has been the cutoff value for a diagnosis of manifest PH since the 1st WSPH. However, the upper level of normal for resting PAPm is 20 mm Hg (5), and it is unclear how to classify and manage patients with PAPm levels between 21 and 24 mm Hg. Most of the relevant epidemiological and therapeutic studies in the field of PAH have used the 25 mm Hg threshold, and little is known about patients with PAPm levels between 21 and 24 mm Hg.

Several studies have suggested that even mildly elevated PA pressures may be of prognostic significance, particularly in patients with lung disease or connective tissue disease (CTD) (6,7). Introduction of the term “borderline PH” for patients with a PAPm ranging from 21 to 24 mm Hg was discussed in Dana Point and in Nice (8). This term could be used to avoid labeling patients with PAPm values between 21 and 24 mm Hg as manifest PH/PAH but at the same time would ensure that such values are not labeled “healthy.” In some circumstances, “borderline” PH might indicate early pulmonary vascular disease, especially when PAWP is low and transpulmonary gradient and PVR are elevated. However, the term “borderline PH” would not be useful in patients with left heart disease and elevated PAWP levels. The natural history of patients with PAPm values between 21 and 24 mm Hg has not been widely studied. One exception are patients with the scleroderma spectrum of

manifest PAH (9). The therapeutic consequences of such findings, however, are unknown.

RECOMMENDATIONS.

- The general definition of PH should remain unchanged. PH is defined by PAPm ≥ 25 mm Hg at rest measured by right heart catheterization (RHC).
- There are still insufficient data to introduce the term “borderline PH” for patients with PAPm levels between 21 and 24 mm Hg, especially because the prognostic and therapeutic implications remain unknown.
- Patients with PAPm values between 21 and 24 mm Hg should be carefully followed, in particular when they are at risk for developing PAH (e.g., patients with CTD, family members of patients with idiopathic pulmonary arterial hypertension [IPAH] or heritable pulmonary arterial hypertension [HPAH]).

Should exercise-induced PH be reintroduced as part of the PH definition? Before the 4th WSPH, PH was defined by resting PAPm > 25 mm Hg or PAPm with exercise > 30 mm Hg. Potential weaknesses of that definition included the fact that the level, type, and posture of exercise had not been specified. Furthermore, the normal exercise PAP varies with age. In a systematic review of the available literature (5), there were no significant differences in PAP at rest according to age groups; however, during exercise, PAPm was significantly higher in older patients (> 50 years of age). Based on these data, a task force at the 4th WSPH concluded that it was impossible to define a cutoff value for exercise-induced PH and recommended eliminating this criterion (1).

Since 2008, several studies have shed more light on exercise-induced PH (10,11), but there is still uncertainty about the most suitable exercise protocol and cutoff levels. In addition, prognostic value and therapeutic consequences of exercise-induced PH in the setting of normal resting hemodynamics have not been elucidated.

RECOMMENDATIONS ON EXERCISE-INDUCED PH.

- Because of the lack of a suitable definition, an exercise

Abbreviations and Acronyms

CO	= cardiac output
CTD	= connective tissue disease
DLCO	= diffusion capacity for carbon monoxide
HFpEF	= heart failure with preserved ejection fraction
HPAH	= heritable pulmonary arterial hypertension
IPAH	= idiopathic pulmonary arterial hypertension
LVEDP	= left ventricular end-diastolic pressure
NT-proBNP	= N-terminal pro-B-type natriuretic peptide
PAH	= pulmonary arterial hypertension
PAPm	= mean pulmonary artery pressure
PAWP	= pulmonary artery wedge pressure
PH	= pulmonary hypertension
PVR	= pulmonary vascular resistance
RHC	= right heart catheterization
Ssc	= scleroderma
WU	= Wood units

- Further studies are needed to define which levels of exercise-induced elevations in PAPm and PVR have prognostic and therapeutic implications.

Should PVR be included in the definition of PH/PAH? HARMONIZATION OF PVR UNITS.

Although PA is always given as mm Hg, various units are used for PVR, most frequently $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ and Wood units ($\text{mm Hg}/\text{l}\cdot\text{min}$). Consistency would be useful, and the working group suggested using Wood units (WU), which can be directly derived from PAP and cardiac output (CO) measurements without multiplication with the factor 80. The use of SI units is not endorsed because they are not commonly being used for hemodynamics in clinical practice.

According to a recent analysis (12), normal PVR at rest is to some extent age dependent, but $\text{PVR} >2$ WU can be considered elevated in all age populations. In the current U.S. guidelines, $\text{PVR} >3$ WU is used as part of the hemodynamic definition of PAH (3).

The working group members unanimously agreed that the general definition of PH should be kept as simple and as broad as possible. Some PH populations (for instance, patients with elevated PAWP levels or patients with high pulmonary blood flow) may have elevated PAP but normal PVR. Thus, PVR should not be part of the general definition of PH.

However, the working group members proposed to include PVR in the hemodynamic definition of PAH for the following reasons: 1) including PVR underscores the need to base the definition of PH on invasive measurements (i.e., RHC); 2) including PVR makes PAWP (or left ventricular end-diastolic pressure [LVEDP]) measurements mandatory; 3) including PVR requires measurements of CO, which would be a substantial advantage because it is current practice in many nonexpert centers to perform RHCs without measuring CO; 4) including PVR will exclude high flow conditions with normal PVR and without pulmonary vasculopathy from the PAH definition; and 5) including PVR will lower the likelihood of patients with left heart disease of being labeled as having PAH.

RECOMMENDATIONS ON PVR.

- To avoid the use of various units, PVR should be given in WU.
- PVR should not become part of the general PH definition.
- PVR should be included in the hemodynamic characterization of patients with PAH as follows: patients with PAH are characterized by pre-capillary PH (i.e., $\text{PAPm} \geq 25$ mm Hg, $\text{PAWP} \leq 15$ mm Hg, and elevated $\text{PVR} [>3$ WU]).
- Although the upper level of normal PVR is approximately 2 WU, the PVR cutoff value for PAH should

setting the cutoff for PAPm at 25 mm Hg, despite the upper limit of normal being 20 mm Hg).

Is PAWP of 15 mm Hg appropriate to distinguish between pre-capillary and post-capillary PH and how should PAWP be measured? PAWP/PAOP/PCWP—HARMONIZATION OF TERMINOLOGY.

The term pulmonary capillary wedge pressure (PCWP) is widely used in the medical literature. For measurement of this pressure, balloon occlusion occurs in the pulmonary arteries, and the obtained value is not equal to the pulmonary capillary pressure in non-occluded areas. Thus, the term PCWP is misleading. Better terms are pulmonary artery occlusion pressure (PAOP) and PAWP. The working group prefers the latter term because the short versions “wedge” and “wedge pressure” are well established in daily clinical practice, even in non-English-speaking countries.

Current guidelines recommend using a PAWP (or LVEDP) ≤ 15 mm Hg to define pre-capillary PH. Higher PAWP values are commonly viewed as indicators of left heart disease. However, patients with the diagnosis of heart failure with preserved ejection fraction (HFpEF) can have a resting PAWP <15 mm Hg and patients with features otherwise indicating the presence of PAH may present with higher PAWP values (13). In addition, PAWP measurements vary between centers, and standardization is necessary to ensure comparisons of patient populations.

STANDARDIZATION OF PAWP MEASUREMENTS. PAWP measurements may be largely affected by swings in the intrathoracic pressure, especially in patients with lung disease. This effect is least pronounced at the end of a normal expiration, which is the point at which PAWP should be determined. Many available devices do not provide end-expiratory but digitized mean PAWP and therefore tend to underestimate the PAWP. For standardization of PAWP measurements, values should be determined at the end of normal expiration (breath holding is not required). Ideally, high-fidelity tracings on paper should be used, rather than small moving tracings on a cardiac monitor.

Normal PAWP values have been explored since the advent of cardiac catheterization and have been found to range from 5 to 12 mm Hg in healthy volunteers. However, these data were generated in younger patients, and it remains unclear whether there is a physiological increase in PAWP with aging. In a comprehensive analysis of the medical literature, Kovacs et al. (12) found that PAWP at rest was independent of age, with values of 9 ± 2 mm Hg found in patients ranging from <24 to ≥ 70 years. Of note, the data of the oldest patient population were derived from 17 patients only. Prasad et al. (14) performed a small but meticulous study comparing hemodynamics and LV function in elderly patients with and without HFpEF, demon-

PAWP levels ≤ 15 mm Hg did not rule out the presence of HFpEF. On the basis of these and other data, it has been suggested to lower the PAWP cutoff for pre-capillary PH to 12 mm Hg. Reasons to reduce the PAWP threshold to 12 mm Hg include the notion that PAWP of 15 mm Hg is associated with a higher chance of misclassifying patients with HFpEF as PAH and that the use of 15 mm Hg has probably contributed to the labeling of patients with HFpEF as PAH with consequences for medical therapy as well as inclusions in clinical trials.

On the other hand, PAWP ≤ 15 mm Hg has a high sensitivity to identify patients with pre-capillary PH, and this cutoff value has been used for decades and has been widely memorized among physicians. Almost all PAH trials have included patients with PAWP ≤ 15 mm Hg, which means that the safety and efficacy of PAH drugs have been evaluated in this patient population. Lowering the PAWP threshold to 12 mm Hg decreases the likelihood of falsely labeling patients with PH due to HFpEF as PAH but at the same time increases the rate at which the presence of PAH is mistakenly excluded.

There is no single PAWP value that allows for correct classification of all patients. PAWP is not a constant number but a biological variable that is affected by various factors, including fluid balance, intrathoracic pressure, and others. In many patients with left heart disease, it will be possible to at least temporarily lower PAWP below 15 mm Hg with meticulous afterload reduction and diuretic medication (15). A comprehensive assessment of the patient's medical history and risk factors together with echocardiographic assessment will provide a more reliable diagnosis than a single PAWP (or LVEDP) measurement. The presence of clinical risk factors (systemic hypertension, older age, obesity, diabetes mellitus, obstructive sleep apnea, coronary artery disease), atrial fibrillation, and echocardiographic findings such as left atrial enlargement or LV hypertrophy indicate a high likelihood of HFpEF (16).

A recent study showed that more than 50% of the patients with PH and PAWP ≤ 15 mm Hg had LVEDP values >15 mm Hg during simultaneous right and left heart catheterization (17). These data raised a debate as to whether the hemodynamic classification as pre- or post-capillary PH might be improved with routine LVEDP measurements. The additional risks and costs associated with routine left heart catheterizations are considerable but might be offset by a more accurate diagnosis and the avoidance of the expensive and potentially harmful use of PAH medications in patients with HFpEF. The working group felt that the current evidence does not support recommending left heart catheterization in all patients with PAH, especially when neither the patient's history nor clinical and echocardiographic findings suggest the presence of LV dysfunction. However, the threshold to perform left heart catheterization should be low in patients with

coronary heart disease or HFpEF. In addition, the finding of an elevated PAWP in a patient when this is unexpected (normal left atrial size, absence of echocardiographic markers of elevated LV filling pressures, absence of risk factors for HFpEF) should prompt the performing physician to measure LVEDP to avoid misclassification.

RECOMMENDATIONS FOR PAWP AT REST.

- The working group does not recommend lowering the threshold to 12 mm Hg in clinical practice.
- The cutoff for pre-capillary PH should remain at ≤ 15 mm Hg because this value has been used in almost all clinical trials generating evidence for the safety and efficacy of PAH-targeted therapies in patients fulfilling these criteria.
- Invasive hemodynamics need to be placed in clinical and echocardiographic context with regard to probability of existence of left heart disease.
- The current evidence does not support recommending left heart catheterization in all patients with PAH.

Should fluid or exercise challenge be used to distinguish patients with PAH from patients with PH due to LV dysfunction? SHOULD FLUID CHALLENGE BE USED TO UNMASK LV DIASTOLIC DYSFUNCTION?

The effect of volume challenge on left-sided end-diastolic pressure has been a subject of interest for some time. Studies in healthy individuals have shown that administration of 1 liter of saline over 6 to 8 min raised the PAWP by a maximum of 3 mm Hg but not to >11 mm Hg (18). In contrast, in a population at high risk for diastolic dysfunction, administration of 500 ml of saline over 5 min was able to reveal patients in whom the PAWP increased to >15 mm Hg (19).

Thus, fluid challenge may identify patients with HFpEF but normal PAWP at baseline and may help reduce the number of inappropriate diagnoses of PAH in patients with LV diastolic dysfunction. A fluid bolus of 500 ml administered over a period of 5 to 10 min appears to be safe and seems to discriminate patients with PAH from those with LV diastolic dysfunction (20). Larger volumes, in contrast, may cause the PAWP to rise even in healthy volunteers (21). The diagnostic performance (sensitivity, specificity, and positive and negative predictive values) of fluid challenge has not yet been sufficiently evaluated, and the same is true for the safety of fluid challenge in patients with severe PH as well as in patients with HFpEF. In addition, fluid challenge adds another layer of complexity to RHC.

RECOMMENDATION ON FLUID CHALLENGE FOR UNMASKING HFPEF.

- Fluid challenge may be useful in identifying patients with occult HFpEF, but this technique requires meticulous evaluation and standardization before its use in clinical practice can be recommended.

distinguish patients with PAH from those with occult LV diastolic dysfunction. The results of this test, however, must be interpreted with caution and should not be used alone to discard a diagnosis of PAH.

SHOULD HEMODYNAMICS BE ASSESSED AT EXERCISE TO UNMASK LV DIASTOLIC DYSFUNCTION? Exercise, with wide swings in airway and pleural pressures, poses particular technical challenges in recording and interpreting cardiac pressures, and few studies have systematically analyzed the PAWP changes during exercise. In a study of healthy non-athletes, the mean wedge pressure rose by up to 5 mm Hg with exercise but did not exceed 15 mm Hg (22). In well-trained athletes, recumbent exercise significantly increased the PAWP, reaching 20 to 25 mm Hg in several individuals (23). In a more recent study on exercise-induced PH, Tolle et al. (11) found PAWP values >15 mm Hg in approximately half of the healthy control group as well as in patients with exercise-induced or resting PH.

Borlaug et al. (24) studied the effects of exercise on hemodynamics in patients with exertional dyspnea and presumed HFpEF but normal resting PAWP levels. At rest, patients with HFpEF had slightly higher PAWP (11 ± 2 vs. 9 ± 3 mm Hg in controls without cardiac disease). During exercise, end-expiration PAWP rose to 32 ± 6 mm Hg in patients with HFpEF compared with 13 ± 5 mm Hg in controls (24). In addition, a recent study suggested that exercise hemodynamics may be useful in distinguishing between PAH and PH associated with LV diastolic dysfunction in patients with the scleroderma (SSc) spectrum of disease (25).

Thus, exercise hemodynamics may identify patients with HFpEF with normal PAWP at rest. However, it is cumbersome and time consuming to exercise patients with a catheter in place, reading of the PAWP during exercise is difficult, and there has been no standardization on the level of exercise, type of exercise, position at exercise, and normal values for various ages.

RECOMMENDATION ON EXERCISE CHALLENGE TO UNMASK HFPEF.

- It is likely that exercise hemodynamics will be useful in uncovering HFpEF. However, further evaluation, standardization, and comparison with volume challenge are necessary before their use in clinical practice can be endorsed.

Additional Recommendations for RHC

Although current guidelines and textbooks recommend RHC for the diagnostic evaluation of patients with PH, specific recommendations on how to perform this procedure are rare. The following points should be noted.

complications (26). Thus, this invasive diagnostic procedure should be performed in expert centers.

- Every RHC should include a comprehensive hemodynamic assessment, including measurements of pressures in the right atrium, right ventricle, and PA; in the “wedge” position; and CO and mixed-venous oxygen saturation.
- The zero level of the pressure transducer varies among centers and should be standardized for future research because the level of the transducer has an important impact on the hemodynamic results, especially on right atrium pressure and PAWP (27). The working group recommends zeroing the pressure transducer at the midthoracic line in a supine patient halfway between the anterior sternum and the bed surface. This represents the level of the left atrium.
- The balloon should be inflated in the right atrium from where the catheter should be advanced until it reaches the PAWP position. Repeated deflations and inflations of the catheter should be avoided because this has been associated with ruptures of PAs (26). The PAWP should be recorded as the mean of 3 measurements at end-expiration.
- The gold standard for CO measurement is the direct Fick method, which requires direct measurement of the oxygen uptake, a technique that is not widely available. Therefore, it has become common practice in many centers to use the indirect Fick method, which uses estimated values for oxygen uptake derived from tables. This approach is acceptable but lacks reliability. Therefore, the preferred method of measuring CO is thermodilution, which has been shown to provide reliable measurements even in patients with very low CO and/or severe tricuspid regurgitation (28).
- Oximetry (i.e., stepwise assessment of oxygen saturation) should be performed in every patient with a PA oxygen saturation >75% and whenever a cardiac left-to-right shunt is suspected.
- Pulmonary vasoreactivity testing for identification of calcium channel blocker “responders” is recommended only for patients with IPAH. In all other forms of PAH or PH, pulmonary vasoreactivity testing is not recommended unless it is completed for scientific purposes because “responders” are exceedingly rare among these patients and the results can be misleading (29). Inhaled nitric oxide at 10 to 20 parts per million is the gold standard for pulmonary vasoreactivity testing (30); intravenous epoprostenol (2 to 12 ng/kg/min), intravenous adenosine (50 to 350 μ g/min), and inhaled iloprost (5 μ g) can be used as alternatives (31,32). The use of oxygen, calcium channel blockers, phosphodiesterase 5 inhibitors, or other vasodilators for acute pulmonary vasoreactivity testing is discouraged.
- Pulmonary angiography can be part of the RHC but

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