Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.032

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 2008 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 and/or conference travel fees from and/or served on advisory boards for Actelion, Bayer, Bristol-Myers Squibb, Digna, Intermone, Gilead, Pfizer, Roche, Sanofi-Aventis, and United Therapeutics; and has received research funding from the National Institutes of Health and the Scleroderma Foundation. Dr. Kurzyna has received speaker and/or conference travel fees from and/or served on advisory boards for Bayer, AOP Orphan, Actelion, Pfizer, and GlaxoSmithKline. Dr. Langleben has received speaker and/or consulting fees from, has served on advisory boards for, and/or has been an investigator in clinical trials for Actelion, Bayer, GlaxoSmithKline, Eli Lilly, Myogen, Northern Therapeutics, Novartis, Pfizer, and United Therapeutics. Dr. Manes has received speaker fees from Actelion, Bayer, and GlaxoSmithKline. Dr. Satoh has received speaker fees from Actelion. Dr. Torres has received grant funding from GENO, Medtronic, Actelion/CoTherix, Gilead, Pfizer, United Therapeutics/Lung Rx, Eli Lilly/ICOS, Bayer, Novartis, Akaria, and ARIES; has served as a consultant (often in the role of steering committee or advisory board member) for Actelion/CoTherix, Gilead, Novartis, Pfizer, United Therapeutics/Lung Rx, GlaxoSmithKline, and Bayer; and is a speaker/advisory board member of Gilead, Actelion, United Therapeutics, Bayer, and Novartis. Dr. Wilkins has received speaker and/or consulting fees from Bayer, GlaxoSmithKline, Pfizer, and Novartis; and has received research funding from the British Heart Foundation, Wellcome Trust, and the National Institutes of Health. Dr. Badesch has received grant funding from Actelion/CoTherix, Gilead, Pfizer, United Therapeutics/Lung Rx, Eli Lilly/ICOS, Bayer, Novartis, Ikaria, and ARIES; has served as a consultant (often in the role of steering committee or advisory board member) for Actelion/CoTherix, Gilead, Pfizer, Mondo-Biotech/Mondogen, United Therapeutics/Lung Rx, GlaxoSmithKline, Eli Lilly/ICOS, Bayer, Ikaria, Reatta, and Arena; and has provided advice in a legal matter to Actelion.

Manuscript received October 11, 2013; accepted October 22, 2013.

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 disease, in whom the presence of "borderline" pressures is associated with a high risk of future development 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]).

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

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 criterion for PH should not be reintroduced at the present time.

- 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 dyn•s•cm^{-5} and Wood units (mm Hg/l•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 PVR >2 WU can be considered elevated in all age populations. In the current U.S. guidelines, 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., PAPm ≥25 mm Hg, PAWP ≤15 mm Hg, and elevated PVR [>3 WU]).
- Although the upper level of normal PVR is approximately 2 WU, the PVR cutoff value for PAH should be kept at 3 WU because patients with lower PVR levels are unlikely to have PAH (this is consistent with 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—HARMONIZTION 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, demonstrating that the normal PAWP slightly increased with age, although usually not beyond 15 mm Hg. Most importantly,

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 echocardiographic signs of systolic and/or diastolic LV dysfunction as well as in patients with risk factors for 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.
- Current evidence suggests that administration of 500 ml of fluid over 5 to 10 min is safe and may help to

JACC Vol. 62, No. 25, Suppl D, 2013
December 24, 2013:D42–50

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 nonathletes, 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.

- RHC in patients with PH can be technically demanding and has been associated with serious, sometimes fatal, 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 μg/min), and inhaled iloprost (5 μg) 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 should be performed after all hemodynamic assessments have been completed.

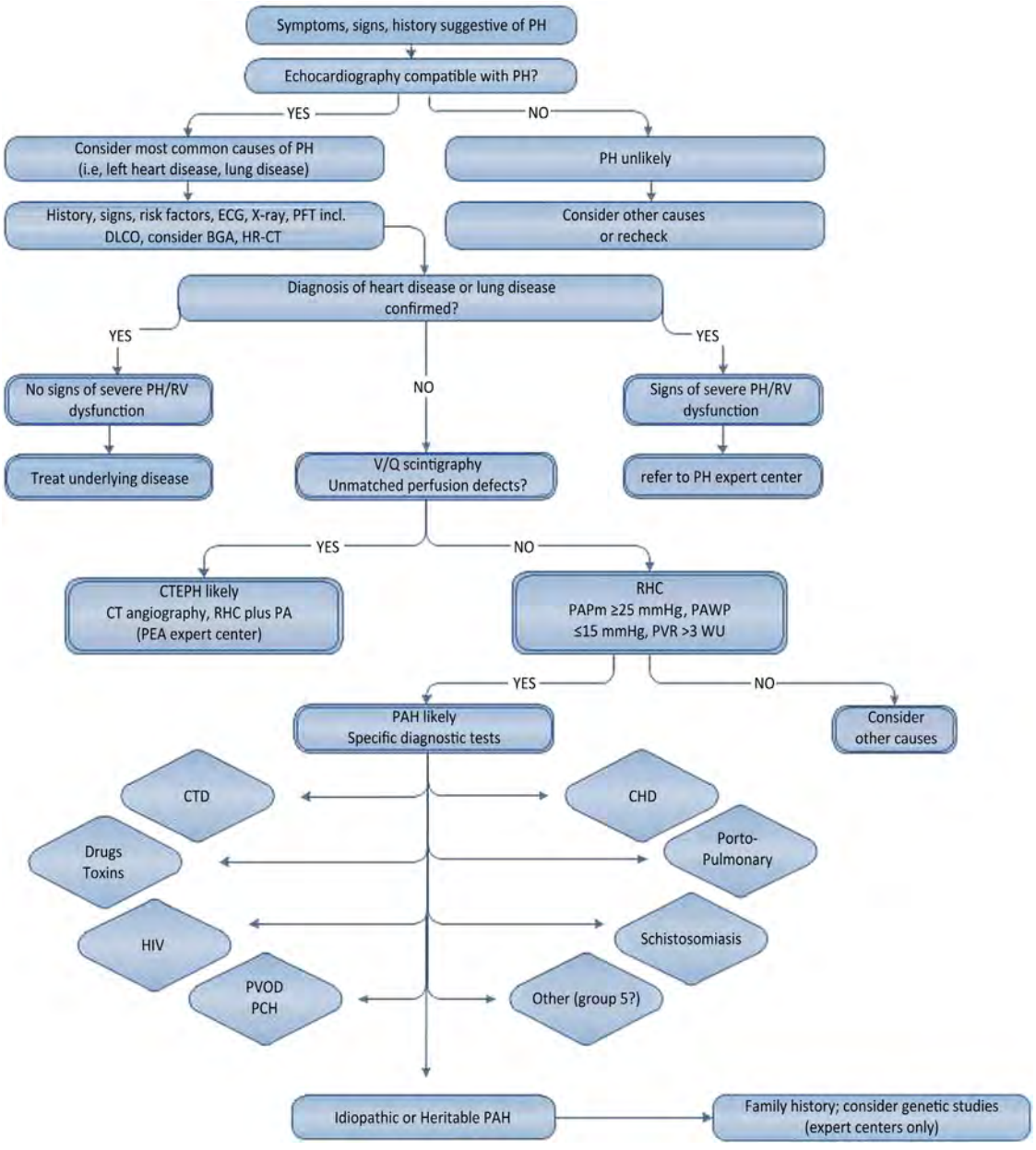

Figure 1 **Diagnostic Approach to Pulmonary Hypertension**

BGA = blood gas analysis; CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; HR-CT = high-resolution computed tomography; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PCH = pulmonary capillary hemangiomatosis; PEA = pulmonary endarterectomy; PFT = pulmonary function testing; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; RHC = right heart catheter; RV = right ventricle; V/Q = ventilation/perfusion; x-ray = chest radiograph.

Diagnostic Approach in Patients With Clinical Suspicion of PH/PAH

The most fundamental principles in the diagnostic workup of patients with clinical suspicion of PH/PAH remain unchanged. PH/PAH should be suspected in any patient with otherwise unexplained dyspnea on exertion, syncope, and/or signs of right ventricular dysfunction. Transthoracic echocardiography continues to be the most important noninvasive screening tool to assess the possibility of PH, but RHC remains mandatory to establish the diagnosis. A diagnosis of PAH requires the exclusion of other causes of PH, and the working group proposes a slightly modified version of the diagnostic algorithm proposed in the 2009

JACC Vol. 62, No. 25, Suppl D, 2013
December 24, 2013:D42–50

European guidelines (2,4) as shown in Figure 1. This revised version has been simplified and, in some aspects, is more specific. The pathway leading from ventilation/perfusion scintigraphy to pulmonary veno-occlusive disease has been deleted (33), and diffusing capacity of the lung for carbon monoxide (DLCO) measurements have been added to the initial assessment because spirometry alone does not always reveal parenchymal lung disease, for instance, in patients with combined pulmonary fibrosis and emphysema (34–36). A comprehensive workup for PH requires expertise and should be performed at expert centers (2).

Early Identification of Patients With PAH

Sporadic cases (IPAH). Despite increasing awareness, there is often considerable delay between onset of symptoms and diagnosis of IPAH. In the recent REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) registry, 21% of patients had symptoms for >2 years before diagnosis (37,38). The vast majority of patients diagnosed with IPAH are in World Health Organization functional classes III and IV (37,39–41), which have been shown to predict poorer survival (42,43). The nature of patients formally diagnosed with IPAH has also changed over recent years, at least in the Western world, with a significant increase in age and number of comorbidities (41,44,45). Identifying patients with IPAH earlier in the disease process is likely to be beneficial, allowing targeted therapies to be started before the development of significant right heart failure (46). Screening is possible in well-defined patient groups at high risk of developing PAH, but this approach is not feasible in the wider population. Identifying patients with IPAH earlier relies on health care professionals having awareness of the condition.

Hereditary cases (HPAH). Approximately 20% of patients with sporadic IPAH and 70% of patients with HPAH have a mutation in bone morphogenetic protein receptor 2 (*BMPR2*), and additional genes associated with HPAH have recently been identified (47,48), which raises the possibility of family screening (49). However, because of reduced penetrance, the lifetime risk of developing PAH is approximately 20% in *BMPR2* mutation carriers (50). The benefits of genetic testing are therefore not certain. A negative test in the context of a known mutation in a family member is reassuring, whereas a positive test can create significant psychological issues (51). Furthermore, the approach to monitoring known mutation carriers for the development of PAH is not clear. Interval echocardiography of mutation carriers has been suggested (53), although in the absence of evidence for benefit of targeted therapies in truly asymptomatic patients, it could be argued that echocardiography should be reserved only for symptomatic carriers. Most importantly, expert counseling should accompany any family screening program.

Detection of PAH and screening in high-risk populations. Various other groups of patients may be considered at high risk of developing PAH and, as such, may be candidates for early detection. These include patients with CTD, congenital heart disease, chronic liver disease, and HIV infection. Except for patients with the SSc spectrum of disease, no new evidence has been generated; therefore, previous recommendations have not been modified.

Screening for PAH in patients with the SSc spectrum of disease. Current guidelines recommend regular screening by echocardiography in patients with SSc spectrum of diseases (defined as patients with systemic sclerosis, mixed connective tissue disease, or other CTDs with prominent scleroderma features such as sclerodactyly, nail fold capillary abnormalities, SSc-specific autoantibodies) (2,4). No such guidelines exist for other CTDs.

The DETECT (Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis) study recently evaluated a 2-step approach in patients with SSc spectrum disorders with DLCO ≤60% and disease duration of >3 years (52). The first step used a simple screening test, such as the presence of telangiectasia, anticentromere antibodies, right-axis deviation on electrocardiogram, and low DLCO and serum biomarkers (urate and N-terminal pro–B-type natriuretic peptide [NT-proBNP]), which gave a sensitivity of 97% (i.e., a low likelihood of falsely excluding PAH). Step 2 was echocardiography (tricuspid regurgitation jet and right atrium area) in patients at risk, followed by RHC. With this algorithm, the number of missed PAH cases was 4%, compared with 29% with the echocardiography-based approach recommended in the current European Respiratory Society/European Society of Cardiology guidelines, suggesting that using a broader panel of diagnostic tools provides more reliable information than echocardiography alone.

The DETECT algorithm is not yet validated in patients with DLCO >60%. Other choices include a combination of echocardiogram, NT-proBNP, and pulmonary function testing (PFT) parameters, which is summarized in the recently published recommendations on screening and early detection of CTD-associated PAH (53,54).

Recommendations on screening of high-risk populations for PAH.

- Annual screening for PAH is recommended in (cardiopulmonary) asymptomatic patients with the SSc spectrum of diseases, although there is a lack of evidence-based data.
- Screening of patients with the SSc spectrum of diseases without clinical signs and symptoms of PH should include a 2-step approach using clinical assessment for the presence of telangiectasia, anticentromere antibodies, PFT and DLCO measurements, electrocardiogram, and biomarkers (NT-proBNP and uric acid) in the initial stage, followed by echocardiography and consideration of RHC in patients with abnormal findings, although there is a lack of data with DLCO >60%.
- The above mentioned screening programs for patients with SSc should be part of a scientific protocol, or a registry, whenever possible.

- Patients with SSc and other CTDs with clinical signs and symptoms of PH should be evaluated by RHC.

Summary and Conclusions

The diagnostic approach to PH proposed at the 4th WSPH has proved useful and largely successful. The general hemodynamic definition of PH (PAPm ≥25 mm Hg at rest) should not be changed. Patients with PAPm values between 21 and 24 mm Hg should be carefully followed, but the term "borderline PH" should be avoided because these patients do not have PH. PVR >3 WU has been added as a hemodynamic criterion for PAH, in an attempt to provide a clearer distinction from other forms of PH. RHC remains an essential tool for the diagnostic workup of patients with PH, and the working group has made several proposals for further standardization of this procedure. Reintroducing exercise criteria for patients with normal hemodynamics at rest but elevated PA pressures during exercise is not recommended because it is currently impossible to define appropriate cutoff levels and there have been few studies assessing what is pathological in terms of affecting exercise capacity and survival.

Data from all over the world indicate that the majority of patients are still diagnosed in a late stage of the disease, and this is not expected to change in the near future. The most significant progress has been made in patients with SSc, for whom the DETECT study has provided important data on screening for PAH (52).

The increased awareness has led to a changing pattern of patients referred for evaluation of PH/PAH. The patients tend to be older and have more comorbidities (41,44,45). Arguably, the majority of these patients have LV diastolic dysfunction as the leading cause of PH, but our current diagnostic tools are often insufficient to provide a clear distinction between PAH and PH due to left heart disease. At the next world meeting in 2018, we hope to have data from well-conducted trials to tell us whether and how fluid challenge, exercise hemodynamics, or other novel tools will help us to paint a clearer picture.

Reprint requests and correspondence: Dr. Marius M. Hoeper, Department of Respiratory Medicine, Hannover Medical School, Carl-Neuberg-Strasse 1, 30623 Hannover, Germany. E-mail: hoeper.marius@mh-hannover.de.

REFERENCES

1. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55–66.
2. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Respir J 2009;34:1219–63.
3. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573–619.
4. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–537.
5. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34:888–94.
6. Kovacs G, Maier R, Aberer E, et al. Borderline pulmonary arterial pressure is associated with decreased exercise capacity in scleroderma. Am J Respir Crit Care Med 2009;180:881–6.
7. Hamada K, Nagai S, Tanaka S, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest 2007;131:650–6.
8. Hoeper MM. The new definition of pulmonary hypertension. Eur Respir J 2009;34:790–1.
9. Bae S, Saggar R, Bolster MB, et al. Baseline characteristics and follow-up in patients with normal haemodynamics versus borderline mean pulmonary arterial pressure in systemic sclerosis: results from the PHAROS registry. Ann Rheum Dis 2012;71:1335–42.
10. Saggar R, Khanna D, Shapiro S, et al. Brief report: effect of ambrisentan treatment on exercise-induced pulmonary hypertension in systemic sclerosis: a prospective single-center, open-label pilot study. Arthritis Rheum 2012;64:4072–7.
11. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension. Circulation 2008;118:2183–9.
12. Kovacs G, Olschewski A, Berghold A, Olschewski H. Pulmonary vascular resistances during exercise in normal subjects: a systematic review. Eur Respir J 2012;39:319–28.
13. Frost AE, Farber HW, Barst RJ, Miller DP, Elliott CG, McGoon MD. Demographics and outcomes of patients diagnosed with pulmonary hypertension with pulmonary capillary wedge pressures 16 to 18 mm Hg: insights from the REVEAL registry. Chest 2013;143:185–95.
14. Prasad A, Hastings JL, Shibata S, et al. Characterization of static and dynamic left ventricular diastolic function in patients with heart failure with a preserved ejection fraction. Circ Heart Fail 2010;3:617–26.
15. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658–66.
16. Hoeper MM, Barbera JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009;54:S85–96.
17. Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. Chest 2009;136:37–43.
18. Bush CA, Stang JM, Wooley CF, Kilman JW. Occult constrictive pericardial disease. Diagnosis by rapid volume expansion and correction by pericardiectomy. Circulation 1977;56:924–30.
19. Robbins IM, Newman JH, Johnson RF, et al. Association of the metabolic syndrome with pulmonary venous hypertension. Chest 2009;136:31–6.
20. Fox BD, Shimony A, Langleben D, et al. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. Eur Respir J 2013;42:1083–91.
21. Fujimoto N, Borlaug BA, Lewis GD, et al. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. Circulation 2013;127:55–62.
22. Holmgren A, Jonsson B, Sjostrand T. Circulatory data in normal subjects at rest and during exercise in recumbent position, with special reference to the stroke volume at different work intensities. Acta Physiol Scand 1960;49:343–63.
23. Bevegard S, Holmgren A, Jonsson B. Circulatory studies in well trained athletes at rest and during heavy exercise. With special reference to stroke volume and the influence of body position. Acta Physiol Scand 1963;57:26–50.

JACC Vol. 62, No. 25, Suppl D, 2013
December 24, 2013:D42–50

24. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588–95.
25. Hager WD, Collins I, Tate JP, et al. Exercise during cardiac catheterization distinguishes between pulmonary and left ventricular causes of dyspnea in systemic sclerosis patients. Clin Respir J 2013; 7:227–36.
26. Hoeper MM, Lee SH, Voswinckel R, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 2006;48:2546–52.
27. Kovacs G, Avian A, Olschewski A, Olschewski H. Zero reference level for right heart catheterization. Eur Respir J 2013;42:1586–94.
28. Hoeper MM, Maier R, Tongers J, et al. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. Am J Respir Crit Care Med 1999;160: 535–41.
29. Montani D, Savale L, Natali D, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. Eur Heart J 2010;31:1898–907.
30. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105–11.
31. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76–81.
32. Jing ZC, Jiang X, Han ZY, et al. Iloprost for pulmonary vasodilator testing in idiopathic pulmonary arterial hypertension. Eur Respir J 2009;33:1354–60.
33. Seferian A, Helal B, Jais X, et al. Ventilation/perfusion lung scan in pulmonary veno-occlusive disease. Eur Respir J 2012;40:75–83.
34. Cottin V, Le Pavec J, Prevot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J 2010;35:105–11.
35. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005;26: 586–93.
36. Trip P, Nossent EJ, de Man FS, et al. Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension—patient characteristics and treatment responses. Eur Respir J 2013;42:1575–85.
37. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023–30.
38. Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. Chest 2011;140:19–26.
39. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. Chest 2010;137:376–87.
40. Hurdman J, Condliffe R, Elliot CA, et al. ASPIRE registry: Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre. Eur Respir J 2012;39:945–55.
41. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol 2013;168:871–80.
42. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164–72.
43. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2012;39:589–96.
44. Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. Chest 2011;139:128–37.
45. Ling Y, Johnson MK, Kiely DG, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 2012;186:790–6.
46. Galie N, Rubin L, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 2008;371: 2093–100.
47. Germain M, Eyries M, Montani D, et al. Genome-wide association analysis identifies a susceptibility locus for pulmonary arterial hypertension. Nat Genet 2013;45:518–21.
48. Ma L, Roman-Campos D, Austin ED, et al. A novel channelopathy in pulmonary arterial hypertension. N Engl J Med 2013;369:351–61.
49. Thomson JR, Machado RD, Pauciulo MW, et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-beta family. J Med Genet 2000;37:741–5.
50. Machado RD, Aldred MA, James V, et al. Mutations of the TGF-beta type II receptor BMPR2 in pulmonary arterial hypertension. Hum Mutat 2006;27:121–32.
51. Machado RD, Eickelberg O, Elliott CG, et al. Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54: S32–42.
52. Coghlan JG, Denton CP, Grunig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2013 May 18 [E-pub ahead of print].
53. Khanna D, Gladue H, Channick R, et al. Recommendations for screening and detection of connective-tissue disease associated pulmonary arterial hypertension. Arthritis Rheum 2013 Sep 10 [E-pub ahead of print].
54. Gladue H, Steen V, Allanore Y, et al. Combination of echocardiographic and pulmonary function test measures improves sensitivity for diagnosis of systemic sclerosis-associated pulmonary arterial hypertension: analysis of 2 cohorts. J Rheumatol 2013;40:1706–11.

Key Words: diagnosis ■ hemodynamics ■ pulmonary hypertension ■ right heart catheterization ■ screening.