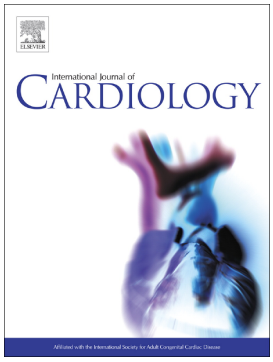

Definition, clinical classification and initial diagnosis of pulmonary hypertension: Updated recommendations from the Cologne Consensus Conference 2018

Gabor Kovacs, Daniel Dumitrescu, Andreas Barner, Sebastian Greiner, Ekkehard Grünig, Alfred Hager, Thomas Köhler, Rainer Kozlik-Feldmann, Irene Kruck, Astrid E. Lammers, Derliz Mereles, Andreas Meyer, Joachim Meyer, Stefan Pabst, Hans-Jürgen Seyfarth, Christoph Sinning, Stephan Sorichter, Gerd Stähler, Heinrike Wilkens, Matthias Held

PII: S0167-5273(18)34347-X
DOI: doi:10.1016/j.ijcard.2018.08.083
Reference: IJCA 26899

To appear in: *International Journal of Cardiology*

Received date: 9 August 2018
Accepted date: 24 August 2018

Please cite this article as: Gabor Kovacs, Daniel Dumitrescu, Andreas Barner, Sebastian Greiner, Ekkehard Grünig, Alfred Hager, Thomas Köhler, Rainer Kozlik-Feldmann, Irene Kruck, Astrid E. Lammers, Derliz Mereles, Andreas Meyer, Joachim Meyer, Stefan Pabst, Hans-Jürgen Seyfarth, Christoph Sinning, Stephan Sorichter, Gerd Stähler, Heinrike Wilkens, Matthias Held , Definition, clinical classification and initial diagnosis of pulmonary hypertension: Updated recommendations from the Cologne Consensus Conference 2018. Ijca (2018), doi:10.1016/j.ijcard.2018.08.083

Definition, clinical classification and initial diagnosis of pulmonary hypertension: Updated Recommendations from the Cologne Consensus Conference 2018

Gabor Kovacs[1,*], Daniel Dumitrescu[2,*], Andreas Barner[3], Sebastian Greiner[4], Ekkehard Grünig[5], Alfred Hager[6], Thomas Köhler[7], Rainer Kozlik-Feldmann[8], Irene Kruck[9], Astrid E. Lammers[10], Derliz Mereles[4], Andreas Meyer[11], Joachim Meyer[12], Stefan Pabst[13], Hans-Jürgen Seyfarth[14], Christoph Sinning[15], Stephan Sorichter[16], Gerd Stähler[17], Heinrike Wilkens[18], Matthias Held[19]

* „equally contributed“

[1]Department of Internal Medicine, Division of Pulmonology, Medical University of Graz and Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria
[2]Clinic III for Internal Medicine, Heart Center, University of Cologne
[3]Hospital & Sanatorium Dr. Barner, Braunlage
[4]Department of Internal Medicine III, Cardiology, Angiology and Pneumology, University Clinic Heidelberg
[5]Center for Pulmonary Hypertension, Thoracic Clinic at the University Clinic Heidelberg
[6]Clinic for Pediatric Cardiology and Congenital Heart Diseases, German Heart Center, Munich
[7]Clinic for Pulmonology, Department Internal Medicine, University Clinic Freiburg
[8]Clinic for Pediatric Cardiology, University Heart Center Hamburg GmbH, University Clinic Eppendorf, Hamburg
[9]Cardio Centrum Ludwigsburg Bietigheim, Ludwigsburg
[10]Pediatric Cardiology, University Clinic Münster
[11]Clinic for Pulmonology, St. Franziskus Hospital, Mönchengladbach
[12]Clinic for Pulmonology, Gastroenterology and Intensive care, Klinikum Harlaching
[13]Medical Clinic II, Department of Pneumology, University Hospital Bonn
[14]Department of Respiratory Medicine; University of Leipzig
[15]University Heart Center Hamburg, Clinic for General and interventional Cardiology, Hamburg
[16]Clinic for Pulmonology, St.-Josef Hospital, RkK-Klinikum Freiburg
[17]Clinic Löwenstein, Medical Clinic I, Löwenstein
[18]Clinic for Internal Medicine V, Pulmonology University Clinic of Saarland, Homburg
[19]Center for Pulmonary Hypertension and Lung Vascular Diseases, Department of Internal Medicine, Missionsklinik Würzburg

Word count: 4822
No. of references: 98
No. of figures: 1
No. of tables: 1

Address correspondence to:
Priv.-Doz. Dr. Gabor Kovacs
Klinische Abteilung für Lungenkrankheiten
Universitätsklinik für Innere Medizin, Medizinische Universität Graz
Auenbruggerplatz 15; 8036 Graz, Österreich
Tel.: +43 (316) 385-12183; FAX: +43 (316) 385-13930
e-mail: gabor.kovacs@medunigraz.at

Summary

In the summer of 2016, delegates from the German Society of Cardiology (DGK), the German Respiratory Society (DGP), and the German Society of Pediatric Cardiology (DGPK) met in Cologne, Germany, to define consensus-based practice recommendations for the management of patients with pulmonary hypertension (PH). These recommendations were built on the 2015 European Pulmonary Hypertension guidelines, aiming at their practical implementation, considering country-specific issues, and including new evidence, where available. To this end, a number of working groups was initiated, one of which was specifically dedicated to the definition, clinical classification and initial diagnosis of PH. While the European guidelines provide a detailed clinical classification and a structured approach for diagnostic testing, their application in routine care may be challenging, particularly given the changing phenotype of PH patients who are nowadays often elderly and may present with multiple potential causes of PH, as well as comorbid conditions. Specifically, the working group addresses the thoroughness of diagnostic testing, and the roles of echocardiography, exercise testing, and genetic testing in diagnosing PH. Furthermore, challenges in the diagnostic work-up of patients with various causes of PH including “PAH with comorbidities”, CTEPH and coexisting conditions are highlighted, and a modified diagnostic algorithm is provided. The detailed results and recommendations of the working group on definition, clinical classification and initial diagnosis of PH, which were last updated in the spring of 2018, are summarized in this article.

Word count summary: 231

Key words: pulmonary hypertension, definition, diagnosis, classification

Defining pulmonary vascular disease

Pulmonary hypertension, pulmonary arterial hypertension

In the updated guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) to ≥25 mmHg at rest as measured invasively by right heart catheterisation (RHC) [1]. The term pulmonary arterial hypertension (PAH) is defined hemodynamically as an mPAP ≥25 mmHg, a pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and a pulmonary vascular resistance (PVR) >3 Wood units (WU) in the absence of other causes of precapillary PH, such as PH due to lung diseases, chronic thromboembolic PH (CTEPH) or other rare diseases. The inclusion of PVR in the definition of PAH emphasises the importance of this parameter in the pathophysiology of the disease. In addition, this makes a complete diagnostic RHC imperative as there is no other way to determine PVR [2]. From a paediatric point of view a definition according to body surface area (in Wood Units × m^2) or in relation to systemic vascular resistance (R_P/R_S) might be an improvement, as healthy infants or small children easily hit the PVR threshold of 3 Wood Units.

There are some patients with a mPAP ≥25 mmHg, a PAWP ≤15 mmHg and a normal PVR <3 Wood units (WU). In these patients an elevated pulmonary blood flow drives the mPAP above 25 mmHg despite a normal PVR. In the ESC/ERS guidelines only patients with haemolytic anaemia were addressed and shifted to group 5 PH. However, numerous congenital shunt defects show this finding in young age as well, and those defects can be closed without relevant additional risk. Potentially, “flow-mediated” PH should become a subgroup of Group 5 PH.

Borderline PAP increase

In healthy individuals, the mPAP at rest is 14.0±3.3 mmHg with an upper limit of normal of approximately 20.6 mmHg. A mPAP between 21 and 24 mmHg is often described as borderline elevated mPAP [3] and is associated with a limited exercise capacity, increased hospitalisation rates and mortality [4,5]. Pulmonary and cardiac comorbidities are common, which may also cause an increase in mPAP, in addition to pulmonary vascular disease [3]. In some patient groups a borderline elevation of mPAP may have prognostic relevance. Recent data show that patients with systemic sclerosis (SSc) and borderline elevated mPAP appear to have a higher risk of developing PH [6]. Therefore, it is recommended that patients who are at risk of developing PAH (e.g. patients with connective tissue diseases or family members of patients with hereditary PAH [HPAH]) and have an

mPAP of 21-24 mmHg be carefully monitored [1]. Based on the current evidence, patients with borderline elevated PAP should not be treated with PAH medications.

Pulmonary hemodynamics during exercise

Due to the lack of reliable data relating to the prognostic relevance of haemodynamic changes in mPAP or PVR during exercise, a disease entity "exercise PH" is not defined in the PH guidelines. Studies conducted in recent years indicate that an abnormal pulmonary haemodynamic reaction during exercise may be characterised by a large increase in pulmonary pressure in relation to flow [3,7-9]. This phenomenon is associated with exercise dyspnoea and limited exercise capacity, and could be referred to as "exercise PH" [10]. The possible causes of a pathological increase in pulmonary pressure during exercise are increases in PVR, left atrial (LA) pressure or left-ventricular end-diastolic pressure (LVEDP), and in intrathoracic pressure. The most common cause of an increase in systolic PAP during exercise as measured by echocardiography is diastolic dysfunction of the left ventricle (LV) causing an increase in LVEDP with exercise, particularly in elderly patients [11]. According to recent studies, "exercise PH" may be defined hemodynamically as mPAP >30 mmHg with a calculated total pulmonary resistance (TPR) >3 WU during maximal exercise [8]. This suggestion refers to patients who develop high mPAP values already at a moderately increased cardiac output during exercise. Close follow-up of these patients is advisable. Outside of clinical studies, patients with "exercise PH" should not be treated with PAH medications. Small studies suggest that patients with exercise PH may have impaired prognosis [12], but large scale studies on the prognostic consequences of "exercise PH" are lacking.

Pulmonary vascular disease without pulmonary hypertension

In patients with univentricular heart after a Fontan-like palliation, the caval veins are directly connected to the pulmonary arteries by the surgeon. These patients do not have a subpulmonary ventricle that raises mPAP to 25 mmHg when PVR is increased. They just run into circulatory failure ("Fontan failure"). Several studies showed that pulmonary vasodilatation works and improves exercise capacity in these patients [13]. Probably this entity should therefore be included into a pulmonary hypertension guideline despite the criteria for PH are not fulfilled.

Clinical classification

The clinical classification of PH categorises multiple clinical conditions into five groups according to similarities in clinical presentation, pathological findings, haemodynamic characteristics and

treatment strategy. Compared with the previous version of the ESC/ERS PH guidelines, minor changes have been made to the clinical disease classification, while the main categories were not changed (**Table 1**).

Elderly patients, patients with comorbidities

Current registry data include an increasing proportion of elderly PH patients [14], who frequently have comorbidities [15]. In patients with PAH or CTEPH, cardiopulmonary comorbidities may be present, however their severity should not explain the severity of symptoms [16]. Patients who pose a particular challenge in this regard are elderly patients who have a haemodynamic profile which is clearly consistent with precapillary PH, but who have relevant cardiovascular comorbidities. The term "atypical PAH" was coined in recent publications for these types of PAH [17], but "PAH with comorbidities" may be a better term. These patients are assigned to Group I according to the Nice classification, but contrast with "classical" PAH patients who are younger/do not have significant cardiopulmonary comorbidities. A distinct classification of patients according to these criteria should be considered in the context of diagnostic assessment (**Figure 1**) as this may influence therapeutic considerations.

Similarly, patients with SSc may frequently have different forms of PH, which can make an exact classification challenging in individual cases [18,19], necessitating a careful diagnostic work-up [20,21]. The classification of interstitial pulmonary involvement in the presence of PH is particularly difficult in individual SSc patients [22].

Patients with chronic thromboembolic disease

Recent data suggests to define chronic thromboembolic disease (CTD) in contrast to chronic thromboembolic pulmonary hypertension (CTEPH) as a disease with chronic thromboembolic vascular obstruction without pulmonary hypertension. These patients may show an objective functional impairment [23]. Optimal therapy needs to be decided on an individual basis. According to recent studies, in carefully selected patients symptoms and quality of life may improve following pulmonary endarterectomy [24].

Initial Diagnosis

A clinical suspicion of PH is based on both symptoms and test results and a diagnosis of PH is confirmed by targeted clinical investigations. The purpose of these tests is not only to confirm that the haemodynamic criteria of PH are met, but also to characterise the aetiology, and the clinical and

haemodynamic severity of the disease. The interpretation of these tests requires expertise in cardiology, respiratory medicine and imaging, and should be done at expert centres. The diagnostic tests should be selected based on the proposed diagnostic algorithm (**Figure 1**).

Symptoms and physical findings

The symptoms of PH are non-specific and include shortness of breath, fatigue, weakness, angina, dry cough, and syncope. Symptoms at rest are only typical in more advanced cases. The clinical presentation of PH can be affected by diseases that cause PH or are associated with it, and also by concomitant comorbidities. Frequently, PH is still diagnosed late [25-27]. Early diagnosis of this condition could result in a better prognosis in many cases [28]. Thus, it is of great importance that P(A)H be considered when determining the cause of dyspnoea in patients who present with non-specific symptoms. Most patients with PAH have a reduced exercise capacity. However, having a normal exercise capacity (relative to the individually calculated reference values) does not rule out pulmonary vasculopathy in isolated cases, particularly in athletes [29].

The physical signs of PH include left parasternal heave, an accentuated pulmonary component of the second heart sound, a third heart sound, a pansystolic murmur of tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation. Elevated jugular venous pressure, hepatomegaly, ascites, and peripheral oedema may be found in patients with advanced disease.

Electrocardiogram

An electrocardiogram (ECG) may provide indirect evidence of PH with signs of right ventricular (RV) strain or RV hypertrophy. A right deviation of the QRS axis in the extremity leads in patients with exercise dyspnea has been described as a key sign of RV strain which has a high positive predictive value for PH [30,31]. However, ECG changes are less sensitive for PH and a normal ECG does not exclude PH.

Chest radiograph

In many patients with PH the chest radiograph shows abnormalities at the time of diagnosis. Relevant findings may include central pulmonary arterial dilatation, and a ‘pruning’ (loss) of peripheral blood vessels. However, a normal chest radiograph does not exclude PH. The evidence for using conventional chest radiographs to diagnose PH is weak.

Transthoracic echocardiography

Transthoracic echocardiography plays a central role in the diagnostic work-up of PH because it visualises cardiac alterations caused by PH and makes it possible to estimate the systolic PAP (sPAP) through continuous wave Doppler measurements. The ESC/ERS guidelines recommend grading the probability of PH as high, intermediate or low, based on the measured tricuspid regurgitation velocity (TRV) at rest and on the presence of additional echocardiographic variables that suggest PH. Based on these echocardiographic parameters and the clinical context, a decision should be made about whether right heart catheterisation (RHC) is necessary.

Although echocardiography is undoubtedly the most important non-invasive test for diagnosing PH, it also has its limitations. Even in tests performed by experienced specialists, only 90% of patients with PH had tricuspid regurgitation [32], which means that it cannot always be used to estimate the sPAP. In certain comorbidities (e.g. pulmonary emphysema), the examination quality is limited, which can produce uncertainty when interpreting echocardiographic readouts [33]. Recently described standard values for echocardiographic right heart parameters promote the detection of pathological changes [34-36], but echocardiographic thresholds have not yet been established for all parameters (e.g. diameter of the central pulmonary artery).

The chart proposed in the current ESC/ERS guidelines for establishing the probability of PH seems practical, but it has not been scientifically evaluated or validated for PH. Current data from a large retrospective analysis confirm that (in experienced hands) determining the sPAP using the TRV and estimated right atrial pressure correlates well with the invasively measured values (r=0.87), and – when the suggested threshold (36 mmHg) is used – it has a specificity of 79% and a sensitivity of 87% [37]. However, in routine clinical practice, large deviations can occur in individual cases [38]: In symptomatic patients with a clinical suspicion of PH, the diagnosis of PH is missed by echocardiography in 10-30% of cases, even if indirect signs are taken into consideration [20,26,32]. For these reasons, further diagnostic testing (e.g. cardiopulmonary exercise testing) should be considered for symptomatic patients with risk factors for PAH or CTEPH, even if the echocardiographic probability for PH is low. In the last few years, echocardiographic tissue Doppler parameters such as strain and strain rate imaging have proven to be prognostically relevant in PAH [39-41], but they need to be prospectively evaluated and better standardized. Echocardiography will also fail to detect chronic thromboembolic disease without pulmonary hypertension at rest (CTED).

Pulmonary function tests (PFT) and arterial blood gas analysis

PFTs and arterial blood gas analysis provide evidence of underlying airway or parenchymal lung diseases and can be helpful in terms of establishing a differential diagnosis. Patients with idiopathic PAH (IPAH) typically have low normal or lowered partial pressure of carbon dioxide (pCO_2) values (33±4 mmHg). In contrast, PH-HFpEF (heart failure with preserved ejection fraction) is associated with normal pCO_2 values (40±5 mmHg). A cut-off value of 36 mmHg might be helpful for distinguishing between these two entities, which are often difficult to seperate, and it can correspondingly impact further diagnostic testing [42]. In addition, hypocapnia as assessed by blood gas analysis appears to be a predictor of an unfavourable disease course [43].

Elevated pCO_2 values (>45 mmHg) and/or elevated bicarbonate values (especially in overweight patients) should involve an assessment for possible obesity hypoventilation syndrome (OHS) [44]. For the diagnosis of sleep-related respiratory disorders, cardiorespiratory polygraphy, including overnight blood gas analysis or transcutaneous capnometry should be conducted and where necessary followed by polysomnography. Overnight oximetry alone is not sufficient to diagnose hypercapnic disorders and to distinguish between an underlying obstructive sleep apnoea and a central sleep apnoea due to PH. The prevalence of a hypoxic sleep disorder was very high in a recent study in patients with precapillary PH [45].

The vital capacity (VC) and forced expiratory volume in one second (FEV1) may also be reduced in PH patients as a result of respiratory muscle limitation [46], and may improve again after non-invasive ventilatory support (see non-invasive ventilation in OHS) [44].

Ventilation/perfusion (V/Q) lung scan

V/Q lung scintigraphy should be performed in patients with PH to definitely exclude or diagnose CTEPH. This is important because CTEPH is a potentially curable disease that generally requires a different therapeutic approach, as compared to PAH. Even today V/Q scans remain superior compared with computed tomography (CT) angiography for detecting chronic thromboembolic changes [26,47]. One reason why CTEPH may not be detected by CT angiography may be the lack of the examiners' experience to recognize signs of CTEPH. Both the technical expertise and the general availability of V/Q scintigraphy show a strong regional variability. In doubt, the examination should take place at a PH expert centre. Storing and transmitting findings digitally is preferable to printouts, as are additional single-photon emission CT images compared to purely planar images [48,49].

High-resolution CT of the chest

High-resolution CT of the chest with contrast enhancement helps to identify patients with lung diseases or CTEPH. In addition, chest CT scans play an important role in detecting pulmonary veno-occlusive disease (PVOD) [50]. In recent years, multiple parameters from static or dynamic CT studies have been described, which make it possible to detect PH or even provide a hemodynamic characterisation of a patient. The most frequently investigated parameters are the diameter of the pulmonary artery and its relationship to the diameter of the aorta. Recent studies, suggesting a threshold value of 29 mm for the diameter of the pulmonary artery and a ratio of 1 for the pulmonary artery/aorta diameter [51] were able to identify PH patients with a high sensitivity and specificity based on these simple measurements [52]. In some studies, this method had even greater specificity than that of echocardiography [53]. Using the ratio of the diameter of the pulmonary artery and the aorta may result in incorrect calculations in terms of PH, specifically in older patients with hypertension-related dilatation of the aorta [54]. Dynamic CT scans may provide valuable information about the flow of the contrast agent through the pulmonary arteries, which can be indicative of PH [55,56].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging provides accurate and reproducible assessments of the size, morphology and function of the RV. Newer sequences have also provided a good visualisation of lung perfusion and chronic perfusion defects [57,58]. In addition, hemodynamic parameters correlated well with invasively measured values as documented in right heart catheter-controlled studies, with a high reliability [59-61].

Blood tests, immunology and abdominal ultrasound

Laboratory tests, immunology and abdominal ultrasound are not primarily used to diagnose PH, but are necessary to determine the aetiology of PH subgroups, and to identify end organ damage. A variety of diagnostic and prognostic biomarkers have been described in the area of PH in recent years [62,63]. Although some of these biomarkers could possibly be used in routine clinical practice in the future, to date none have outperformed N-terminal pro-brain natriuretic peptide (NT-proBNP) or BNP. The combinations of different biomarkers (coupled with clinical parameters) appear promising, and in the future will likely help improve their prognostic value [64].

Right heart catheterisation (RHC)

RHC is essential for confirming a diagnosis of PAH or CTEPH, for assessing the severity of hemodynamic impairment, and for vasoreactivity testing of the pulmonary circulation in selected patients.

Suboptimally treated cardiac or pulmonary disease, such as coronary heart disease, arterial hypertension, congestive heart failure, COPD or sleep apnoea, can considerably influence the hemodynamics in the pulmonary circulation. In order to obtain an accurate picture of hemodynamics during RHC, any pre-existing medical conditions should be optimally controlled at the time of RHC. This applies in particular to anti-hypertensive, anti-obstructive, and diuretic therapies. Diagnostic RHC should be performed only after these therapies have been optimised.

RHC is an invasive test that has very low complication rates at experienced centres [65]. There are “typical” sources of errors that can greatly affect the measurements. One of the most significant errors is incorrectly determining the zero reference level. According to current recommendations, this should be at mid-chest level in the supine position [66,67]. Other zero levels may falsify the test results and thus lead to an incorrect diagnosis. Pulmonary pressures should be measured either at the end of expiration during continuous breathing or by averaging the values over 3-4 respiratory cycles. Calculating PVR is important because current ESC/ERS guidelines require this parameter to diagnose PAH. If mixed venous oxygen saturation shows a pathological increase, serial oximetry is needed for the detection of rare anomalous connections of the pulmonary veins or a systemic-to-pulmonary shunt (e.g. atrial septal defect). In these cases, an increase in oxygen saturation in the pulmonary artery is observed.

In order to identify patients who can be treated with calcium channel blockers, pulmonary vasoreactivity testing should be performed in patients with IPAH, HPAH and drug-induced PAH, but not in patients with associated forms of PAH or in patients with other forms of PH. Worldwide, vasoreactivity tests are most often performed using nitric oxide (NO), but inhaled iloprost can also be used to identify acute responders [68,69]. For NO, the maximum effect of pulmonary vasodilation is achieved during inhalation, while this effect is observed for iloprost during the first 5 minutes after the end of the inhalation (in a few cases minimum PAP values may be observed up to 30 minutes after inhalation). A recent study showed that the vasodilatory reserve determined in the context of vasoreactivity testing may have prognostic relevance in non-responders as well [70]. A volume challenge during RHC is a promising approach which may unmask latent left heart failure in unclear clinical situations [71], but is currently not recommended due to partially contradictory results and a lack of standardisation.

Additional left heart catheterisation including measurement of the left ventricular enddiastolic pressure and coronary angiography is recommended in PH patients with a relevant cardiovascular risk profile, and generally also in patients with PH secondary to left heart disease.

Diagnostic algorithm: Concept of the current ESC/ERS guidelines

According to the ESC/ERS guidelines, the diagnostic process **(Figure 1)** starts with the suspicion of PH on the basis of medical history, symptoms, clinical findings, and echocardiography results compatible with PH. In the event of a low probability of PH based on echocardiography, no additional investigations are necessary according to the PH guidelines, and other causes for the symptoms should be considered together with follow-up monitoring. If echocardiography indicates a high or intermediate probability of PH, the guidelines recommend considering relevant left heart disease (PH group 2) or lung disease (PH group 3) by additional evaluation of risk factors, ECG, blood gas analysis, PFT, chest radiograph, and high-resolution CT. If a significant left heart disease or lung disease is confirmed, appropriate treatment for this disease should be initiated. In the presence of severe PH and/or RV dysfunction, patients should be referred to a PH expert centre for further evaluation.

If no significant left heart disease or lung disease is found, V/Q scintigraphy should be performed to obtain a differential diagnosis between CTEPH and PAH. At the same time, affected patients should be referred to a PH expert centre. If the V/Q scintigraphy shows segmental perfusion defects, this suggests Group 4 PH (CTEPH). As even in CTEPH patients left heart disease and chronic obstructive pulmonary disease may appear as coexistent comorbidities, differential diagnosis may be challenging and needs careful evaluation [72]. The final diagnosis of CTEPH (and the assessment of suitability for pulmonary endarterectomy or balloon pulmonary angioplasty) will require CT pulmonary angiography, RHC and selective pulmonary angiography.

PAH is characterised by an unremarkable or a diffuse heterogeneous appearance on perfusion scintigraphy. PAH should be considered in particular if there are associated conditions and/or risk factors for the development of PAH, such as a positive family history, connective tissue disease, congenital heart defects, human immunodeficiency virus infection, portal hypertension or a history of the use of drugs or toxins known to induce PAH. A hemodynamic diagnosis is made by means of RHC. By using additional specific diagnostic tests, including haematology, clinical chemistry, immunology, serology, ultrasonography and genetics, the final diagnosis can be refined.

Comments: Specific diagnostic questions and recommendations

Thoroughness of testing

In practice, the diagnostic algorithm is often not fully completed (only 6% of patients undergo all of the recommended tests). Forty-three percent of patients do not receive V/Q scintigraphy to exclude CTEPH [73]. Given this current state of practice, emphasis should be placed on following all of the steps of the diagnostic algorithm.

Screening of asymptomatic patients at risk of PH continues to be recommended only for patients with connective tissue disorders and first-degree relatives of patients with hereditary PAH.

The outcomes from the paediatric TOPP (Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension) registry have shown that ECG, chest radiography and echocardiography were the most frequently performed non-invasive diagnostic tests. Of all of the 456 patients enrolled, none of the patients with PH had normal results for all three tests, suggesting the potential diagnostic value of using a combination of straightforward tests and the importance of a comprehensive work-up [74]. The transferability of these results to adults is unknown.

Central role of echocardiography

Echocardiography is a key component of the current diagnostic algorithm, determining whether a further diagnostic work-up for PH should be conducted. In routine clinical practice a number of "upstream" tests, e.g. those performed for a diagnostic clarification of dyspnoea, may indicate the presence of PH and deserve consideration. In symptomatic patients with risk factors for PAH or CTEPH, even if the echocardiographic probability is low, a further diagnostic test (e.g. cardiopulmonary exercise testing – see below) should be considered because PH may be missed on echocardiography (see comments on echocardiography) [20,32,75].

Role of exercise testing in diagnosing PH

Exercise tests are not mentioned in great detail in the current ESC/ERS guidelines in the context of diagnosing PH. However, recent studies indicate that ***cardiopulmonary exercise testing (CPET)*** *can be used not only to estimate the prognosis of patients with confirmed PH [76,77], but it may also be helpful to detect precapillary PH [78]. A decreased peak oxygen uptake, signs of inefficient ventilation (elevated ventilatory equivalent for CO_2 (VE/VCO_2), reduced end-tidal CO_2 pressure ($PETCO_2$) without a ventilatory cause) and particularly, pathological alveolar/arterial gas differences for O_2 and CO_2 have been described for PAH and CTEPH patients [75,79,80]. CPET may prove objective functional limitation and detect ineffective ventilation and gas exchange disturbance in patients with CTED [23]. In patients with SSc the pattern of findings differs between those with PAH and those with LV dysfunction [80]. Similarly, in patients with pulmonary diseases and mild PH, a lowered VE/VCO_2 slope*

*and higher $PETCO_2$ values are to be expected, compared to patients with severe PH and concomitant lung disease [81]. Therefore, CPET is able to provide important information for differential diagnostic considerations of patients with PH and cardiac and/or pulmonary diseases. An increase in the difference between arterial and end-tidal CO_2 partial pressures is clinically valuable, in particular, when diagnosing CTEPH [75] and for differentiating between IPAH and CTEPH [82]. In a retrospective study, CPET was also helpful for identifying CTEPH in patients with unspecific echocardiographic findings [75]. Thus, CPET may constitute a valuable complementary test. There is no single perfect CPET parameter that sufficiently confirms a suspected diagnosis of PH. Rather, it is the overall pattern assessment of characteristic changes in several specific parameters that is required. Since CPET thus provides significant additional information in the diagnostic work-up of suspected PH, it has been included in the proposed diagnostic algorithm of the Cologne Consensus Conference (**Figure 1**).*

***Exercise echocardiography** is a promising technique that is being used at PAH centres in the context of clinical trials [83]. Exercise echocardiography may help to non-invasively detect an excessive pulmonary pressure increase during exercise, which may be a reason for closer monitoring in risk groups for PH [84,85]. In addition, exercise echocardiography may increase the sensitivity of detecting PH in SSc compared to echocardiography conducted at rest, but with reduced specificity [86]. Relevant left heart involvement in particular may be the reason for exercise-induced increase in PAP, rather than PAH. So far, there have been insufficient data to establish diagnostic or therapeutic consequences based on exercise echocardiography. In addition to its potential diagnostic value, exercise echocardiography may have prognostic significance in PH patients by assessing the pulmonary arterial pressure increase and estimating the right ventricular contractile reserve during exercise [87].*

Diagnostic work-up in patients with CTEPH and comorbidities

V/Q scintigraphy is primarily recommended to be performed after the exclusion of cardiopulmonary diseases. However, significant cardiopulmonary diseases may be present as comorbidities in patients with CTEPH [72]. Because CTEPH is potentially curable, the indication for V/Q scintigraphy of the lung in symptomatic patients with risk factors for CTEPH should be kept wide, even if the medical history and/or non-invasive tests suggest PH due to lung or left heart diseases. If there is no sufficient improvement upon treatment of the underlying disease in these patients, re-evaluation of PH aetiology, particularly for CTEPH, is advisable.

Diagnostic genetic testing

For the first time, diagnostic molecular genetic testing and genetic counselling have been included in the ESC/ERS guidelines as an important new element of patient care [1]. Both are subject to strict local regulations and patients must receive comprehensive genetic counselling before testing. Patients with idiopathic or familial PAH or PVOD/pulmonary capillary haemangiomatosis (PCH) should be informed about the possibility of genetic counselling and testing, because of their increased probability of having a mutation. A recent study showed, that genetic counselling is still hardly used in clinical practice, possibly due to lack of knowledge and awareness [88].

Genetic testing and counselling should only be performed by specifically trained professionals and should in the first instance include testing for mutations of the genes that encode BMPR2 (bone morphogenetic protein receptor type 2), ALK1 (activin receptor-like kinase 1) and endoglin. If the tests are negative, testing for other genes such as KCNK3 (potassium channel subfamily K member 3) or CAV1 (caveolin 1) can be considered. According to the ESC/ERS guidelines, patients with idiopathic or familial PVOD/PCH should be tested for EIF2AK4 (eukaryotic translation initiation factor 2 alpha kinase 4) mutations [89].

In addition to patients with IPAH, HPAH, appetite suppressant-induced PAH, or PVOD/PCH, patients with CHD-APAH (congenital heart disease-associated PAH), CTEPH or paediatric PAH may also benefit from genetic counselling and testing [90,91].

Genetic testing should be expanded to other less commonly affected genes [90]. New screening methods, such as next generation sequencing may be used to analyse selected candidate genes more quickly and at a lower cost [92]. It appears that this method may replace conventional Sanger sequencing of the main genes BMPR2, endoglin and ALK1 in the future. The occurrence of two or more mutations in one patient may explain the different penetrance and clinical manifestation of the disease in the sense of the "second-hit" hypothesis [93,94].

In addition to receiving genetic testing and counselling, it is recommended that patients at a higher risk for developing PH, such as BMPR2 mutation carriers or relatives of patients with a mutation, be offered a clinical screening test. BMPR2 mutation carriers have a lifetime risk of developing PAH of approximately 20% [95]. It is not currently possible to predict who will ultimately develop PAH, although women are at a higher risk than men [96]. Annual echocardiographic screening tests are currently being offered to asymptomatic individuals with a PAH-related mutation and to first-degree family members of HPAH patients who do not carry any known mutations.

Clinical testing of high-risk patients using exercise echocardiography might help to detect the disease earlier. It has already been shown that family members of PAH patients have an abnormally high increase in PAP during exercise significantly more often than healthy controls [97]. In a large HPAH

family that was tracked over a period of 12 years, a clinical manifestation of the disease occurred only in those family members who carried a mutation and had previously exhibited an increase in sPAP during exercise [98].

Conflicts of interest / Author disclosures

GK: received fees for lectures and/or consulting from Actelion, Bayer, GSK, MSD, Novartis, Pfizer, Chiesi, Boehringer-Ingelheim

DD: received fees for lectures and/or consulting from Actelion, Bayer, GSK, Novartis, Pfizer, Servier

AB: none reported

SG: none reported

EG: received fees for lectures and/or consulting from Actelion, Bayer, GSK, MSD, Novartis, Pfizer, United Therapeutics

AH: received fees for lectures and/or consulting from Actelion, AOP Orphan Pharmaceuticals, Encysive, GSK, Lilly, OMT, Pfizer, Novartis

TK: received fees for lectures and/or consulting from Actelion, Bayer, GSK

RKF: none reported

IK: none reported

AEL: received fees for lectures and/or consulting from Actelion

DM: none reported

AM: none reported

JM: none reported

SP: none reported

HJS: received fees for lectures and/or consulting from Actelion, Bayer, GSK

CS: none reported

SS: none reported

GS: none reported

HW: received fees for lectures and/or consulting from Actelion, Bayer, Boehringer, GSK, Pfizer, Roche

MH: received fees for lectures and/or consulting from Actelion, Bayer, Berlin Chemie, Boehringer, GSK, MSD, Novartis, Pfizer, United Therapeutics

Table 1. Detailed clinical classification of pulmonary hypertension [1].

1. Pulmonary arterial hypertension	➢ idiopathic
	➢ heritable (BMPR2 or other mutation)
	➢ drugs or toxins induced
	➢ associated with
	  ➢ connective tissue disease
	  ➢ HIV infection
	  ➢ portal hypertension
	  ➢ congenital heart disease
	  ➢ schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis	➢ idiopathic ➢ heritable (EIF2AK4 or other mutation) ➢ drugs/toxins/radiation induced ➢ associated with connective tissue disease or HIV infection
1''. Persistent pulmonary hypertension of the newborn	
2. Pulmonary hypertension due to left heart disease	➢ left ventricular systolic dysfunction ➢ left ventricular diastolic dysfunction ➢ valvular disease ➢ congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies ➢ congenital /acquired pulmonary vein stenosis
3. Pulmonary hypertension due to lung diseases and/or hypoxia	➢ chronic obstructive pulmonary disease ➢ interstitial lung disease ➢ other pulmonary diseases with mixed restrictive and obstructive pattern ➢ sleep-disordered breathing ➢ alveolar hypoventilation syndromes ➢ chronic exposure to high altitude ➢ developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions	➢ chronic thromboembolic pulmonary hypertension
	➢ other pulmonary artery obstructions
	  ➢ angiosarcoma
	  ➢ other intravascular tumours
	  ➢ arteritis
	  ➢ congenital pulmonary artery stenosis
	  ➢ parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms	➢ haematological disorders (chronic haemolytic anaemia, myeloproliferative disorders, splenectomy) ➢ systemic disorders (sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis) ➢ metabolic disorders (glycogen storage disease, Gaucher disease, thyroid disorders) ➢ others (pulmonary tumoral thrombotic microangiopathy, fibrosing

mediastinitis, chronic renal failure with/without dialysis, segmental pulmonary hypertension)

BMPR2: bone morphogenic protein receptor type 2, EIF2AK4: eukaryotic translation initiation factor 2 alpha kinase 4

Figure legend

Figure 1. Proposed diagnostic algorithm in case of suspected pulmonary hypertension, according to the 2016 Cologne Consensus Conference (modified from [1]).

* PAH, differentiation of typical/atypical PAH

[a]In case of echocardiographic evidence of PH, even in patients who show signs of PH due to left heart or lung disease according to tests, an exclusion of CTEPH by scintigraphy should be considered in the presence of typical risk factors for CTEPH.

[b]In case of echocardiographic evidence of PH, even in patients who show signs of PH due to left heart or lung disease according to tests, consultation with a PH expert centre should be considered in the presence of risk factors for PAH if there is uncertainty as to whether these constitute a cause or comorbidity.

PH: pulmonary hypertension, CTEPH: chronic thromboembolic pulmonary hypertension, DLCO: diffusing capacity for carbon monoxide, PAH: pulmonary arterial hypertension, PVOD: pulmonary veno-occlusive disease, PCH: pulmonary capillary haemangiomatosis, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial Wedge pressure, PVR: pulmonary vascular resistance. Original version from [1].

References

[1] Galie N, Humbert M, Vachiery JL*, et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46:903-975.

[2] Hoeper MM, Bogaard HJ, Condliffe R*, et al.* Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013; 62:D42-50.

[3] Kovacs G, Avian A, Tscherner M*, et al.* Characterization of patients with borderline pulmonary arterial pressure. Chest 2014; 146:1486-1493.

[4] Heresi GA, Minai OA, Tonelli AR*, et al.* Clinical characterization and survival of patients with borderline elevation in pulmonary artery pressure. Pulm Circ 2013; 3:916-925.

[5] Maron BA, Hess E, Maddox TM*, et al.* Association of Borderline Pulmonary Hypertension With Mortality and Hospitalization in a Large Patient Cohort: Insights From the VA-CART Program. Circulation 2016.

[6] Valerio CJ, Schreiber BE, Handler CE, Denton CP, Coghlan JG. Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. Arthritis Rheum 2013; 65:1074-1084.

[7] Lau EM, Godinas L, Sitbon O*, et al.* Resting pulmonary artery pressure of 21-24 mmHg predicts abnormal exercise haemodynamics. Eur Respir J 2016; 47:1436-1444.

[8] Herve P, Lau EM, Sitbon O*, et al.* Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J 2015; 46:728-737.

[9] Naeije R, Vanderpool R, Dhakal BP*, et al.* Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. Am J Respir Crit Care Med 2013; 187:576-583.

[10] Lau EM, Chemla D, Whyte K, Kovacs G, Olschewski H, Herve P. Does exercise pulmonary hypertension exist? Curr Opin Pulm Med 2016; 22:400-407.

[11] Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. Circulation 2009; 119:2663-70.

[12] Stamm A, Saxer S, Lichtblau M*, et al.* Exercise pulmonary haemodynamics predict outcome in patients with systemic sclerosis. Eur Respir J 2016.

[13] Hebert A, Mikkelsen UR, Thilen U*, et al.* Bosentan improves exercise capacity in adolescents and adults after Fontan operation: the TEMPO (Treatment With Endothelin Receptor Antagonist in Fontan Patients, a Randomized, Placebo-Controlled, Double-Blind Study Measuring Peak Oxygen Consumption) study. Circulation 2014; 130:2021-2030.

[14] 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; 168:871-880.

[15] Badesch DB, Raskob GE, Elliott CG*, et al.* Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010; 137:376-387.

[16] Seeger W, Adir Y, Barbera JA*, et al.* Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol 2013; 62:D109-16.

[17] Opitz CF, Hoeper MM, Gibbs JS*, et al.* Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension: A Pathophysiological Continuum. J Am Coll Cardiol 2016; 68:368-378.

[18] Giordano N, Montella A, Corallo C*, et al.* Pulmonary hypertension: a correct diagnosis for a suitable therapy in scleroderma patients. Clin Exp Rheumatol 2015; 33:S182-9.

[19] Avouac J, Airo P, Meune C*, et al.* Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010; 37:2290-2298.

[20] Coghlan JG, Denton CP, Grunig E*, et al.* Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014; 73:1340-1349.

[21] Visovatti SH, Distler O, Coghlan J*, et al.* Borderline pulmonary arterial pressure in systemic sclerosis patients: a post-hoc analysis of the DETECT study. Arthritis Res Ther 2014; 16:493.

[22] Fischer A, Swigris JJ, Bolster MB*, et al.* Pulmonary hypertension and interstitial lung disease within PHAROS: impact of extent of fibrosis and pulmonary physiology on cardiac haemodynamic parameters. Clin Exp Rheumatol 2014; 32:S-109-14.

[23] Held M, Kolb P, Grun M*, et al.* Functional Characterization of Patients with Chronic Thromboembolic Disease. Respiration 2016; 91:503-509.

[24] Taboada D, Pepke-Zaba J, Jenkins DP*, et al.* Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. Eur Respir J 2014; 44:1635-1645.

[25] Rich S, Dantzker DR, Ayres SM*, et al.* Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987; 107:216-223.

[26] Held M, Grun M, Holl R*, et al.* Chronic thromboembolic pulmonary hypertension: Time delay from onset of symtoms to diagnosis and clinical condition at diagnosis. Dtsch Med Wochenschr 2014; 139:1647-1652.

[27] Mayer E, Jenkins D, Lindner J*, et al.* Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. J Thorac Cardiovasc Surg 2011; 141:702-710.

[28] Humbert M, Yaici A, de Groote P*, et al.* Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011; 63:3522-3530.

[29] Dumitrescu D, Gerhardt F, Viethen T, Schmidt M, Mayer E, Rosenkranz S. Case report: Subjective loss of performance after pulmonary embolism in an athlete- beyond normal values. BMC Pulm Med 2016; 16:21-016-0180-x.

[30] Al-Naamani K, Hijal T, Nguyen V, Andrew S, Nguyen T, Huynh T. Predictive values of the electrocardiogram in diagnosing pulmonary hypertension. Int J Cardiol 2008; 127:214-218.

[31] Kovacs G, Avian A, Foris V*, et al.* Use of ECG and Other Simple Non-Invasive Tools to Assess Pulmonary Hypertension. PLoS One 2016; 11:e0168706.

[32] Held M, Linke M, Jany B. Echocardiography and right heart catheterization in pulmonal hypertension. Dtsch Med Wochenschr 2014; 139:1511-1517.

[33] Fisher MR, Criner GJ, Fishman AP*, et al.* Estimating pulmonary artery pressures by echocardiography in patients with emphysema. Eur Respir J 2007; 30:914-21.

[34] D'Andrea A, Naeije R, Grunig E*, et al.* Echocardiography of the pulmonary circulation and right ventricular function: exploring the physiologic spectrum in 1,480 normal subjects. Chest 2014; 145:1071-1078.

[35] Grunig E, Henn P, D'Andrea A*, et al.* Reference values for and determinants of right atrial area in healthy adults by 2-dimensional echocardiography. Circ Cardiovasc Imaging 2013; 6:117-124.

[36] Lang RM, Badano LP, Mor-Avi V*, et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16:233-270.

[37] Greiner S, Jud A, Aurich M*, et al.* Reliability of noninvasive assessment of systolic pulmonary artery pressure by Doppler echocardiography compared to right heart catheterization: analysis in a large patient population. J Am Heart Assoc 2014; 3:10.1161/JAHA.114.001103.

[38] Fisher MR, Forfia PR, Chamera E*, et al.* Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179:615-21.

[39] Kittipovanonth M, Bellavia D, Chandrasekaran K, Villarraga HR, Abraham TP, Pellikka PA. Doppler myocardial imaging for early detection of right ventricular dysfunction in patients with pulmonary hypertension. J Am Soc Echocardiogr 2008; 21:1035-1041.

[40] Sachdev A, Villarraga HR, Frantz RP*, et al.* Right ventricular strain for prediction of survival in patients with pulmonary arterial hypertension. Chest 2011; 139:1299-1309.

[41] Haeck ML, Scherptong RW, Marsan NA*, et al.* Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. Circ Cardiovasc Imaging 2012; 5:628-636.

[42] Olsson KM, Sommer L, Fuge J, Welte T, Hoeper MM. Capillary pCO2 helps distinguishing idiopathic pulmonary arterial hypertension from pulmonary hypertension due to heart failure with preserved ejection fraction. Respir Res 2015; 16:34-015-0194-6.

[43] Hoeper MM, Pletz MW, Golpon H, Welte T. Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2007; 29:944-950.

[44] Held M, Walthelm J, Baron S, Roth C, Jany B. Functional impact of pulmonary hypertension due to hypoventilation and changes under noninvasive ventilation. Eur Respir J 2014; 43:156-165.

[45] Jilwan FN, Escourrou P, Garcia G, Jais X, Humbert M, Roisman G. High occurrence of hypoxemic sleep respiratory disorders in precapillary pulmonary hypertension and mechanisms. Chest 2013; 143:47-55.

[46] Meyer FJ, Lossnitzer D, Kristen AV*, et al.* Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. Eur Respir J 2005; 25:125-130.

[47] Tunariu N, Gibbs SJ, Win Z*, et al.* Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med 2007; 48:680-684.

[48] Bajc M, Neilly JB, Miniati M*, et al.* EANM guidelines for ventilation/perfusion scintigraphy : Part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. Eur J Nucl Med Mol Imaging 2009; 36:1356-1370.

[49] Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan M, Jonson B. EANM guidelines for ventilation/perfusion scintigraphy : Part 2. Algorithms and clinical considerations for diagnosis of pulmonary emboli with V/P(SPECT) and MDCT. Eur J Nucl Med Mol Imaging 2009; 36:1528-1538.

[50] Montani D, Lau EM, Dorfmuller P*, et al.* Pulmonary veno-occlusive disease. Eur Respir J 2016.

[51] Truong QA, Massaro JM, Rogers IS*, et al.* Reference values for normal pulmonary artery dimensions by noncontrast cardiac computed tomography: the Framingham Heart Study. Circ Cardiovasc Imaging 2012; 5:147-154.

[52] Dornia C, Lange TJ, Behrens G*, et al.* Multidetector computed tomography for detection and characterization of pulmonary hypertension in consideration of WHO classification. J Comput Assist Tomogr 2012; 36:175-180.

[53] Iyer AS, Wells JM, Vishin S, Bhatt SP, Wille KM, Dransfield MT. CT scan-measured pulmonary artery to aorta ratio and echocardiography for detecting pulmonary hypertension in severe COPD. Chest 2014; 145:824-832.

[54] Ng CS, Wells AU, Padley SP. A CT sign of chronic pulmonary arterial hypertension: the ratio of main pulmonary artery to aortic diameter. J Thorac Imaging 1999; 14:270-278.

[55] Pienn M, Kovacs G, Tscherner M*, et al.* Non-invasive determination of pulmonary hypertension with dynamic contrast-enhanced computed tomography: a pilot study. Eur Radiol 2014; 24:668-676.

[56] Pienn M, Kovacs G, Tscherner M*, et al.* Determination of cardiac output with dynamic contrast-enhanced computed tomography. Int J Cardiovasc Imaging 2013; 29:1871-1878.

[57] Rajaram S, Swift AJ, Telfer A*, et al.* 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. Thorax 2013; 68:677-678.

[58] Wirth G, Bruggemann K, Bostel T, Mayer E, Duber C, Kreitner KF. Chronic Thromboembolic Pulmonary Hypertension (CTEPH) - Potential Role of Multidetector-Row CT (MD-CT) and MR Imaging in the Diagnosis and Differential Diagnosis of the Disease. Rofo 2014.

[59] Kreitner KF, Wirth GM, Krummenauer F*, et al.* Noninvasive assessment of pulmonary hemodynamics in patients with chronic thromboembolic pulmonary hypertension by high temporal resolution phase-contrast MRI: correlation with simultaneous invasive pressure recordings. Circ Cardiovasc Imaging 2013; 6:722-729.

[60] Swift AJ, Rajaram S, Hurdman J*, et al.* Noninvasive estimation of PA pressure, flow, and resistance with CMR imaging: derivation and prospective validation study from the ASPIRE registry. JACC Cardiovasc Imaging 2013; 6:1036-1047.

[61] Reiter G, Reiter U, Kovacs G, Olschewski H, Fuchsjager M. Blood Flow Vortices along the Main Pulmonary Artery Measured with MR Imaging for Diagnosis of Pulmonary Hypertension. Radiology 2015; 275:71-79.

[62] Foris V, Kovacs G, Tscherner M, Olschewski A, Olschewski H. Biomarkers in pulmonary hypertension: what do we know? Chest 2013; 144:274-283.

[63] Tiede SL, Gall H, Dorr O*, et al.* New potential diagnostic biomarkers for pulmonary hypertension. Eur Respir J 2015; 46:1390-1396.

[64] Calvier L, Legchenko E, Grimm L*, et al.* Galectin-3 and aldosterone as potential tandem biomarkers in pulmonary arterial hypertension. Heart 2016; 102:390-396.

[65] 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; 48:2546-2552.

[66] Kovacs G, Avian A, Olschewski A, Olschewski H. Zero reference level for right heart catheterisation. Eur Respir J 2013; 42:1586-1594.

[67] Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. Am J Respir Crit Care Med 2014; 190:252-257.

[68] Jing ZC, Jiang X, Han ZY*, et al.* Iloprost for pulmonary vasodilator testing in idiopathic pulmonary arterial hypertension. Eur Respir J 2009; 33:1354-1360.

[69] Opitz CF, Rubin LJ. Acute vasodilator testing in idiopathic pulmonary arterial hypertension: must we take NO for the answer? Eur Respir J 2009; 33:1247-1249.

[70] Leuchte HH, Baezner C, Baumgartner RA, Muehling O, Neurohr C, Behr J. Residual pulmonary vasodilative reserve predicts outcome in idiopathic pulmonary hypertension. Heart 2015; 101:972-976.

[71] D'Alto M, Romeo E, Argiento P*, et al.* Clinical Relevance of Fluid Challenge in Patients Evaluated for Pulmonary Hypertension. Chest 2017; 151:119-126.

[72] Pepke-Zaba J, Delcroix M, Lang I*, et al.* Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011; 124:1973-1981.

[73] McLaughlin VV, Langer A, Tan M*, et al.* Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: an initiative to close the care gap. Chest 2013; 143:324-332.

[74] Beghetti M, Berger RM, Schulze-Neick I*, et al.* Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice. Eur Respir J 2013; 42:689-700.

[75] Held M, Grun M, Holl R*, et al.* Cardiopulmonary exercise testing to detect chronic thromboembolic pulmonary hypertension in patients with normal echocardiography. Respiration 2014; 87:379-387.

[76] Wensel R, Opitz CF, Anker SD*, et al.* Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation 2002; 106:319-24.

[77] Wensel R, Francis DP, Meyer FJ*, et al.* Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol 2013; 167:1193-1198.

[78] Dumitrescu D, Nagel C, Kovacs G*, et al.* Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. Heart 2017.

[79] Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. Chest 2005; 127:1637-1646.

[80] Dumitrescu D, Oudiz RJ, Karpouzas G*, et al.* Developing pulmonary vasculopathy in systemic sclerosis, detected with non-invasive cardiopulmonary exercise testing. PLoS One 2010; 5:e14293.

[81] Boerrigter BG, Bogaard HJ, Trip P*, et al.* Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. Chest 2012; 142:1166-1174.

[82] Scheidl SJ, Englisch C, Kovacs G*, et al.* Diagnosis of CTEPH versus IPAH using capillary to end-tidal carbon dioxide gradients. Eur Respir J 2012; 39:119-124.

[83] van Riel AC, Opotowsky AR, Santos M*, et al.* Accuracy of Echocardiography to Estimate Pulmonary Artery Pressures With Exercise: A Simultaneous Invasive-Noninvasive Comparison. Circ Cardiovasc Imaging 2017; 10:10.1161/CIRCIMAGING.116.005711.

[84] Grunig E, Janssen B, Mereles D*, et al.* Abnormal pulmonary artery pressure response in asymptomatic carriers of primary pulmonary hypertension gene. Circulation 2000; 102:1145-50.

[85] Condliffe R, Kiely DG, Peacock AJ*, et al.* Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 2009; 179:151-7.

[86] Nagel C, Henn P, Ehlken N*, et al.* Stress Doppler echocardiography for early detection of systemic sclerosis-associated pulmonary arterial hypertension. Arthritis Res Ther 2015; 17:165-015-0673-7.

[87] Grunig E, Tiede H, Enyimayew EO*, et al.* Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. Circulation 2013; 128:2005-2015.

[88] Jacher JE, Martin LJ, Chung WK, Loyd JE, Nichols WC. Pulmonary arterial hypertension: Specialists' knowledge, practices, and attitudes of genetic counseling and genetic testing in the USA. Pulm Circ 2017; 7:372-383.

[89] Eyries M, Montani D, Girerd B*, et al.* EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. Nat Genet 2014; 46:65-69.

[90] Machado RD, Southgate L, Eichstaedt CA*, et al.* Pulmonary Arterial Hypertension: A Current Perspective on Established and Emerging Molecular Genetic Defects. Hum Mutat 2015; 36:1113-1127.

[91] Xi Q, Liu Z, Zhao Z, Luo Q, Huang Z. High Frequency of Pulmonary Hypertension-Causing Gene Mutation in Chinese Patients with Chronic Thromboembolic Pulmonary Hypertension. PLoS One 2016; 11:e0147396.

[92] Song J, Eichstaedt CA, Viales RR*, et al.* Identification of genetic defects in pulmonary arterial hypertension by a new gene panel diagnostic tool. Clin Sci (Lond) 2016; 130:2043-2052.

[93] Viales RR, Eichstaedt CA, Ehlken N*, et al.* Mutation in BMPR2 Promoter: A 'Second Hit' for Manifestation of Pulmonary Arterial Hypertension? PLoS One 2015; 10:e0133042.

[94] Wang G, Knight L, Ji R*, et al.* Early onset severe pulmonary arterial hypertension with 'two-hit' digenic mutations in both BMPR2 and KCNA5 genes. Int J Cardiol 2014; 177:e167-9.

[95] Soubrier F, Chung WK, Machado R*, et al.* Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol 2013; 62:D13-21.

[96] Larkin EK, Newman JH, Austin ED*, et al.* Longitudinal analysis casts doubt on the presence of genetic anticipation in heritable pulmonary arterial hypertension. Am J Respir Crit Care Med 2012; 186:892-896.

[97] Grunig E, Weissmann S, Ehlken N*, et al.* Stress Doppler echocardiography in relatives of patients with idiopathic and familial pulmonary arterial hypertension: results of a multicenter European analysis of pulmonary artery pressure response to exercise and hypoxia. Circulation 2009; 119:1747-57.

[98] Hinderhofer K, Fischer C, Pfarr N*, et al.* Identification of a new intronic BMPR2-mutation and early diagnosis of heritable pulmonary arterial hypertension in a large family with mean clinical follow-up of 12 years. PLoS One 2014; 9:e91374.

Highlights

In the summer of 2016, delegates from the German Society of Cardiology (DGK), the German Respiratory Society (DGP), and the German Society of Pediatric Cardiology (DGPK) met in Cologne, Germany, to define consensus-based practice recommendations for the management of patients with pulmonary hypertension (PH). These recommendations were built on the 2015 European Pulmonary Hypertension guidelines, aiming at their practical implementation, considering country-specific issues, and including new evidence, where available. To this end, a number of working groups was initiated, one of which was specifically dedicated to the definition, clinical classification and initial diagnosis of PH. While the European guidelines provide a detailed clinical classification and a structured approach for diagnostic testing, their application in routine care may be challenging, particularly given the changing phenotype of PH patients who are nowadays often elderly and may present with multiple potential causes of PH, as well as comorbid conditions. Specifically, the working group addresses the thoroughness of diagnostic testing, and the roles of echocardiography, exercise testing, and genetic testing in diagnosing PH. Furthermore, challenges in the diagnostic work-up of patients with various causes of PH including “PAH with comorbidities”, CTEPH and coexisting conditions are highlighted, and a modified diagnostic algorithm is provided. The detailed results and recommendations of the working group on definition, clinical classification and initial diagnosis of PH, which were last updated in the spring of 2018, are summarized in this article.

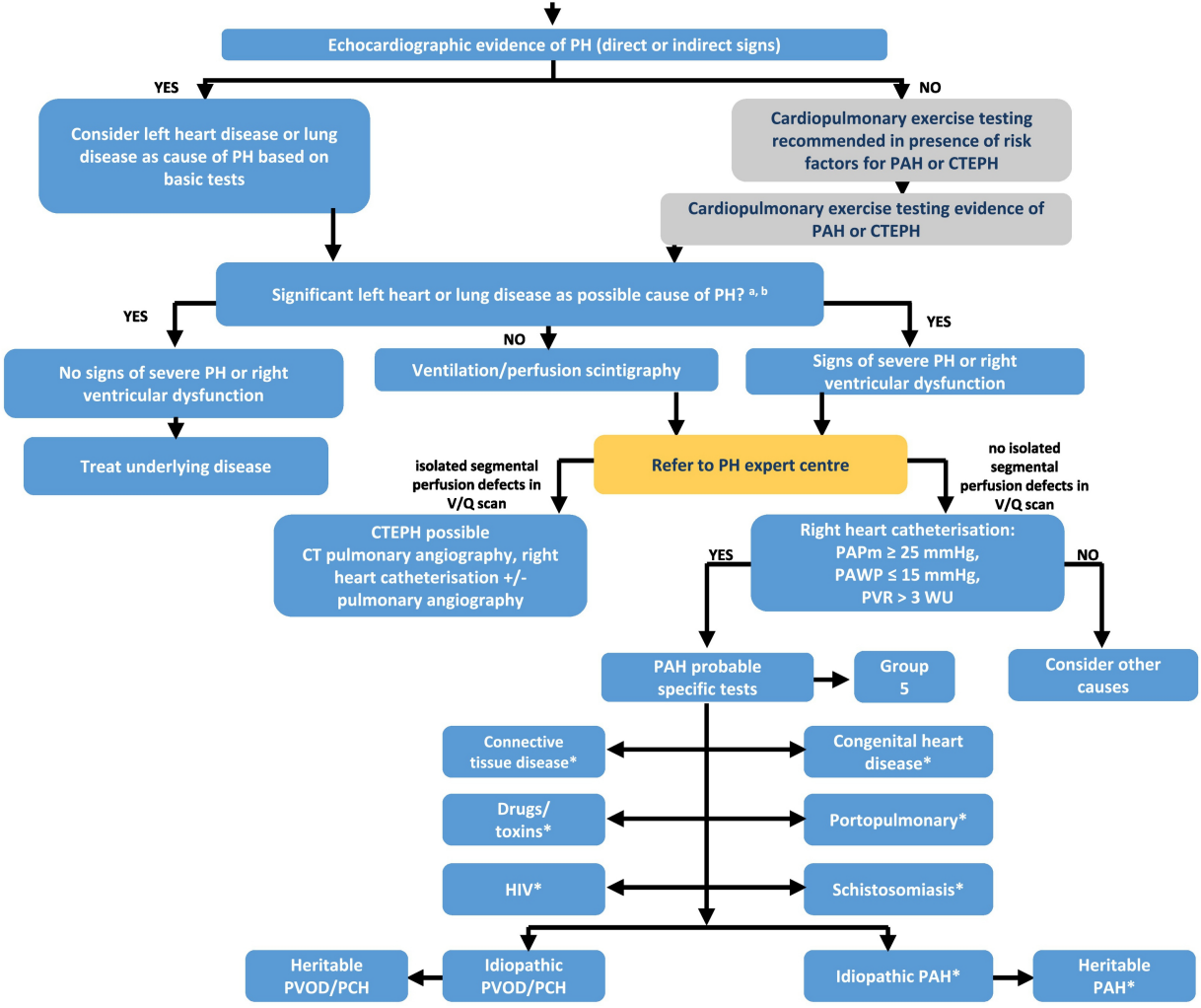

Figure 1