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


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

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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.

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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 × m²) or in relation to systemic vascular resistance (Rₚ/Rₛ) 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 (pCO₂) values (33±4 mmHg). In contrast, PH-HFpEF (heart failure with preserved ejection fraction) is associated with normal pCO₂ 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 separate, 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 pCO₂ 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**

**Thorroughness 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 CO₂ (VE/VCO₂), reduced end-tidal CO₂ pressure (PETCO₂) without a ventilatory cause) and particularly, pathological alveolar/arterial gas differences for O₂ and CO₂ 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/VCO₂ 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

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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
   - valvar 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

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.

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.

References


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.
Echocardiographic evidence of PH (direct or indirect signs)

- **YES**
  - Consider left heart disease or lung disease as cause of PH based on basic tests

- **NO**
  - Cardiopulmonary exercise testing recommended in presence of risk factors for PAH or CTEPH

  - **YES**
    - Cardiopulmonary exercise testing evidence of PAH or CTEPH

  - **NO**
    - Significant left heart or lung disease as possible cause of PH? ^a,^b

      - **YES**
        - No signs of severe PH or right ventricular dysfunction
          - Treat underlying disease

      - **NO**
        - Ventilation/perfusion scintigraphy
          - Refer to PH expert centre
            - isolated segmental perfusion defects in V/Q scan

            - **YES**
              - CTEPH possible
                - CT pulmonary angiography, right heart catheterisation +/- pulmonary angiography

            - **NO**
              - Signs of severe PH or right ventricular dysfunction
                - Right heart catheterisation: PAPm ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 WU
                  - **YES**
                    - PAH probable specific tests
                    - Group 5

                  - **NO**
                    - Consider other causes

- **NO**
  - Refer to PH expert centre
    - no isolated segmental perfusion defects in V/Q scan

- **NO**
  - No signs of severe PH or right ventricular dysfunction

  - Refer to PH expert centre

  - CTEPH possible
    - CT pulmonary angiography, right heart catheterisation +/- pulmonary angiography

  - **NO**
    - Connective tissue disease*
      - Congenital heart disease*
      - Drugs/toxins*
      - Portopulmonary*
      - HIV*
      - Schistosomiasis*
      - Heritable PVOD/PCH
      - Idiopathic PVOD/PCH
      - Heritable PAH*
      - Idiopathic PAH*

*connective tissue disease, congenital heart disease, drugs/toxins, portopulmonary, HIV, schistosomiasis, heritable PVOD/PCH, idiopathic PVOD/PCH, heritable PAH, idiopathic PAH

Figure 1