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Pulmonary hypertension due to chronic lung disease: Updated Recommendations of the Cologne Consensus Conference 2011☆

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ABSTRACT

The 2009 European Guidelines on Pulmonary Hypertension did not cover only pulmonary arterial hypertension (PAH) but also some aspects of pulmonary hypertension (PH) in chronic lung disease. These guidelines point out that the drugs currently used to treat patients with PAH (prostanoids, endothelin receptor antagonists and phosphodiesterase type-5 inhibitors) have not been sufficiently investigated in other forms of PH. Therefore, the use of these drugs in patients with chronic lung disease and PH is not recommended. This recommendation, however, is not always in agreement with medical needs as physicians feel sometimes inclined to also treat other forms of pulmonary hypertension which may affect the quality of life and survival of these patients in a similar manner as in PAH. In June 2010, a consensus conference was held in Cologne, Germany, to discuss open and controversial issues surrounding the practical implementation of the European Guidelines. The conference was sponsored by the German Society of Cardiology, the German Society of Respiratory Medicine and the German Society of Pediatric Cardiology (DGK, DGP and DGPK). To this end, a number of working groups were initiated, one of which was specifically dedicated to the diagnosis and treatment of PH due to chronic lung disease. This manuscript describes in detail the results and recommendations of this working group which were last updated in October 2011.

Preliminary remarks

This article is part of a supplement of the *International Journal of Cardiology* in which the results of a German Consensus Conference on pulmonary hypertension are described that was held in June 2010 in Cologne, Germany, and was organized by the pulmonary hypertension (PH) working groups of the German Societies of Cardiology (Deutsche Gesellschaft für Kardiologie, DGK)

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and Respiratory Medicine (Deutsche Gesellschaft für Pneumologie, DGP) and the German Society of Pediatric Cardiology (Deutsche Gesellschaft für Pädiatrische Kardiologie, DGPK). This conference addressed practical issues surrounding the implementation of the European Guidelines for diagnosis and therapy of pulmonary hypertension in Germany. To this end, a number of working groups were initiated, one of which was specifically dedicated to PH due to chronic lung disease. The authors were members of this working group, and the recommendations were updated in October 2011. Below, the corresponding sections of the European Guidelines are summarized [1–3] whereby comments and additions appear in italics. The information on class of recommendation and level of evidence correspond to the tables listed in the preamble of this supplement.

1. Introduction

The diagnosis and treatment of patients with pulmonary hypertension due to chronic lung disease according to group 3 of the current classification (Table 1) are discussed only briefly in the European guidelines. This article addresses these issues in detail and in some sections falls back on the recommendations of the 4th World Symposium on Pulmonary Hypertension that took place in 2008 in Dana Point, California [4]. Focus is on pulmonary hypertension in chronic obstructive or interstitial lung disease. The other types of pulmonary hypertension associated with lung disease that are listed in Table 1, cannot be discussed in detail. This applies to the diseases listed for group 3 as well as for specific diseases from group 5 such as sarcoidosis or pulmonary Langerhans cell granulomatosis. The statements throughout this article can be applied in principle to all diseases named in groups 3 and 5.

2. Hemodynamic definition of pulmonary hypertension

Pulmonary hypertension has been defined as a mean pulmonary arterial pressure (PAPm) $\geq$25 mmHg. Normal PAPm values are 14 $\pm$ 3 mmHg with an upper limit of normal (defined as mean value + 2 SD) of 20 mmHg [5,6]. The "grey area" between 20 and 25 mmHg at rest has yet to be sufficiently defined. The criterion of increase in PAPm >30 mmHg on exercise that was valid until recently has been abandoned, after a structured review of previously published right heart catheterizations in healthy subjects demonstrated that physiological pressure values on exercise can be much higher, especially in elderly patients [5]. With the currently available data it is not possible to specify a threshold above which an increase in pulmonary pressure on exercise is pathological.

Comment:

The current hemodynamic definition of PH is basically oriented on the previous treatment studies on PH which enrolled only patients with a PAPm $\geq$25 mmHg. Data on PH associated with chronic lung disease which indicated that lower mean pulmonary arterial values could also be of clinical and prognostic significance, was not taken into account (see below). On the other hand, it is not yet clear if the treatment of patients with mildly elevated pulmonary pressure values will provide a clinical benefit. Lower cut-off values would furthermore automatically increase the number of patients who were incorrectly diagnosed with PH or PAH. In view of these uncertainties, the current hemodynamic definition of PH seems justified. Currently, this also applies to the elimination of exercise cut-off values since, at present, it is not possible to determine general cut-off values for pulmonary pressure on exercise on the one hand, and, on the other hand, there is no evidence yet that patients with normal pulmonary pressures at rest but "elevated" pressures on exercise benefit from pulmonary vasodilator therapy at all.

Table 1
Updated clinical classification of pulmonary hypertension (Dana Point, 2008).

1. **Pulmonary arterial hypertension (PAH)**
   - 1.1. Idiopathic PAH
   - 1.2. Heritable PAH
     - 1.2.1. BMPR2 mutations
     - 1.2.2. ALK1, endoglin mutations (with and without hereditary hemorrhagic telangiectasia)
     - 1.2.3. Unknown mutations
   - 1.3. Drugs or toxins induced
   - 1.4. Associated with:
     - 1.4.1. Connective tissue diseases
     - 1.4.2. HIV infection
     - 1.4.3. Portal hypertension
     - 1.4.4. Congenital heart disease
     - 1.4.5. Schistosomiasis
     - 1.4.6. Chronic hemolytic anemia
   - 1.5. Persistent pulmonary hypertension of the newborn

1'. **Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**

2. **Pulmonary hypertension due to left heart disease**
   - 2.1. Systolic dysfunction
   - 2.2. Diastolic dysfunction
   - 2.3. Valvular disease

3. **Pulmonary hypertension due to lung diseases and/or hypoxemia**
   - 3.1. Chronic obstructive pulmonary disease
   - 3.2. Interstitial lung disease
   - 3.3. Other pulmonary diseases with mixed restrictive/obstructive pattern
   - 3.4. Sleep-disordered breathing
   - 3.5. Alveolar hypoventilation syndrome
   - 3.6. Chronic exposure to high altitude
   - 3.7. Developmental abnormalities

4. **Chronic thromboembolic pulmonary hypertension (CTEPH)**

5. **Pulmonary hypertension with unclear or multifactorial mechanisms**
   - 5.1. Hematological disorders: myeloproliferative disorders, splenectomy
   - 5.2. Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on hemodialysis

BMPR-2, bone morphogenetic protein receptor type-2; ALK-1, activin receptor-like kinase 1 gene.

3. Pulmonary hypertension due to chronic lung disease: prevalence and prognostic significance

PH occurs frequently in patients with chronic obstructive lung disease (COPD) as well as in patients with interstitial lung disease (ILD); in some series the prevalence of PH was >50% [7,8]. In the majority of these cases, PH was only mild and demonstrated other characteristics than PAH, i.e. pulmonary pressures were less elevated (mean pulmonary arterial pressures rarely exceeded 35 mmHg), cardiac output usually remained normal, and pulmonary vascular resistance was only slightly to moderately increased (only in exceptional cases >480 dyn s cm^{-5}) [7,8]. However, there are reports indicating that mild forms of PH in patients with chronic lung disease may also be of prognostic significance (see below).

Comment:

Information on the incidence of PH in patients with chronic lung disease varies depending on the chosen definition of PH as well as the investigated patient population and method of examination (echocardiography versus right heart catheterization). A study by the National Emphysema Treatment Trials (NETT) published in 2002, showed that 90% of all patients with advanced pulmonary emphysema who were evaluated for lung volume reduction (LVR) had a mean pulmonary arterial pressure (PAPm) >20 mmHg and approx. 50% had a PAPm >25 mmHg [9]. Another patient population with severe

COPD that was evaluated for LVR or lung transplantation, also showed PAPm values >25 mmHg in 50% of all cases [10]. Similar numbers were published for patients with interstitial lung disease [11]. At least in selected case series of patients who were evaluated for lung transplantation due to advanced pulmonary fibrosis, the prevalence of PH with PAPm values >25 mmHg was between 30 and 70% [8,12,13].

No concrete information is available on the incidence of PH in patients with less advanced lung disease since naturally these patients are not systematically examined with right heart catheterization. Echocardiographic examinations are not accurate enough to generate epidemiological data (see below).

Irrespective of this, PH is less pronounced in most patients with lung disease than in patients with "true" PAH and right ventricular systolic pump failure does generally not occur. Nevertheless, there are numerous studies indicating that even mild forms of PH may be clinically significant in patients with COPD as well as in patients with pulmonary fibrosis, since they are associated with worse oxygenation, decreased exercise capacity, and poorer prognosis. Oswald-Mammoser et al. were able to demonstrate that a PAPm >25 mmHg in COPD is associated with increased mortality. In a study by Weitzenblum et al., the 4-year survival rate of COPD patients was 72% if the PAPm was below 20 mmHg but only 49% with a PAPm >20 mmHg [14]. Similar findings were established in patients with pulmonary fibrosis [11]. A prospective study with 87 patients with idiopathic pulmonary fibrosis published in 2007, a PAPm >17 mmHg was already linked to a poorer prognosis [15]. At least 50% of all patients with combined pulmonary fibrosis and emphysema (CPFE) also have PH which likewise constitutes an independent risk factor for increased mortality [16,17].

The most recent NETT data on PH in patients with pulmonary emphysema was presented by Minai et al. in May 2010 during the American Thoracic Society's annual convention. 1,866 patients had been enrolled making this series one of the largest in this patient population. All patients underwent echocardiographic assessment; systolic pulmonary arterial pressure (PA pressure) ≥45 mmHg was determined as cut-off value. No further investigation was carried out in patients with a systolic PA pressure <45 mmHg (n = 1,069; 57%), while patients with a systolic PH pressure ≥45 mmHg underwent right heart catheterization. This procedure confirmed PH with a PAPm of ≥25 mmHg in 302 (38%) patients, which once more underlines the insufficient accuracy of determining PA pressure with echocardiography (see below). Prespecified criteria for severe pulmonary hypertension were (i) PAPm >35 mmHg, or (ii) PAPm ≥25 mmHg with a cardiac index <2.0 l/min/m^2, or (iii) pulmonary vascular resistance (PVR) >6 Wood units (corresponding to 480 dyn s cm^{-5}). According to these criteria, 18 (2.2%) patients had severe PH, including only one patient with a PAPm >35 mmHg (Minai O et al. ATS 2010). Surprisingly, in this population the presence of PH did not affect the survival rates after 1, 2 and 5 years (p = 0.19 for patients with a PAPm ≥25 mmHg versus <25 mmHg).

The issue of which degree of PH can be expected within the context of lung disease is of paramount importance, since in some cases the lung disease may not be the only cause of PH so that further diagnostic procedures are necessary to e.g. rule out causative heart disease, liver disease, or CTEPH. In some cases it is even possible that the PH is a "true" PAH with a coexisting lung disease and no causal significance. If a population has a high prevalence of a disease such as COPD, it should be expected that it will also occur at a comparative prevalence in patients with PAH.

Chaouat et al. were able to demonstrate that 27 out of 998 patients with COPD and chronic respiratory failure who underwent right heart catheterization had severe pulmonary hypertension, defined as PAPm ≥40 mmHg. Besides the already known COPD, 16 of these 27 patients had at least one other disease that may have caused PH [18]. In the other patients (approx. 1% of the study population) it was unclear if the severe PH was actually secondary to COPD or an independent disease, in other words ultimately an idiopathic PAH.

Table 2
Criteria for the presence of severe pulmonary hypertension in patients with chronic lung disease*.

At least 2 of the following criteria must be met:
1. Mean PA pressure (PAPm) >35 mmHg
2. PAPm ≥25 mmHg with limited cardiac output (CI <2.0 l/min/m^2)
3. Pulmonary vascular resistance (PVR) >480 dyn s cm^{-5}

*As a rule, these criteria only apply if other causes of PH (e.g. chronic thromboembolic PH or left ventricular failure) have been excluded.

Thabut et al. assessed 215 patients with very advanced COPD prior to scheduled LVR or lung transplantation with right heart catheterization: PAPm values of >25 mmHg, >35 mmHg, and >45 mmHg were found in 50.2%, 9.8% and 3.7% of patients, respectively.

One problem of such kind of studies is that they are conducted predominantly in selected patient populations with very advanced lung disease. Therefore there is little reliable data on the prevalence and degree of PH in patients with less severe forms of chronic lung disease. The summarized data above from the NETT registry could most likely be regarded as representative, not only because of the very large number of cases but also because not only patients with severe emphysema were enrolled.

The available data on patients with pulmonary fibrosis is still uncertain since almost all studies with invasive hemodynamics originated from pre-transplantation populations and the patients had been preselected accordingly. Larger-scale studies are almost exclusively based on echocardiographic examinations with the corresponding limitations.

If pulmonary hypertension is more severe than expected, it is always suspected that PH cannot be attributed to the pulmonary disease alone. But what range can be expected? In the most recent data from the NETT registry mentioned above, 38% of the examined COPD patients suffered from pulmonary hypertension with a PAPm ≥25 mmHg, but only approx. 1% of all patients met the criteria for severe PH (PAPm >35 mmHg or PAPm ≥25 mmHg with a cardiac index < 2.0 l/min/m^2, or PVR >480 dyn s cm^{-5}) chosen for this study. As opposed to previous studies on PH due to chronic lung disease, not only the level of PA pressure was chosen as criterion for severity from the NETT registry, but at the same time cardiac index and PVR were used so that the impact of pulmonary hypertension on right ventricular function was taken into account as well.

The German consensus group agreed to adopt the above-mentioned definition of severe PH from the NETT registry in a modified, stricter form (Table 2). Although this definition has been derived from patients with COPD, it sufficiently corresponds with the available findings from patient populations with different interstitial lung diseases [19] to be used by the consensus group for all other lung diseases as well. This definition ensures that only hemodynamically relevant pulmonary hypertension with distinct right ventricular load is classified as severe. Since only a negligible minority of patients (<5%) with lung disease presents such pronounced pulmonary hypertension, it satisfies the "out of proportion" concept. At the time, this definition requires a complete right heart catheterization including measurement of cardiac output (see below).

4. Diagnosis of pulmonary hypertension due to chronic lung disease

The diagnostic procedure in patients with suspected PH requires a number of tests to confirm the diagnosis, to determine the clinical classification of PH, and evaluate the severity of the functional as well as the hemodynamic impairment. It is especially important to fully clarify the diagnosis of patients with severe PH, since chronic lung disease alone is generally not sufficient to cause severe PH (see above). After the description of each procedure, an integrated diagnostic algorithm of the guidelines is shown in Fig. 1.

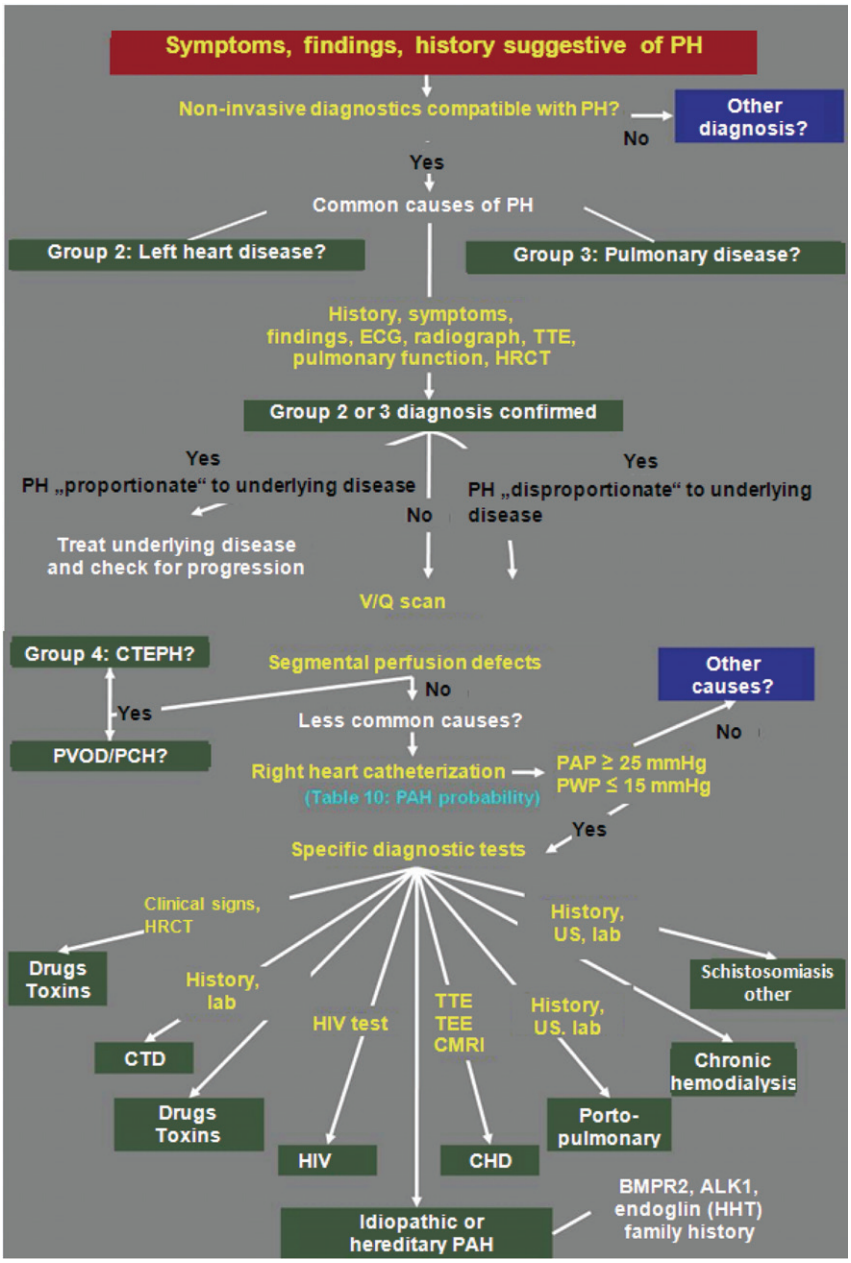

Fig. 1. Diagnostic algorithm. Explanation: TTE, transthoracic echocardiography; HRCT, high-resolution CT; V/Q scan, ventilation/perfusion lung scan; PAPm, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CTEPH, chronic thromboembolic pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; CTD, connective tissue disease; CHD, congenital heart disease; TEE, transesophageal echocardiography; CMRI, cardiac magnetic resonance imaging; US, ultrasonography abdomen; ALK-1, activin-receptor-like kinase; BMPR2, bone morphogenetic protein receptor 2; HHT, hereditary hemorrhagic telangiectasia (Osler's disease)

4.1. Symptoms and clinical findings

The symptoms of PH are non-specific. This applies especially to the main symptom, exercise dyspnea, which is naturally also a key symptom of the underlying disease. Therefore the issue of whether the extent of dyspnea can be explained by the level of limited ventilatory function constitutes an important aspect of the diagnostic clarification of such patients. Otherwise the presence of PH should be taken into consideration.

The physical examination findings that may indicate PH include visible and palpable left parasternal pulsations, an accentuated pulmonary component of second heart sound, a left parasternal systolic murmur of tricuspid regurgitation, and a diastolic murmur of pulmonary valve insufficiency. Jugular vein distention, hepatomegaly, peripheral edema, and ascites indicate severe PH. However, edema may occur in chronic lung disease, especially in exacerbated chronic obstructive pulmonary disease (COPD), even without the presence of PH.

4.2. Electrocardiogram (ECG)

The ECG may provide evidence of PH in the presence of typical signs (P-pulmonale, RV hypertension, depolarization disorder over the anterior wall leads and inferior leads, right bundle branch block). Signs of right ventricular load in the ECG of patients with COPD are relevant for prognosis [20].

Sensitivity and specificity of the ECG to detect PH have not been sufficiently investigated in patients with chronic lung disease. Just as in other forms of PH, absence of the above-mentioned signs of right ventricular load by no means rule out the presence of PH.

4.3. Radiology

Dilation of central pulmonary vessels (>15 mm for the right lower lobe branch in the chest radiograph, >25 mm for the pulmonary trunk in the CT scan) is regarded as an indication for the presence of PH. The degree of PH does not correlate with the radiological finding and normal radiographic findings do not rule out PH.

4.4. Pulmonary function and blood gas analysis

The findings of spirometry and body plethysmography are determined by the underlying lung disease and are not significantly affected by concomitant PH. Decreased lung diffusion capacity for carbon monoxide (DLCO) and inadequate severe hypoxemia may be possible indicators of PH. Patients with chronic hypercapnia are at increased risk of PH. On the other hand, pronounced hyperventilation can be an indicator of severe PH especially in patients with chronic lung disease.

4.5. Echocardiography

Transthoracic echocardiography plays a central role in the initial confirmation of suspected PH. The estimation of PAP is based on the Doppler-echocardiographic measurement of the peak velocity of the tricuspid regurgitation jet (V_{max}). The simplified Bernoulli equation ($\Delta P = 4 \times V_{max^2}$) is used to determine the pressure gradient between right ventricle and right atrium. Right atrial pressure is usually estimated based on the diameter and respiratory variation of the inferior vena cava. This procedure, however, was proven to be unreliable especially in patients with COPD. A Doppler signal over the tricuspid valve can only be measured in 38–70% of these patients [21–23]. In current studies, 50% of invasively assessed systolic pulmonary arterial pressures deviated from the values determined with echocardiography by more than 10 mmHg [24,25]. Overestimated right arterial pressure values as well as inadequate Doppler signals were identified as essential sources of errors in echocardiography [25]. Studies with a V_{max} cut-off value of 2.5–2.8 m/s for PH at rest, had yielded false positive results in 45–72% of cases [24,26].

Indications for echocardiography to evaluate PH in patients with COPD or interstitial lung disease include: (i) confirmation or exclusion of PH, (ii) clarification of concomitant left heart disease, and (iii) the selection of patients for right heart catheterization necessary for the conclusive diagnosis of PH.

Comment:

Despite its limitations, echocardiography in patients with chronic lung disease remains the most important initial method of investigation when PH is suspected. In the current NETT registry data, echocardiography had a positive predictive value of 0.56 and a negative predictive value of 0.82 (Minai et al. ATS 2010), whereby the cut-off value was set at a systolic PA pressure of 45 mmHg. It is decisive that the examiner is aware of the limitations of this procedure and interprets the findings with the necessary prudence. As in other types of PH, the diagnosis should, in principle, not be established on echocardiography alone, especially if therapeutic consequences are being considered.

4.6. Ventilation/perfusion lung scan/V/Q scan)

The ventilation/perfusion lung scan is used to exclude or confirm chronic thromboembolic pulmonary hypertension (CTEPH).

Comment:

Sensitivity and specificity of the V/Q scan decrease with increasing severity of obstructive or restrictive lung disease. If therapeutic consequences can be expected, contrast-enhanced computed tomography (CT) should be preferred in advanced lung disease.

4.7. Computed tomography of the chest

High-resolution CT (HR-CT) is an integral part of the diagnosis of interstitial lung disease and pulmonary emphysema. In addition, the CT can provide evidence of pulmonary hypertension (central pulmonary vessels >25 mm) or right ventricular load.

4.8. Laboratory tests

The determination of the BNP or NTproBNP values can be helpful within the scope of the initial diagnosis and for follow-up assessments. However, elevated BNP/NTproBNP levels are not specific for PH since increased values are also present in left ventricular failure. Then again, normal BNP/NT-proBNP values do not exclude PH [27].

4.9. Right heart catheterization and vasoreactivity test

Right heart catheterization (RHC) is required to confirm the diagnosis of PH and to assess its severity. The examination should generally only be performed at centers that have extensive experience in the diagnosis and therapy of PH. When performed at experienced centers, the rate of complications associated with this examination is low (morbidity 1.1%, mortality 0.055%) [28].

Indications for right heart catheterization in patients with chronic lung disease may include: (i) confirmation of diagnosis or exclusion of PH in patients prior to surgical interventions (transplantation, LVR), (ii) suspected out of proportion PH, (iii) repeated episodes of right ventricular failure, (iv) uncertain echocardiographic findings with coexisting clinical indications of PH.

The following parameters must be determined with each right heart catheterization: right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure (if technically feasible), cardiac output (thermodilution or Fick method with measured oxygen consumption, tabular oxygen consumption is not reliable enough), as well as mixed venous oxygen saturation.

Comment:

The recommendations for right heart catheterization in patients with chronic lung disease sometimes lead to misunderstandings. On no account do the guidelines require RHC in all patients with chronic lung disease and clinical signs of PH. This type of intervention is only deemed necessary if therapeutic consequences are expected or if important prognostic information is needed for continued patient management (e.g. placing on the lung transplant list). Since the European guidelines generally do not recommend targeted drug therapy of PH in patients with chronic lung disease, RHC will only be necessary in exceptional cases (see below).

RHC should only be performed at locations where the above-mentioned hemodynamic parameters can be fully collected, otherwise the patients should be referred to appropriate centers.

Vasoreactivity testing should be considered in patients with PH due to chronic lung disease.

The significance of exercise hemodynamics during right heart catheterization is currently not established.

5. Treatment of pulmonary hypertension due to chronic lung disease

At present there is no specific treatment for PH due to chronic lung disease. Long-term oxygen treatment (LTOT) reduces progression in PH due to COPD. Only in rare cases does this treatment lead to the normalization of pulmonary pressures and the structural

Table 3
Recommendations of the European guidelines for pulmonary hypertension associated with lung disease and/or hypoxia.

Recommendation	Class of recommendation	Level of evidence
Echocardiography is a recommended screening method for PH due to lung disease	I	C
In patients with PH due to lung disease, RHC is recommended to confirm diagnosis	I	C
The optimization of treatment of patients with PH due to lung disease including long-term oxygen therapy for hypoxemia is recommended	I	C
Patients with out or proportion PH due to lung disease should be enrolled in RCTs for PAH-targeted drugs	IIa	C
The treatment of patients with PH due to lung disease with PAH-targeted drugs is not recommended	III	C

PH, pulmonary hypertension; RCTs, randomized controlled trials; PAH, pulmonary arterial hypertension; RHC, right heart catheterization.

changes of lung vessels are not affected [29]. The role of LTOT for the progression of PH in interstitial lung disease is even less well established.

The treatment of PH due to chronic lung disease with conventional vasodilators (e.g. calcium channel blockers) is not recommended, since the inhibition of hypoxic vasoconstriction can lead to worsening of gas exchange and these agents provide no long-term benefit [30–34]. The available data on the use of "PAH drugs", in other words prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors [35–37], in these patients is insufficient and limited to a few studies on acute effects as well as uncontrolled studies with only few case numbers.

The treatment of choice for hypoxemic patients with COPD or interstitial lung disease and concomitant PH is LTOT. Patients with "out of proportion" PH (characterized by the fact that the extent of dyspnea can not be explained by the lung disease alone and a PAPm >40 mmHg at rest) should be referred to expert centers and enrolled in clinical studies. The use of "PAH drugs" is not advised in these patients since systematic studies on safety and efficacy are not available. The recommendations of the European guidelines on PH due to chronic lung disease are summarized in Table 3. The definitions for the class of recommendations or levels of evidence correspond to the tables in the preamble of this brochure.

Comment:

Some treatment principles for patients with chronic lung disease and PH are undisputable even if there is only little reliable data to this end. For instance, this applies to long-term oxygen treatment for patients with chronic hypoxemia regardless of the underlying lung disease, even if corresponding reliable data is only available for patients with COPD.

The obstructive sleep apnea syndrome generally does not lead to clinically relevant PH, a fact that must be considered when clarifying the causes as well as in the treatment of PH or PAH. By contrast, the presence of chronic hypercapnia associated with hypoventilation syndromes of various origins can lead to severe PH. This is particularly common in patients with kyphoscoliosis and in patients with obesity hypoventilation syndrome. In these cases, causal treatment, usually with non-invasive ventilation, is top priority especially since PH can regress in these cases with efficient treatment and normalization of $paCO_2$ values.

In the presence of PH and central sleep apnea, PH should not be automatically classified as a result of sleep apnea. As in left ventricular failure, severe PH also favors the occurrence of central sleep apnea [38].

There is insufficient data on the issues of if and when patients with chronic lung disease and pulmonary hypertension should receive anticoagulation. This must currently be decided on an individual basis only.

Use of "PAH drugs" in chronic lung disease

Up to now, no solid data is available on drug therapy for PH in the context of chronic lung disease. This applies to COPD as well as to pulmonary fibrosis and mixed forms. A small placebo controlled study with the endothelin receptor antagonist bosentan in patients with COPD without severe pulmonary hypertension showed no improvement in exercise capacity but worsening of oxygenation [39]. Acute data is available on the use of sildenafil in patients with COPD and PH which also demonstrates worsening of gas exchange with simultaneous improvement of hemodynamic parameters [40]. There is, however, no reliable long-term data on safety and tolerability for sildenafil in this patient group.

The recently published STEP-IPF study was not able to demonstrate an improvement in exercise capacity in patients with IPF on a 12-week therapy with sildenafil but showed significant albeit minor benefits with regard to oxygenation, DLCO, as well as dyspnea and quality of life scores as compared to the placebo group. In these studies the presence of PH was not required for study enrollment, but rather a DLco <35% of the predicted value was used as inclusion criterion, intending an enrichment of the study population with patients with IPF-associated PH [41].

In view of this data, the working group agrees with the recommendations of the guidelines not to systematically treat patients with lung disease and PH with PAH drugs as long as there is no solid corresponding data. This applies irrespective of the underlying lung disease.

However, patients with lung disease and severe pulmonary hypertension must be viewed separately, especially if the lung disease has not progressed enough to be regarded as the sole cause of PH. The guidelines refer to these cases as "out of proportion PH" without clearly defining this term. Because of the above-mentioned reasons, the German consensus conference has decided to adopt the definition in the NETT registry of severe PH due to chronic lung disease in modified form (Table 2).

Patients with chronic lung disease have not been systematically assessed in clinical studies with PAH drugs, so that there is no sufficient evidence on the safety and benefit of these drugs in these patient groups. Some of these patients show clinical characteristics that apply more to PH than to their lung disease [18]. In such borderline cases it may be difficult or even impossible to differentiate if a patient is suffering from chronic lung disease with resulting PH or from PAH with concomitant but not causative chronic lung disease. In the latter case it would not be justifiable to deny a patient targeted PAH therapy. Such patients should be enrolled in clinical studies in accordance with the recommendations of the European guidelines. Several Phase II and Phase III studies are currently under way but the majority of patients will not meet the inclusion and exclusion criteria. This option can, therefore, not be considered in general. The decision regarding targeted therapy will then fall within the discretion of the treating physician.

The following constellation of findings indicates that patients who suffer from chronic lung disease also have severe PH, whereby it is not always possible to clearly differentiate between PH within the scope of the underlying disease and PAH: Mild to moderate severity of ventilatory limitation, i.e. total lung capacity (TLC) in pulmonary fibrosis > approx. 60% of the predicted value, in COPD FEV_1 > ca. 50% of the predicted value, hyperventilation or at least absence of hypercapnia and coexistence of severe PH corresponding to the criteria in Table 2 which cannot be explained by a further disease (e.g. left ventricular failure, pulmonary embolism).

These hemodynamic values should not be measured immediately after exacerbation of the underlying disease (if applicable at an interval

of ≥6 weeks). Furthermore, these patients should be screened for other causes of PH in accordance with the above diagnostic algorithm (Fig. 1).

Recommendations of the working group

General remarks

With regard to these cut-off values and the potential consequences for the medical treatment of patients with chronic lung disease, this consensus document differs from the European guidelines.

- *In the majority of cases, the pathology and pathophysiology PH in chronic lung diseases is clearly different from PAH. In individual cases, especially in the presence of severe pulmonary hypertension, there are pathological and pathophysiological similarities between PAH and severe PH due to chronic lung disease.*
- *It is conceivable that in individual cases, lung disease could "trigger" the development of PAH (analog to other diseases such as collagen vascular disease, HIV infection, or portal hypertension).*
- *In patients with mild to moderately severe ventilation disorder but concomitant severe increased pulmonary pressure, PH may dominate the clinical symptoms. In some cases, it is almost impossible to distinguish the clinical symptoms from PAH.*
- *Some studies on PAH drugs have enrolled patients with mild to moderate obstructive and restrictive ventilation disorders in accordance with the above criteria (TLC >60% of the target value, FEV_1 >50% of the target value).*
- *There is limited clinical experience on the use of "PAH drugs" in patients with chronic lung disease. Since these patients are suffering from life-threatening illnesses, there is a medical-ethics dilemma between the availability of evidence-based data and the vital need for treatment. This is all the more true since it will hardly be possible to generate sufficient data for all conceivable chronic lung diseases with concomitant PH that meet the requirements of evidence-based medicine. In such cases, the essential task of the physician consists of applying the best possible treatment for the patient taking into consideration benefits, risks, and costs.*

Specific recommendations of the working group on the treatment of PH in patients with chronic lung disease

- *The targeted treatment with "PAH drugs" is generally not recommended and should be reserved for exceptional cases. The treatment decisions in these cases should be made only at expert centers (definition according to the European guidelines, Table 4).*
- *Use of such treatment requires comprehensive diagnostic procedures according to the recommendations of the guidelines, including right heart catheterization. The patients should meet the following criteria: (i) invasive assessment of severe PH according to the criteria in Table 2, (ii) mild to moderate severity of ventilatory limitation as defined above, (iii) exclusion of other causes of PH, including left heart disease and CTEPH.*
- *Before these patients are treated with "PAH drug", it should be assessed if they are eligible for a clinical study. Large PH centers as well as PH self-help groups (pheV) will provide information about this.*
- *Even if the patients thus characterized are potentially suffering from PAH, they have so far not been systematically enrolled in clinical studies due to their limited pulmonary function. Accordingly, the safety as well as the efficacy of "PAH drugs" is not sufficiently characterized in such cases so that patients should be closely monitored. This includes controls of arterial or capillary blood gases.*
- *Because of the limited available scientific data, no recommendations can be made about which substance group should be preferred.*
- *Unlike in PAH, it not yet known if the "PAH drugs" have a positive effect on disease progression in patients with chronic lung disease and PH. Hence, a treatment attempt should initially be made over a limited period of 3–6 months in order to decide then, after careful re-evaluation, if an objective clinical effect has occurred that would justify the continuation of therapy. Otherwise the treatment should be discontinued. This approach should be discussed with the patient before the start of treatment.*
- *A special situation arises if patients have end-stage lung disease and are on a lung transplant waiting list. Here, the treatment of severe pulmonary hypertension is justified in individual cases under clinically controlled conditions with the foreseeable goal of reaching transplantation, especially if a clinical improvement can be documented on this treatment.*

Table 4
Definition of a pulmonary hypertension referral center.

Recommendation	Class of recommendation	Level of evidence
A pulmonary hypertension referral center must provide a professional, interdisciplinary team (cardiologists, respiratory medicine physicians, clinical nurse specialists, radiologists, psychologists, social work support, appropriate on-call expertise in PH)	I	C
Pulmonary hypertension referral centers are required to have direct lines and quick referral patterns to other departments, experts, and programs (rheumatology centers, family planning service, PEA program, lung transplantation service, center for adult patients with congenital heart disease)	I	C
A pulmonary hypertension referral center should follow at least 50 patients with PAH or CTEPH and should treat at least two new patients per month with documented PAH or CTEPH.	IIa	C
Pulmonary hypertension referral centers should perform at least 20 vasoreactivity tests in patients with PAH per year.	IIa	C
Pulmonary hypertension referral centers should participate in clinical research in PAH (including Phase II and III studies)	III	C

CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension, PH, pulmonary hypertension; PAP, pulmonary arterial pressure; PEA, pulmonary endarterectomy.

Closing remarks

The recommendations of the Cologne Consensus Conference differ in some parts from the current European guidelines, especially with regard to the treatment of PH due to chronic lung disease. Large parts of the European guidelines are strictly evidence-based. The consensus conference adopted these guidelines in essence but at the same time attempted to make recommendation for patients presenting in a grey zone where it is very difficult to distinguish between PH due to chronic lung disease and PAH. This is a difficult and sometimes unsatisfying endeavor, since on the one hand the uncritical and unjustified use of "PAH drugs" should be avoided but on the other hand it must be prevented that patients do not receive these drugs for formal reasons even though experienced physicians see a realistic chance that patients may benefit from them.

The members of this working group have observed with great unease that "PAH drugs" are increasingly used by non-experts and oftentimes for patients for whom these drugs are not indicated or the indication has not been carefully assessed. In many of these cases, the treating physicians do not seem to understand the difference between PAH and other forms of PH. This development may have negative consequences: Those patients not suffering from PAH may be treated with drugs they will not benefit from while patients with established PH are denied comprehensive and competent treatment at specialized centers. In addition, the unjustified use of "PAH drugs" results is an economic burden to the health care system.

Only carefully designed clinical trials and registries will help to further elucidate which patients may benefit for "PAH drugs", and which not. Until more data is available, the best way to avoid over-, under- and mistreatment of patients with PH and chronic lung disease is referring them to expert centers, as recommended by the European guidelines.

Conflicts of interest

M.M. Hoeper: Remunerations for lectures and/or consultancy for Actelion, Bayer, Gilead, GSK, Lilly, LungRx, and Pfizer.

S. Andreas: Remunerations for lectures for Actelion and Pfizer. Clinical studies with Actelion.

A. Bastian: none.

M. Claussen: Remunerations for lectures for Actelion, Bayer, and Pfizer.

H.A. Ghofrani: Remunerations for lectures and/or consultation of Actelion, Bayer, Gilead, GSK, Lilly, LungRx, and Pfizer.

M. Gorenflo: Remunerations for lectures and/or consultation of Bayer.

C. Grohé: Remunerations for lectures and/or consultancy for Pfizer, Lilly, Bayer, Actelion.

A. Günther: Remunerations for lectures and/or consultation of Actelion and Bayer. Clinical studies with Actelion and Bayer.

M. Halank: Remunerations for lectures and/or consultancy for Actelion, Bayer, GSK, Lilly, Pfizer, and United Therapeutics.

P. Hammerl: Lecturer Actelion/GSK.

M. Held: Remunerations for lectures and/or consultation of Actelion, GSK, Pfizer; Lilly, Novartis, Boehringer.

S. Krüger: Remunerations for lectures and/or consultancy for Actelion, Bayer, GSK, Lilly, and Pfizer.

T. J. Lange: Remunerations for lectures and/or consultancy for Encysive, GSK, Lilly, and Pfizer.

F. Reichenberger: Honorarium from Actelion and Pfizer.

A. Sablotzki: Remunerations for lectures and/or consultancy, as well as assistance in research projects for Bayer, CSL Behring, Edwards Lifesciences, Lilly, Löser Medizintechnik, NovoNordisk.

G. Staehler: Remunerations for lectures and/or consultation of Actelion, Bayer, Lilly, and Pfizer.

W. Stark: none.

H. Wirtz: Lecturer Actelion.

C. Witt: Remunerations for lectures and/or consultancy for Actelion, Bayer-Schering-Pharma, GSK, and Pfizer.

J. Behr: Remunerations for lectures and/or consultancy for Actelion, Bayer, Gilead, GSK, Lilly, and Pfizer.

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