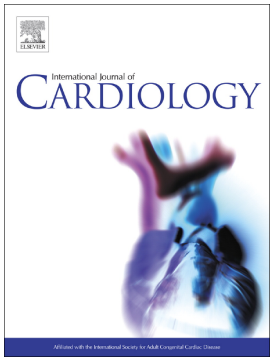

Pulmonary hypertension due to lung diseases: Updated recommendations from the Cologne Consensus Conference 2018

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Pulmonary hypertension due to lung diseases: Updated recommendations from the Cologne Consensus Conference 2018

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Summary

The 2015 European Guidelines on Pulmonary Hypertension did not only cover pulmonary arterial hypertension (PAH) but also some aspects of pulmonary hypertension (PH) associated with chronic lung disease. The European Guidelines point out that the drugs currently used to treat patients with PAH (prostanoids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, sGC stimulators) have not been sufficiently investigated in other forms of PH. Therefore, the European Guidelines do not recommend the use of these drugs in patients with chronic lung disease and PH. This recommendation, however, is not always in agreement with medical ethics as physicians sometimes feel inclined to treat other forms of PH which may affect quality of life and survival of these patients in a similar manner. To this end, it is crucial to consider the severity of both PH and the underlying lung disease. In June 2016, a Consensus Conference organized by the PH working groups of the German Society of Cardiology (DGK), the German Society of Respiratory Medicine (DGP) and the German Society of Paediatric Cardiology (DGPK) was held in Cologne, Germany, to discuss open and controversial issues surrounding the practical implementation of the European Guidelines. Several working groups were created, one of which was dedicated to the diagnosis and treatment of PH in patients with chronic lung disease. The 2018 updated recommendations of this working group are summarized in the present paper.

Word count summary: 226

Key words: pulmonary hypertension - lung disease - COPD – pulmonary fibrosis - therapy

Clinical significance of pulmonary hypertension in patients with lung disease

At the 2013 World Symposium on Pulmonary Hypertension (PH) in Nice, a separate working group for PH due to lung disease was convened for the first time, and its findings were published in high-impact journals before the year was out [1]. The chapter on this topic in the 2015 ESC/ERS guidelines is based on these recommendations, although not before being further revised by the authors of the guidelines and approved by the respective medical societies: the *European Society of Cardiology* (ESC) and *European Respiratory Society* (ERS) [2]. Both of these publications state that PH in patients with lung disease is associated with a less favorable prognosis, that most of these patients have chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) or combined pulmonary fibrosis and emphysema (CPFE), and that there are other rare lung diseases which are often associated with PH, e.g. pulmonary Langerhans cell histiocytosis and sarcoidosis.

Comments: *The prognosis is very poor for patients with lung disease and overt PH (Group 3 PH). Based on data from the Swiss PH registry and the English ASPIRE registry, this patient population has the poorest prognosis of all of the PH groups, although the mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) in Group 3 PH were less elevated on average than in most of the PH groups [3;4].*

In COPD, an elevated mPAP is associated with higher mortality [5-8]. Furthermore, having an elevated mPAP predisposes patients to more hospitalizations [9]. In IPF, an elevated mPAP is likewise associated with increased mortality [10;11]. The studies mentioned above suggest that exceeding an mPAP of approximately 19 mmHg worsens the prognosis in both COPD and IPF.

Among the hemodynamic factors, elevated PVR and low pulmonary arterial oxygen saturation (SvO_2) were especially strongly associated with mortality in COPD [12]. An elevated PVR was also strongly associated with mortality in IPF [13].

Most patients with severe emphysema have an mPAP between 20 and 25 mmHg [14]. In contrast COPD patients very rarely (approximately 1%) have an mPAP >40 mmHg, provided there is no other condition causing PH [15]. The prevalence of PH in interstitial lung disease (ILD) correlates only weakly with the degree of restriction [16;17]. Patients with CPFE develop PH in 47-90% of cases [18-21]. In these patients, the diffusing capacity of the lungs for carbon monoxide (DLCO) is severely restricted (in most cases to 20-45% of the predicted reference range), while lung volumes are normal or slightly changed and severe airway obstructions are absent. The mortality rate for this disease is high and is also strongly associated with pulmonary pressure [18;22;23].

In some of these patients, abnormalities of the lung parenchyma seen on computed tomography (CT) scans are rather discrete, which makes it difficult to differentiate the disease from idiopathic pulmonary arterial hypertension (IPAH). A Dutch working group compared their IPAH patients who had a substantially decreased DLCO (<45% of the predicted reference range) with other IPAH patients [24]. The patients with the low DLCO were similar to the CPFE patients described in other publications in terms of their hemodynamics, age, proportion of males, and similarly high number of pack years. Some of them had pathological changes on high resolution CT scans, although they were not very pronounced. In these patients, in whom the low DLCO would constitute a global indicator of possible lung disease, PH could be referred to as "atypical PAH" or "PAH with pulmonary comorbidities".

Definitions

The new terms 'PH-COPD, PH-IPF, PH-CPFE' and 'severe PH-COPD, PH-IPF, PH-CPFE' were coined in the publication from the Nice working group and in the ESC/ERS guidelines [1;2]. 'Non-severe' disease refers to the respective lung diseases with an mPAP ≥25 mmHg, 'severe' disease to those with an mPAP ≥35 mmHg or an mPAP ≥25 mmHg and decreased cardiac output. The wording in the ESC/ERS guidelines is: '...in the presence of a low cardiac output (CI <2.5 L/min)'. Apparently what was meant was a CI <2.5 L/min/m^2, as stated in the online version of the ESC/ERS guidelines [http://erj.ersjournals.com/content/46/6/1855]. In the Nice working group [1], the CI criterion in question was <2.0 L/min/m^2. According to the consistent statements of the Nice working group and the ESC/ERS guidelines, PAH therapy should in principle be considered for patients with 'severe PH due to lung disease'.

Comments: *The change in the CI criterion from 2.0 to 2.5 L/min/m^2 increases the number of patients with lung disease who qualify as having 'severe PH due to lung disease'. The reason for this is that very few patients with chronic lung disease have an mPAP >35 mmHg, but many have an mPAP ≥25 mmHg. On the other hand, patients with an mPAP between 25 and 35 mmHg rarely have a CI of <2.0 L/min/m^2, but frequently have a CI between 2.0 and 2.5 L/min/m^2. No reason was given for choosing the value of 2.5 L/min/m^2, which makes it difficult to comprehend the underlying rationale.*
The criteria for severe PH due to lung disease in the paper published by the Nice working group [1] originally came from the 2010 Cologne Consensus Conference [25], some of the authors of which also worked on the current comments. Then, as now, the evidence for the criteria for 'severe PH due to lung disease' is weak. The aim of the criteria is to identify those patients who have a good chance of responding well to PAH therapy. The recent disappointing treatment outcomes from the RISE-IIP study (NCT 02 138 825) make this yet another in a long line of negative controlled studies in which Group 3 PH patients were enrolled without due consideration of the criteria for 'severe PH'. Therefore,

the 2016 Consensus Conference recommends going back to the original criteria for severe PH due to lung disease, which have also been taken up by and are being used by our American and French colleagues [26;27].

The criteria for severe PH due to lung disease are:

- *PAP >35 mmHg*
- *PAP ≥25 mmHg and CI <2.0 L/min/m^2*
- *PVR >6 WU*

To make a diagnosis, at least two of these criteria must be met.

In practical terms this means that patients must have a clearly elevated PVR, either based on a high mPAP or on a clearly reduced cardiac output or CI. This will ensure that PAH drugs, which as is generally known act primarily on PVR, will find a relevant target. This PVR criterion is supported by the research conducted by Corte and colleagues, and the findings from the ASPIRE study [12; 13].

The Nice working group [1] proposed specific criteria for differentiating between PH due to lung disease (Group 3 PH) and PAH (Group 1 PAH) with a concomitant but independent lung disease. The criteria listed for Group 1 PAH were:

1) normal or slightly decreased ventilatory function, which is defined as a forced expiratory volume in 1 second of >60% of the normal range for COPD and a vital capacity of >70% for IPF
2) absence of serious lung parenchymal changes on high resolution CT scans
3) predominantly circulatory limitation on physical exercise.

Comments: *Unfortunately, the above Nice working group criteria were not included in the ESC/ERS guidelines, so the important and difficult process of differential diagnosis is still subject to the experience and judgment of the individual physician. Interestingly, the DLCO is therefore not taken into account despite it being known to have a high sensitivity for detection of parenchymal lung disease. There is a lack of clarity how patients with low DLCO but without extensive lung parenchymal pathologies on high resolution CT scans should be categorized. Therefore it is also difficult to state criteria for DLCO that suggest a distinct lung disease. Independent of this consideration, it should be noted here that a low DLCO is a strong predictor of an unfavorable prognosis, both in IPAH and in diastolic left heart failure with preserved ejection fraction (HFpEF) [24;28].*

Recommendations for management

The recommendations of the ESC/ERS Guidelines for PH due to lung disease [2] (Table 1) were all given evidence level C, which means that they are not based on controlled studies or meta-analyses. The recommendation classes range from I (unconditional recommendation) and IIa (strong recommendation for) to III (clear recommendation against). Comments on all six recommendations are given below.

1) Echocardiography is recommended as the first non-invasive diagnostic step in suspected PH in patients with lung disease (I).

   Comments: *This recommendation does not mean that echocardiography is a very reliable method, only that it is the best of the methods available.*

2) Referral to an expert centre is recommended for patients with echocardiographic signs of severe PH / right ventricular dysfunction (I).

   Comments: *This recommendation is very reasonable, but it does not take into account that severe PH can be due to an underlying disease such as severe left heart disease, which requires a different type of expertise than that required to treat PAH.*

3) Optimal treatment of the underlying disease, including long-term oxygen therapy, is recommended in patients with PH due to lung disease (I).

   Comments: *Unfortunately, as the guidelines correctly state, there is no evidence for this pragmatic recommendation. The most positive outcomes associated with optimized treatment of the underlying disease have been observed in patients who have severe hypercapnic respiratory failure without severe lung disease, who are stabilized on long-term non-invasive ventilation outside of the hospital setting [29-31], as well as those with diseases that are responsive to steroids, in which PH may improve alongside the underlying disease.*

4) Referral to a PH expert centre should be considered for patients with severe PH / severe RV failure for individualized treatment (IIa).

   Comments: *This statement should be viewed in the context of the definition of an 'expert centre for PH' (ESC/ERS Guidelines) and the definition of 'severe PH due to lung disease' (see above).*

5) Right heart catheterization is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are anticipated, e.g.

- lung transplantation
- alternative diagnoses such as PAH/CTEPH, and/or
- potential enrolment in a clinical trial (III).

Comments: *This statement implies that right heart catheterization should be performed only at an expert centre and nowhere else. The expert centre will check whether RHC is indicated. Among other things, this approach ensures that the expert centre does not have to repeat a recently conducted invasive procedure.*

6) PAH drugs are not recommended for patients with PH due to lung disease (III).

Comments: *This recommendation applies to the majority of patients with PH due to lung disease. The few patients who might benefit from PAH treatments should primarily be referred to an expert centre.*

Experience with PAH drugs for PH due to lung disease

The ESC/ERS guidelines do not go into detail about the treatment studies conducted so far for group 3 PH. They note that treatment with conventional vasodilators, such as calcium channel blockers, is not recommended because these drugs may impair gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction and because they were not effective in long-term studies.

Comments: *The literature cited by the ESC/ERS guidelines for this section includes not only studies investigating 'conventional vasodilators', but also studies investigating phosphodiesterase-5 inhibitors and experimental PAH therapies. One of these studies [32] is worth noting, even though it had limited statistical power and was negative: sildenafil was investigated in patients with IPF in a prospective, double-blind, placebo-controlled study. While the primary endpoint (a significant improvement in the 6-minute walk distance) was not achieved, several clinically relevant secondary endpoints were achieved, including improvement in quality of life and oxygenation.*

In addition, based on smaller case series, one can see that selected PH patients with fibrotic lung disease might benefit from targeted PH treatment, in particular prostanoids given via the inhaled route or orally administered PDE-5 inhibitors [33;34]. Although smaller case series have also suggested beneficial effects for riociguat [41,44,52], recently a phase IIb study of riociguat in patients with idiopathic interstitial pneumonia (IIP) and PH had to be terminated early for safety reasons. Even without a detailed analysis available, IIP represents a new contraindication for riociguat.

In randomized controlled trials, the endothelin receptor antagonist (ERA) ambrisentan led to more rapid progression in IPF patients, more side effects and increased mortality, without fundamentally

improving the additional PH [35;36]. In fibrosing IIP, bosentan reduced neither the PVR nor the functional capacity after 16 weeks of treatment [37].

Currently, there are no specific treatment recommendations for CPFE. Potential treatments can be based on the recommendations for pulmonary fibrosis or pulmonary emphysema [38;39].

In patients with PH-COPD who meet the definition of 'severe PH' proposed above, there have been no large randomized controlled studies from Western countries investigating the efficacy of PAH therapies. In small observational studies, in a very select group of patients, there was evidence of a benefit for PAH therapy with regard to exercise capacity and symptoms [40]. In contrast, for patients with COPD without severe PH, the findings of randomized controlled studies investigating PAH therapies have been consistently negative [41-43].

In clinical practice some patients receive a compassionate PAH therapy for PH due to lung disease. Findings from the COMPERA registry for a subgroup of patients with IIP who received PAH therapy at expert centres were published recently [44]. According to these findings, the short-term effects are indeed comparable to those in PAH, but the longer-term prognosis is much less favorable.

Very few controlled studies have analyzed the efficacy of PAH therapies in severe Group 3 PH. A current retrospective study is comparing patients who received PAH therapy with a control cohort which received no PAH therapy. Although the patients who received PAH therapy were older and had much worse hemodynamics, their survival was significantly better [45]. This study has a number of limitations that make the results difficult to interpret. Nonetheless, the findings are encouraging for conducting prospective controlled studies (see below) that are required for an evidence-based analysis.

Future study concepts

The Nice working group and the ESC/ERS guidelines do not specifically address this topic.

Comments: *Controlled prospective studies with sufficient power are necessary to obtain clarity about the potential indication of PAH drugs in patients with PH due to lung disease. The treatment has two main aims: to improve clinical symptoms, and to improve the course of the disease.*

If vasodilatory PAH drugs, which are known to act primarily on PVR, are used as they have been in the past, the inclusion criteria should require a sufficiently high PVR. The Cologne Consensus Conference proposes the same criteria as for a 'severe group 3 PH' (see above). Patients with mild cardiac comorbidities should explicitly be included because there is a very high prevalence of heart disease in

the typical patient population, although patients with overt pulmonary venous congestion (PAWP >15 mmHg) and a history of pulmonary edema should be excluded for safety reasons.

Given that mortality is very high in severe PH due to lung disease, it is recommended that cardiorespiratory mortality and death due to any cause be used, ideally as the primary endpoint. Patient-oriented treatment goals such as quality of life, oxygenation and exercise capacity should also be considered.

The study duration should be long enough to be able to definitively evaluate effects on the disease course.

Invasive measurement of hemodynamics

Measuring pulmonary hemodynamics with a fluid-filled catheter is the gold standard for determining pulmonary pressures and PVR in group 3 PH [2]. However, neither the Nice working group [1] nor the ESC/ERS guidelines [2] discuss the special considerations which relate to carrying out invasive hemodynamic investigations in patients with lung disease.

Comments: *Invasive pulmonary vascular pressure measurement uses mPAP to determine the classifications of overt PH and severe PH, PAWP to decide on whether pulmonary venous congestion is present, and right atrial pressure (RAP) to guide volume management. In this situation, intrathoracic pressure has greater significance than in patients without lung disease. The pressure measured during catheterization is known to be equivalent to the sum of the transmural plus the intrathoracic pressures, relative to a previously defined zero level [46]. In group 3 PH, abnormal intrathoracic pressure values are very common, which may result in the measured pressure values being misinterpreted. While patients with obstructive lung disease often have a positive intrathoracic pressure, it is highly negative in patients with restrictive lung disease. This affects all values measured during catheterization in the same way – irrespective of whether this is mPAP, PAWP or RAP.*

One conclusion from the PH World Conference in Nice was that the zero level should be placed at the level of the left atrium (mid-thoracic) [2;46;47].

Comments: *This recommendation is an important deviation from earlier conventions and may also be relevant for longitudinal catheterization studies of individual patients. If, for example, the zero point was placed at the 2/3 or 3/5 thoracic level during earlier examinations but is now placed at 1/2 thoracic level, the pressure readings will be around 2-3 mmHg higher. If the examination is not performed with the patient completely supine, the zero point should also be set at the level of the left atrium. Based on the 'phlebostatic axis' [48] a modified method ('phlebostatic point') is recommended, which can be used with the body in any position [46].*

The ESC/ERS guidelines leave it up to the investigator to decide whether to measure pulmonary pressures at the end of expiration or to take an average of several respiratory cycles.

Comments: *The Cologne Consensus Conference working group recommends using only the second method for patients with obstructive lung disease. Rationale: in patients with severe obstructive lung disease, usually the 'pressure at the end of expiration' corresponds to the pressure in the last phase of active expiration and not the pressure at the end of the passive expiratory flow, where it can be recorded for those with healthy lungs, at least at rest. Thus, in patients with obstructive disease, the intrathoracic pressure during this phase of respiration is in the positive range, leading to an overestimation of mean pulmonary artery pressure. The expiratory intrathoracic pressure increases with the severity of the obstruction and increasing ventilation during physical exercise. If 'air-trapping' also occurs during exercise, the intrathoracic pressure may increase very dramatically. This also has a considerable effect on the average value over several respiratory cycles. The extent of this rapid pressure change can be estimated based on the increase in RAP [49].*

For reasons of comparability, it is recommended that the same method be used for all lung diseases, even if no obstruction is present.

In order to correctly determine the PVR, the mPAP and PAWP must be determined using exactly the same technique. This applies to the zero level and the respiratory manoeuvre. It is therefore recommended to pay close attention to the zero level, to always avoid a single respiratory manoeuvre and to average the pressure over several respiratory cycles. A detailed rationale can be found in [46].

Table 1: Definitions and management of pulmonary hypertension due to chronic lung disease

Underlying lung disease	**mPAP < 25 mmHg**	**mPAP ≥ 25 and < 35 mmHg and CI ≥ 2.0 L/min/m²**	**mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg and CI < 2.0 L/min/m²**
• COPD with FEV_1 ≥ 60% pred • IPF with FVC ≥ 70% pred • No or only few bronchial or parenchymal changes on CT	• No PH • PAH drugs not recommended	• PH classification unclear • Currently no data to support treatment with PAH drugs	• PH classification unclear: differentiate between PAH (Group 1) with concomitant lung disease or PH due to lung disease (Group 3)
• COPD with FEV_1 <60% pred • IPF with FVC <70% pred • On CT combined fibrosis and emphysema	• No PH • PAH drugs not recommended	• PH-COPD, PH-IPF, PH-CPFE • Currently no data to support treatment with PAH drugs	• Severe PH-COPD, severe PH-IPF, severe PH-CPFE: Transfer to a centre with expertise in PH and lung disease for individualised decisions due to poor prognosis; randomised controlled studies are needed

CI: cardiac index, COPD: chronic obstructive pulmonary disease, CPFE: combined pulmonary fibrosis and emphysema, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, IPF: idiopathic pulmonary fibrosis, mPAP: mean pulmonary artery pressure, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, pred: predicted.

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