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Pulmonary hypertension in chronic obstructive pulmonary disease

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Abstract

Pulmonary hypertension (PH) is a common complication of advanced chronic obstructive pulmonary disease (COPD) and is defined by a mean pulmonary artery pressure (PAP) ≥ 25 mm Hg at rest in the supine position. Owing to its frequency, COPD is a common cause of PH; in fact, it is the second most frequent cause of PH, just after left heart diseases. PH is due to the elevation of pulmonary vascular resistance, which is caused by functional and morphological factors, chronic alveolar hypoxia being the most important. In COPD PH is generally mild to moderate, PAP usually ranging between 25 and 35 mm Hg in a stable state of the disease. A small proportion of COPD patients may present a severe or "disproportionate" PH with a resting PAP > 35 –40 mm Hg. The prognosis is particularly poor in these patients. In COPD PH worsens during exercise, sleep and severe exacerbations of the disease, and these acute increases in afterload may favour the development of right heart failure.

The diagnosis of PH relies on Doppler echocardiography, and right heart catheterization is needed in a minority of patients. Treatment of PH in COPD relies on long-term oxygen therapy (≥ 16 h/day) which generally stabilizes or at least attenuates the progression of PH. Vasodilator drugs, which are commonly used in idiopathic pulmonary arterial hypertension, have rarely been used in COPD, and we lack studies in this field. Patients with severe PH should be referred to a specialist PH centre where the possibility of inclusion in a controlled clinical trial should be considered.

Key words: COPD, pulmonary hypertension, chronic respiratory failure, pulmonary vascular resistance, out of proportion pulmonary hypertension

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide, with an increasing prevalence in recent years [1]. One well-known complication of COPD is pulmonary hypertension (PH), a condition that was denominated "cor pulmonale" in the past [2–4].

In the updated WHO classification of pulmonary hypertension [5] PH secondary to COPD is placed in group 3, i.e. PH associated with lung diseases and/or hypoxemia (Tab. 1). Owing to its frequency COPD is by far the most common cause of PH in this group, far more common than interstitial lung disease and obesity-hypoventilation syndrome. When considering the five groups of

classification, COPD is the most frequent cause of PH just after PH secondary to left heart disease. With time, PH may lead to the development of right ventricular enlargement, which may result in right ventricular failure, but it should be emphasized that PH is only one among other complications of advanced COPD and that the prognosis of COPD is linked to the severity of respiratory insufficiency rather than to the occurrence of PH, which is essentially a "marker" of long-standing hypoxaemia [6]. Indeed, this does not apply to severe or "disproportionate" PH, but very few COPD patients exhibit this severe form of PH [7].

This review article gives an overview of PH resulting from COPD and tries to cover all aspects from epidemiology to treatment.

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Table 1. Group 3 of the present classification of pulmonary hypertension. Pulmonary hypertension due to lung disease and/or hypoxia

3.1	Chronic obstructive pulmonary disease (COPD)
3.2	Interstitial lung disease
3.3	Other pulmonary diseases
3.4	Sleep disordered breathing
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental abnormalities

Adapted from Simonneau et al. [5]

Definitions

The current definition of PH is a resting mean pulmonary artery pressure (PAP) measured by right heart catheterization (RHC) ≥ 25 mm Hg [8, 9]. It is accepted that normal PAP is between 8 and 20 mm Hg [8–10]. In the past, PH complicating chronic respiratory disease was generally defined by a resting PAP > 20 mm Hg [11], which is slightly different from the present definition of PH [8, 9] and is explained by the fact that a resting PAP > 20 mm Hg was considered as being abnormal, even in elderly subjects. These various definitions should be kept in mind when comparing studies, particularly in terms of prevalence of PH in COPD [12].

Severe PH in COPD could be defined by a PAP > 35 [13] or > 40 mm Hg [7] in patients investigated at rest during a stable state of the disease. In fact, there is no consensual definition of severe PH in COPD.

In the “natural history” of COPD PH is often preceded by an abnormally large increase in PAP during exercise [14], generally defined by a mean pressure > 30 mm Hg for a mild level of exercise. The term “exercising” pulmonary hypertension has been used, but we believe that the term pulmonary hypertension should be reserved to resting PH [4].

Prevalence of PH in COPD

Determination of the prevalence of PH in COPD has been impeded by difficulties in obtaining valid data from an adequate sample of COPD patients. The main reason is that right heart catheterization (RHC), the gold standard for the diagnosis of PH, cannot be performed on a large scale in COPD patients for ethical reasons, and Doppler echocardiography, which is the best noninvasive method [15], is often inaccurate in COPD [16].

Only studies from hospital-based samples are presently available, but they have no real epidemiologic value. The prevalence of PH, defined by PAP

> 20 mm Hg, ranges from 35% to more than 90% [7, 13, 17–19]. In the studies conducted by Scharf et al. [19], Thabut et al. [13] and Chaouat et al. [7], 5%, 13.5% and 5.8%, respectively, of the COPD patients had severe PH (PAP > 35 or 40 mm Hg).

To our knowledge, the only population-based study that aimed to determine the prevalence of subjects in the general population at risk of developing PH (i.e. markedly hypoxemic subjects with severe COPD) is that of Williams and Nicholl [20]. They estimated that in Sheffield (UK) 0.3% of adults aged ≥ 45 years were at risk. Extrapolating for England and Wales, this would represent 60,000 subjects. However, these data were obtained more than 20 years ago, whereas the incidence and prevalence of COPD have markedly increased in recent years. The prevalence of COPD is estimated to be approximately 5% in the adult population in most European countries [21], and 6% of COPD patients have severe or very severe disease and are at risk of PH [12]; this would represent approximately 1.5 million patients for Europe.

Pathology

The structural basis of PH in COPD includes three potential mechanisms: remodelling, reduction in the total number of pulmonary vessels, and pulmonary thrombosis. However, the only demonstrated morphological basis is the remodelling of the pulmonary arteries and arterioles. Remodelling includes muscularization of pulmonary arterioles ($< 80 \mu\text{m}$) which can extend to the periphery in precapillary vessels ($20 \mu\text{m}$), and changes in the intima: intimal thickening is observed in muscular pulmonary arteries and in pulmonary arterioles [22, 23]. These intimal lesions are characterized by the development of longitudinal muscle and fibrosis. The other component of intimal thickness is the occurrence of inner muscular tubes, i.e. a new layer of circular smooth muscle sandwiched between internal and external lamina in pulmonary arterioles [24].

It has been known for many years that pulmonary vascular remodelling is present not only in advanced COPD, but also in patients with mild COPD [25, 26]. It has been shown in recent years that smokers with normal lung function may develop intimal thickening in pulmonary muscular arteries [26]. These structural abnormalities could be the consequence of endothelial dysfunction of pulmonary arteries, probably induced by cigarette smoke [26]. However, the clinical relevance of these early abnormalities is presently unknown, and it should be emphasized that they have been observed in smokers and in mild COPD patients not exhibiting PH.

Mechanisms of PH in COPD

PAP represents the sum of the pulmonary artery “capillary” (wedge) pressure (PCWP), which is equivalent to the left atrial pressure (LAP), and of the driving pressure across the pulmonary circulation (DP). The latter is the product of cardiac output (\dot{Q}) and pulmonary vascular resistance (PVR). Accordingly,

$$\begin{aligned} \text{PAP} &= \text{PCWP (or LAP)} + \text{DP} \\ \text{PAP} &= \text{PCWP} + \dot{Q} \times \text{PVR} \end{aligned}$$

Thus, three variables can contribute to an elevation of PAP: wedge pressure, cardiac output and pulmonary vascular resistance. In COPD the role of an elevated cardiac output is almost negligible. An abnormally elevated wedge pressure has been observed in a relatively high percentage of COPD patients in some studies [19, 27]. However, many of these patients had an associated left heart disease [19, 27]. One hypothesis is that the increase in intrathoracic pressure in emphysematous patients may induce an increase in PCWP. This has been frequently observed during exercise [28] and has been attributed to dynamic hyperinflation [29].

Actually, at rest and during a steady state of the disease, PCWP is most often normal in COPD patients not exhibiting associated significant left heart disease. Thus, in COPD PH is precapillary, almost exclusively accounted for by the increased PVR [4, 30].

The factors leading to an increased PVR in COPD are numerous, but alveolar hypoxia is the predominant one [31]. Two distinct mechanisms of action of alveolar hypoxia must be considered: acute hypoxia causes pulmonary vasoconstriction, and chronic hypoxia induces, with time, structural changes in the pulmonary vascular bed, i.e. remodelling of the pulmonary vasculature [32].

Acute alveolar hypoxia induces a rise of PVR and PAP in humans as well as in almost all species of mammals that is accounted for by hypoxic pulmonary vasoconstriction (HPV) [33, 34]. HPV is observed in normal subjects [34] as well as in patients with chronic respiratory disease [35]. This vasoconstriction is localized in the resistance pulmonary arteries ($< 500 \mu\text{m}$) and its precise mechanism is now better understood. In particular, there has been a marked improvement of the knowledge of smooth muscle cell potassium channels involved in the regulation of the pulmonary vascular tone [36] and of the endothelium-derived mediators [37].

In normal humans the reactivity of the pulmonary circulation to acute hypoxia varies from one individual to another and this interindividual variability is also found in COPD patients [38], but the potential clinical consequences of this variability are presently unknown. The situations which bear the closest analogy with acute hypoxic challenges are severe exacerbations of COPD leading to acute respiratory failure [39] and the sleep-related episodes of worsening hypoxaemia [40].

Chronic alveolar hypoxia induces, in healthy people living at altitudes > 3500 m, precapillary PH similar to that observed in COPD [41], and morphological studies have shown remodelling of the pulmonary vascular bed. There is some degree of similarity between these structural changes and those observed in COPD patients with PH, and it is accepted that chronic alveolar hypoxia is the main cause of pulmonary vascular remodelling in COPD, even though one morphological study led to different conclusions [22].

Chronic alveolar hypoxia is not the only factor leading to elevated PVR. Patients with advanced COPD have marked morphological changes of the lung (including loss of capillaries and reduction of the pulmonary vascular bed), particularly when emphysema is severe, and these changes could partly account for the increased PVR [19, 22].

It has been hypothesized that inflammation of the pulmonary arteries could contribute to pulmonary vascular remodelling in COPD, and to the elevation of PVR [42]. However, few studies have confirmed this hypothesis [43]. It has also recently been shown that systemic inflammation increases the risk of developing PH in COPD [44, 45]. The issue of the role of inflammation in PH complicating COPD remains controversial [46].

Finally, the occurrence and the degree of severity of PH in COPD could be modulated by genetic factors, as suggested by recent studies [47, 48]. More studies are needed in this field.

Diagnosis of PH in COPD

Symptoms and physical signs are of little help in the diagnosis of PH. Dyspnoea is generally present in advanced COPD patients with and without PH. Dyspnoea is the consequence of airflow limitation and pulmonary hyperinflation rather than PH.

Physical signs occur late, being observed at an advanced stage of the disease far after the development of PH. Peripheral (ankle) oedema is the best sign of right heart failure (RHF), but it is not specific and can arise from other causes [49]. In some patients with PH it does not occur at all.

A murmur of tricuspid regurgitation, suggesting right ventricular dilatation, is rarely present in COPD patients, which can be explained by the mild to moderate degree of PH in most COPD patients.

The sensitivity of the electrocardiogram (ECG) for the diagnosis of PH is poor (20–40%) whereas the specificity of signs of right ventricular hypertrophy is high [50]. A normal ECG does not exclude the presence of PH in COPD patients. The radiological prediction of PH is even more problematic since radiological signs lack both sensitivity and specificity [50].

Magnetic resonance imaging is probably the best method for the measurement of right ventricular ejection fraction [51], right ventricular mass and the diameter of the pulmonary artery, but its role in the diagnosis strategy of PH in COPD is not well established.

Doppler echocardiography is by far the best method for the noninvasive diagnosis of PH [15]. The maximum velocity of the tricuspid regurgitation jet allows the calculation of the right ventricular to right atrial gradient according to the Bernoulli equation. The gradient is added to right atrial pressure (5 or 10 mm Hg) to give an estimated value of right ventricular systolic pressure that is equal to pulmonary artery systolic pressure. With the same technique (continuous wave Doppler echocardiography) it is possible, in cases of pulmonary regurgitation, to estimate the pulmonary artery diastolic pressure.

However, in COPD the chance of obtaining tricuspid regurgitation signals of sufficient quality is generally low [52]. In the large series ($n = 374$) of candidates for lung transplantation (most of them being COPD) investigated by Arcasoy et al. [16] the estimation of systolic PAP was possible in only 44% of the patients, and 52% of pressure estimations were found to be inaccurate when compared with pressures measured during RHC (> 10 mm Hg difference). In a recent study [53] the bias of Doppler echocardiography in the measurement of systolic PAP compared with RHC was 2.8 mm Hg (95% CI: -18.7 – 24.0 mm Hg), which is high when one takes into account the modest level of PH in most COPD patients.

Systolic PAP can also be estimated from Doppler pulmonary flow velocity curves since the correlations between systolic PAP and the time to peak pulmonary blood velocity (acceleration time measured by pulsed Doppler echocardiography) are strong [54]. To our knowledge, the evaluation of right ventricular dysfunction with the Tei index and the tricuspid annular displacement has not been performed in COPD patients [12].

Plasma brain natriuretic peptide could be a biomarker of PH in chronic lung diseases [55], but studies are needed to determine whether it is a useful diagnostic tool in COPD patients.

RHC continues to be the gold standard for the diagnosis of PH [18, 30]. It allows the direct measurement of PAP, PCWP, right heart filling pressures, and cardiac output by thermodilution or according to Fick's principle. Measurements are performed at rest in the supine position and can be obtained during steady-state exercise and after therapeutic interventions (O_2 , NO and other vasodilators). PVR is calculated according to the formula: $PVR = \frac{PAP - PCWP}{\dot{Q}}$, where \dot{Q} is the cardiac output.

The major drawback of RHC is indeed its invasive nature. The procedure has some risks and can not be performed on a large scale in COPD patients. Furthermore, there is no evidence-based study demonstrating its clinical value in advanced COPD [12]. Therefore, RHC can not be used routinely.

In COPD patients, Doppler echocardiography must be performed when PH is suspected (patients with chronic hypoxaemia, severe and very severe COPD, i.e. stages 3 and 4 of the GOLD classification). The indications of RHC should be limited to the cases where there is a suspicion of severe PH (systolic pressure estimated from Doppler echocardiography > 50 – 60 mm Hg). RHC can help to differentiate diastolic left heart failure from precapillary PH in COPD since it allows the measurement of capillary (wedge) pressure (PCWP). Accordingly, RHC may be useful for prescribing the most appropriate treatment.

Characteristics of PH in COPD

PH is precapillary with an increased pressure difference between PAP and PCWP reflecting the increased PVR (Fig. 1). In almost all COPD patients marked oscillations of systolic and diastolic pulmonary pressure are observed with respiration (Fig. 1). These oscillations reflect the elevated intrathoracic pressure changes due to increased airway resistance.

The main characteristic of PH in COPD is probably its mild to moderate degree, with resting PAP in a stable state of the disease usually ranging between 20–25 and 35 mm Hg [14, 18]. This modest degree of PH, also observed in other chronic respiratory diseases [56, 57], is very different from other causes of PH, such as chronic pulmonary thromboembolic disease (CTEPH) and in particular idiopathic pulmonary arterial hypertension (IPAH) in which PAP is usually > 40 mm Hg and may exceed 80 mm Hg in some patients. Table 2

compares the pulmonary haemodynamic data of COPD patients exhibiting PH [18], a series of patients with idiopathic pulmonary fibrosis (IPF) [56] and obesity-hypoventilation syndrome (OHS) [57], a series of patients with IPAH (French Registry) [58], and a series of CTEPH from San Diego (USA)

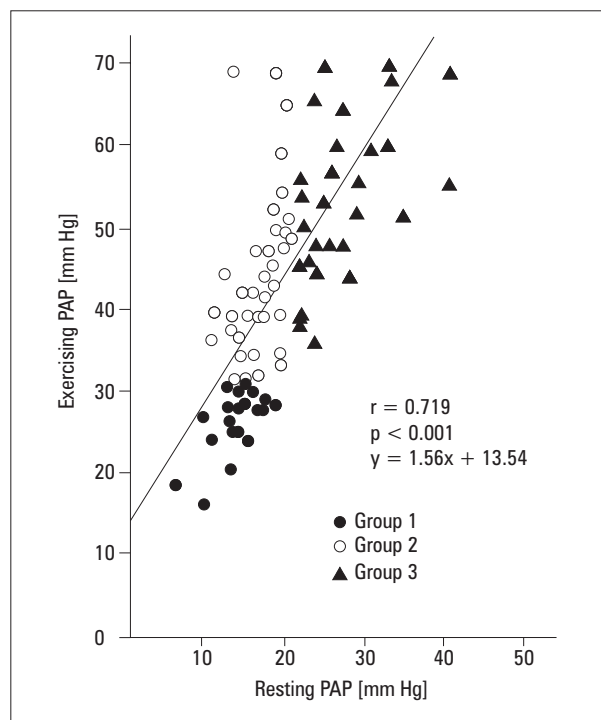


Figure 1. Resting and exercising pulmonary artery mean pressure (PAP) in a large series of chronic obstructive pulmonary disease patients. Group 1: resting PAP < 20 mm Hg and exercising PAP < 30 mm Hg. Group 2: resting PAP < 20 mm Hg and exercising PAP > 30 mm Hg. Group 3: resting PAP > 20 mm Hg (personal data)

[59]. It can be seen that PH is severe in IPAH (mean PAP of 56 mm Hg) and in CTEPH (46 mm Hg) but is rather mild in COPD (26 mm Hg), as well as in IPF (24 mm Hg) and in OHS (26 mm Hg).

In COPD, when PH occurs, PVR is moderately increased and cardiac output is in the normal range, contrasting with IPAH and CTEPH (Tab. 2). A PAP > 40 mm Hg is unusual in COPD patients, except when they are investigated during an acute exacerbation [4] or when there is an associated cardiopulmonary disease [7]. The consequences of the modest level of PH include the absence or late occurrence of RHF. However, PH, even if mild at baseline, may worsen during exercise, sleep and acute exacerbation of the disease [4].

PAP increases markedly during steady state exercise in COPD patients with resting PH [4, 17, 60], as illustrated in Figure 2, which shows that in these patients' (Group 3) PAP rises from a mean of 27 to 55 mm Hg during a 30–40 watt exercise of 7–10 min. duration. This is explained by the fact that PVR does not decrease during exercise in these patients whereas it does in healthy subjects.

Acute increases of PAP during sleep have been observed in COPD patients with respiratory failure [40]. They are principally observed in REM sleep, during which dips in oxygen saturation are more severe. These episodes are not caused by apnoeas, except if COPD is associated with a sleep apnoea syndrome, but by alveolar hypoventilation and/or ventilation-perfusion mismatching [40]. PAP can increase by > 10 mm Hg from its baseline value [4].

In patients with advanced COPD severe exacerbations can lead to acute respiratory failure characterized by a worsening of hypoxaemia and

Table 2. Comparison of pulmonary hypertension in chronic hypoxic lung disease (COPD, IPF, OHS) to idiopathic pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)

	COPD	IPF	OHS	Idiopathic PAH	CTEPH
References	18	56	57	58	59
Number of patients	62	31	36	259	500
Age (years)	55 ± 8	58 ± 16	62 ± 12	50	–
FEV ₁ [mL]	1170 ± 390	1655 ± 650	1610 ± 600	–	–
FEV ₁ (% of predicted)	–	–	–	> 70	–
PaO ₂ [mm Hg]	60 ± 9	68 ± 12	59 ± 8	–	–
PaCO ₂ [mm Hg]	45 ± 6	35 ± 5	50 ± 4	–	–
PAP [mm Hg]	26 ± 6	24 ± 11	26 ± 10	56	46
PCWP [mm Hg]	8 ± 2	7 ± 4	–	8	–
Q̇ [L/min/m ²]	3.8 ± 1.1	3.4 ± 0.8	2.9 ± 0.9	2.3	2.2

Mean values ± standard deviation. COPD — chronic obstructive pulmonary disease; FEV₁ — forced expiratory volume in 1 second; IPF — idiopathic pulmonary fibrosis; OHS — obesity-hypoventilation syndrome; PAP — pulmonary artery mean pressure; PCWP — pulmonary capillary wedge pressure; Q̇ — cardiac output

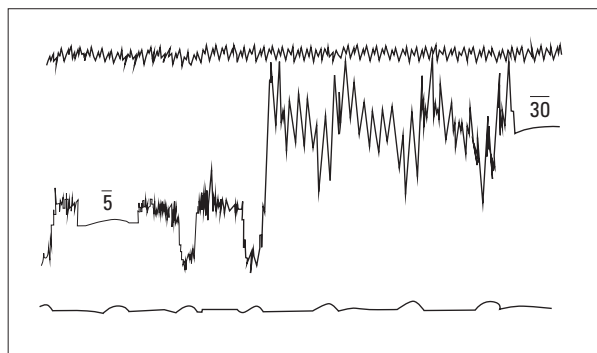


Figure 2. In chronic obstructive pulmonary disease (COPD) pulmonary hypertension is “precapillary”: the pulmonary “capillary” wedge pressure (left part of the trace) is normal (5 mm Hg), whereas pulmonary artery mean pressure (right part of the trace) is elevated (30 mm Hg) owing to the elevation of pulmonary vascular resistance. In COPD patients, important swings of systolic and diastolic pulmonary artery pressure from inspiration to expiration are observed, which reproduce the elevated intrathoracic pressure changes

hypercapnia. In patients exhibiting PH there is a simultaneous increase of PAP from its baseline value [39]. PAP may increase by as much as 20 mm Hg but usually returns to baseline after recovery [4]. The striking parallel between changes in PaO₂ and PAP suggests the presence of hypoxic pulmonary vasoconstriction.

Thus, even though PH is usually mild to moderate in COPD patients, it may increase markedly during exercise, sleep and exacerbations of the disease; these acute increases of afterload, especially during exacerbations, can favour the development of RHF [49].

Severe and “out of proportion” PH in COPD

As mentioned previously, PH in COPD is usually mild to moderate with a resting PAP ranging between 20 and 35 mm Hg. A minority of COPD patients exhibit severe PH, which can be defined by resting PAP > 35 mm Hg [13, 19] or > 40 mm Hg [7]. This level of PH is considered to be “out of proportion” in COPD patients investigated during a stable state of the disease, and recent studies have aimed to evaluate its frequency and understand its mechanisms [7, 13]. Chaouat et al. [7] observed that from 998 COPD patients investigated, when clinically stable with right heart catheterization performed between 1990 and 2002, only 27 had resting PAP ≥ 40 mm Hg. Of the 27 patients, 16 had an associated disease that could explain in part the severity of PH: 4 had a left heart disease responsible for an increased PCWP and a decreased left ventricular ejection fraction; 2 patients had CTEPH; and

Table 3. Comparison of COPD patients with severe (PAP > 40 mm Hg) pulmonary hypertension to patients with usual pulmonary hypertension (PAP 20–40 mm Hg)

Variables	Severe PH without associated disease (n = 11)	Usual PH (n = 16)
Age (years)	67 (62–68)	66 (63–73)
FEV ₁ (% predicted)	50 (44–56)	27 (23–34)
FEV ₁ /VC (%)	49 (39–53)	34 (26–38)
DLCO [mL/min/mm Hg]	4.6 (4.2–6.7)	10.3 (8.9–12.8)
PaO ₂ [mm Hg]	46 (41–53)	56 (54–64)
PaCO ₂ [mm Hg]	32 (28–37)	47 (44–49)
A–aO ₂ [mm Hg]	56 (50–68)	30 (27–37)
PAP [mm Hg]	48 (46–50)	25 (22–37)
PCWP [mm Hg]	6 (4–7)	7 (6.5–7.5)
Q̇ [L/min/m ²]	2.3 (1.8–2.5)	2.8 (2.4–3.1)
TPR [IU/m ²]	21.3 (17.6–36.6)	9.0 (7.4–9.9)

A–A_o — alveolar arterial PO₂ difference; DLCO — diffusion capacity for carbon monoxide; FEV₁ — forced expiratory volume in 1 second; PAP — pulmonary artery mean pressure; PCWP — pulmonary capillary wedge pressure; PH — pulmonary hypertension; TPR — total pulmonary resistance; VC — vital capacity. Values are median (interquartile range). Adapted from Chaouat et al. [7]

6 had an associated restrictive lung disease (mainly severe obesity plus obstructive sleep apnoeas). In these 6 latter patients PaO₂ was very low (44 ± 4 mm Hg), with a further decrease during sleep. Finally, just 11 patients had COPD as the only cause of severe PH [7]. In view of these results, it must be recommended that the presence of an associated disease should be investigated in COPD patients with severe PH. This severe PH is uncommon in COPD (1.1% of the patients investigated) [7]. Table 3 indicates that these patients have less severe bronchial obstruction than COPD patients with “usual” PH, and their mean FEV₁ was 50% of the predicted value; they had profound hypoxaemia and exhibited hypocapnia.

Thabut et al. [13] identified, by statistical analysis, a similar subgroup of 16 patients with moderately severe bronchial obstruction contrasting with severe PH. The patients of Thabut et al. [13] and Chaouat et al. [7] with severe PH represent a subset of COPD patients in whom pulmonary vascular disease is predominant. Actually, some characteristics of these patients (low cardiac output, hypocapnia, low DLCO) are similar to those observed in idiopathic PAH. Due to the severity and the scattered number of COPD patients with severe (or “out of proportion”) PH, these patients should be referred to an expert centre of pulmonary vascular disease so that RHC can be performed, and they should be included in registries and clinical trials [8].

Table 4. Evolution of arterial blood gases and haemodynamic variables before (T1) and during (T2) an episode of peripheral oedema in severe COPD patients

	RVEDP [mm Hg]		PAP [mm Hg]		\dot{Q} [l/min/m ²]		PaO ₂ [mm Hg]		PaCO ₂ [mm Hg]	
	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
Group 1 (n = 9)	7.5 ± 3.9	13.4 ± 1.2*	27 ± 5	40 ± 6*	3.23 ± 0.82	3.19 ± 1.07	63 ± 4	49 ± 7*	46 ± 7	50 ± 14*
Group 2 (n = 7)	5.5 ± 2.4	5.1 ± 1.5	20 ± 6	21 ± 5	3.63 ± 0.36	3.29 ± 1.32	66 ± 7	59 ± 7	42 ± 6	45 ± 6

PAP — pulmonary artery mean pressure; \dot{Q} — cardiac output; RVEDP — right ventricular end-diastolic pressure. T1 — stable state of the disease; T2 — episode of oedema. Group 1 — patients with haemodynamic signs of right heart failure (elevated RVEDP); group 2 — patients without haemodynamic signs of right heart failure. Values are mean ± SD. Adapted from Weitzenblum et al. [49]

*Difference between T1 and T2 statistically significant, $p < 0.001$

Evolution and prognosis of pulmonary hypertension in COPD

The “natural history” of PH in COPD is not fully understood [14], but several studies have shown that the progression of PH is generally slow and that PAP may remain stable over periods of 2 to 5 years [61, 62]. In a study in which 93 patients were followed-up for 5–12 years, the changes in PAP were rather small: + 0.5 mm Hg/year for the group as a whole [63]. Nevertheless, a minority of advanced COPD patients exhibit a marked worsening of PAP during follow-up [63]. These patients are characterized by a progressive deterioration of PaO₂ and PaCO₂ during the follow-up [62, 63]. A study on the “natural history” of pulmonary haemodynamics in COPD patients with an initial PAP < 20 mm Hg showed that only 33 of 121 developed PH (PAP > 20 mm Hg) after a mean interval of 6.8 ± 2.9 years [14].

Does PH lead, with time, to RHF? Peripheral oedema are frequently observed in advanced COPD patients and are considered to reflect RHF, but the possible occurrence of RHF in these patients has been questioned [64], particularly because the degree of PH is most often mild in COPD. Peripheral oedema may simply indicate the presence of secondary hyperaldosteronism induced by functional renal insufficiency and is not synonymous with heart failure [3, 64].

The role of pressure overload (i.e. pulmonary hypertension) in the development of RHF in these patients has been debated. It has been denied by MacNee et al. [65], but another study from our group [49] has led to different conclusions: in 9 of 16 patients with marked peripheral oedema during an exacerbation of COPD, haemodynamic signs of RHF were present during the episode of oedema and were probably accounted for by a significant worsening of PH (from 27 ± 5 to 40 ± 6 mm Hg, $p < 0.001$) which, in turn, was explained by a worsening of hypoxemia. Thus, many patients

with advanced COPD will never develop RHF; however, some patients will experience episodes of “true” RHF during exacerbations of the disease accompanied by a worsening of PH [49] (Tab. 4).

The level of PAP is a good indicator of prognosis in COPD (18,66). The prognosis is worse in patients with PH compared with patients without PH [18, 66] and is particularly poor in patients with severe PH, including patients with disproportionate PH [7]. The 5-year survival rate of COPD patients with PH (PAP > 20 mm Hg) is about 50% [18, 66], but these results were obtained before the era of long-term oxygen therapy (LTOT), which significantly improves the prognosis of markedly hypoxaemic patients, most of them exhibiting PH [67, 68]. Of interest is that PAP remains an excellent prognostic indicator in COPD patients treated with LTOT [6].

Treatment of pulmonary hypertension in COPD

The treatment of PH in COPD is based on LTOT. This raises the important question as to whether it is necessary to treat PH in COPD with methods other than LTOT. PH, even if modest in most patients, may worsen during acute exacerbations, and these acute increases in PAP may contribute to the development of RHF [62]. This could represent an argument for the treatment of PH, which must be also considered in all cases of severe PH (PAP > 35–40 mm Hg).

Long-term oxygen therapy

Alveolar hypoxia is considered to be the major determinant of the elevation of PVR and PAP in COPD patients. Accordingly, LTOT is a logical treatment of PH in COPD. The well-known Nocturnal Oxygen Therapy Trial (NOTT) [67] and Medical Research Council (MRC) study [69] were not principally devoted to pulmonary haemodynamics, but RHC was performed at the onset in all patients and

follow-up dates were available for a relatively high number of patients. In the MRC study [68] LTOT patients had a stable PAP after one year whereas control patients had a significant increase in PAP. In the NOTT study [67] continuous LTOT (≥ 18 h/day) slightly but significantly decreased resting and exercising PAP after 6 months whereas nocturnal LTOT (10–12 h/day) did not.

Further studies more specifically devoted to the pulmonary haemodynamic evolution under LTOT [69, 70] have shown either a tendency towards the reversal of the progression of PH [69] or a stabilization of PH under LTOT [70] over periods of two to six years. However, PAP seldom returned to normal. It must be emphasized that the best haemodynamic results have been obtained in studies in which the daily duration of LTOT was the longest (≥ 16 –18 h/day) [67, 69]. Accordingly, one should recommend continuous oxygen therapy.

Vasodilator drugs

Experience with vasodilators (prostanoids, endothelin receptors antagonists, phosphodiesterase 5 inhibitors) has come from the treatment of IPAH. It is tempting to use these drugs in cases of PH complicating COPD, particularly in the (rare) cases of severe (“disproportionate”) PH. Unfortunately, there have been very few studies in this field. In the only (to our knowledge) controlled study in which COPD patients with mild resting PH or no resting PH at all received bosentan or placebo, the results were disappointing and included a worsening of hypoxaemia [71], which is a well-known deleterious effect of vasodilators in COPD.

Nitric oxide is a selective and potent pulmonary vasodilator. One long-term study (3 months) in 40 patients already on LTOT showed that the addition of nitric oxide produced significant improvement in PAP, PVR and cardiac output [72]. However, the technological and toxicological problems related to the prolonged use of inhaled NO are far from being solved, and, to our knowledge, inhaled NO is not used at present in stable COPD patients.

It is presently recommended not to treat COPD patients with drugs dedicated to IPAH outside of trials and to refer patients with severe PH to a regional specialist PH centre [8].

Finally, single-lung transplantation could be considered in COPD patients with severe PH aged < 65 years and without severe comorbidities [12], but we lack studies in this field [73].

Conflict of interest

The Authors declare no conflict of interest.

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