



SERIES “PULMONARY HYPERTENSION: BASIC CONCEPTS FOR PRACTICAL MANAGEMENT”

Edited by M.M. Hoeper and A.T. Dinh-Xuan
Number 6 in this Series

Pulmonary hypertension in COPD

A. Chaouat*, R. Naeije# and E. Weitzenblum[†]

ABSTRACT: Mild-to-moderate pulmonary hypertension is a common complication of chronic obstructive pulmonary disease (COPD); such a complication is associated with increased risks of exacerbation and decreased survival. Pulmonary hypertension usually worsens during exercise, sleep and exacerbation. Pulmonary vascular remodelling in COPD is the main cause of increase in pulmonary artery pressure and is thought to result from the combined effects of hypoxia, inflammation and loss of capillaries in severe emphysema.

A small proportion of COPD patients may present with “out-of-proportion” pulmonary hypertension, defined by a mean pulmonary artery pressure >35–40 mmHg (normal is no more than 20 mmHg) and a relatively preserved lung function (with low to normal arterial carbon dioxide tension) that cannot explain prominent dyspnoea and fatigue. The prevalence of out-of-proportion pulmonary hypertension in COPD is estimated to be very close to the prevalence of idiopathic pulmonary arterial hypertension.

Cor pulmonale, defined as right ventricular hypertrophy and dilatation secondary to pulmonary hypertension caused by respiratory disorders, is common. More studies are needed to define the contribution of cor pulmonale to decreased exercise capacity in COPD. These studies should include improved imaging techniques and biomarkers, such as the B-type natriuretic peptide and exercise testing protocols with gas exchange measurements.

The effects of drugs used in pulmonary arterial hypertension should be tested in chronic obstructive pulmonary disease patients with severe pulmonary hypertension. In the meantime, the treatment of cor pulmonale in chronic obstructive pulmonary disease continues to rest on supplemental oxygen and a variety of measures aimed at the relief of airway obstruction.

KEYWORDS: Chronic obstructive pulmonary disease, hypoxaemia, inflammation, oxygen therapy, pulmonary hypertension, vasodilator agents

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide with an increasing prevalence during the past decades [1]. One established complication of COPD is the development of pulmonary hypertension (PH). Typically, PH appears when airflow limitation is severe and is associated with chronic hypoxaemia, the main pathophysiological cause being chronic alveolar hypoxia, although new mechanisms have emerged recently. In older studies, mean pulmonary artery pressure (\bar{P}_{pa}) was significantly linked to the severity of COPD and

was considered to be an important prognostic factor and part of the justification for long-term oxygen therapy (LTOT). Nowadays, in a time of LTOT, PH is a significant risk factor for hospitalisation [2] and is still associated with a shorter life expectancy [3]. In most cases, PH is mild to moderate [4–6] but it may be severe and could be observed without major airflow limitation. This latter condition has been termed “out-of-proportion” PH. In a recent study [6], it has been reported that, unlike “usual” PH in COPD patients undergoing LTOT (the most common situation), out-of-proportion PH often leads

AFFILIATIONS

*Dept for Respiratory Diseases and Respiratory Intensive Care, Centre Hospitalier Universitaire de Nancy, Vandoeuvre-les-Nancy and [†]Dept of Pneumology, Centre Hospitalier Universitaire de Strasbourg, Strasbourg, France, and #Dept of Pathophysiology, Erasme Campus, Brussels, Belgium.

CORRESPONDENCE

A. Chaouat
Service des Maladies Respiratoires et Réanimation Respiratoire
Hôpital de Brabois
Allée du Morvan
54511 Vandoeuvre-lès-Nancy Cedex
France
Fax: 33 383154023
E-mail: a.chaouat@chu-nancy.fr

Received:

February 01 2008

Accepted after revision:

May 29 2008

STATEMENT OF INTEREST

Statements of interest for A. Chaouat and R. Naeije can be found at www.erj.ersjournals.com/misc/statements.shtml

Previous articles in this series: No. 1: Dupuis J, Hoeper MM. Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* 2008; 31: 407–415. No. 2: Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2008; 31: 891–901. No. 3: Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Respir J* 2008; 31: 1357–1367. No. 4: Wilkins MR, Wharton J, Grimminger F, Ghofrani HA. Phosphodiesterase inhibitors for the treatment of pulmonary hypertension. *Eur Respir J* 2008; 32: 198–209. No. 5: Warwick G, Thomas PS, Yates DH. Biomarkers in pulmonary hypertension. *Eur Respir J* 2008; 32: 503–512.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

rapidly to right heart failure and death. Given the increasing number of patients, the recognition of susceptibility factors for PH in this disease has important implications for a clear understanding of the natural history of COPD. A better diagnosis strategy for PH in COPD is also mandatory, as is new treatment, particularly in out-of-proportion PH. It must be emphasised that out-of-proportion PH does not match with any group of the last published classification of PH [7] and, thus, there is a need for a consensual definition of this condition.

PH is defined as $\bar{P}_{pa} > 20$ mmHg and is placed in the heterogeneous group of PH associated with disorders of the respiratory system and/or hypoxaemia [7]. The reason for setting such a threshold is that in healthy subjects \bar{P}_{pa} is always < 20 mmHg at rest and, as stated above, a $\bar{P}_{pa} > 20$ mmHg is associated with increased morbidity and mortality. However, in some recent studies PH was defined by $\bar{P}_{pa} > 25$ mmHg [8, 9]. These various definitions should be kept in mind when comparing studies, particularly in terms of prevalence of PH in populations of COPD. Although severe PH in COPD could be defined by $\bar{P}_{pa} > 35$ mmHg in patients undergoing optimal treatment (including LTOT), it must be emphasised that this is not a consensual definition. Cor pulmonale is defined as right ventricular hypertrophy and dilatation or both, secondary to PH caused by respiratory disorders [10]. This article is part of a review series on pulmonary hypertension [11–16].

EPIDEMIOLOGY OF PH IN COPD

Prevalence of PH in COPD

Determination of prevalence of PH in COPD has been hampered by difficulties in obtaining valid data from an adequate population-based sample of COPD. The main reason is that right heart catheterisation (RHC) cannot be performed on a large scale for ethical reasons and it is well known that echocardiography alone is subject to some error [17]. Only studies of hospitalised subjects are available. BURROWS *et al.* [18] reported 36 yrs ago that 50 patients with COPD and severe airflow limitation (forced expiratory volume in one second (FEV₁)/vital capacity (VC) ratio of 37%) had an average \bar{P}_{pa} value of 26 mmHg. In a larger sample of 175 patients with a mean FEV₁/VC ratio of 40%, WEITZENBLUM *et al.* [19] observed a prevalence of PH (defined as $\bar{P}_{pa} > 20$ mmHg) of 35%.

The 120 patients with severe emphysema evaluated for participation in the National Emphysema Treatment Trial [20] had a mean \pm SD \bar{P}_{pa} of 26.3 ± 5.2 mmHg. The 95% confidence interval (CI) of the true mean in such a population was 25.4–27.2 mmHg. These results obtained when LTOT was readily available confirmed that PH when present in patients with severe COPD is mild to moderate, but also extremely prevalent, since in this series of patients 91% had $\bar{P}_{pa} > 20$ mmHg. VIZZA *et al.* [21], in a cohort of 168 patients with COPD listed for lung transplantation, observed similar results in terms of \bar{P}_{pa} , with a 95% CI of 24.1–25.9 mmHg. THABUT *et al.* [8], investigating the two types of population, *i.e.* candidates for lung volume reduction surgery (LVRS) and candidates for lung transplantation, had comparable results. Mild (\bar{P}_{pa} 26–35 mmHg), moderate (36–45 mmHg) and severe (> 45 mmHg) PH was present in 36.7, 9.8 and 3.7% of the 215 patients, respectively. In a large series of 998 patients with COPD [6] with less airway limitation and hypoxaemia than the two studies quoted above, the \bar{P}_{pa} was 20.3 ± 8.1 mmHg. This latter

study demonstrated that the prevalence of $\bar{P}_{pa} > 20$ mmHg in hospitalised COPD patients is $\sim 50\%$. When considering patients listed for LVRS or lung transplantation the prevalence of PH would lie between 70–90%.

In the large population of patients with COPD, it is worthwhile to estimate the proportion of those with severe PH. In the study reported by SCHARF *et al.* [20] considering pulmonary haemodynamics of patients with severe emphysema, only 5% of the population as a whole had $\bar{P}_{pa} > 35$ mmHg. It should be made clear that this latter figure is underestimated since severe PH was a criterion of exclusion in the National Emphysema Treatment Trial [20]. In the studies conducted in France by THABUT *et al.* [8] and by CHAOUAT *et al.* [6], 13.5% and 5.8% of the population had severe PH ($\bar{P}_{pa} \geq 35$ mmHg), respectively. Interestingly, in these two studies \bar{P}_{pa} was positively skewed, indicating that a significant number of patients with COPD had severe PH (fig. 1). Importantly, all the patients in both studies, even those with a high elevation of \bar{P}_{pa} , were in a stable state of the disease and had optimal treatment including LTOT.

The other method by which the prevalence of PH in COPD can be estimated is to look at recent epidemiological studies devoted to COPD. The prevalence of COPD among adults in eight European cities has been estimated to be as high as 6.2% [22]. Knowing that COPD is usually progressive, many patients will be at risk of PH in the near future [23]. Furthermore, it must be considered that this population of COPD has lot of comorbidities that could raise the level of PH. Indeed, ischaemic heart disease, hypertensive cardiomyopathy, chronic heart failure and worsening of chronic respiratory failure due to obesity are frequently encountered [24]. According to a prevalence of COPD of $\sim 5\%$ in the adult population in most European countries, and that 6% of patients have severe or very severe disease, the number of patients in Europe with severe PH (1% of the severe and very severe COPD patients are likely to have $\bar{P}_{pa} > 40$ mmHg [6]) may be $\sim 7,500$. When related to the adult French population, the figure would be 650, which is very close to a prevalence of 15 cases per million patients with pulmonary arterial hypertension (PAH) in the same country [25]. In light of all these studies, it is highly probable that

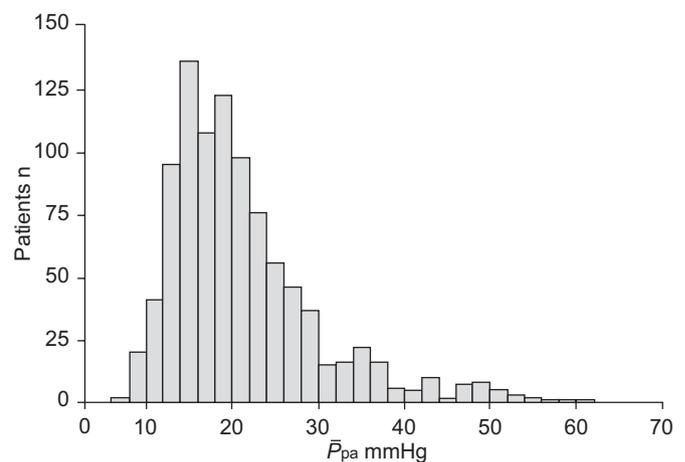


FIGURE 1. Mean pulmonary artery pressure (\bar{P}_{pa}) in a hospital-based cohort of 998 chronic obstructive pulmonary disease (COPD) patients with a mild to very severe airflow limitation. It can be seen that severe pulmonary hypertension is uncommon in COPD but does exist. Data taken from [6].

the number of COPD patients with PH is high, with a mild-to-moderate increase in \bar{P}_{pa} in most cases, but undoubtedly there are also a significant number of patients with severe PH.

Prognostic impact of PH in patients with COPD

Before the introduction of LTOT, it was shown that PH in COPD was an independent prognostic factor. Indeed, patients with similar airflow limitation had lower life expectancy when \bar{P}_{pa} was above the normal value [19, 26]. Now, LTOT improves the survival of hypoxaemic COPD patients. It has been suspected, but not clearly demonstrated, that the increased life expectancy was due to the improvement of pulmonary haemodynamics. Interestingly, \bar{P}_{pa} remains an excellent prognostic factor in patients undergoing LTOT [3, 27, 28]. In the most recent study [3], patients with $\bar{P}_{pa} > 25$ mmHg had a significantly lower survival rate at 5 yrs compared with patients without PH (33 versus 66%; $p < 0.001$; fig. 2a). Importantly, $\bar{P}_{pa} > 18$ mmHg was associated with an increased risk of severe exacerbation in COPD patients with moderate to severe airflow limitation (fig. 2b) [2].

PATHOLOGY

The structural basis of PH in COPD includes three potential mechanisms: remodelling, reduction in the total number of pulmonary vessels, and pulmonary thrombosis [29, 30]. In fact, the only structural basis of PH that is well investigated in pathology is the remodelling of pulmonary arteries and arterioles. However, loss of pulmonary vessels has been shown in experimental models of emphysema and is likely to play an important role in human disease too.

The anatomic abnormalities of pulmonary vasculature in COPD have been documented from necropsy material from patients with severe disease [31, 32]. These studies have shown a muscularisation of pulmonary arterioles. This part of the pre-capillary vascular bed, < 80 μm in diameter, is without muscular layer in normal subjects. In transverse section, pulmonary arterioles in severe COPD patients have distinct media of circularly oriented smooth muscle bounded on its outer and inner aspects by elastic laminae. The muscularisation of pulmonary arterioles can extend to the periphery in pre-capillary vessels as little as 20 μm in diameter. This phenomenon is due to hypertrophy, proliferation and transformation of the phenotype of contractile cells called pericytes, which are precursors of smooth muscle cell, or transformation of intermediate cells. In larger pulmonary arteries (80–1,000 μm in diameter in humans) the media can be thickened or focally atrophied [31, 33, 34]. Muscularisation also occurs in the post-capillary vessels of patients with COPD [35] with a more important amount of extracellular matrix in veins and venules than in pulmonary arteries.

Changes in intima are an important part of the remodelling of pulmonary arteries in patients with COPD. These changes have been observed in patients with end-stage COPD and also in mild disease. Intimal thickening is observed in muscular pulmonary arteries and in pulmonary arterioles [31, 32]. However, pathological studies in COPD have not shown complex lesions, which are frequently encountered in patients with PAH [36], such as plexiform lesions (irregular mass of endothelial cells) or angiomatoid lesions, characteristic of severe PH.

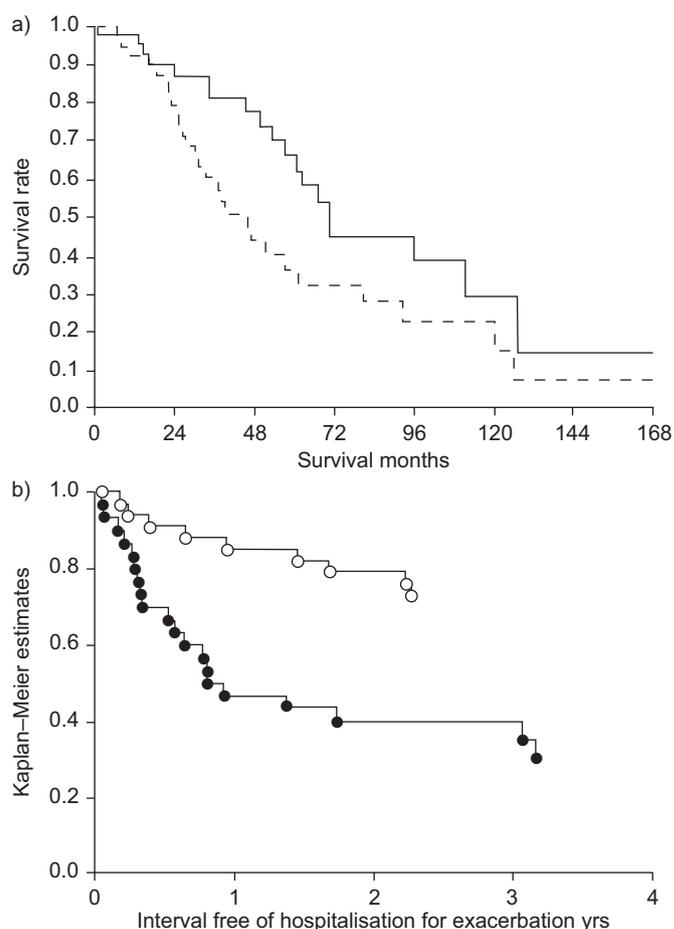


FIGURE 2. Prognostic impact of pulmonary hypertension. a) Chronic obstructive pulmonary disease (COPD) patients with a mean pulmonary artery pressure (\bar{P}_{pa}) ≥ 25 mmHg (---) at the beginning of long-term oxygen therapy have a significantly ($p < 0.001$) shorter life expectancy compared with patients with $\bar{P}_{pa} < 25$ mmHg (—). Reproduced from [3] with permission from the publisher. b) COPD patients with $\bar{P}_{pa} > 18$ mmHg (●) in a stable state of the disease have an increased risk of hospitalisation for exacerbation compared with patients with $\bar{P}_{pa} \leq 18$ mmHg (○). Reproduced from [2] with permission from the publisher.

It has been known for many years that pulmonary artery lesions appear not only in patients with end-stage COPD but also in patients with mild COPD, and even in smokers with normal lung function [32, 37, 38]. Inhaled noxious particles and gases in smokers lead to an inflammatory process with an increased number of CD8+ T-lymphocytes in the wall of central and peripheral airways of smokers and patients with COPD [39, 40]. Interestingly, the same infiltrate of inflammatory cells is present in pulmonary vascular lesions.

PATHOPHYSIOLOGY

\bar{P}_{pa} represents the sum of the pulmonary artery wedge pressure (P_{pw}) and of the driving pressure across the pulmonary circulation. The latter is the product of cardiac output and pulmonary vascular resistance (PVR). Accordingly, one can write:

$$\bar{P}_{pa} = P_{pw} + (\text{CO} \times \text{PVR}) \quad (1)$$

where CO is cardiac output. Thus, three variables can contribute to an elevation of \bar{P}_{pa} : P_{pw} , cardiac output and PVR.

In a large series of COPD patients, a relatively high proportion (19%) of COPD patients with increased P_{pw} at rest has been reported [41]. However, most of these patients had an associated left heart disease. In the haemodynamic study of the National Emphysema Treatment Trial, 61.4% of the 120 patients investigated at entry to the study had an abnormally high P_{pw} (>12 mmHg) [20]. One hypothesis is that the increase in intrathoracic pressure in emphysematous patients may induce an increase in P_{pw} . During exercise, an almost constant increase in P_{pw} in patients of the emphysema type has been observed. Since right atrial pressure, pulmonary artery pressure (P_{pa}) and intra-oesophageal pressure increased in the same proportion as P_{pw} , it was concluded 20 yrs ago that this increase in P_{pw} was due to dynamic hyperinflation [42]. The increase in P_{pw} observed in some COPD patients could also be due to left ventricular diastolic dysfunction secondary to cardiovascular comorbidities or to the so-called ventricular interdependence. This latter mechanism can occur only when the right ventricle is significantly dilated.

Therefore, PH complicating COPD is mostly of the pre-capillary type. A post-capillary component can participate to the increase in P_{pa} , particularly during exercise and acute exacerbations.

The factors leading to an increased PVR in COPD are listed table 1. These factors are numerous but alveolar hypoxia is predominant. In addition, recent reports have suggested that inflammation may contribute to pulmonary vascular remodelling in COPD. In severe emphysema \bar{P}_{pa} and PVR were weakly correlated with diffusing capacity of the lung for carbon monoxide (DL_{CO}), suggesting that, in patients with markedly predominant emphysema, loss of pulmonary capillaries may play a role in the development of PH [20, 43].

Inflammation

It has been hypothesised that the development of structural and functional abnormalities of pulmonary arteries in COPD is related to inflammatory cells in the vascular wall [44]. However, few studies have confirmed this hypothesis. PEINADO *et al.* [40] have reported a relationship between the number of inflammatory cells infiltrating the wall of pulmonary arteries on the one hand, and the enlargement of the intimal layer and endothelial

dysfunction on the other. It is important to note that pulmonary vascular remodelling in this context does not necessary induce PH. The remodelling may take place in an outward direction and, therefore, does not reduce the vascular lumen. However, it has been shown recently that systemic inflammation in COPD appears to increase the risk for developing PH in COPD. Indeed, C-reactive protein [45], as well as pro-inflammatory cytokines, interleukin (IL)-6 and monocyte chemoattractant protein-1 [46], were correlated with the level of \bar{P}_{pa} in two recent studies. In one of these studies, one form of a functional polymorphism of the IL-6 gene accountable for a higher expression of the gene was associated with a higher risk for the development of PH in a population of patients with severe and very severe COPD [46]. The issue of the role of inflammation in PH complicating COPD remains controversial [47]; however, *in vitro* and animal models of pulmonary artery remodelling related to tobacco smoke studies support such a mechanism [48].

Hypoxic PH

Alveolar hypoxia is probably the most important factor leading to an increased PVR [49]. Acute hypoxia induces in humans, as well as in almost all species of mammals, a rise of PVR and P_{pa} that is accounted for by hypoxic pulmonary vasoconstriction (HPV) [50]. This vasoconstriction is localised in the resistance pulmonary arteries (<500 μ m). Its precise mechanism has recently been better identified. In particular, there has been a marked improvement of the knowledge of the smooth muscle cell potassium channels involved in the regulation of the pulmonary vasomotor tone [51] and of the endothelium-derived mediators [48, 52].

In normal humans, the reactivity of the pulmonary circulation to acute hypoxia varies from one subject to another [53] and this interindividual variability is also found in COPD patients [54]. This means that some patients are "responders" to acute hypoxia, exhibiting a marked increase in PVR and P_{pa} during hypoxic challenge, whereas others are "poor responders" or even "nonresponders" (fig. 3) [54].

Although HPV is less active in patients with significant structural changes of small pulmonary arteries, as observed in patients with severe COPD, this response of the pulmonary vascular bed to alveolar hypoxia can have important consequences in many clinical situations. Indeed, HPV can be involved during acute exacerbations of COPD, sleep-related hypoxaemia and exercise. The acute HPV onsets and resolves rapidly and is mainly due to a contraction of small pulmonary artery smooth muscle cells [55–57].

Chronic effects of hypoxia on the pulmonary circulation are mainly known from animal models of hypoxia-induced PH and *in vitro* studies [48]. There are changes in structure and function of all cells and extracellular matrix of the pulmonary vascular wall. For instance, chronic hypoxia increases the synthesis and release of endothelin from endothelial cells [52] and, therefore, amplifies and extends the acute effect of hypoxia on voltage-dependent potassium (K_v) channels. Nitric oxide and prostacyclin, two potent vasodilators synthesised by endothelial cells, are affected by chronic hypoxia. This produces an imbalance in favour of an increase of pulmonary vascular tone and a proliferative state of cells of the vascular wall.

TABLE 1 Confirmed and suspected factors leading to an increased pulmonary vascular resistance in chronic obstructive pulmonary disease (COPD)

Factors of PH in COPD	Consequences on pulmonary vessels
Airflow limitation	Pressure swings
Emphysema	Reduction of the vascular bed
Alveolar hypoxia	Vasoconstriction, remodelling
Hypercapnic acidosis	Vasoconstriction
Polycythaemia	Hyperviscosity
Lung and systemic inflammation	Remodelling, including fibrosis

PH: pulmonary hypertension.

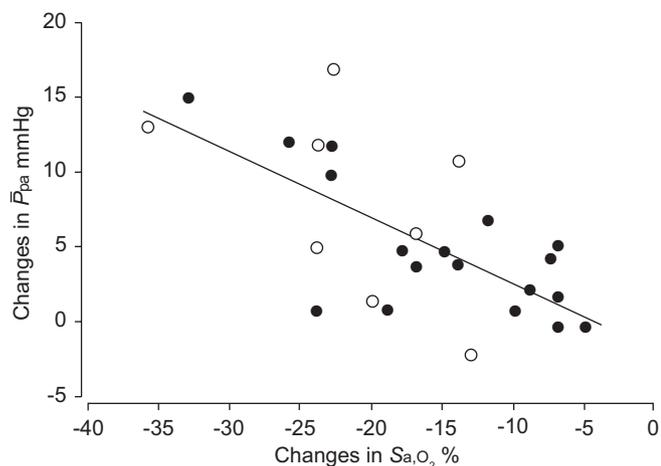


FIGURE 3. Changes in mean pulmonary artery pressure (\bar{P}_{pa}) as a function of changes in arterial oxygen saturation (S_{a,O_2}) from inspiratory oxygen fraction (F_{i,O_2}) 0.21 to 0.13 or 0.15. ●: level of S_{a,O_2} at F_{i,O_2} of 0.21 >90%; ○: level of S_{a,O_2} at F_{i,O_2} of 0.21 <90%. Although there is a statistical significant correlation between changes in \bar{P}_{pa} and changes in S_{a,O_2} ($n=26$, $r=-0.665$, $p<0.001$), an important interindividual variability can be seen. Reproduced from [54] with permission from the publisher.

Numerous components of the cellular “machinery”, such as K_V channels, G-protein-coupled receptors, 5-HT transporter, growth factors, pro-inflammatory cytokines and RhoA/Rho kinase signalling pathway contributes in complex interplays to the remodelling process of pulmonary arteries under chronic hypoxia [48, 58–62].

These observations suggest that pulmonary inflammation, systemic inflammation, chronic hypoxia, loss of pulmonary capillaries in severe emphysema and perhaps mechanical injury due to hyperinflation, in complex interactions, contribute to the development of PH in COPD (fig. 4).

NATURAL HISTORY OF PH IN COPD

Exercising PH

In COPD, it has been noted that PH may first appear during exercise and during sleep. KESSLER *et al.* [63] followed up 131

COPD patients with mean \pm SD FEV₁ $45 \pm 16\%$ predicted and mild hypoxaemia (71 ± 13 mmHg) during a mean time interval of 7 ± 3 yrs. None of these patients had PH at baseline (\bar{P}_{pa} 15 ± 3 mmHg). Among them, 76 had exercising PH defined by $\bar{P}_{pa} \geq 30$ mmHg. In that study, patients having exercising P_{pa} at onset were more prone to develop resting PH with time. The other important finding of the study by KESSLER *et al.* [63] is the slow progression of \bar{P}_{pa} with time ($+0.4$ mmHg·yr⁻¹). It is also important to note that the change of \bar{P}_{pa} during the follow-up was correlated with the change of arterial oxygen tension (P_{a,O_2}), the more P_{a,O_2} worsened the more \bar{P}_{pa} increased. The slow progression of \bar{P}_{pa} was also demonstrated in more advanced COPD patients with PH at rest in an earlier study [64].

In advanced COPD, patients with resting PH have a marked increase in P_{pa} during steady-state exercise [42, 65, 66]: a COPD patient whose baseline \bar{P}_{pa} is modestly elevated (25–30 mmHg) may exhibit severe PH (50–60 mmHg) during moderate exercise (30–40 W). This is explained by the fact that PVR does not decrease during exercise in advanced COPD patients [65, 66], whereas it does in healthy subjects; as cardiac output is doubled for this level of exercise, \bar{P}_{pa} increases by $\sim 100\%$. From a practical viewpoint, this means that daily activities, such as climbing stairs, or even walking, can induce marked PH.

Peaks of PH during sleep

Some COPD patients who are normoxaemic or mildly hypoxaemic during the day develop moderate to severe hypoxaemia during sleep [67, 68]. These episodes of hypoxaemia are due to alveolar hypoventilation which occurs mainly in rapid eye movement (REM) sleep. They coincide with transient increase in P_{pa} [69, 70]. It has been hypothesised that intermittent episodes of PH during sleep in COPD could lead to permanent PH [71]. However, the investigations performed in this area are rather controversial. Indeed, one group found that desaturations during sleep is a risk factor for developing permanent PH [72] and is associated with a worse prognosis [73], while another group found the opposite to be the case [74, 75].

Rise of PAP during exacerbation

It has also been observed that some COPD patients have a pronounced increase in P_{pa} during acute respiratory failure.

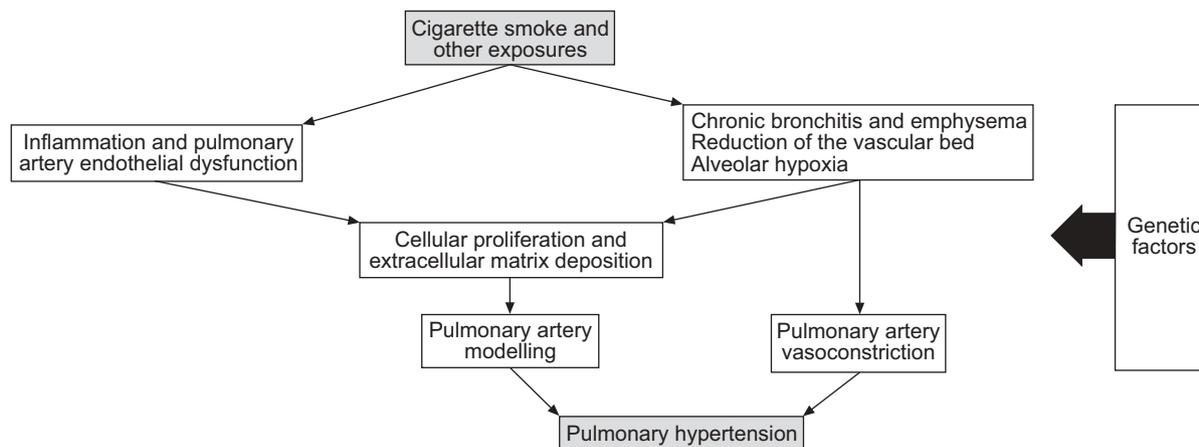


FIGURE 4. Confirmed and suspected mechanisms leading to pulmonary hypertension in chronic obstructive pulmonary disease, which, as shown, are influenced by genetic factors.

\bar{P}_{pa} may increase by as much as 20 mmHg and returns to its baseline value after the recovery of the exacerbation [76]. WEITZENBLUM *et al.* [77] have investigated 16 COPD patients exhibiting marked peripheral oedema. Nine out of the 16 patients had an important increase in \bar{P}_{pa} compared with baseline values (fig. 5) associated with haemodynamic signs of right heart failure (right ventricular end-diastolic pressure >12 mmHg). It is noteworthy that the change in \bar{P}_{pa} during the episode of peripheral oedema compared to a stable state of the disease was highly correlated with the change in P_{a,O_2} ($r = -0.75$, $p = 0.02$). ANAND *et al.* [78] have observed similar behaviour of pulmonary haemodynamics and arterial blood gases under comparable circumstances. Frequent exacerbations of COPD can result in both more rapid declines in lung function and worse outcomes [79]. It is also known that COPD patients with PH have an increased risk of having severe exacerbations [2]. The occurrence of exacerbation is due to an interaction between the host on one hand and viruses, bacteria and environmental pollution on the other [79]. The exact link between exacerbations and the natural history of permanent PH in COPD is not precisely known. It can be speculated that the repetition of exacerbation associated with transient increase in P_{pa} could lead to permanent PH, this latter state being classically associated with a worse prognosis [19].

Pulmonary haemodynamics during a period of disease stability

During stable disease state, most patients with advanced COPD have mildly or moderately increased P_{pa} at rest. For instance, in a recent study investigating a large series of COPD patients during in a stable state of the disease, the average value of \bar{P}_{pa} was at the limit of the normal range (20 ± 8 mmHg), although the airway limitation was of great magnitude (FEV1 $33 \pm 11\%$ pred) [6]. This confirmed earlier reports establishing that when

present in COPD, PH is mild or moderate and contrasts with the severity of PH in idiopathic PAH.

The most recent classification of PH was designed for associating entities with common pathophysiological and clinical features [7]. Table 2 compares the pulmonary haemodynamic data of COPD patients exhibiting PH [6, 19], a series of patients from the French registry of PAH [25] and a series of chronic thromboembolic PH from San Diego (CA, USA) [80]. From these data it can be concluded that when PH occurs in COPD, PVR is moderately increased on the one hand, and right ventricular pre-load pressures and cardiac output are usually in the normal range on the other, contrasting with the large increase in PVR and haemodynamic signs of right ventricular dysfunction observed in patients with PAH and chronic thromboembolic PH.

Right ventricular dysfunction in COPD

Patients with stable COPD having moderate to severe airway limitation without hypoxaemia have preserved right ventricular systolic function at rest [81]. Indeed, in a series of 25 patients with an FEV1 of $41 \pm 15\%$ pred and a P_{a,O_2} 82 ± 10 mmHg (10.9 ± 1.3 kPa), right ventricular ejection fraction measured by magnetic resonance imaging (MRI) method was $53 \pm 12\%$, and was similar in 26 normal controls ($53 \pm 7\%$). In 158 patients with COPD evaluated for lung transplantation, the prevalence of right ventricular dysfunction was 59% [21]. In 120 patients with severe emphysema SCHARF *et al.* [20] found a mean right ventricular ejection fraction of $34 \pm 8\%$. The same study showed that \bar{P}_{pa} and P_{a,O_2} were the only covariates included in a multivariate regression analysis to predict right ventricular ejection fraction. These two covariates explained only 13% of the variance of right ventricular ejection fraction. It must be kept in mind that right ventricular ejection fraction is the result of complex interaction between pre-load, afterload and right ventricular contractility, and most published studies have not assessed all these

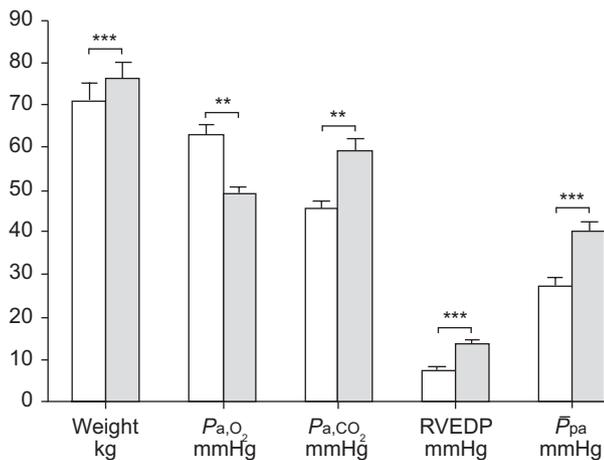


FIGURE 5. Evolution of weight, arterial oxygen (P_{a,O_2}) and carbon dioxide (P_{a,CO_2}) tensions, right ventricular end-diastolic pressure (RVEDP) and mean pulmonary artery pressure (\bar{P}_{pa}) from baseline (□) to an episode of oedema due to right heart failure mostly associated with an acute exacerbation of the disease (■) in nine chronic obstructive pulmonary disease patients. Notably, the changes in \bar{P}_{pa} were significantly correlated with the changes in P_{a,O_2} ($r = -0.75$, $p = 0.02$). Data are presented as mean and SEM. 1 mmHg=0.133 kPa. **: $p < 0.01$; ***: $p < 0.001$. Data are taken from [77].

	COPD	COPD	iPAH	CTEPH
Reference	[19]	[6]	[25]	[80]
Subjects n	62	16	259	500
Age yrs	55	66	50	
FEV1 mL	1170			
FEV1 % pred		27	>70	
P_{a,O_2} mmHg	60	56		
P_{a,CO_2} mmHg	45	47		
\bar{P}_{pa} mmHg	26	25	56	46
P_{pw} mmHg	8.0	7.0	8.0	
Cardiac output $L \cdot min^{-1} \cdot m^{-2}$	3.8	2.8	2.3	~2.2

Values are presented as means, unless otherwise stated. FEV1: forced expiratory volume in one second; % pred: % predicted; P_{a,O_2} : arterial oxygen tension; P_{a,CO_2} : arterial carbon dioxide tension; \bar{P}_{pa} : mean pulmonary artery pressure; P_{pw} : pulmonary wedge pressure. 1 mmHg=0.133 kPa.

interactions. The best manner in which to study right ventricular function is to determine the end-systolic pressure–volume relationship. Studies performed with this method have shown that decreased right ventricular contractility is observed only during acute exacerbation with the presence of marked peripheral oedema [82]. Apart from acute exacerbation, indicators of right heart failure could be hardly observed in COPD patients even in the most advanced stage of the disease.

Severe and out-of-proportion PH

As aforementioned, PH in COPD is usually mild to moderate; however, owing to the high prevalence of COPD, it can be observed as an associated disease which could also impact on the pulmonary circulation in an additive manner. In a large series of COPD patients investigated during a period of disease stability, 27 had a $\bar{P}_{pa} \geq 40$ mmHg and, among them, 16 had an associated disease explaining, in part, the severity of PH [6]. Four had a left heart disease responsible for an increased P_{pw} and a decreased left ventricular ejection fraction. Two patients had chronic thromboembolic PH and six had an associated restrictive lung disease (mainly severe obesity plus obstructive sleep apnoeas), which also falls into the group of PH associated with hypoxaemic pulmonary disorders in the latest classification of PH [7]. In these six latter patients, P_{a,O_2} was very low (44 ± 4 mmHg; 5.9 ± 0.5 kPa) with a further decrease during sleep and was associated with an increased arterial carbon dioxide tension. Consequently, it must be emphasised that hypoxaemic pulmonary disease could lead to the development of severe PH and right heart failure. Alveolar hypoxia due to alveolar hypoventilation must be a predominant cause of PH in such a circumstance. In the view of these results, it must be recommended that the presence of an associated disease should be investigated in COPD patients

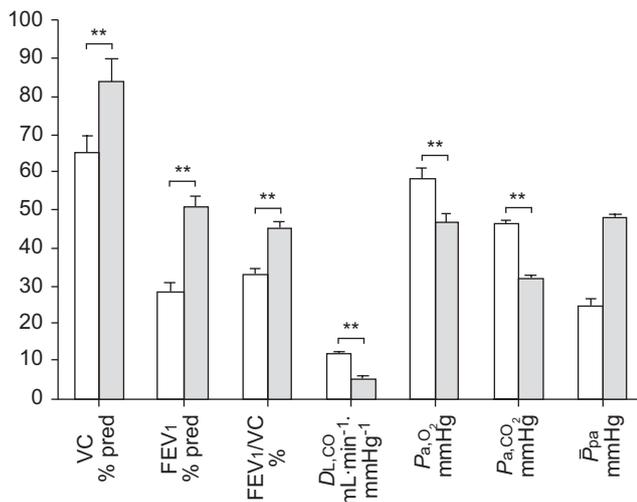


FIGURE 6. Comparisons of vital capacity (VC), forced expiratory volume in one second (FEV₁), FEV₁/VC ratio, diffusion capacity for carbon monoxide (DLCO), arterial oxygen (P_{a,O_2}) and carbon dioxide (P_{a,CO_2}) tensions and mean pulmonary artery pressure (\bar{P}_{pa}) between 16 chronic obstructive pulmonary disease (COPD) patients with no associated disease and a $\bar{P}_{pa} \geq 20$ and < 40 mmHg (□) and 11 COPD patients with no associated disease and a $\bar{P}_{pa} > 40$ mmHg (■). It can be seen that in the group of patients with severe pulmonary hypertension (■), P_{a,O_2} and DLCO was significantly lower, although airway obstruction was less severe. 1 mmHg=0.133 kPa. **: $p < 0.01$. Data are taken from [6].

with severe PH, since treatable associated conditions covered up by COPD could be found. In the same study devoted to severe PH in COPD, 11 patients had COPD as the only cause of severe PH [6]. These patients exhibit a distinctive pattern with less severe airflow limitation but more severe hypoxaemia, hypocapnia and decreased DLCO (fig. 6). THABUT *et al.* [8] have found similar characteristics in a group of 16 COPD patients [83]. These two studies do not supply information of the natural history of the disease, but it is unlikely that severe PH was the result of the progression of COPD, knowing that airflow limitation was not severe [6, 8]. Therefore, such a condition could be termed out-of-proportion PH and may be defined by $\bar{P}_{pa} > 35$ –40 mmHg and a mild-to-moderate airflow limitation. In the current authors' opinion, in a time of LTOT it is probably the sole situation in which right heart failure can be observed in COPD patients in a stable state of disease at some distance from an acute exacerbation. It must be clarified that the cause of hypoxaemia in this situation is a worsening of ventilation–perfusion mismatch and probably, in some patients, the development of a right-to-left shunt, and not alveolar hypoventilation due to severe airflow limitation.

Due to the severity and the scattered number of COPD patients with out-of-proportion PH, these patients should be referred to an expert centre of pulmonary vascular diseases to perform an RHC and to include them in registries and clinical trials.

DIAGNOSIS STRATEGY

Recognition of PH in COPD is often hampered by the clinical picture of the causal disease. Symptoms such as dyspnoea on exertion and fatigue are generally present in advanced COPD patients with or without PH; they are essentially the consequence of airflow limitation and hyperinflation rather than PH. However, one study has shown that patients with out-of-proportion PH in COPD have more severe dyspnoea on exertion in comparison with COPD patients, with more-severe airflow limitation but lower P_{pa} [6].

Physical signs that are observed in severe PH, and particularly in idiopathic PAH, such as a loud pulmonary component of the second heart sound and a pansystolic murmur owing to tricuspid regurgitation (TR), are rarely noticed in COPD patients with PH, except during severe exacerbations of the disease. This can be explained by the presence of mild-to-moderate PH in most of the patients and by the late occurrence (or no occurrence at all) of right heart failure. Peripheral oedema occurs rather late in the course of COPD and is not synonymous with right heart failure [78].

ECG may predict the presence of right ventricular hypertrophy, which is not exactly synonymous with PH. Most recognised ECG changes have a good specificity (>85%) but their sensitivity is poor (~40%), particularly in patients with mild PH [84]. Similarly, chest radiography is poorly sensitive in the diagnosis of PH in COPD. Nevertheless, these two conventional tests may be useful, on account of their simplicity and low cost, in raising suspicion of PH.

Prediction of P_{pa} from pulmonary function data

Spirometry is mandatory for the diagnosis of COPD; however, VC, FEV₁ and FEV₁/VC have no utility in the prediction of P_{pa}

in COPD. This is not surprising, since PH itself has little effect on lung mechanics [85].

Significant correlations between P_{a,O_2} or arterial oxygen saturation (S_{a,O_2}) and P_{pa} have been regularly demonstrated and there have been attempts to predict the level of P_{pa} from arterial blood gases. A predictive equation of P_{pa} from S_{a,O_2} and pH was proposed >20 yrs ago [86]. It later appeared that this formula was unreliable for predicting P_{pa} in individuals, because the margin of error was too great. This is not surprising, since correlations between P_{a,O_2} and P_{pa} are loose, with P_{a,O_2} explaining only 25% of the variance of P_{pa} .

Better results could perhaps be obtained by a multivariate analysis including arterial blood gases and pulmonary volumes [86]: stepwise multiple regression analyses generally explained <50% of the total variance of P_{pa} . A qualitative diagnosis of PH is often possible, but the prediction of the level of P_{pa} is too imprecise. DL_{CO} is reduced in patients with severe PH; however, on this sole measurement PH cannot be predicted since the decrease in DL_{CO} can also result from lung emphysema.

Although there are important limitations of pulmonary function data in predicting PH, it must be mentioned that unusual patterns have been described in two studies that underlined out-of-proportion PH [6, 8]. Indeed, in both studies, most patients with the highest \bar{P}_{pa} have relatively preserved lung mechanics, very low P_{a,O_2} , a huge increase in alveolar-arterial oxygen tension difference and a tendency to have hypocapnia. One of these studies also showed that DL_{CO} was more reduced than usual in lung emphysema [6]. Therefore, such a pattern of pulmonary function tests associated with severe dyspnoea should guide the clinician to suspect out-of-proportion PH.

Doppler echocardiography

Doppler echocardiography is by far the best method for the noninvasive diagnosis of PH [87, 88], which allows estimation of systolic P_{pa} from the measurement of the maximum velocity of the TR, using continuous wave Doppler echocardiography. With the same technique, in case of pulmonary regurgitation, it is possible to estimate the pulmonary artery diastolic pressure.

There are strong correlations between values obtained with the measurement of the maximum velocity of TR and those found on RHC [89]. While a TR signal can be recorded in 90–100% of patients with clinical signs of right heart failure [90], the rate of success decreases in the absence of these signs [91]. In COPD patients, recovery rates of TR signals of sufficient quality are lower, ranging 24–77% [92–94]. In a recent study the bias of Doppler echocardiography in the measurement of systolic P_{pa} compared with RHC was 2.8 mmHg (95% CI -18.7–24.0 mmHg) [9], which is high when one takes into account the modest level of PH (\bar{P}_{pa} <35 mmHg) in most COPD patients. ARCASOY *et al.* [17] have investigated a large series of patients (n=374) who were candidates for lung transplantation, most of whom had COPD. The estimation of systolic P_{pa} by echocardiography was possible in only 44% of the patients (hyperinflation precluded optimal visualisation of the heart) and 52% of pressure estimations were found to be inaccurate (>10 mmHg difference compared with measured pressure obtained during RHC). It must be mentioned that it is possible

to improve these low recovery rates of TR, mainly due to inflated chest, by the use of saline contrast enhancement.

Estimation of P_{pa} from Doppler pulmonary flow velocity curves has been reported [93, 95]. Correlations between P_{pa} and the time to peak pulmonary blood velocity (acceleration time) are strong. Even if this method does not allow a precise measurement of P_{pa} in individuals, decreased acceleration time is a better evaluation of right ventricular afterload than \bar{P}_{pa} measured invasively.

The evaluation of right ventricular dysfunction with Doppler echocardiography has been performed in severe PH [96]. Indeed, the Tei index [97] and tricuspid annular displacement [98] predict survival of patients with idiopathic PAH. To the current authors' knowledge, no recent study has been performed in order to determine the clinical value of these measurements of right ventricular dysfunction in COPD.

A good evaluation of pulmonary haemodynamics can be performed with Doppler echocardiography using, in association, several measurements, for example: maximal velocity of TR, pulmonary blood flow velocity and new indices of right ventricular dysfunction. Again, Doppler echocardiography is the best noninvasive method for PH diagnosis, even in COPD, and in spite of technical difficulty. Furthermore, when RHC is mandatory, as in severe PH [99], Doppler echocardiography complements it, since it provides different information [88].

B-type natriuretic peptide

B-type natriuretic peptide (BNP) release is due to increased wall stretch of atria and ventricles and may have a relatively good sensitivity and specificity for the identification of PH in COPD patients [100, 101]. However, more and larger studies are needed to determine the benefit of BNP plasma level in the diagnosis procedure of PH in COPD.

Isotopic ventriculography and MRI

Isotopic right ventriculography is a technique used to assess right ventricular global function. Studies performed ~20 yrs ago have shown significant correlation between right ventricular ejection fraction measured with isotopic ventriculography and P_{pa} [102, 103]. However, this method does not allow diagnosis of PH, owing to the important overlap of this measurement in COPD patients in a stable disease state, compared with normal subjects [102]. Therefore, isotopic right ventriculogram adds little information compared to echocardiography, and this method is costly.

MRI allows the measurement of volumes and blood flow in the thorax. New generation devices are not hindered by cardiac motion. At present, it is probably the best method for the measurement of right ventricular ejection fraction and right ventricular mass [81, 104], but its role in the diagnosis strategy of PH in COPD must be determined.

Other tests

Ventilation–perfusion scans and spiral computed tomographic angiography may be useful in patients with severe PH in order to exclude chronic pulmonary thromboembolism. Similarly, COPD associated with sleep apnoeas may lead to severe PH [105]. Subsequently, when PH is severe, sleep study may be useful.

Assessment of functional capacity can be performed with a physician-supervised cardiopulmonary exercise test (CPET). Severe PH and particularly out-of-proportion PH in these patients may be associated with a typical “heart failure profile”. This profile is distinguished by increased ventilatory equivalents, decreased maximum oxygen consumption, early anaerobic threshold, failure of stroke volume and oxygen pulse to increase, and altered chronotropic responses, without demonstrable ventilatory limitation, as defined by maximum ventilation reaching maximum voluntary ventilation [106–109]. The benefit of studies on CPET is that PH may be an uncommon cause of decreased exercise capacity in COPD patients, particularly in patients with out-of-proportion PH. More data is needed to identify those patients with COPD, probably with more severe PH, who present with a predominantly cardiovascular limitation to exercise capacity.

The 6-min walk distance is generally used as a reproducible, easy and low-cost surrogate to a complete CPET. However, in COPD, the 6-min walk test may be less sensitive to clinical changes than reported in heart failure and in PAH, with an average of 54 m needed to be associated with a perceivable change in clinical condition [110]. This is probably due to the fact that exercise capacity would be less exclusively dependent on maximum cardiac output than in heart failure and in PAH. Only one study, which included 45 patients with COPD, has shown that patients with $\bar{P}_{pa} > 35$ mmHg have a 6-min walk distance significantly lower than patients with lower \bar{P}_{pa} . More studies are needed to determine the usefulness of exercise testing for the diagnosis of clinically significant PH in COPD.

RHC

RHC is the gold standard for the diagnosis of PH [87, 99]. It allows the direct measurement of pressures in the right atrium, the right ventricle, the pulmonary artery and in the wedge position to estimate left heart filling pressures. RHC is generally carried out using a Swan–Ganz catheter type.

RHC has two main drawbacks: first, it is an invasive procedure including some risks. It needs hospitalisation which may be inconvenient for patients. The second drawback is the inherent methodological limitation of this technique: the fluid-filled Swan–Ganz catheter is incapable of measuring instantaneous pressures and does not give information about the natural pulsing of the pulmonary circulation [88, 111]. More importantly, there is no evidenced-based study demonstrating the clinical value of RHC in advanced COPD. At present, invasive measurement of P_{pa} is of little help for assessment of domiciliary oxygen therapy. Therefore, RHC cannot be used routinely in COPD patients.

The collective body of evidence described above shows that the diagnosis of PH in COPD is not easy and there is not a unique and simple test to confirm or exclude PH. More importantly, at present it is not known whether the recognition of PH in COPD has a clinical impact in the management of patients with COPD, except during the pre-operative evaluation of patients who are candidates for lung transplantation or LVRS. However, the present authors suspect that an unrecognised and untreated severe PH or out-of-proportion PH could have a harmful effect. Indeed, the current authors believe that RHC can help to differentiate diastolic (left) heart failure in COPD

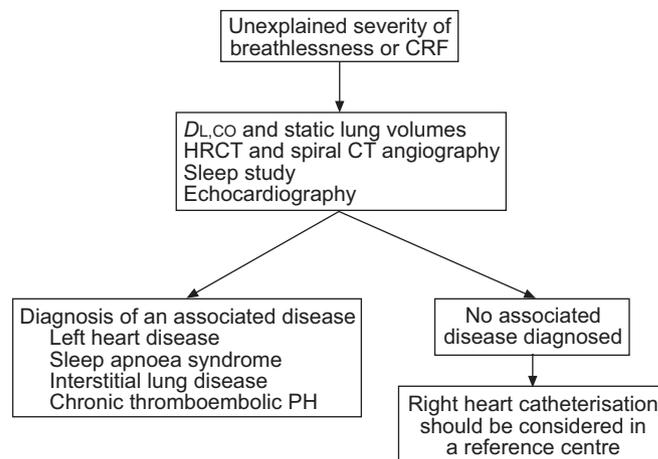


FIGURE 7. Proposal for a diagnostic strategy for the identification of “out-of-proportion” pulmonary hypertension (PH) in chronic obstructive pulmonary disease. An important elevation of systolic pulmonary artery pressure and a normal left ventricular ejection fraction without an associated disease should encourage a right heart catheterisation. CRF: chronic respiratory failure; DL,CO: diffusion capacity for carbon monoxide; HRCT: high-resolution computed tomography; CT: computed tomography.

and pre-capillary out-of-proportion PH; subsequently it is of use to consider RHC to prescribe the more appropriate treatment. A diagnosis strategy for PH in COPD patients is shown in figure 7.

TREATMENT

The treatment of PH in COPD is based on oxygen therapy. An important question is: is it necessary to treat PH in COPD with methods other than oxygen therapy? It is known that PH is mild to moderate in most patients with COPD and the necessity of treating this hypertension can be questioned. The main argument in favour of treatment is that PH, even when modest, may worsen, particularly during acute exacerbations, and these acute increases in P_{pa} may contribute to the development of right heart failure [4, 5]. Table 3 summarises

TABLE 3 Methods of treatment of pulmonary hypertension in chronic obstructive pulmonary disease

Methods	References	At least one randomised trial?
LTOT	[112–116]	Yes
Nocturnal oxygen therapy	[117, 118]	Yes
Medical treatment dedicated to PAH	[119, 120]	Yes
Ca ²⁺ channel blockers	[121]	No
Urapidil	[122]	No
Angiotensin inhibitors	[123, 124]	Yes
Inhaled nitric oxide	[125]	Yes
Pulmonary rehabilitation	[126]	No
LVRS	[127–130]	Yes
Lung transplantation	[131]	No

LTOT: long-term oxygen therapy; PAH: pulmonary arterial hypertension; LVRS: lung volume reduction surgery.

all methods of treatments of PH in COPD. The treatment of right heart failure during an exacerbation will not be reviewed.

LTOT

Alveolar hypoxia is considered to be a determinant of the elevation of PVR and P_{pa} in COPD patients. One of the aims of LTOT is the improvement of PH induced by chronic alveolar hypoxia.

The well-known Nocturnal Oxygen Therapy Trial (NOTT) [112] and Medical Research Council (MRC) [113] studies were not mainly devoted to the pulmonary haemodynamic evolution under LTOT, but pulmonary haemodynamic data were available at the onset in all patients and follow-up RHC was performed in a relatively high number of patients. In the MRC study, 42 patients who survived >500 days from the onset of the study were catheterised again after at ≥ 1 yr of follow-up [113]. \bar{P}_{pa} was stable in the subgroup of 21 patients administered LTOT, whereas it increased significantly ($+2.8$ mmHg \cdot yr $^{-1}$) in the control group of 21 patients. In the NOTT study, haemodynamic data at the onset and after 6 months of LTOT were available in 117 patients [114]. Continuous (≥ 18 h \cdot day $^{-1}$) LTOT decreased slightly but significantly resting (mean -3 mmHg) and exercising \bar{P}_{pa} (mean -6 mmHg) and PVR, whereas nocturnal oxygen therapy (10–12 h \cdot day $^{-1}$) did not.

WEITZENBLUM *et al.* [115] have compared the pulmonary haemodynamic evolution before and after onset of oxygen therapy, with 16 patients acting as their own controls. A reversal of the progression of PH was observed under LTOT; \bar{P}_{pa} was not normalised but returned to its baseline level a mean of 6 yrs earlier. When changes in \bar{P}_{pa} were expressed as changes per year, the difference was also significant, with an increase of 1.5 mmHg \cdot yr $^{-1}$ before the onset of LTOT *versus* a decrease of 2.1 mmHg \cdot yr $^{-1}$ after the initiation of LTOT ($p < 0.01$).

More recently, ZIELINSKI *et al.* [116] investigated COPD patients under LTOT (15 h \cdot day $^{-1}$). In 12 patients who completed 6 yrs of LTOT, \bar{P}_{pa} fell from 25 ± 7 to 21 ± 4 mmHg after 2 yrs but slightly increased to 26 ± 6 mmHg after 6 yrs. On average there was a long-term stabilisation of PH on LTOT.

The best haemodynamic results have been obtained in the continuous oxygen group of the NOTT study [114] and in a study reported by WEITZENBLUM *et al.* [115], that is in the studies where the daily duration of oxygen therapy was the longest (17–18 h of oxygen per day). Accordingly, continuous oxygen therapy is recommended.

In summary, LTOT stabilises, or at least attenuates, and sometimes reverses, the progression of PH, but P_{pa} seldom returns to normal. The longer the daily duration of LTOT, the better the pulmonary haemodynamic results.

Nocturnal oxygen therapy in patients with isolated sleep-related hypoxaemia

COPD patients who are hypoxaemic while awake will also be hypoxaemic during sleep. In most COPD patients, hypoxaemia does, in fact, worsen during sleep and especially during REM sleep, as mentioned above. It follows that it is particularly important to oxygenate these patients during sleep. It is

sometimes recommended to add 1 L \cdot min $^{-1}$ oxygen flow to the daytime resting prescription [132].

Some COPD patients do not have significant hypoxaemia when awake ($P_{a,O_2} > 60$ mmHg; > 8.0 kPa) but are hypoxaemic during sleep with a mean nocturnal transcutaneous $S_{a,O_2} < 88$ – 90% . It has been hypothesised that sleep-related hypoxaemia, occurring in COPD patients without significant daytime hypoxaemia, could lead to permanent (daytime) PH [71]. If this was the case, prescription of nocturnal oxygen therapy to these patients would be justified. In fact, this hypothesis has not yet been demonstrated [117].

Two controlled studies [117, 118] have investigated the effects of nocturnal oxygen therapy administered to COPD patients exhibiting sleep-related hypoxaemia, but without significant daytime hypoxaemia. FLETCHER *et al.* [118] have compared 19 desaturators receiving nocturnal oxygen to 19 comparable desaturators treated with room air. In fact, only 16 patients could complete the 3-yr study: \bar{P}_{pa} increased by a mean value of 3.9 mmHg in the control group ($n=9$) and decreased by 3.7 mmHg in patients ($n=7$) treated with nocturnal oxygen ($p < 0.02$). FLETCHER *et al.* [118] concluded that nocturnal oxygen therapy had favourable effects on pulmonary haemodynamics. A more recent European multicentric study has compared the evolution of P_{pa} in 41 nocturnal desaturators randomly allocated to nocturnal oxygen and 35 similar patients receiving no nocturnal oxygen [117]. The duration of the study was 2 yrs. A total of 24 patients in the nocturnal oxygen group and 22 in the control group completed the study. Nocturnal oxygen therapy did not modify the evolution of pulmonary haemodynamics, which was the same in the two groups.

The present data, related to the evolution of pulmonary haemodynamics, are not sufficient for justifying the use of nocturnal oxygen in COPD patients who do not qualify for conventional oxygen therapy according to current criteria [1, 132].

Medical treatments dedicated to PAH

Treatments of PAH have shown a dramatic change in the past few years [133]. Synthetic prostacyclin (epoprostenol), prostacyclin analogues, endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors were tested in randomised controlled trials, leading to the approval of several drugs in each class. It is tempting to use these drugs in PH complicating COPD. Unfortunately, only a few studies [109, 119] have been published in this field (long-term effect) and they were, for the most part, uncontrolled. A recent report has shown that one endothelin-1 receptor antagonist had deleterious effects on gas exchanges in a randomised trial performed in COPD patients [120]. Therefore, it is strongly recommended to not treat COPD patients with drugs dedicated to PAH outside trials. More randomised controlled studies are required in this area.

Other medical treatments

Experience with vasodilators has come from the treatment of idiopathic PAH. This is based on the belief that pulmonary vasoconstriction is an important component of PH, although this may not be true in most patients. The acute effects of some drugs, such as calcium channel blockers and urapidil, have been somewhat favourable [55, 121] but there have been very few long-term studies, and their results have been disappointing

and have shown deleterious effects on gas exchanges [122]. Only two studies of angiotensin inhibitors testing a long-term effect (>30 days) on PH in COPD patients have been performed [123, 124]. Both studies showed no significant difference in terms of pulmonary haemodynamic variables. Calcium channel blockers, α_1 -antagonists and angiotensin inhibitors should not be used to treat PH in COPD.

Inhaled nitric oxide is a selective and potent pulmonary vasodilator. It may improve pulmonary haemodynamics and hypoxaemia in COPD [134], but some studies have shown that it worsens ventilation-perfusion mismatch and hypoxaemia [4, 135]. There has been one long-term study, that of VONBANK *et al.* [125] in 40 COPD patients already on LTOT. Patients were randomly assigned to receive either oxygen alone or “pulsed” inhalation of nitric oxide with oxygen over a period of 3 months. The addition of nitric oxide allowed a significant improvement in P_{pa} , PVR and cardiac output. These results are promising but the technological and toxicological problems related to the prolonged use of inhaled nitric oxide are far from being solved, and clearly further studies in this field are required.

Exercise and respiratory training designated as pulmonary rehabilitation in COPD has a positive impact. It improves exercise capacity and quality of life and reduces dyspnoea on exertion with a high level of evidence [126]. Conversely, in severe PH it is believed that physical activities have a negative impact and may favour a worsening of the disease [99]. However, the recent American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation suggests that severe PH is not a contraindication to exercise training [126]. Pulmonary rehabilitation has been performed in patients with PAH or severe chronic thromboembolic PH and has shown beneficial results [136]. Thus, exercise and respiratory training can be accomplished in COPD patients with PH. It is probably wise to refer patients with severe PH to an expert centre in order to start and monitor pulmonary rehabilitation.

LVRS and lung transplantation

Patients with advanced emphysema may benefit from LVRS [137]. Generally, COPD with severe PH ($P_{pa} \geq 35$ mmHg) are not candidates for LVRS and should rather be considered for lung transplantation. LVRS could have favourable pulmonary haemodynamic effects, since it improves pulmonary function and arterial blood gases. Conversely, it could have deleterious effects, since it may cause a reduction of the pulmonary vascular tree.

There have been few studies on pulmonary haemodynamics before and after LVRS [127–129]. LVRS may have adverse effects on pulmonary haemodynamics owing to the reduction of the vascular bed after the resection of lung tissue. Early studies have shown conflicting results, with increases in P_{pa} after LVRS in one study [130] but not in others [127, 128]. A recent study as part of the National Emphysema Treatment Trial has shown no significant differences in terms of \bar{P}_{pa} and PVR, 6 months after medical treatment or LVRS [129].

Lung transplantation is performed in selected COPD patients with end-stage disease. BJORTUFT *et al.* [131] have investigated a group of 24 patients, including 19 with COPD, who underwent

single lung transplantation. The majority (15 out of 24) of patients had mild-to-moderate PH at the onset and in these patients \bar{P}_{pa} mean \pm SEM significantly decreased from 28 ± 1 mmHg to 18 ± 1 mmHg after transplantation; there was a similar decrease in PVR. These results were maintained after 2 yrs of follow-up. Therefore, COPD patients with PH normalise pulmonary haemodynamics after single lung transplantation. Lung transplantation may be considered in all patients with severe PH aged <65 yrs and without comorbidities.

CONCLUSION

Chronic obstructive pulmonary disease is a frequent cause of pulmonary hypertension in the population of patients with chronic respiratory failure. Pulmonary hypertension is usually mild to moderate and, nowadays, most of these patients in industrialised countries are undergoing long-term oxygen therapy which stabilises, attenuates, or sometimes reverses the progression of pulmonary hypertension. Conversely, few patients, in spite of long-term oxygen therapy, have severe pulmonary hypertension. In these latter patients a cause of pulmonary hypertension other than chronic obstructive pulmonary disease, which may be treatable, should be sought. When no other causes of pulmonary hypertension are detectable, these patients frequently exhibit a distinctive clinical pattern which shares similarities with other pulmonary vasculopathies, such as idiopathic pulmonary arterial hypertension, a condition termed “out-of-proportion” pulmonary hypertension. The potential impact of drugs indicated in pulmonary arterial hypertension need to be tested in randomised controlled trials in patients with out-of-proportion pulmonary hypertension.

REFERENCES

- 1 Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
- 2 Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 158–164.
- 3 Oswald-Mammosser M, Weitzenblum E, Quoix E, *et al.* Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest* 1995; 107: 1193–1198.
- 4 Barbera JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 892–905.
- 5 Weitzenblum E. Chronic cor pulmonale. *Heart* 2003; 89: 225–230.
- 6 Chaouat A, Bugnet AS, Kadaoui N, *et al.* Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 189–194.
- 7 Simonneau G, Galie N, Rubin LJ, *et al.* Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 5S–12S.
- 8 Thabut G, Dauriat G, Stern JB, *et al.* Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* 2005; 127: 1531–1536.

- 9 Fisher MR, Criner GJ, Fishman AP, *et al.* Estimating pulmonary artery pressures by echocardiography in patients with emphysema. *Eur Respir J* 2007; 30: 914–921.
- 10 Han MK, McLaughlin VV, Criner GJ, Martinez FJ. Pulmonary diseases and the heart. *Circulation* 2007; 116: 2992–3005.
- 11 Hoepfer MM, Dinh-Xuan AT. Pulmonary hypertension: basic concepts and practical management. *Eur Respir J* 2008; 31: 236–237.
- 12 Dupuis J, Hoepfer MM. Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* 2008; 31: 407–415.
- 13 Gombert-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2008; 31: 891–901.
- 14 Wilkins MR, Wharton J, Grimminger F, Ghofrani HA. Phosphodiesterase inhibitors for the treatment of pulmonary hypertension. *Eur Respir J* 2008; 32: 198–209.
- 15 Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Respir J* 2008; 31: 1357–1367.
- 16 Warwick G, Thomas PS, Yates DH. Biomarkers in pulmonary hypertension. *Eur Respir J* 2008; 32: 503–512.
- 17 Arcasoy SM, Christie JD, Ferrari VA, *et al.* Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003; 167: 735–740.
- 18 Burrows B, Kettel LJ, Niden AH, Rabinowitz M, Diener CF. Patterns of cardiovascular dysfunction in chronic obstructive lung disease. *N Engl J Med* 1972; 286: 912–918.
- 19 Weitzenblum E, Hirth C, Ducolone A, Mirhom R, Rasaholinjanahary J, Ehrhart M. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1981; 36: 752–758.
- 20 Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE. Hemodynamic characterization of patients with severe emphysema. *Am J Respir Crit Care Med* 2002; 166: 314–322.
- 21 Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998; 113: 576–583.
- 22 Boutin-Forzano S, Moreau D, Kalaboka S, *et al.* Reported prevalence and co-morbidity of asthma, chronic bronchitis and emphysema: a pan-European estimation. *Int J Tuberc Lung Dis* 2007; 11: 695–702.
- 23 Lindberg A, Bjerg-Backlund A, Ronmark E, Larsson LG, Lundback B. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking. Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med* 2006; 100: 264–272.
- 24 Viegi G, Pistelli F, Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. *Eur Respir J* 2007; 30: 993–1013.
- 25 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
- 26 Bishop JM, Cross KW. Physiological variables and mortality in patients with various categories of chronic respiratory disease. *Bull Eur Physiopathol Respir* 1984; 20: 495–500.
- 27 Keller R, Ragaz A, Borer P. Predictors for early mortality in patients with long-term oxygen home therapy. *Respiration* 1985; 48: 216–221.
- 28 Skwarski K, MacNee W, Wraith PK, Sliwinski P, Zielinski J. Predictors of survival in patients with chronic obstructive pulmonary disease treated with long-term oxygen therapy. *Chest* 1991; 100: 1522–1527.
- 29 Bignon J, Houry F, Even P, Andre J, Brouet G. Morphometric study in chronic obstructive bronchopulmonary disease. Pathologic, clinical, and physiologic correlations. *Am Rev Respir Dis* 1969; 99: 669–695.
- 30 Wagenvoort CA, Mulder PG. Thrombotic lesions in primary plexogenic arteriopathy. Similar pathogenesis or complication? *Chest* 1993; 103: 844–849.
- 31 Wilkinson M, Langhorne CA, Heath D, Barer GR, Howard P. A pathophysiological study of 10 cases of hypoxic cor pulmonale. *Q J Med* 1988; 66: 65–85.
- 32 Magee F, Wright JL, Wiggs BR, Pare PD, Hogg JC. Pulmonary vascular structure and function in chronic obstructive pulmonary disease. *Thorax* 1988; 43: 183–189.
- 33 Dunnill MS. Fibrinoid necrosis in the branches of the pulmonary artery in chronic non-specific lung disease. *Br J Dis Chest* 1960; 54: 355–358.
- 34 Smith P, Rodgers B, Heath D, Yacoub M. The ultrastructure of pulmonary arteries and arterioles in emphysema. *J Pathol* 1992; 167: 69–75.
- 35 Harris P, Heath D. The pulmonary circulation at high altitude. In: Harris P, Heath D, eds. *The Human Pulmonary Circulation*. Edinburgh, Churchill Livingstone, 1986; pp. 493–506.
- 36 Pietra GG, Capron F, Stewart S, *et al.* Pathologic assessment of vasculopathies in pulmonary hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 25S–32S.
- 37 Hale KA, Niewoehner DE, Cosio MG. Morphologic changes in the muscular pulmonary arteries: relationship to cigarette smoking, airway disease, and emphysema. *Am Rev Respir Dis* 1980; 122: 273–278.
- 38 Wright JL, Lawson L, Pare PD, *et al.* The structure and function of the pulmonary vasculature in mild chronic obstructive pulmonary disease. The effect of oxygen and exercise. *Am Rev Respir Dis* 1983; 128: 702–707.
- 39 Santos S, Peinado VI, Ramirez J, *et al.* Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J* 2002; 19: 632–638.
- 40 Peinado VI, Barbera JA, Abate P, *et al.* Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 1605–1611.
- 41 Chabot F, Schrijen F, Poincelot F, Polu JM. Interpretation of high wedge pressure on exercise in patients with chronic obstructive pulmonary disease. *Cardiology* 2001; 95: 139–145.
- 42 Butler J, Schrijen F, Henriquez A, Polu JM, Albert RK. Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988; 138: 350–354.
- 43 Oswald-Mammosser M, Apprill M, Bachez P, Ehrhart M, Weitzenblum E. Pulmonary hemodynamics in chronic obstructive pulmonary disease of the emphysematous type. *Respiration* 1991; 58: 304–310.
- 44 Wright JL, Levy RD, Churg A. Pulmonary hypertension in chronic obstructive pulmonary disease: current theories of pathogenesis and their implications for treatment. *Thorax* 2005; 60: 605–609.

- 45 Joppa P, Petrasova D, Stancak B, Tkacova R. Systemic inflammation in patients with COPD and pulmonary hypertension. *Chest* 2006; 130: 326–333.
- 46 Eddahibi S, Chaouat A, Tu L, et al. Interleukin-6 gene polymorphism confers susceptibility to pulmonary hypertension in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; 3: 475–476.
- 47 Hoepfer MM, Welte T. Systemic inflammation, COPD, and pulmonary hypertension. *Chest* 2007; 131: 634–635.
- 48 Stenmark KR, Fagan KA, Frid MG. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. *Circ Res* 2006; 99: 675–691.
- 49 Fishman AP. Hypoxia on the pulmonary circulation. How and where it acts. *Circ Res* 1976; 38: 221–231.
- 50 Fishman AP, Mc CJ, Himmelstein A, Cournand A. Effects of acute anoxia on the circulation and respiration in patients with chronic pulmonary disease studied during the steady state. *J Clin Invest* 1952; 31: 770–781.
- 51 Archer S, Michelakis E. The mechanism(s) of hypoxic pulmonary vasoconstriction: potassium channels, redox O₂ sensors, and controversies. *News Physiol Sci* 2002; 17: 131–137.
- 52 Faller DV. Endothelial cell responses to hypoxic stress. *Clin Exp Pharmacol Physiol* 1999; 26: 74–84.
- 53 Grover RF. Chronic hypoxic pulmonary hypertension. In: Fishman A, ed. *The Pulmonary Circulation: Normal and Abnormal*. Philadelphia, University of Pennsylvania Press, 1990; pp. 283–299.
- 54 Weitzenblum E, Schrijen F, Mohan-Kumar T, Colas des Francs V, Lockhart A. Variability of the pulmonary vascular response to acute hypoxia in chronic bronchitis. *Chest* 1988; 94: 772–778.
- 55 Simonneau G, Escourrou P, Duroux P, Lockhart A. Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. *N Engl J Med* 1981; 304: 1582–1585.
- 56 Tolins M, Weir EK, Chesler E, Nelson DP, From AH. Pulmonary vascular tone is increased by a voltage-dependent calcium channel potentiator. *J Appl Physiol* 1986; 60: 942–948.
- 57 Weir EK, Lopez-Barneo J, Buckler KJ, Archer SL. Acute oxygen-sensing mechanisms. *N Engl J Med* 2005; 353: 2042–2055.
- 58 Davie NJ, Crossno JT Jr, Frid MG, et al. Hypoxia-induced pulmonary artery adventitial remodeling and neovascularization: contribution of progenitor cells. *Am J Physiol Lung Cell Mol Physiol* 2004; 286: L668–L678.
- 59 Eddahibi S, Raffestin B, Hamon M, Adnot S. Is the serotonin transporter involved in the pathogenesis of pulmonary hypertension? *J Lab Clin Med* 2002; 139: 194–201.
- 60 Marcos E, Adnot S, Pham MH, et al. Serotonin transporter inhibitors protect against hypoxic pulmonary hypertension. *Am J Respir Crit Care Med* 2003; 168: 487–493.
- 61 Eddahibi S, Chaouat A, Morrell N, et al. Polymorphism of the serotonin transporter gene and pulmonary hypertension in chronic obstructive pulmonary disease. *Circulation* 2003; 108: 1839–1844.
- 62 Girgis RE, Mozammel S, Champion HC, et al. Regression of chronic hypoxic pulmonary hypertension by simvastatin. *Am J Physiol Lung Cell Mol Physiol* 2007; 292: L1105–L1110.
- 63 Kessler R, Faller M, Weitzenblum E, et al. “Natural history” of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. *Am J Respir Crit Care Med* 2001; 164: 219–224.
- 64 Weitzenblum E, Sautegau A, Ehrhart M, Mammosser M, Hirth C, Roegel E. Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984; 130: 993–998.
- 65 Horsfield K, Segel N, Bishop JM. The pulmonary circulation in chronic bronchitis at rest and during exercise breathing air and 80 per cent oxygen. *Clin Sci* 1968; 34: 473–483.
- 66 Fletcher EC, Luckett RA, Miller T, Fletcher JG. Exercise hemodynamics and gas exchange in patients with chronic obstruction pulmonary disease, sleep desaturation, and a daytime PaO₂ above 60 mmHg. *Am Rev Respir Dis* 1989; 140: 1237–1245.
- 67 Fletcher EC, Miller J, Divine GW, Fletcher JG, Miller T. Nocturnal oxyhemoglobin desaturation in COPD patients with arterial oxygen tensions above 60 mmHg. *Chest* 1987; 92: 604–608.
- 68 Levi-Valensi P, Weitzenblum E, Rida Z, et al. Sleep-related oxygen desaturation and daytime pulmonary haemodynamics in COPD patients. *Eur Respir J* 1992; 5: 301–307.
- 69 Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. The effect of short- and long-term oxygen. *Chest* 1984; 85: 6–14.
- 70 Weitzenblum E, Muzet A, Ehrhart M, Ehrhart J, Sautegau A, Weber L. Variations nocturnes des gaz du sang et de la pression artérielle pulmonaire chez les bronchitiques insuffisants respiratoires [Nocturnal changes in blood gases and pulmonary arterial pressure in chronic bronchitis patients with respiratory insufficiency]. *Nouv Presse Med* 1982; 11: 1119–1122.
- 71 Block AJ, Boysen PG, Wynne JW. The origins of cor pulmonale; a hypothesis. *Chest* 1979; 75: 109–110.
- 72 Fletcher EC, Luckett RA, Miller T, Costarangos C, Kutka N, Fletcher JG. Pulmonary vascular hemodynamics in chronic lung disease patients with and without oxyhemoglobin desaturation during sleep. *Chest* 1989; 95: 757–764.
- 73 Fletcher EC, Donner CF, Midgren B, et al. Survival in COPD patients with a daytime PaO₂ greater than 60 mmHg with and without nocturnal oxyhemoglobin desaturation. *Chest* 1992; 101: 649–655.
- 74 Chaouat A, Weitzenblum E, Kessler R, et al. Sleep-related O₂ desaturation and daytime pulmonary haemodynamics in COPD patients with mild hypoxaemia. *Eur Respir J* 1997; 10: 1730–1735.
- 75 Chaouat A, Weitzenblum E, Kessler R, et al. Outcome of COPD patients with mild daytime hypoxaemia with or without sleep-related oxygen desaturation. *Eur Respir J* 2001; 17: 848–855.
- 76 Abraham AS, Cole RB, Green ID, Hedworth-Whitty RB, Clarke SW, Bishop JM. Factors contributing to the reversible pulmonary hypertension of patients with acute respiratory failure studies by serial observations during recovery. *Circ Res* 1969; 24: 51–60.

- 77 Weitzenblum E, Apprill M, Oswald M, Chaouat A, Imbs JL. Pulmonary hemodynamics in patients with chronic obstructive pulmonary disease before and during an episode of peripheral edema. *Chest* 1994; 105: 1377–1382.
- 78 Anand IS, Chandrashekhar Y, Ferrari R, et al. Pathogenesis of congestive state in chronic obstructive pulmonary disease. Studies of body water and sodium, renal function, hemodynamics, and plasma hormones during edema and after recovery. *Circulation* 1992; 86: 12–21.
- 79 Mannino DM, Watt G, Hole D, et al. The natural history of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27: 627–643.
- 80 Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. *Ann Thorac Surg* 2003; 76: 1457–1462.
- 81 Vonk-Noordegraaf A, Marcus JT, Holverda S, Roseboom B, Postmus PE. Early changes of cardiac structure and function in COPD patients with mild hypoxemia. *Chest* 2005; 127: 1898–1903.
- 82 MacNee W, Wathen CG, Flenley DC, Muir AD. The effects of controlled oxygen therapy on ventricular function in patients with stable and decompensated cor pulmonale. *Am Rev Respir Dis* 1988; 137: 1289–1295.
- 83 Weitzenblum E, Chaouat A. Severe pulmonary hypertension in COPD: is it a distinct disease? *Chest* 2005; 127: 1480–1482.
- 84 Oswald-Mammosser M, Oswald T, Nyankiye E, Dickele MC, Grange D, Weitzenblum E. Non-invasive diagnosis of pulmonary hypertension in chronic obstructive pulmonary disease. Comparison of ECG, radiological measurements, echocardiography and myocardial scintigraphy. *Eur J Respir Dis* 1987; 71: 419–429.
- 85 Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987; 107: 216–223.
- 86 Bishop JM, Cross KW. Use of other physiological variables to predict pulmonary arterial pressure in patients with chronic respiratory disease. Multicentre study. *Eur Heart J* 1981; 2: 509–517.
- 87 McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: Suppl. 1, 14S–34S.
- 88 Naeije R, Torbicki A. More on the noninvasive diagnosis of pulmonary hypertension: Doppler echocardiography revisited. *Eur Respir J* 1995; 8: 1445–1449.
- 89 Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coll Cardiol* 1985; 6: 359–365.
- 90 Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984; 70: 657–662.
- 91 Chan KL, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery pressure. *J Am Coll Cardiol* 1987; 9: 549–554.
- 92 Tamarin R, Torbicki A, Marchandise B, Laaban JP, Morpurgo M. Doppler echocardiographic evaluation of pulmonary artery pressure in chronic obstructive pulmonary disease. A European multicentre study. Working Group on Noninvasive Evaluation of Pulmonary Artery Pressure. European Office of the World Health Organization, Copenhagen. *Eur Heart J* 1991; 12: 103–111.
- 93 Torbicki A, Skwarski K, Hawrylkiewicz I, Pasiński T, Miskiewicz Z, Zielinski J. Attempts at measuring pulmonary arterial pressure by means of Doppler echocardiography in patients with chronic lung disease. *Eur Respir J* 1989; 2: 856–860.
- 94 Laaban JP, Diebold B, Zelinski R, Lafay M, Raffoul H, Rochemaure J. Noninvasive estimation of systolic pulmonary artery pressure using Doppler echocardiography in patients with chronic obstructive pulmonary disease. *Chest* 1989; 96: 1258–1262.
- 95 Boyd MJ, Williams IP, Turton CW, Brooks N, Leech G, Millard FJ. Echocardiographic method for the estimation of pulmonary artery pressure in chronic lung disease. *Thorax* 1980; 35: 914–919.
- 96 Burgess MI, Ray S, Mogulkoc N, et al. Doppler echocardiographic index of global right ventricular function. *Circulation* 2000; 101: E117.
- 97 Tei C, Dujardin KS, Hodge DO, et al. Doppler echocardiographic index for assessment of global right ventricular function. *J Am Soc Echocardiogr* 1996; 9: 838–847.
- 98 Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006; 174: 1034–1041.
- 99 Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25: 2243–2278.
- 100 Bozkanat E, Tozkoparan E, Baysan O, Deniz O, Ciftci F, Yokusoglu M. The significance of elevated brain natriuretic peptide levels in chronic obstructive pulmonary disease. *J Int Med Res* 2005; 33: 537–544.
- 101 Leuchte HH, Baumgartner RA, Nounou ME, et al. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir Crit Care Med* 2006; 173: 744–750.
- 102 Biernacki W, Flenley DC, Muir AL, MacNee W. Pulmonary hypertension and right ventricular function in patients with COPD. *Chest* 1988; 94: 1169–1175.
- 103 Mols P, Huynh CH, Dechamps P, Naeije N, Guillaume M, Ham H. Prediction of pulmonary arterial pressure in chronic obstructive pulmonary disease by radionuclide ventriculography. *Chest* 1989; 96: 1280–1284.
- 104 Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. *Am J Respir Crit Care Med* 2005; 171: 1292–1297.
- 105 Chaouat A, Weitzenblum E, Krieger J, Ifoundza T, Oswald M, Kessler R. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. *Am J Respir Crit Care Med* 1995; 151: 82–86.
- 106 Deboeck G, Niset G, Lamotte M, Vachiery JL, Naeije R. Exercise testing in pulmonary arterial hypertension and in chronic heart failure. *Eur Respir J* 2004; 23: 747–751.
- 107 Holverda S, Bogaard HJ, Groepenhoff H, Postmus PE, Boonstra A, Vonk-Noordegraaf A. Cardiopulmonary exercise test characteristics in patients with chronic

- obstructive pulmonary disease and associated pulmonary hypertension. *Respiration* 2008; 76: 160–167.
- 108** Hansen JE, Ulubay G, Chow BF, Sun XG, Wasserman K. Mixed-expired and end-tidal CO₂ distinguish between ventilation and perfusion defects during exercise testing in patients with lung and heart diseases. *Chest* 2007; 132: 977–983.
- 109** Rietema H, Holverda S, Bogaard HJ, *et al.* Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur Respir J* 2008; 31: 759–764.
- 110** Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997; 155: 1278–1282.
- 111** Raeside D, Peacock A. Making measurements in the pulmonary circulation: when and how? *Thorax* 1997; 52: 9–11.
- 112** Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980; 93: 391–398.
- 113** Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
- 114** Timms RM, Khaja FU, Williams GW. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. *Ann Intern Med* 1985; 102: 29–36.
- 115** Weitzenblum E, Sautegau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985; 131: 493–498.
- 116** Zielinski J, Tobiasz M, Hawrylkiewicz I, Sliwinski P, Palasiewicz G. Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. *Chest* 1998; 113: 65–70.
- 117** Chaouat A, Weitzenblum E, Kessler R, *et al.* A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. *Eur Respir J* 1999; 14: 1002–1008.
- 118** Fletcher EC, Lockett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO₂ above 60 mm Hg. *Am Rev Respir Dis* 1992; 145: 1070–1076.
- 119** Alp S, Skrygan M, Schmidt WE, Bastian A. Sildenafil improves hemodynamic parameters in COPD—an investigation of six patients. *Pulm Pharmacol Ther* 2006; 19: 386–390.
- 120** Stolz D, Rasch H, Linka A, *et al.* A randomized, controlled trial of bosentan in severe COPD. *Eur Respir J* 2008; 32: 619–628.
- 121** Adnot S, Defouilloy C, Brun-Buisson C, Abrouk F, Piquet J, Lemaire F. Hemodynamic effects of urapidil in patients with pulmonary hypertension. A comparative study with hydralazine. *Am Rev Respir Dis* 1987; 135: 288–293.
- 122** Saadjian AY, Philip-Joet FF, Vestri R, Arnaud AG. Long-term treatment of chronic obstructive lung disease by Nifedipine: an 18-month haemodynamic study. *Eur Respir J* 1988; 1: 716–720.
- 123** Bertoli L, Fusco M, Lo Cicero S, Micallef E, Busnardo I. Influence of ACE inhibition on pulmonary haemodynamics and function in patients in whom β -blockers are contraindicated. *Postgrad Med J* 1986; 62: Suppl. 1, 47–51.
- 124** Morrell NW, Higham MA, Phillips PG, Shakur BH, Robinson PJ, Beddoes RJ. Pilot study of losartan for pulmonary hypertension in chronic obstructive pulmonary disease. *Respir Res* 2005; 6: 88.
- 125** Vonbank K, Ziesche R, Higenbottam TW, *et al.* Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. *Thorax* 2003; 58: 289–293.
- 126** Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390–1413.
- 127** Oswald-Mammosser M, Kessler R, Massard G, Wihlm JM, Weitzenblum E, Lonsdorfer J. Effect of lung volume reduction surgery on gas exchange and pulmonary hemodynamics at rest and during exercise. *Am J Respir Crit Care Med* 1998; 158: 1020–1025.
- 128** Kubo K, Koizumi T, Fujimoto K, *et al.* Effects of lung volume reduction surgery on exercise pulmonary hemodynamics in severe emphysema. *Chest* 1998; 114: 1575–1582.
- 129** Criner GJ, Scharf SM, Falk JA, *et al.* Effect of lung volume reduction surgery on resting pulmonary hemodynamics in severe emphysema. *Am J Respir Crit Care Med* 2007; 176: 253–260.
- 130** Weg IL, Rossoff L, McKeon K, Michael Graver L, Scharf SM. Development of pulmonary hypertension after lung volume reduction surgery. *Am J Respir Crit Care Med* 1999; 159: 552–556.
- 131** Bjortuft O, Simonsen S, Geiran OR, Fjeld JG, Skovlund E, Boe J. Pulmonary haemodynamics after single-lung transplantation for end-stage pulmonary parenchymal disease. *Eur Respir J* 1996; 9: 2007–2011.
- 132** Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: S77–S121.
- 133** McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation* 2006; 114: 1417–1431.
- 134** Adnot S, Kouyoumdjian C, Defouilloy C, *et al.* Hemodynamic and gas exchange responses to infusion of acetylcholine and inhalation of nitric oxide in patients with chronic obstructive lung disease and pulmonary hypertension. *Am Rev Respir Dis* 1993; 148: 310–316.
- 135** Roger N, Barbera JA, Roca J, Rovira I, Gomez FP, Rodriguez-Roisin R. Nitric oxide inhalation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 156: 800–806.
- 136** Mereles D, Ehlken N, Kreuscher S, *et al.* Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 2006; 114: 1482–1489.
- 137** Fishman A, Martinez F, Naunheim K, *et al.* A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.