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Pulmonary Hypertension in Patients with Chronic Obstructive Pulmonary Disease

Advances in Pathophysiology and Management

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Abstract

Pulmonary hypertension (PH) is an important complication in the natural history of chronic obstructive pulmonary disease (COPD). Its presence is associated with reduced survival and greater use of healthcare resources. The prevalence of PH is high in patients with advanced COPD, whereas in milder forms it might not be present at rest but may develop during exercise. In COPD, PH is usually of moderate severity and progresses slowly, without altering right ventricular function in the majority of patients. Nevertheless, a small

subgroup of patients (1–3%) may present with out-of-proportion PH, that is, with pulmonary arterial pressure largely exceeding the severity of airway impairment. These patients depict a clinical picture similar to more severe forms of PH and have higher mortality rates.

PH in COPD is caused by the remodelling of pulmonary arteries, which is characterized by the intimal proliferation of poorly differentiated smooth muscle cells and the deposition of elastic and collagen fibres. The sequence of changes that lead to PH in COPD begins at early disease stages by the impairment of endothelial function, which is associated with impaired release of endothelium-derived vasodilating agents (nitric oxide, prostacyclin) and increased expression of growth factors. Products contained in cigarette smoke play a critical role in the initiation of pulmonary endothelial cell alterations.

Recognition of PH can be difficult because symptoms due to PH are not easy to differentiate from the clinical picture of COPD. Suspicion of PH should be high if clinical deterioration is not matched by the decline in pulmonary function, and in the presence of profound hypoxaemia or markedly reduced carbon monoxide diffusing capacity. Patients with suspected PH should be evaluated by Doppler echocardiography and, if confirmed, undergo right-heart catheterization in those circumstances where the result of the procedure can determine clinical management.

To date, long-term oxygen therapy is the treatment of choice in COPD patients with PH and hypoxaemia because it slows or reverses its progression. Conventional vasodilators are not recommended because of their potential detrimental effects on gas exchange, produced by the inhibition of hypoxic pulmonary vasoconstriction and their lack of effectiveness after long-term treatment. In the subgroup of patients with out-of-proportion PH, new specific therapy available for pulmonary arterial hypertension (PAH) [prostanoids, endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors] may be considered in the setting of clinical trials. The use of specific PAH therapy in COPD patients with moderate PH is discouraged because of the potential detrimental effect of some of these drugs on gas exchange and there are no data demonstrating their efficacy.

Chronic obstructive pulmonary disease (COPD) is defined in terms of airflow obstruction that results from an inflammatory process affecting the airways and lung parenchyma. Despite major abnormalities affecting the airways and lung parenchyma, changes in pulmonary vessels represent an important component of the disease. Alterations in vessel structure are very common, and abnormalities in their function impair gas exchange and result in pulmonary hypertension (PH), the presence of which is associated with reduced survival.[1] Studies conducted at early disease stages revealing significant structural and functional abnormalities in pulmonary vessels[2-4] have opened a new avenue for a better understanding of the pathogenesis of this process, which might translate into clinical practice.

In this review, we examine the clinical relevance of PH in COPD, the current understanding on its pathobiology, its detection and diagnosis, and, finally, we address its management and the potential usefulness of new specific treatments for pulmonary arterial hypertension (PAH) in the particular setting of COPD.

1. Prevalence

The actual prevalence of PH in COPD is unknown because it has not been screened systematically using right-heart catheterization in the

wide clinical spectrum of the disease. Furthermore, the criteria used to define PH in COPD vary among different studies. Whereas some authors have used the conventional criteria used to define PAH, that is, a mean pulmonary artery pressure (PAP) >25 mmHg,[5] others have used a PAP of 20 mmHg as cut-off value. In this review, we consider the latter criterion, based on recently reported data indicating that the upper limit of PAP in healthy individuals is 20 mmHg.[6]

The majority of haemodynamic studies in COPD have been performed in patients with advanced disease (stage III or IV of the Global Initiative on Obstructive Lung Disease [GOLD] classification[7]). Three studies have provided data in large series of patients.[8-10]

Scharf et al.[8] evaluated 120 patients with severe emphysema (mean forced expiratory volume in the first second [FEV_1], 27% of predicted), screened for lung volume reduction surgery (LVRS). The incidence of PH (PAP >20 mmHg) was very high (91%), although in the majority of patients (86%) it was in the mild to moderate range (20–35 mmHg). Only 5% of patients showed PAP >35 mmHg. The correlation between PAP and lung function was very weak. Indeed, PAP was more closely related to pulmonary artery occlusion pressure, which was slightly increased in the majority of patients, suggesting the potential effect of gas trapping or some degree of left ventricular dysfunction in raising pulmonary capillary pressure.

Chaouat et al.[9] retrospectively evaluated the haemodynamic studies of 998 COPD patients. They identified 27 patients with severe PH, defined by PAP >40 mmHg. Whereas 16 of them had another disease capable of causing PH, in 11 (1.1% of the whole group), COPD was the only cause. The latter group of patients had moderate airway obstruction (FEV_1 50% predicted), severe hypoxaemia, hypocapnia, very low carbon monoxide diffusing capacity (DLCO) and shorter survival. These findings indicate that there is a small subset of COPD patients with out-of-proportion PH who share some clinical features with idiopathic PAH.

Thabut et al.[10] evaluated 215 patients with severe COPD (FEV_1 24% predicted), candidates for LVRS or lung transplantation. PH (PAP >25 mmHg) was present in 50% of the patients, although in the majority it was mild (26–35 mmHg). In 9.8% of patients, it was moderate (36–45 mmHg) and in 3.7% it was severe (>45 mmHg). A cluster analysis identified a subset of patients characterized by moderate impairment of airway function and high levels of PAP, along with severe arterial hypoxaemia. This observation supports the concept raised by Chaouat et al.[9] on the existence of a reduced subgroup of COPD patients with out-of-proportion PH.

In patients with less severe disease, the prevalence of PH is considered to be low. However, in these patients, PH might not be present at rest but develop during exercise.[11] The exact prevalence of exercise-induced PH in patients with moderate COPD is unknown, but may be high.[11]

Furthermore, histological evaluation of lung tissue samples from patients with mild to moderate COPD reveals significant vascular changes in the majority,[2,3,12] although the clinical significance of these anatomical abnormalities remains to be established.

2. Prognostic Significance of Pulmonary Hypertension

Patients with COPD and PH have shorter survival than patients with normal PAP.[13] Burrows et al.[14] showed that survival was inversely related to pulmonary vascular resistance (PVR). In a 15-year follow-up study conducted in 200 patients, Traver et al.[15] showed that, after adjusting for age, the presence or absence of cor pulmonale was one of the best predictors of mortality. These studies were conducted before long-term oxygen therapy (LTOT) was introduced as regular treatment for chronic respiratory failure in COPD. Nevertheless, in a recent study conducted in 84 patients receiving LTOT, it has been shown that PAP is the single best predictor of mortality.[16] The 5-year survival was 36% in patients with PAP >25 mmHg, whereas in patients with PAP <25 mmHg survival was 62%.[16] Furthermore, echocardiographic signs of right ventricular dysfunction[17] and ECG signs of right ventricular hypertrophy or

right atrial overload[18] are also predictive of survival in COPD.

In addition to the prognostic significance in relation to survival, the presence of PH in COPD is also associated with poor clinical evolution and more frequent use of healthcare resources.[19] It has been shown that the presence of PAP >18 mmHg is one of the best predictors of increased risk of hospitalization for COPD exacerbation, suggesting that patients with an abnormal pulmonary vascular bed might have lesser functional reserve to overcome the changes that occur during exacerbation episodes.

3. Pulmonary Vascular Remodelling

Vascular remodelling is a process that causes thickening of the arterial wall and increases resistance by causing the vessel wall to encroach into the lumen and reduce its diameter. In COPD, pulmonary vascular remodelling affects small and precapillary arteries, and has been identified at different degrees of disease severity. Patients with end-stage COPD and PH show deposition of longitudinal muscle, fibrosis and elastosis that enlarge the intima in pulmonary muscular arteries.[20,21] Intimal enlargement of muscular arteries is also present in patients with very severe COPD without PH.[22] In the arterioles, there is development of a medial coat of circular smooth muscle, bounded by a new elastic lamina, with deposition of longitudinal muscle and fibrosis of the intima.[20,21]

In mild to moderate COPD, pulmonary muscular arteries show intimal enlargement with reduction of the lumen size, which is more pronounced in small arteries.[2,3,23] Intimal hyperplasia results from the proliferation of poorly differentiated smooth muscle cells (SMCs), and deposition of elastic and collagen fibres (figure 1).[4] In addition, there is muscularization of the arterioles.[24]

Changes in the tunica media are less conspicuous in COPD and the majority of morphometric

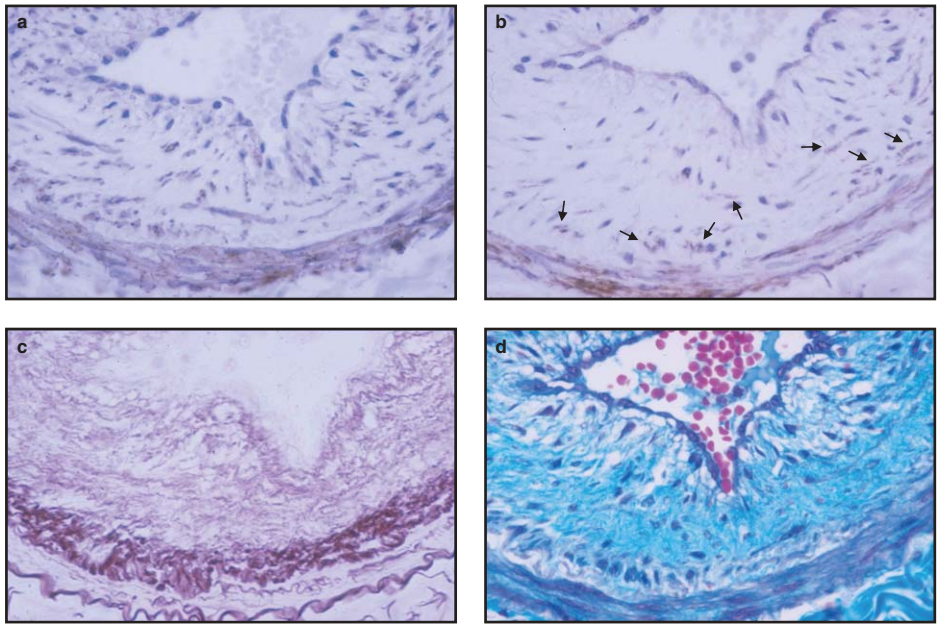

Fig. 1. Pulmonary vascular remodelling in chronic obstructive pulmonary disease. Serial sections of a pulmonary muscular artery with prominent intimal hyperplasia and luminal narrowing. Immunostaining for α-smooth muscle actin (**a**) reveals intimal proliferation of smooth muscle cells, although not all of them show immunoreactivity to desmin [arrows] (**b**), a contractile filament expressed in mature smooth muscle cells, thus indicating a poorly differentiated state. Staining for elastic (**c**) and collagen (**d**) fibres showed marked elastosis and fibrosis in the intima.

studies have failed to demonstrate differences in the thickness of the muscular layer when comparing COPD patients with control subjects.[2,3,23]

Remodelling of pulmonary arteries is not restricted to patients with an established diagnosis of COPD. Indeed, intimal thickening, the magnitude of which does not differ from that seen in patients with mild to moderate COPD, is also present in heavy smokers with normal lung function.[4]

3.1 Inflammatory Changes

COPD is an inflammatory disease; hence, inflammatory cells might contribute to the alterations of pulmonary vessels. Indeed, the extent of pulmonary vascular remodelling correlates with the severity of inflammatory cell infiltrate in small airways.[2,24] Patients with COPD have an increased number of inflammatory cells infiltrating the adventitia of pulmonary muscular arteries compared with nonsmokers.[12] This inflammatory infiltrate is largely constituted by activated T lymphocytes with a predominance of the CD8+ subset.[12,25] By contrast, the number of neutrophils, macrophages and B lymphocytes are minimal, and do not differ from those of control subjects.

In patients with mild to moderate COPD the intensity of inflammatory cell infiltrate in pulmonary arteries correlates with the degree of airflow obstruction, suggesting that, as the disease progresses, the inflammatory reaction in pulmonary arteries may become more severe.[12]

Interestingly, smokers with normal lung function also show an increased number of CD8+ T cells in the arterial adventitia, with a reduction in the CD4+/CD8+ ratio compared with nonsmokers, which does not differ from patients with mild to moderate COPD.[12]

4. Endothelial Dysfunction

Endothelial cells play a crucial role in the regulation of vascular homeostasis.[26] In pulmonary vessels, endothelial cells contribute to the reduced vascular tone,[27] regulate vessel adaptation to increased flow[28] and modulate hypoxic vasoconstriction.[29,30] Endothelial dysfunction of pulmonary arteries has been shown at different degrees of COPD severity: patients with end-stage COPD who underwent lung transplantation[31] and patients with mild to moderate disease (figure 2).[3] Impairment of endothelial function may be associated with or result from changes in the expression or balanced release of vasoactive mediators with vasodilator properties, such as nitric oxide (NO) or prostacyclin, and mediators with vasoconstrictive properties, such as endothelin-1 (ET-1) or angiotensin.

Indeed, the expression of endothelial NO synthase (eNOS) in pulmonary arteries, which is diminished in patients with idiopathic PAH,[32] is also reduced in COPD patients[33] and in smokers without airflow obstruction.[34]

Nana-Sinkam et al.[35] have recently shown that the expression of prostacyclin synthase in pulmonary arteries is also reduced in patients with severe emphysema. Similarly, Tuder et al.[36] demonstrated loss of expression of prostacyclin synthase in endothelial cells of pulmonary arteries of inpatients with associated forms of PH.

Giaid et al.[37] showed that the expression of ET-1 in pulmonary arteries was increased in both primary and secondary forms of PH.

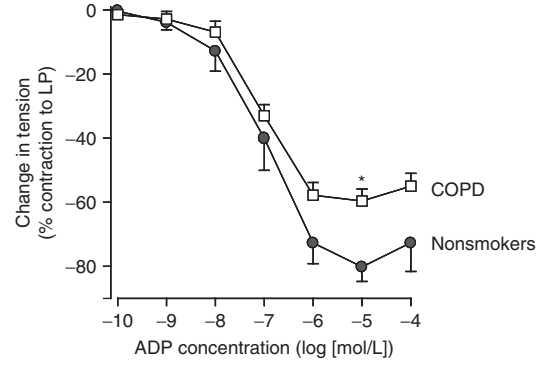

Fig. 2. Endothelial dysfunction in chronic obstructive pulmonary disease (COPD). Change in tension of pulmonary artery rings, precontracted with L-phenylephrine (LP), in response to cumulative concentrations of adenosine diphosphate (ADP), an endothelium-dependent vasodilator, in patients with mild to moderate COPD and nonsmokers. Patients with COPD showed reduced endothelium-dependent relaxation as compared with nonsmokers (from Peinado et al.[3]). * $p < 0.05$ vs non smokers.

Nevertheless, studies conducted in patients with mild to moderate COPD or severe emphysema have failed to show differences in ET-1 expression in pulmonary arteries when compared with nonsmokers.[33,34] However, the latter finding could be because patients evaluated in these series did not have PH.

5. Pathobiology of Pulmonary Vascular Changes

Hypoxia has been classically considered the main pathogenic mechanism of PH in COPD. However, its role is currently being reconsidered because pulmonary vascular remodelling and endothelial dysfunction can be observed in patients with mild COPD who do not have hypoxaemia and in smokers with normal lung function,[2,4,12] and because LTOT does not fully reverse PH.[38]

Recent observations have indicated that cigarette smoke products may be at the origin of pulmonary vascular impairment in COPD.[1] This suggestion arises from the observation that smokers with normal lung function show prominent changes in pulmonary arteries, such as SMC proliferation,[4] impairment of endothelial function,[3] reduced expression of eNOS,[34] increased expression of growth factors[22] and inflammatory cell infiltrate,[12] that are indistinguishable from those seen in patients with mild to moderate COPD, and clearly differ from nonsmokers.

Furthermore, guinea-pigs exposed long term to cigarette smoke develop PH and vessel remodelling,[39] changes that appear when there is no evidence of emphysema, indicating that cigarette smoke-induced vascular abnormalities precede its development.[40] In this animal model, cigarette smoke exposure induces rapid changes in gene expression of vascular endothelial growth factor (VEGF), VEGF receptor-1, ET–1 and inducible NOS,[41] mediators that regulate vascular cell growth and vessel contraction, and are likely to be involved in the pathogenesis of pulmonary vascular changes of COPD. In addition, exposure of pulmonary artery endothelial cells to cigarette smoke extract causes an irreversible inhibition of eNOS activity, which is as a result of diminished protein content and messenger RNA.[42] Cigarette smoke contains a number of products that have the potential to produce endothelial injury, among which the aldehyde acrolein seems to play a prominent role, since it reduces the expression of prostacyclin synthase in endothelial cells.[35]

In summary, there is compelling evidence suggesting that the initial event in the natural history of pulmonary PH in COPD could be the injury of endothelium by cigarette-smoke products (figure 3). Indeed, lesions of endothelial cells in pulmonary arteries from COPD patients can be identified on microscopic observation as areas of denuded endothelium.[43] More subtle, but no less important, is the alteration of endothelial synthesis and release of vasoactive mediators associated with cigarette smoking.[34] Endothelial damage also results in an imbalance among factors that regulate cell growth, thereby favouring the proliferation of SMC and

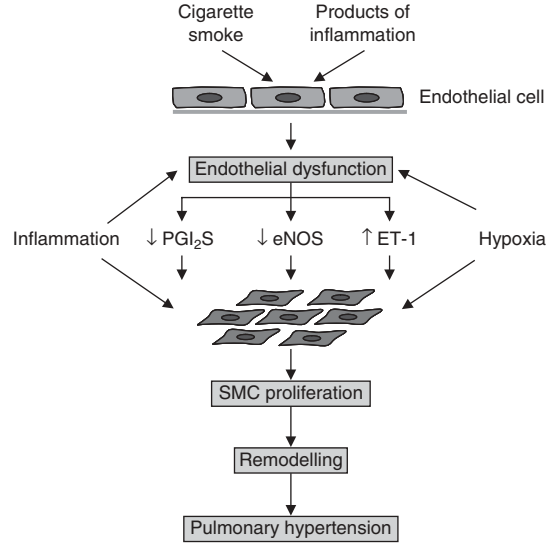

Fig. 3. Pathobiology of pulmonary hypertension in chronic obstructive pulmonary disease. Cigarette smoke or inflammation products may initiate the sequence of changes by producing endothelial dysfunction. The imbalance between endothelium-derived vasoactive agents promotes smooth muscle cell (SMC) proliferation, vessel wall remodelling and pulmonary hypertension. In the natural course of the disease, inflammation and hypoxia contribute to enhance and perpetuate this process by acting on endothelial and SMCs. **eNOS** = endothelial nitric oxide synthase; **ET-1** = endothelin-1; **PGI_2S** = prostacyclin (prostaglandin I_2) synthase.

extracellular matrix deposition (figure 3). All these changes may contribute to intimal hyperplasia with the ensuing reduction of arterial lumen, which increases pulmonary vascular resistance.

Arteries with endothelial dysfunction are more susceptible to the action of additional factors. Among those, sustained arterial hypoxaemia and alveolar hypoxia in poorly ventilated lung units play a crucial role, since they may induce further endothelial impairment and vessel remodelling, either directly or through VEGF-dependent mechanisms, thus amplifying the initial effects of cigarette smoke products. Similar effects may be produced by cytokines released by inflammatory cells (figure 3).

6. Pathophysiology and Natural History of Pulmonary Hypertension

As mentioned in section 1, in COPD, PH is usually of low to moderate severity and mean PAP rarely exceeds 35–40 mmHg. Patients exceeding these values are considered to have out-of-proportion PH and represent only 1–3% of COPD patients.[9,10] Both right atrial pressure and pulmonary artery occlusion pressure tend to be normal, in addition to cardiac output.[14,44,45] This haemodynamic profile contrasts with other types of PH (PAH, thromboembolic PH) where PAP can reach extremely high values, close to those of the systemic circulation, and where cardiac output is usually reduced.

PH in COPD progresses over time and its severity correlates with the degree of airflow obstruction and the impairment of pulmonary gas exchange.[8,46] The rate of progression of PH is slow, with PAP increasing at an average rate of 0.6 mmHg per year.[46]

At the initial stage, PH in COPD may not be apparent at rest, but may develop during exercise. Kessler et al.[11] assessed the evolution of pulmonary haemodynamics in patients with moderate COPD without PH at rest, although 58% of patients developed it during exercise. In a second assessment performed 7 years later, PAP had increased by 2.6 mmHg, with an annual rise of 0.4 mmHg. In this second assessment, 25% of patients already had PH at rest. Interestingly, the incidence of resting PH was twice as high in the group of patients who at the initial catheterization developed PH during exercise (32%) as in those without exercise-induced PH (16%).[11] These results indicate that in COPD changes in pulmonary circulation may start several years before PH is apparent at rest, and that exercise testing may be useful to show up abnormalities of pulmonary circulation. These observations are consistent with morphometric studies showing conspicuous changes in the structure of pulmonary muscular arteries in patients with mild COPD.[2,3]

6.1 Hypoxic Pulmonary Vasoconstriction

Pulmonary arteriolar constriction in response to hypoxia reduces perfusion in poorly ventilated or nonventilated lung units and diverts it to better ventilated units, thereby restoring ventilation-perfusion (V_A/Q) equilibrium and increasing partial pressure of arterial oxygen (PaO_2) [figure 4]. Hypoxic pulmonary vasoconstriction (HPV) plays an important role in matching pulmonary blood flow to alveolar ventilation in COPD where hypoxaemia and hypercapnia are predominantly due to V_A/Q mismatching.[47] The contribution of HPV to V_A/Q matching is greater in patients with less severe COPD.[2,30] Indeed, HPV is less active in patients with severe structural impairment of pulmonary muscular arteries.[2] Furthermore, in isolated pulmonary artery rings the magnitude of contraction induced by hypoxic stimulus is inversely related to the endothelial function and directly related to PaO_2,[48] suggesting that the impairment of endothelial function is associated with an altered response to hypoxic stimulus that further worsens gas exchange. The inhibition of HPV with oxygen breathing or vasodilators impairs V_A/Q matching and in the case of vasodilating agents worsens arterial hypoxaemia (figure 5). Accordingly, the potential deleterious effects on gas exchange of drugs that may inhibit HPV (table I) must be considered when treating PH in patients with COPD.

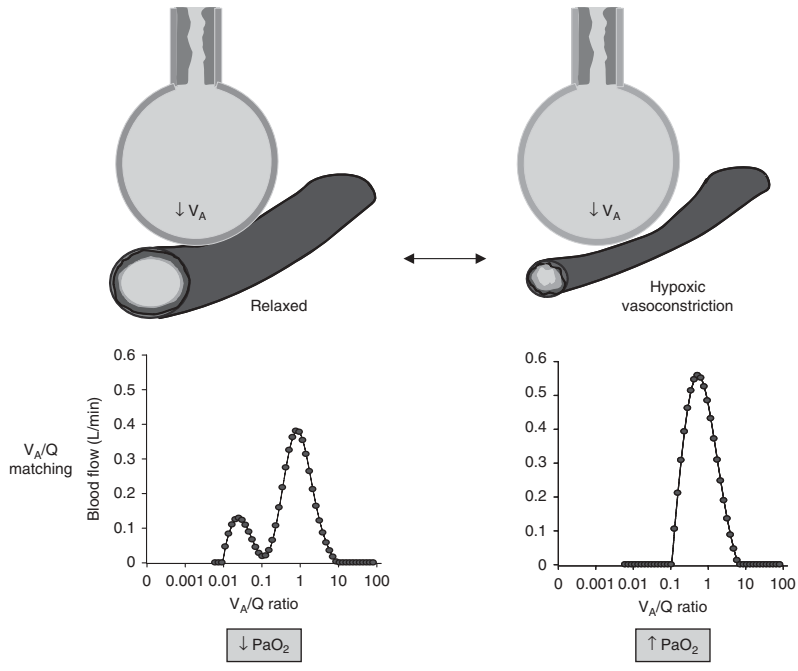

Fig. 4. Hypoxic pulmonary vasoconstriction in chronic obstructive pulmonary disease (COPD). Airway narrowing, which is characteristic of COPD, reduces effective ventilation (V_A), and hence arterial oxygen tension, in dependent alveolar units. Perfusion of these units results in ventilation-perfusion (V_A/Q) imbalance, reflected in a significant proportion of blood flow diverted to areas with low V_A/Q ratio (lower panel), which is the main determinant of arterial hypoxaemia in COPD. When hypoxic vasoconstriction operates, blood flow is diverted away from poorly ventilated alveolar units to units with better V_A/Q matching, thus raising the partial pressure of arterial oxygen (PaO_2). Inhibition of hypoxic vasoconstriction re-establishes V_A/Q mismatching and reduces PaO_2.

6.2 Right Ventricular Function

Because the PAP is only moderately elevated and its rate of progression is slow in patients with COPD and PH, the right ventricle has time to adapt to such a modest increase in afterload. When PAP is chronically elevated, the right ventricle dilates and both end-diastolic and end-systolic volumes increase. The stroke volume of the right ventricle is usually maintained, whereas the ejection fraction decreases. Subsequent hypertrophy of the right ventricular wall in persistent PH reduces its tension and improves the coupling between right ventricle and pulmonary circulation.

The reduction in right ventricular ejection fraction (RVEF) is inversely related to PAP.[63] Nonetheless, a decrease in RVEF does not mean that there is true ventricular dysfunction.[64] Assessment of end-systolic pressure-volume relationships has shown that in clinically stable COPD patients the contractility of the right ventricle lies within normal limits, irrespective of the PAP value.[65,66] However, during exacerbations, when PAP increases markedly, the contractility of the right ventricle is reduced in patients presenting clinical signs of right heart failure.[67,68]

In COPD, the cardiac output is usually preserved and may rise during exacerbation episodes,[69,70] even when there are apparent signs of right heart failure (peripheral oedema). Therefore, the usual definition of heart failure as a reduction in cardiac output does not apply in this condition. For this reason, the classical term cor pulmonale is being abandoned and it is now regarded as the expression of diastolic dysfunction of the right ventricle.

6.3 Peripheral Oedema

Peripheral oedema may be a sign of venous congestion secondary to upstream transmission of right ventricular filling pressures. However, in advanced COPD oedema is more related to hypercapnia rather than to raised jugular pressures.[71,72] Some patients may present peripheral oedema without haemodynamic signs of right heart failure or significant changes in PAP.[73,74] This has led to the reconsideration of peripheral oedema formation in COPD.[67,68,72,75,76]

In COPD, peripheral oedema results from a complex interaction between the haemodynamic changes and the balance between oedema-promoting and oedema-protective mechanisms. In patients with PH associated with chronic respiratory failure, both hypoxaemia and hypercapnia aggravate venous congestion by further activating the sympathetic nervous system, which

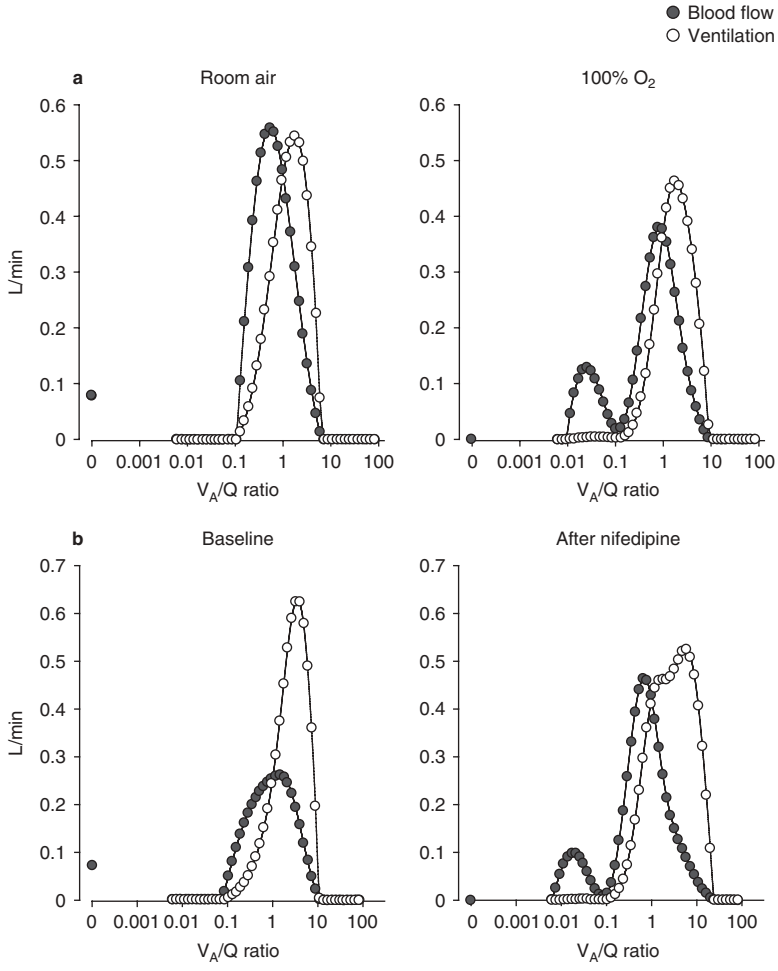

Fig. 5. Effects of inhibiting hypoxic pulmonary vasoconstriction in chronic obstructive pulmonary disease (COPD). (**a**) Plots of ventilation and blood flow in alveolar units with different ventilation-perfusion (V_A/Q) ratios in a patient with COPD while breathing room air and 100% oxygen. Inhibition of hypoxic vasoconstriction by oxygen breathing worsened V_A/Q distributions, as shown by increased perfusion in poorly ventilated alveolar units with low V_A/Q ratio. (**b**) Ventilation-perfusion distributions in a patient with COPD, before and after nifedipine 20 mg. After nifedipine, V_A/Q distributions worsened (increased perfusion in areas of low V_A/Q ratio) in a similar way to that after oxygen, as a result of the inhibition of hypoxic vasoconstriction. The latter reduced arterial oxygenation.

Table I. Drugs that may inhibit hypoxic pulmonary vasoconstriction in chronic obstructive pulmonary disease

Vasodilators
Calcium channel antagonists[49-52]
Atrial natriuretic factor[53]
Acetylcholine[54]
Inhaled nitric oxide[30,55-57]
Epoprostenol[58]
Sildenafil[59]
Bronchodilators
β_2-Adrenergic receptor agonists[60,61]
Theophylline[62]

is already stimulated by right atrial distension. Sympathetic activation decreases renal plasma flow, stimulates the renin-angiotensin-aldosterone system, and promotes tubular absorption of bicarbonate, sodium and water. Vasopressin also contributes to oedema formation. It is released when patients become hyponatraemic and the plasma vasopressin levels rise in patients with hypoxaemia and hypercapnia.[75]

Atrial natriuretic peptide is released from distended atrial walls and may act as an oedema-protective mechanism, since it has vasodilator, diuretic and natriuretic effects. Nevertheless, these effects are usually insufficient to counterbalance the oedema-promoting mechanisms.

Peripheral oedema may develop or worsen during exacerbation episodes. Analysing the changes from stable conditions that took place during an exacerbation episode, Weitzenblum et al.[70] identified a subgroup of patients with more marked peripheral oedema that was attributed to haemodynamic signs of right heart failure (increase in end-diastolic pressure). Compared with patients with normal end-diastolic pressure, patients with right heart failure had more marked increase in PAP and more severe hypoxaemia and hypercapnia. This suggests that during exacerbations PH worsening contributes to oedema formation in a subgroup of COPD patients.

7. Evaluation and Diagnosis

Recognition of PH in COPD is difficult, especially in its mildest form, because symptoms due to PH, such as dyspnoea or fatigue, are difficult to differentiate from the clinical picture of COPD. Furthermore, the identification of some clinical signs may be obscured by chest hyperinflation or large swings in intrathoracic pressure. In addition, the presence of peripheral oedema may not be a sign of right ventricular failure in COPD. Cardiac sounds may be disturbed by the presence of bronchial rales or overinflated lungs. Thus, the typical auscultatory findings of PH (ejection click or increased pulmonary component of the second heart sound, and pansystolic murmur of tricuspid regurgitation) are uncommon in COPD patients.

7.1 Routine Examinations

7.1.1 Chest Radiography

The most characteristic radiographic pattern of PH is the increase of the vascular hilum size with oligohaemia in the peripheral lung fields. Widening of the hilum can be assessed by the hilar thoracic index (distance between the start of divisions of the right and left main pulmonary arteries divided by the transverse diameter of the thorax).[77] Values >0.36 are suggestive of PH.[77,78] Other signs are cardiomegaly as a result of an enlarged right ventricle, enlarged pulmonary trunk, widening of the descending right pulmonary artery diameter (normally <16 mm) and encroachment of the retrosternal airspace on the lateral view. However, the sensitivity of chest radiography to detect PH in COPD is low.[79]

7.1.2 ECG

The sensitivity of the ECG to detect right ventricular hypertrophy is relatively low and ECG changes are not closely related to the severity of PH.[78] ECG changes associated with PH include (i) a P-pulmonale pattern suggesting right atrial overload in leads II, III and aVF; (ii) an $S_1S_2S_3$ pattern; (iii) an S_1Q_3 pattern; (iv) incomplete right bundle-branch block; and (v) right ventricular hypertrophy with QRS axis ≥120°, a predominant R wave in V1, or an R/S amplitude ratio in V5 and V6 of <1. At least two of these three latter criteria are sufficient to raise suspicion of right ventricular hypertrophy.[18,78] In COPD, both the $S_1S_2S_3$ pattern and signs of right

atrial overload have been associated with shorter survival.[18] ECG changes in COPD have a specificity of 86% and a sensitivity of 51% in detecting PH.

7.1.3 Lung Function Testing

Lung function testing is mandatory for the diagnosis of COPD.[7] Unfortunately, there are no specific patterns of pulmonary function impairment associated with the development of PH. Pulmonary hypertension has little effect *per se* on lung mechanics or gas exchange. In conditions of preserved lung parenchyma, PH can reduce DLCO. However, the latter cannot be attributed to PH in COPD, since it can be caused by lung emphysema. Yet, in patients with moderate airflow obstruction and markedly reduced DLCO, PH should be ruled out. Indeed, COPD patients with out-of-proportion PH display very low values of DLCO, along with marked hypoxaemia.[9]

7.2 Echocardiography

Echocardiography is an essential diagnostic step in any patient with suspected PH. It is noninvasive and easily available, it allows the assessment of right ventricular hypertrophy and/or dilatation, and ejection flow dynamics, and may also provide an estimate of systolic PAP.[80] However, this method presents technical difficulties in COPD patients because overinflated chests may alter sound-wave transmission. Furthermore, a measurable tricuspid regurgitation (TR) velocity is less likely to be observed in patients with COPD than in patients with more severe forms of PH.[80-82] Even if a TR jet is observed, echocardiographic estimates of the PAP are often inaccurate and result in both false positive and false negative diagnosis of PH. Compared with right heart catheter measurements, estimations of systolic PAP by echocardiography were found to be inaccurate in 52% of patients with COPD, and 48% of patients were misclassified as having PH by echocardiography.[83] In two large series comparing echocardiographic data and findings from right heart catheterization in patients with COPD, the positive predictive values of echocardiography were 32% and 68%, and the negative predictive values 67% and 93%, respectively.[83,84]

Systolic indices of tricuspid valve annular motion measured by tissue Doppler imaging appear to be useful for the prediction of right ventricular failure in COPD.[85] Furthermore, exercise echocardiography allows the identification of abnormal ventricular septal motion with distortion of left ventricle in COPD, findings that may help to detect occult right ventricular dysfunction.[86]

7.3 Biomarkers

Plasma levels of brain natriuretic peptide (BNP) or the N-terminal fragment of proBNP have also been evaluated as predictors of PH in patients with lung disease.[87] It has been found that BNP increases when PH is 'significant' (PAP >35 mmHg) and has some prognostic significance.[87] A cut-off value of 33 pg/mL had an 87% sensitivity and 81% specificity to detect 'significant' PH.[87] However, in patients with milder PH, which is more usual in COPD, BNP lacks sufficient sensitivity and specificity.

7.4 Right Heart Catheterization

Right heart catheterization is the gold standard for the diagnosis of PH. The procedure allows direct measurements of PAP, cardiac output and PVR. It can also be used to assess the acute effects of therapeutic interventions. Right heart catheterization is a safe procedure in expert hands but, because of its invasive nature, it is not routinely recommended in the assessment of patients with COPD. Nevertheless, in the following selected populations right heart catheterization may be indicated: (i) patients with suspected out-of-proportion PH (estimated systolic PAP >50 mmHg at echocardiography) who may be potentially suitable for specific PH treatment; (ii) patients with frequent episodes of right ventricular failure; and (iii) in the preoperative evaluation of candidates for lung transplant or LVRS.[88]

In summary, clinical suspicion of PH in patients with COPD should be high if clinical deterioration is not matched to the decline in pulmonary function. Profound hypoxaemia,

hypocapnia and low DLCO are indicators of possible PH. Once PH is suspected patients should be evaluated by Doppler echocardiography and, if confirmed, undergo right heart catheterization in those circumstances where the result of the procedure can determine clinical management.

8. Treatment

In patients with associated PH, COPD should be optimally treated according to existing guidelines.[7] Treatment addressed to ameliorate PH in COPD includes LTOT, vasodilators and, eventually, new specific PAH therapy.

8.1 Long-Term Oxygen Therapy

Chronic hypoxaemia plays a key role in the development of PH in COPD. Therefore, its correction with supplemental oxygen seems to be an appropriate treatment. In patients with advanced COPD, acute administration of oxygen exerts little effect on pulmonary haemodynamics[30,68,89] or RVEF[66] in patients studied at rest under stable clinical conditions. During acute exacerbation episodes, when PAP increases significantly, controlled administration of oxygen also results in minimal or no change of PAP.[89,90] By contrast, when oxygen is administered during exercise, it often improves pulmonary haemodynamics[14] and RVEF.[91]

LTOT has been shown to improve survival in COPD patients with chronic hypoxaemia. In the two classical studies that showed survival benefits in patients treated with LTOT, the Medical Research Council (MRC)[92] and NOTT (Nocturnal Oxygen Therapy Trial),[93] pulmonary haemodynamic measurements were performed before initiating LTOT and after a long period of follow-up. In the MRC study, PAP remained unaltered in patients receiving LTOT (more than 15 h/day), whereas in the control group PAP rose by a mean of 2.7 mmHg per year.[92] In the NOTT study, 117 patients were re-evaluated after 6 months of treatment. Whereas in patients receiving continuous LTOT (more than 18 h/day) PAP decreased by an average of 3 mmHg, it did not change in the group receiving nocturnal LTOT (10–12 h/day).[93,94] It should be noted that despite the haemodynamic improvement shown in some patients, in the majority of them PAP values recorded in the follow-up study did not return to normal levels. These results indicate that LTOT may slow the evolution of PH in COPD and even reverse its progression when it is administered continuously. Nevertheless, both the MRC and the NOTT studies showed that the decrease in mortality in patients receiving LTOT was unrelated to changes in pulmonary haemodynamics.[92,93] Indeed, the NOTT study did not demonstrate that ameliorating PH resulted in improved mortality.[93]

The beneficial effects of LTOT on the progression of PH in COPD were confirmed by Weitzenblum et al.[38] in a small group of patients who were followed for long periods before and after initiating LTOT. Before the onset of LTOT, PAP rose by an average 1.5 mmHg per year. By contrast, patients receiving LTOT showed a progressive decrease of PAP (–2.2 mmHg per year).[38] However, it should be noted that despite this improvement, normalization of PAP was rarely observed in the study performed 31 months after initiating LTOT.[38] Furthermore, necropsy studies have failed to show significant differences in the structural abnormalities of pulmonary vessels in patients receiving LTOT for long periods, when compared with patients who did not receive oxygen treatment.[20]

Considering that the haemodynamic response to oxygen administration might be widely variable in COPD, Ashutosh et al.[95] evaluated the long-term effects of oxygen therapy according to its acute effects on pulmonary haemodynamics. These authors showed that survival benefit of LTOT was greater in patients who showed a significant decrease in PAP during the acute administration of oxygen (acute responders).[95]

In summary, LTOT appears to be the most appropriate treatment for PH in hypoxaemic COPD patients, since its administration slows, and sometimes reverses, its progression. Nevertheless, PAP rarely returns to normal values and the structural abnormalities of pulmonary vessels

remain unaltered. It is likely that, in agreement with other forms of PH,[96] a subgroup of patients who are acute responders to oxygen administration may obtain greater benefit from LTOT.

8.2 Vasodilators

Calcium channel antagonists have been extensively evaluated for the treatment of PH in COPD. Acute administration of nifedipine has been shown to reduce PAP and increase cardiac output in COPD patients studied both at rest and during exercise.[49,97,98] However, nifedipine inhibits HPV,[50] thus worsening V_A/Q relationships and lowering arterial oxygen tension (PO_2) [figure 5].[49,99] Similar effects of nifedipine have been shown in exercise-induced PH.[49] The deleterious effects of vasodilators on V_A/Q distributions and gas exchange in COPD have been also shown with felodipine,[51] atrial natriuretic factor[53] and acetylcholine[54] (table I).

In addition, clinical results of long-term treatment with calcium channel antagonists in COPD have been disappointing. Despite the fact that slight haemodynamic improvement has been observed in some studies,[100] in others both pulmonary haemodynamics and clinical status either deteriorated or remained unchanged after several weeks or months of treatment.[101,102] In a recent study, 1 year of treatment with the angiotensin-II receptor antagonist losartan also resulted in no significant benefit on systolic PAP, exercise capacity or symptoms in COPD patients with associated PH.[103]

The effects of selective pulmonary vasodilators have also been investigated in COPD. Inhaled NO acts as a selective vasodilator of the pulmonary circulation, owing to its inactivation when combined with haemoglobin, for which it has a very high affinity. Low concentrations of inhaled NO do not exert any effect on gas exchange, whereas it decreases PAP in a dose-dependent manner.[54] When administered in high concentrations (40 parts per million [ppm]), it usually decreases PAP but at the same time worsens V_A/Q distributions,[30] as a result of the inhibition of HPV,[55] and decreases PaO_2.[30,56,57]

The effects of inhaled NO on gas exchange in COPD appear to be different during exercise, since in this condition it may promote better V_A/Q matching without altering arterial PO_2.[56] Such a different effect of inhaled NO during exercise might be explained by enhanced distribution of the gas to well ventilated lung units with faster time constants, which are more efficient in terms of gas exchange. In clinical terms, these findings may imply that if inhaled NO could be delivered specifically to well ventilated alveolar units with fast time constants, the beneficial vasodilator effect of NO would not be offset by its deleterious impact on gas exchange. This notion has led to the development of the so-called spiked or pulsed delivery of NO.[104] With this system a small bolus of NO is administered at the beginning of inspiration, with the aim that it will be specifically distributed to alveolar units with fast time constants.

Yoshida et al.[105] showed that the combined administration of low doses of NO and oxygen resulted in a significant improvement of pulmonary haemodynamics and provided better oxygenation than when breathing oxygen alone. Whereas the haemodynamic effects of combined NO and oxygen appear to be related to the NO dose, the amelioration in gas exchange seems to have a ceiling effect at a concentration of 5 ppm.[106] Vonbank et al.[107] evaluated the combined effect of oxygen and pulsed NO inhalation, compared with oxygen alone, in a randomized study of 3 months' duration. Compared with oxygen alone, the combined inhalation of NO and oxygen caused a significant decrease in PAP and PVR, without decreasing arterial oxygenation.[107]

Overall, it can be concluded that in COPD systemic vasodilators may produce a slight reduction in PAP and increase cardiac output, but their administration is usually accompanied by gas exchange worsening, and there is no evidence that long-term treatment is of clinical benefit. For these reasons, they are not recommended for the treatment of PH associated with COPD. Selective vasodilators, such as inhaled NO, exert similar haemodynamic and gas exchange effects and, if used, should be administered using systems of

pulsed delivery and in combination with oxygen. Despite some preliminary promising data,[107] the long-term effect of selective vasodilators in terms of survival and symptom relief remains to be established.

8.3 Other Treatments

Diuretics are recommended in patients with peripheral oedema in order to reduce sodium and water retention and hence right ventricular workload. Nevertheless, diuretics should be given with caution, since they may induce metabolic alkalosis that may aggravate arterial hypercapnia.[108] Furthermore, excessive intravascular volume depletion may compromise adequate filling of the afterloaded right ventricle and promote further blood viscosity in polycythaemic patients.[78] Diuretic treatment is usually instituted with low doses of loop diuretics, such as furosemide (20–40 mg/day). Monitoring of plasma electrolytes is mandatory and potassium or magnesium supplementation may be necessary.

Bronchodilators may exert some beneficial effects on pulmonary haemodynamics in patients with COPD. Theophylline reduces PVR slightly, and improves both right and left ventricular ejection fractions.[109] Nevertheless, patients with right ventricular failure have decreased clearance of theophylline and their plasma concentrations should be closely controlled. Short-acting β-adrenergic receptor agonists given by the intravenous route increase cardiac output and reduce PVR.[60,110] However, these effects are frequently accompanied by a worsening of arterial oxygenation as a result of the inhibition of HPV.[60-62] The detrimental effects of β-adrenergic receptor agonists on gas exchange are not seen when they are administered by inhalation.[60]

8.4 New Specific Therapy for Pulmonary Arterial Hypertension

Experience accumulated in PAH, mainly in the idiopathic form and in some associated conditions, indicates that specific therapy of PAH, addressed to revert or compensate the unbalanced release of endothelium-derived vascular mediators, improves symptoms, exercise performance, pulmonary haemodynamics and survival.[111] Based on this experience and taking into account that the pathogenesis of PH in COPD shares some common pathways with that of PAH, it is conceivable that drugs that may correct the endothelial vasoconstrictor-dilator imbalance could be of clinical benefit in COPD.[112,113]

There are currently three types of drugs that have been successfully used in PAH: prostanoids (prostacyclin and its analogues), ET-1 receptor antagonists and phosphodiesterase (PDE)-5 inhibitors.[5]

Prostanoids must be administered by the intravenous, subcutaneous or inhaled route. Stevens et al.[114] reported the use of intravenous epoprostenol (synthetic prostacyclin) in two patients with severe COPD and PH. After 7 months of treatment one patient had died and the other was still alive.[114] Nevertheless, a placebo-controlled study has shown that intravenous administration of prostacyclin worsens arterial oxygenation in patients with a COPD exacerbation,[58] an effect that can be attributed to the inhibition of HPV. The acute effects of inhaled iloprost, a prostacyclin analogue, were evaluated in six patients with COPD and a mean systolic PAP, estimated by Doppler echocardiography, of 40 mmHg.[115] The administration of iloprost 5 μg by inhalation resulted in improvement of exercise tolerance with no effect on gas exchange.[115]

The effects of bosentan, a dual antagonist of ET-1 receptors, in COPD have been evaluated in a randomized, placebo-controlled study.[116] Thirty COPD patients with a mean systolic PAP (echocardiography) of 37 mmHg were treated with bosentan 125 mg twice daily during 3 months. At the end of the treatment period there were no changes in exercise tolerance or echocardiographically assessed PAP, whereas the arterial oxygenation worsened significantly[116] (table II). Sildenafil, a PDE-5 inhibitor, has been evaluated in three uncontrolled studies including a small number of subjects[117-119] (table II). In two of these studies, sildenafil, at doses higher than those currently approved for PAH treatment, improved exercise tolerance and pulmonary

Table II. New specific therapy for pulmonary arterial hypertension in chronic obstructive pulmonary disease (COPD)

Study	Drug	Design	No. pts	Dose (mg)	Time (mo)	6MWD (m)		PAP (mmHg)		PaO_2 (mmHg)	
						pre	post	pre	post	pre	post
Alp et al.[117]	Sildenafil	Uncontrolled	6	50 bid	3	351 ± 49	433 ± 52*	30 ± 6	25 ± 4*	NR	NR
Madden et al.[118]a	Sildenafil	Uncontrolled	7	50 tid	2	107 ± 76	145 ± 96*	39 ± 10	35 ± 9	NR	NR
Rietema et al.[119]	Sildenafil	Uncontrolled	14	20 tid	3	385 ± 135	394 ± 116	20 ± 9	NR	NR	NR
Stolz et al.[116]	Bosentan	Double-blind, placebo-controlled	30	125 bid	3	331 ± 123	329 ± 94	32 (29–38)b	30 (26–34)b	65 ± 11	61 ± 8*

a Four patients had COPD and three idiopathic pulmonary fibrosis.

b Measured by echocardiography; values are median (interquartile range).

bid = twice daily; **NR** = not reported; **PAP** = pulmonary artery pressure; **PaO_2** = partial pressure of arterial oxygen; **pts** = patients; **tid** = three times daily; **6MWD** = distance covered in the 6-minute walk test; * $p < 0.05$ vs pretreatment value.

haemodynamics (table II).[117,118] In the third study, where patients were treated with conventional doses, exercise tolerance, assessed by both the 6-minute walk test and an incremental cardiopulmonary exercise tests, did not change after 3 months' treatment (table II).[119] Furthermore, the stroke volume, measured by magnetic resonance, did not increase after sildenafil treatment, neither at rest nor during exercise.[119] No data on the effects of sildenafil on gas exchange have been reported in any of these studies. However, sildenafil has the potential for worsening gas exchange in patients with COPD,[120] since it inhibits HPV, as shown in healthy volunteers.[59]

These preliminary reports on the effects of specific PAH therapy in COPD should be taken with caution, since the majority of the studies involved a small number of subjects and had an uncontrolled design, and some of them included patients without PH. Furthermore, one of the major safety concerns in COPD, which is the potential detrimental effect on gas exchange, has not been reported in the majority of studies. The safety and efficacy of specific PAH therapy for the treatment of PH associated with COPD warrants further evaluation in appropriately designed trials.

In summary, the treatment of choice in patients with PH associated with COPD who are hypoxaemic is LTOT. In the subgroup of patients with out-of-proportion PH, an exhaustive work-up should be completed to exclude other causes (i.e. sleep disordered breathing, left heart disease). Once confirmed, specific PAH therapy might be considered, although ideally this should be done in the setting of clinical trials in experienced PH centres. The use of specific PAH therapy in patients with COPD and moderate PH is currently discouraged because there are no systematic data regarding its efficacy and there is compelling evidence indicating that these drugs might worsen pulmonary gas exchange.

9. Conclusions

Pulmonary hypertension is a serious complication of COPD that is associated with greater mortality and a worse clinical course. In advanced COPD, PH is highly prevalent, affecting more than 50% of patients, although in the majority of patients it is of mild to moderate severity. Endothelial cell damage and dysfunction is at the origin of PH in COPD. It is currently thought to be produced by the effects of cigarette smoke products.

Echocardiography is the best screening tool for the assessment of PH in COPD, although its diagnostic performance is lower than in other forms. The proper diagnosis of PH relies on right heart catheterization, although the procedure is essentially restricted to patients with suspected out-of-proportion PH. The treatment of choice for COPD patients with associated PH who are hypoxaemic is LTOT. Conventional vasodilators are not recommended because they may impair gas exchange and their lack of efficacy after long-term use. The use of specific PAH therapy in patients with moderate PH is currently

discouraged until more data regarding its safety and efficacy are available.

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