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Themed Issue: Pulmonary hypertension and right heart failure: new therapeutic avenue/approaches

REVIEW ARTICLE

Pulmonary hypertension in chronic obstructive pulmonary disease

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Even mild pulmonary hypertension (PH) is associated with increased mortality and morbidity in patients with chronic obstructive pulmonary disease (COPD). However, the underlying mechanisms remain elusive; therefore, specific and efficient treatment options are not available. Therapeutic approaches tested in the clinical setting, including long-term oxygen administration and systemic vasodilators, gave disappointing results and might be only beneficial for specific subgroups of patients. Preclinical studies identified several therapeutic approaches for the treatment of PH in COPD. Further research should provide deeper insight into the complex pathophysiological mechanisms driving vascular alterations in COPD, especially as such vascular (molecular) alterations have been previously suggested to affect COPD development. This review summarizes the current understanding of the pathophysiology of PH in COPD and gives an overview of the available treatment options and recent advances in preclinical studies.

Abbreviations: 6MWD, 6-min walking distance; CDDO-Im, 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole; CI, cardiac index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; ET-1, endothelin-1; FEV_1, forced expiratory volume in 1 s; HF, heart failure; HPV, hypoxic pulmonary vasoconstriction; IPAH, idiopathic pulmonary arterial hypertension; L-NIL, N^6-(1-iminoethyl)-L-lysine dihydrochloride; LTOT, long-term oxygen therapy; mPAP, mean pulmonary arterial pressure; MPO, myeloperoxidase; mTOR, mechanistic target of rapamycin kinase; Nrf2, nuclear factor, erythroid 2-like 2; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; RH, right heart; RHC, right heart catheterization; Rtp801/DDIT4, DNA-damage-inducible transcript 4; RV, right ventricle; RVSP, right ventricular systolic pressure; S1P, sphingosine 1-phosphate; SAR, small airway remodelling; sGC, soluble GC; V/Q, ventilation/perfusion; WSPH, World Symposium on Pulmonary Hypertension.

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1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive and incurable disease that represents one of the five leading causes of death worldwide. Pathological changes in COPD are caused by the inhalation of toxic agents such as cigarette smoke and include permanent bronchoconstriction, small airway remodelling (SAR), alveolar destruction, activation of the innate immune system, and pulmonary vascular remodelling (Vestbo et al., 2013). COPD comprises chronic bronchitis as well as lung emphysema. In addition to the effects on the lung, COPD patients present with numerous systemic effects, and in up to 90% of patients, mean pulmonary arterial pressure (PAP) is higher than 20 mmHg at rest (Scharf et al., 2002; Thabut et al., 2005). Although pulmonary hypertension (PH) is associated with increased risk of exacerbations and decreased survival in COPD patients, treatment options for this complication are limited (Chaouat, Naeije, & Weitzenblum, 2008; Peinado, Pizarro, & Barbera, 2008).

PH is characterized by increased mean pulmonary arterial BP (Simonneau et al., 2019). The subsequently increased afterload for the right ventricle (RV) of the heart causes right heart (RH) hypertrophy. This adaptive hypertrophy helps the heart to cope with the high pulmonary vascular resistance (PVR). However, beneficial adaptive hypertrophy can culminate in maladaptation, RV dilatation, and failure.

The complex aetiology of the vascular alterations in COPD is not fully understood but is likely to involve the direct effects of cigarette smoke on the pulmonary vasculature as well as hypoxia, activation of inflammatory cells, polycythaemia, vascular pruning, and lung hyperinflation (Peinado et al., 2008; Shujaat, Minkin, & Eden, 2007). Although there is no doubt that hypoxia occurring in advanced COPD can trigger pulmonary vascular remodelling, PH, and subsequent RH hypertrophy, recent evidence from human COPD and smoke-exposed animals suggest that (a) vascular alterations occur as an early phenomenon prior to emphysema development and (b) they are an important player in the pathology of COPD and might be even driving parenchymal destruction. This novel concept emphasizes the need for an efficient treatment of COPD–PH, as the curative therapies for vascular alterations could prevent or even contribute to the reversal of emphysema.

This article summarizes the current understanding of the pulmonary vascular structural and molecular changes in COPD. Additionally, it reviews available treatment options, as well as the recent advances in preclinical studies investigating potential therapies for COPD–PH.

2 | PHYSIOLOGICAL AND PATHOLOGICAL MECHANISMS AND THE PREVALENCE OF PH IN COPD PATIENTS

2.1 | Mechanisms of PAP elevation in COPD

The main underlying mechanisms for an increase in mean PAP (mPAP) consist of three principal factors, which can, one by one or simultaneously, cause PH. The first factor is hyperinflation of the lung, causing elevation of all thoracic pressure readings and a decrease of blood volume in all cardiac chambers, decreasing stroke volume, and increasing sympathetic drive. The second factor is an increased filling pressure of the left ventricle due to systolic, diastolic, or combined heart failure (HF), causing an elevated PAP even in the presence of normal PVR. The third factor is elevated PVR, causing both an elevated transpulmonary arterio-venous pressure gradient and, in severe cases, a decreased cardiac output (CO).

2.2 | Hyperinflation, cor pulmonale, and right and left ventricular dysfunction

Based on autopsy findings, the term "cor pulmonale" was used to describe an RV dilatation due to chronic lung disease. In contrast, current studies using modern imaging in patients with mild-to-moderate COPD demonstrated reduced RV volumes, compared with healthy controls (Kawut et al., 2014). This apparent paradox may be explained by the fact that the majority of patients with severe COPD primarily suffer from increased intrathoracic pressures due to hyperinflation, airway obstruction, and airway collapse and not from decompensated RH failure. Increased intrathoracic pressures reduce venous blood return into the thorax, thus contributing to reduced volumes in all cardiac chambers. The recent CLAIM study has elegantly demonstrated that this can be reversed by means of combined long-acting bronchodilators, causing deflation of the lung and increased end-diastolic filling of both the right and left ventricle and a significant increase in stroke volume (Hohlfeld et al., 2018). As expected, these changes were associated with a substantial improvement of dyspnoea.

Another cardiac factor relates to left ventricular changes: Up to 30% of COPD patients suffer from systolic or diastolic left HF (Funk et al., 2008; Rennard et al., 2015; Rutten et al., 2005), leading to increases in both pulmonary arterial wedge pressure (PAWP) and mPAP on top of the increased pressure due to lung hyperinflation. Episodes of left heart decompensation cause increasing PAP and may be difficult to differentiate from COPD exacerbations (Krahnke et al.,

2015), because, among other similarities, both complications are associated with acute mPAP elevation (Abraham et al., 2011; Weitzenblum, Apprill, Oswald, Chaouat, & Imbs, 1994). Frequent mPAP elevations may cause a dilation of the central pulmonary arteries. This might explain why a large prospective study found that a pulmonary artery/aorta diameter ratio >1 on the chest CT was the strongest baseline predictor of severe exacerbations (Wells et al., 2012).

As mentioned, COPD is a disease frequently associated with HF that constitutes a short-term prognostic indicator of cardiovascular morbidity and mortality in patients admitted through this process. Both conditions share some risk factors including cigarette smoking, advanced age, and systemic inflammation (Hawkins et al., 2009). The relationship between COPD and cardiovascular events is not fully clarified. COPD patients do not have an increased risk of having arterial hypertension or hypertrophy of the left ventricle. However, there is evidence that the systemic inflammation that accompanies these patients may play an important role in the pathogenesis of atherosclerosis (Sin & Man, 2003). One hypothesis to explain the high prevalence of left ventricular systolic dysfunction in individuals with COPD is that systemic inflammation accelerates the progression of coronary atherosclerosis, which leads to the development of ischaemic heart disease. The high incidence of motor disorders of the left ventricle wall seen in patients with COPD and left ventricular dysfunction could also justify the relationship between both chronic processes.

In patients with COPD, associated or not with HF, it is often difficult to make a differential diagnosis of dyspnoea. The symptoms and physical signs of both diseases can coexist with each other and often do not correlate with the patient's haemodynamic state.

Performing an echocardiogram in patients with COPD can detect alterations in left ventricular function, both diastolic and systolic, associated with the presence of cardiovascular disease in a high percentage of cases.

In terms of treatment, COPD should be treated according to clinical guidelines in patients with HF as there is no direct evidence that this respiratory disease should be treated differently in the presence of HF. This statement is based on findings from large long-term studies in patients with HF and co-morbid COPD (Calverley et al., 2010).

Additional studies providing new data on the pathogenesis and management of patients with COPD and HF are needed, with the purpose of trying to improve quality of life as well as survival of these patients, and also, these patients would definitely benefit from greater integration between cardiology and pulmonology (Canepa et al., 2019).

2.3 | Increased PVR

Several mechanisms may be involved in the increase of PVR in COPD patients, and augmented PVR leads to an elevated PAP and in severe cases to decreased CO.

2.3.1 | Pulmonary vascular remodelling

Pulmonary vascular remodelling is an important factor contributing to the increased PVR. Changes in the pulmonary vasculature are present in all stages of the disease and involve the intimal and medial layers of the vascular wall (Magee, Wright, Wiggs, Pare, & Hogg, 1988; Wilkinson, Langhorne, Heath, Barer, & Howard, 1988; Wright, Petty, & Thurlbeck, 1992). Intimal thickening is evident in patients with mild-to-moderate disease whose PAP is within the normal range at rest (Magee et al., 1988) and also in smokers without airway obstruction (Santos et al., 2002) and includes occurrence of longitudinally oriented smooth muscle cells and deposition of elastic and collagen fibres (Santos et al., 2002; Wilkinson et al., 1988). Changes in the medial layer were found in patients with established COPD–PH and included hypertrophy of the muscular layer (Magee et al., 1988; Wright et al., 1992) and development of a circular smooth muscle coat confined by a new internal elastic lamina in the arterioles (Wilkinson et al., 1988). It is worth mentioning that severe COPD–PH presents with higher degree of vascular remodelling of the pulmonary microvessels, compared with the situation seen in COPD patients with moderate PH (Bunel et al., 2019). Additionally, inflammatory infiltrates largely consisting of T lymphocytes were found in the adventitia of pulmonary muscularized arteries in patients with mild COPD. The number of leukocytes found in adventitia correlated with the intimal thickening (Peinado et al., 1999).

2.3.2 | Loss of small pulmonary vessels

Pruning of small blood vessels is another feature of pulmonary vascular remodelling in COPD patients (Bunel et al., 2019; Estepar et al., 2013; Washko et al., 2019), which may also contribute to the increase in PVR. Here again, the capillary density in COPD lungs appears to be dependent on PH severity (Bunel et al., 2019). The loss of distal arterial vasculature is associated with RV enlargement in patients with mild COPD, and relative preservation of that vasculature in those patients with emphysema is protective against RV enlargement and the consequences of this condition (Washko et al., 2019). These findings indicate that there is indeed a subgroup of COPD patients with predominant vascular involvement and suggest that therapies focused on vascular disease may improve the cardiovascular outcomes in patients with less severe COPD. Importantly, a recent study from Rahaghi et al. (2019) demonstrated that loss of small vessel volume in lungs of smokers measured by CT was well correlated with the reduction of vascular cross-sectional area, quantified histologically.

2.3.3 | Hypoxic pulmonary vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) is another important factor contributing to increased PVR in COPD. Airway obstruction, loss

of alveolar septae, and loss of small airways (Hogg, 2004) in lungs of COPD patients often exhibit a patchy distribution pattern all over the lung, resulting in ventilation (V) and perfusion (P) heterogeneity. Therefore, HPV plays an important role for the matching V/Q at the lung level. HPV, as a physiological mechanism, explains why patients with severe structural lung disease may have normal or near-normal arterial blood gas pressures and why strong vasodilator drugs or endogenous inflammatory mediators attenuating HPV may severely deteriorate V/Q matching and arterial oxygenation. However, prolonged hypoxia and persisting HPV in many lung areas may lead to chronic vasoconstriction and remodelling of the pulmonary vessels with thickening of the vessel walls and reduced vascular lumen and thus contribute to the increase of PVR and the development of PH (Blanco, Piccari, & Barbera, 2016; Kovacs & Olschewski, 2018; Nathan et al., 2019).

2.4 | Tobacco smoking, endothelial and epithelial dysfunction, and inflammation

In addition to hypoxia-driven mechanisms described above, recent studies provided evidence that tobacco smoking may cause remodelling of the pulmonary arteries, independent of changes in lung function (Santos et al., 2002). Animals with chronic cigarette smoke exposure developed pulmonary vascular remodelling prior to lung emphysema development (Ferrer et al., 2009; Seimetz et al., 2011; Weissmann et al., 2014; Wright & Churg, 1991). Cigarette smoke acts through either a direct effect on endothelial cells, epithelial cells, (endothelial and epithelial dysfunction), and/or pulmonary arterial smooth muscle cells or through an inflammatory mechanism (Ferrer et al., 2009; Lee, Taneja, & Vassallo, 2012; Nyunoya et al., 2014; Xu et al., 2010). Endothelial dysfunction causes vascular stiffness, for example, due to lack of **NO** and **prostacyclin** and overproduction of **thromboxane A_2** and **endothelin-1 (ET-1)**, and is frequently present in COPD (Polverino et al., 2017). Some studies suggest that endothelial dysfunction of the small pulmonary vessels also causes lung emphysema (Taraseviciene-Stewart & Voelkel, 2008). In addition, endothelial dysfunction also results in left HF, which again contributes to an increase in mPAP. Cigarette smoke is also associated with epithelial cell apoptosis causing lung emphysema. Inflammatory cytokines like C-reactive protein, **TNF-α**, the chemokine **CCL2**, soluble **intercellular adhesion molecule-1**, and PDGF can contribute to pulmonary vascular disease by directly affecting the pulmonary artery smooth muscle cells and pulmonary artery endothelial cells (Joppa, Petrasova, Stancak, & Tkacova, 2006; Wouters, Groenewegen, Dentener, & Vernooy, 2007). In addition, tobacco smoke may directly target pulmonary artery smooth muscle cells (Seimetz et al., 2011).

In addition to the above mechanisms, genetic heterogeneity might play a role in development of a vascular phenotype in COPD patients. For details, the reader is referred to the Supporting Information.

3 | THE CLINICAL PICTURE OF PH IN COPD

3.1 | Clinical classification

In COPD, PH can be defined as pre- or post-capillary, depending on the PAWP reading during RH catheterization (RHC; Simonneau et al., 2019). Precapillary PH can be due to pulmonary arterial hypertension (PAH; group 1) in patients with mild lung disease, due to lung diseases and/or hypoxia (group 3), or due to chronic thromboembolic PH (group 4). This last possibility needs to be taken into consideration, as COPD is a risk factor for venous thromboembolism. In addition, other causes for PH may be present (group 5 PH). Increased PAWP can be due to left heart disease (group 2) in patients with increased left ventricular filling pressures as a consequence of cardiovascular co-morbidities (true post-capillary PH) or due to lung hyperinflation (group 3).

There is a potential overlap between group 3 and group 1 PH, as even some patients with idiopathic PAH (IPAH) present with airway obstruction and low diffusing capacity of the lung for carbon monoxide (Trip et al., 2014). In IPAH patients, COPD may develop as well, most probably as a consequence of smoking. Because it is not always easy to distinguish PAH patients with COPD (group 1) from patients with PH due to COPD (group 3), the 6th World Symposium on Pulmonary Hypertension (WSPH) suggested some specific diagnostic criteria to aid clinicians in the differential diagnosis. If the airway obstruction is mild and PH is severe, if there is a familial PAH or an associated PAH (e.g., systemic sclerosis or portal hypertension) or if the development of PH precedes the development of airway obstruction, the patient may qualify as PAH (group 1 PAH) with a concomitant lung disease. On the other hand, COPD patients should be assigned to group 3 PH, if forced expiratory volume in 1 s (FEV_1) is below 60% predicted or severe structural changes are visible in the lung parenchyma as assessed by thin-slice CT. Further criteria relate to the findings of cardiopulmonary exercise test, where ventilatory limitation supports group 3 PH classification and circulatory limitation supports group 1 PAH classification (Nathan et al., 2019).

3.2 | The relevance of elevated PAP in COPD

A mPAP between 21 and 30 mmHg is a common finding in COPD patients. Such mPAP values are mildly elevated in relation to normal mPAP of 14.0 ± 3.3 mmHg (Kovacs, Berghold, Scheidl, & Olschewski, 2009; Simonneau et al., 2019). Independent of the underlying disease, a resting mPAP above 20 mmHg is associated with increased mortality (Douschan et al., 2018; Kovacs et al., 2014) and an increased risk of severe exacerbations (Kessler, Faller, Fourgaut, Mennecier, & Weitzenblum, 1999; Medrek, Sharafkhaneh, Spiegelman, Kak, & Pandit, 2017). Enlarged pulmonary arteries, as detected by CT imaging, were better baseline predictors of exacerbations than any lung function parameter (Wells et al., 2012). In the ASPIRE registry from the United Kingdom, patients with PH due to lung disease had a worse prognosis than other PH groups including PAH (Hurdman et al., 2012).

In order to better stratify COPD patients based on their resting mPAP, the working group on PH in lung diseases during the 6th WSPH suggested the following definitions (Nathan et al., 2019):

- chronic lung disease without PH (mPAP < 21 mmHg or mPAP 21–24 mmHg with PVR < 3 Wood units),
- chronic lung disease with PH (mPAP ≥ 21–24 mmHg with PVR ≥ 3 Wood units or mPAP 25–34 mmHg, PH–COPD, PH–idiopathic pulmonary fibrosis, and PH–combined pulmonary fibrosis and emphysema), and
- chronic lung disease with severe PH (mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg with low cardiac index [CI < 2.0 $L \cdot min^{-1} \cdot m^{-2}$]).

The thresholds for "severe PH" were based on previous recommendations (Hoeper et al., 2011; Olschewski et al., 2018; Seeger et al., 2013) relying on studies such as that presented by Minai et al. during the American Thoracic Society Annual Conference 2010, which suggested that there is a small cluster of COPD patients with predominant vascular involvement, which may be called a "pulmonary vascular phenotype" (Kovacs et al., 2018). The features of the COPD "pulmonary vascular phenotype" include less severe airflow limitation, more extensive arterial hypoxemia, normocapnia or hypocapnia, very low diffusing capacity of the lung for carbon monoxide, severe dyspnoea during exercise (Kovacs et al., 2018), and a cardiovascular exercise limitation pattern.

In most COPD patients, the increase of mPAP per increase in CO (mPAP/CO slope) is elevated during exercise, causing limitation of cardiac reserves and additional dyspnoea. The underlying mechanisms again relate not only to hyperinflation and left HF but also to an increased PVR (Kovacs et al., 2017). A significant increase in PAP during exercise is associated with poor exercise capacity (Boerrigter et al., 2012; Cuttica et al., 2010; Sims et al., 2009).

3.3 | Clinical consequences of PAP elevation

Despite the clinical relevance of increased PAP in COPD, PAH therapies are not recommended for most of the COPD patients, even if their mPAP meets the criteria for PH. The main reasons are (a) many COPD patients will not meet the criteria for precapillary PH (mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR ≥ 3 Wood units; Simonneau et al., 2019), (b) PAH therapies have only been approved for group 1 PH (PAH) and not for group 3 PH (due to lung disease), to which group most COPD patients belong, and (c) PAH therapies may lead to severe complications in COPD patients (e.g., due to increased V/Q mismatch and hypoxemia).

3.4 | Prevalence of PAP elevation and PH in COPD

The prevalence of PH in COPD is difficult to assess. Non-invasive assessment is not reliable, and large series of RHC are only available in patients with severe COPD. Several studies in patients with severe airway obstruction showed that up to 90% of these patients have an mPAP > 20 mmHg (Scharf et al., 2002; Thabut et al., 2005). However, just 3–5% were in a mPAP range above 35–40 mmHg (Nathan et al., 2019), and in a carefully examined COPD cohort from Strasbourg, only 1.1% presented with mPAP > 40 mmHg with no other explanation for PH than COPD (Chaouat et al., 2005).

In a French cohort of transplant candidates with severe emphysema, cluster analysis revealed a rare subgroup of patients with an "out-of-proportion" increase in mPAP (Thabut et al., 2005). This cluster accounted for 7.4% of the emphysema cohort. When the more general ECLIPSE cohort with Global Initiative for COPD (GOLD) 2–4 patients was subjected to cluster analysis, about 15% belonged to the severe emphysema cluster (Rennard et al., 2015). If this cluster corresponds to the above French transplant cohort, it would mean that 15% out of 7.4%, that is, 1.1% of all COPD patients in GOLD stages 2–4, may present with out-of-proportion PH. This percentage corresponds very well to the Strasbourg cohort and offers the chance to estimate the overall burden of severe PH in COPD. If just 6.5% of the general population >25 years suffer from COPD (Ford et al., 2013), and only half of these patients are in GOLD stages 2–4, this would still translate to 0.036% prevalence of severe PH due to severe emphysema in a general population, that is, 36/100,000, which is about 10 times higher than the PAH prevalence (Galie et al., 2016).

PH imposes a high degree of morbidity and mortality on COPD patients. As the mechanisms are not elucidated yet, preclinical research in relevant animal models may help to clarify these aspects and pave the way to new treatment options in COPD patients with PH.

4 | ANIMAL MODELS OF COPD–PH

Animal models are helpful to determine the molecular pathways of the complex pathophysiology of COPD and to identify potential drug targets for novel therapies. Various animal models mimic different features of COPD, most commonly emphysema, induced by different triggers, such as intratracheal elastase (pancreatic or neutrophil elastase) application, LPS application, and inorganic dusts exposure or by diverse genetic modifications of mice, reproducing some of the hallmarks of the disease. Cigarette smoke exposure models have been suggested to have the best translational value for COPD, sharing the same aetiology and reproducing pathological alterations and the majority of the morphological lesions seen in humans (Wright, Cosio, & Churg, 2008). Accordingly, we here focus mainly on tobacco smoke exposure animal models, in which PH develops. In different species, smoke-induced changes include emphysema, epithelial cell metaplasia, airway remodelling and activation of innate immunity, and also pulmonary vascular remodelling and PH as early phenomena of this disease (Churg & Wright, 2007). PH is seen also in elastase models of emphysema, but the pathological mechanisms leading to the elevation of PAP in this model probably have different underlying causes (Luthje et al., 2009).

4.1 | Cigarette smoke exposure in animals

4.1.1 | Methods of smoke exposure

There are two ways for tobacco smoke administration in animal models, the whole-body and the nose-only administration (Leberl, Kratzer, & Taraseviciene-Stewart, 2013). In addition, effects of mainstream or side-stream exposure can be investigated. The advantage of the whole-body exposure is that animals are not restrained, causing less stress for the animals including stress-related confounding effects. It is also feasible for a large number of animals. One disadvantage might be that animals can ingest nicotine or tar orally by licking the coat. However, a study conducted by Mauderly et al. (1989) showed that there was less acute toxicity and less weight loss in the animals with whole-body exposure compared with nose-only application.

Cigarettes used in these kinds of experiments should be standardized (use of research-grade cigarettes), assuring a defined composition, a specified dose of total suspended particles, and total particulate matter in smoke (Leberl et al., 2013).

4.2 | Smoke-induced pathological changes

4.2.1 | Emphysema

Parenchymal destruction and enlargement of the alveolar space in lungs of COPD patients is the pathological change that, historically, has attracted the most attention and became the focus of most animal models.

Functional changes in the lungs of smoke-exposed mice and guinea pigs can nowadays be precisely measured and include increase of compliance and loss of elastic recoil, evident from the shift of the pressure/volume curve upwards and to the left (Wright et al., 2008).

Smoke-induced emphysema in mice and guinea pigs is similar to a mild, centrilobular form commonly found in human smokers, progresses with the prolonged exposure to smoke, but, in general, remains milder than seen in patients with GOLD stage 4 COPD. Moreover, smoke induces abnormalities in the parenchyma between alveolar ducts, with increase in size and number of the pores of Kohn—a phenomenon also found in human smokers (Wright et al., 2008).

It is important to mention that in lungs of smoke-exposed mice, development of the described functional and morphological changes consistent with emphysema depends on the strain. Guerassimov et al. (2004) compared five different strains of mice and characterized AKR/J strain as supersusceptible, C57BL/6/J, A/J, and SJ/L strains as mildly susceptible, and the NZWLac/J as resistant.

Similar to the proposed mechanisms of emphysema development in humans, cigarette smoke in mice induces both oxidative stress and the infiltration of inflammatory cells, which release proteases that overwhelm the anti-proteolytic defence (Leberl et al., 2013).

4.2.2 | Small airway remodelling

SAR is an important contributor to the airflow limitation in COPD. For modelling this aspect of COPD pathology, the guinea pig is the species of choice. In this animal model, smoke-induced SAR is more marked than in mice and includes secretory cell metaplasia that can be reduced by smoke cessation, thickening of the small airway walls by deposition of collagen and fibronectin, and mild aggregation of lymphocytes around the bronchioles, analogous to those seen in humans (Lapperre et al., 2007; Wright et al., 2008; Wright & Churg, 2002).

4.2.3 | Inflammation and inflammatory mediators

Chronic inflammation is an important component of the COPD pathology and one of the mechanisms driving parenchymal destruction and SAR (and, possibly, vascular remodelling). An excessive and self-amplifying immune response in lungs from COPD patients is characterized by increased numbers of alveolar macrophages, neutrophils, and cytotoxic T lymphocytes and by the release of multiple inflammatory mediators and proteases and induction of oxidative and nitrosative stress (Barnes, 2004; Barnes, Shapiro, & Pauwels, 2003).

The feasibility of smoke exposure in mice mimicking features of COPD in humans was addressed in some studies investigating the time course of the changes in the composition and abundance of inflammatory cells in the lungs upon smoke exposure (D'Hulst, Vermaelen, Brusselle, Joos, & Pauwels, 2005; Kemeny et al., 2017). D'Hulst et al. observed a progressive biphasic infiltration of inflammatory cells, including dendritic cells, neutrophils, macrophages, and T and B lymphocytes in the broncho-alveolar lavage compartment. Dendritic cells, macrophages, and lymphocytes, but not neutrophils, also accumulated in the lungs following smoke exposure (D'Hulst et al., 2005). Confirmation of their data has been found in numerous studies (Dominguez-Fandos et al., 2012; Hodge-Bell et al., 2007; Phillips et al., 2015). Along these lines, several pharmacological interventions targeting the inflammatory response show promising results in preclinical studies employing the smoke model (Churg et al., 2012; Sussan et al., 2009; Wright et al., 2011).

4.2.4 | Vascular remodelling

In addition to emphysema development and inflammation, cigarette smoke models in animals mimic important features of COPD-associated vascular pathology seen in humans. These changes involve, for example, the intimal and medial layer of the small pulmonary vessels (at least in the later stages) and lead to PH and RH hypertrophy (Ferrer et al., 2009; Magee et al., 1988; Seimetz et al., 2011; Shujaat et al., 2007).

Going further, studies in smoke-exposed guinea pigs and mice clearly support the suggestion derived from findings in humans that pulmonary vascular alterations and PH can occur prior to emphysema development (Ferrer et al., 2009; Seimetz et al., 2011; Wright &

Churg, 1991). In smoke-exposed guinea pigs, an increase in mPAP and muscularization of small pulmonary vessel was found already after 1 month, when there was no evidence of emphysema. Confirming this report and going beyond, Ferrer et al. (2009) reported that there is selective endothelial dysfunction in pulmonary arteries and smooth muscle cell proliferation in small pulmonary vessels of guinea pigs after 3 months of smoke exposure, preceding emphysema development. Similarly, 3 months of smoke exposure in mice resulted in pulmonary vascular remodelling and an increase in right ventricular systolic pressure (RVSP), without detectable changes in lung function or alveolar structure (Seimetz et al., 2011). Moreover, Seimetz et al. (2011) reported a smoke-induced increase in the alveoli/vessel ratio, indicating that in this mouse model, similar to the situation seen in COPD patients, smoke-induced changes in vasculature include pruning of the small vessels. Evidence was provided that smoke-induced PH can develop independently of hypoxia (Seimetz et al., 2011), and it has been hypothesized that vascular molecular and/or structural alterations can even trigger emphysema.

4.2.5 | RV hypertrophy

Abnormalities in pulmonary vasculature are accompanied by RV hypertrophy and impairment of RV function (Seimetz et al., 2011; Sussan et al., 2009; Weissmann et al., 2014) in mice and guinea pigs. Seimetz et al. investigated the time course of these changes in mice and found that RV hypertrophy developed after 6 months of smoke exposure, while an increase in RVSP and muscularization of small pulmonary vessels was largely detectable at earlier time points. However, thus far, RV failure has not been reported, most likely due to the mild PH occurring in these models.

4.3 | Elastase application in animals

4.3.1 | Emphysema

In rodents, single or repetitive intratracheal instillation of porcine elastase was shown to induce dramatic enlargement of the alveoli, accompanied by severe functional changes, which, in some instances, were reported to be progressive (Luthje et al., 2009; Wright et al., 2008). The important advantages of this model are the fast induction of emphysema and severity of the disease. However, although the postulated mechanistic simplicity of this model is now challenged because of the observed inflammatory response and systemic effects (Luthje et al., 2009), it is nevertheless a very good model to mimic the effects of alpha-1 antitrypsin deficiency in humans. Only a few studies have investigated the occurrence of PH and RH hypertrophy after elastase application. It has been speculated that the primary cause of PH is loss of the capillary bed and, possibly, hypoxemia (Icochea, Cooper, & Kuhn, 1982; Luthje et al., 2009; Oliveira et al., 2016).

Taken together, findings in animal models support the importance of and the need to investigate the lung vascular compartment to understand early molecular changes and pathological mechanisms leading to PH in COPD and also emphysema development. In addition, animal models of the disease are needed for preclinical testing of novel therapeutic approaches in both preventive and curative settings.

5 | PHARMACOLOGICAL THERAPIES FOR PH IN ANIMAL MODELS OF COPD

Findings obtained mainly in animal models of smoke exposure, together with the intriguing observation that vascular alterations appear in human smokers who had not developed COPD (Santos et al., 2002), prompted the hypothesis that COPD–PH is an early phenomenon of disease that can be caused directly by tobacco smoke and its mediators, rather than by hypoxemia and loss of the vascular bed. Independently, chronic hypoxia caused by COPD may of course lead to PH development (Burger, 2009). Obviously, largely independent mechanisms can trigger PH/vascular remodelling in COPD. Going beyond, it could even be hypothesized that lung vascular structural and/or molecular alterations trigger emphysema development, a hypothesis that has to be explored further. If such a change of paradigm holds true, it may offer new strategies for the treatment of this devastating disease.

However, most studies hitherto have focused mainly on pharmacological interventions in terms of parenchymal destruction and SAR (main findings from smoke models summarized in Leberl et al., 2013) but not on vascular alterations. Only few vascular-based therapeutic approaches have been tested for the treatment of PH in COPD/emphysema animal models as well as for their impact on emphysema development. Those include treatments approved or investigated for ameliorating IPAH, as well as interventions targeted primarily against inflammation, protease–antiprotease imbalance, and oxidative and nitrosative stress, all mutually interconnected causes of emphysema development.

5.1 | Therapies targeting the NO pathway: soluble GC and PDEs

5.1.1 | Soluble GC stimulation

Several therapies directed against PH focus on the **soluble GC** (sGC)–**cGMP** axis, an important regulator of vascular tone, known to be down-regulated in PAH (Schermuly et al., 2008), and also reduced in smoke-exposed animals and COPD patients (Weissmann et al., 2014). Besides the vasodilatory effect, cGMP may be beneficial due to its effects on proliferation, platelet aggregation, and inflammatory cell recruitment (Ghofrani et al., 2017). Along these lines, stimulation of sGC by **riociguat** (approved for PAH and chronic thromboembolic PH treatment; Ghofrani et al., 2017) not only prevented tobacco smoke-driven PH development but intriguingly also prevented airspace enlargement in smoke-exposed mice (Weissmann et al., 2014).

Similarly, stimulation of sGC by **BAY 41-2272** in tobacco smoke-exposed guinea pigs reduced PVR and vascular remodelling and prevented emphysema development (Weissmann et al., 2014). In a recently published study, riociguat was also shown to be effective in reversing fully established emphysema and decreasing RVSP, muscularization of small pulmonary vessels, and RH hypertrophy in smoke-exposed mice and had beneficial effects on PH without disturbing oxygenation in a, however, small cohort of COPD patients (Pichl et al., 2019). For the potential downstream signalling events mediating therapeutic effects of sGC stimulation on parenchymal integrity, the authors propose down-regulation of **MMPs** and **inducible NOS (iNOS)** and up-regulation of **FGF10** expression. Similarly, therapeutic intervention with sGC stimulator BAY 41-2272 decreased extent of emphysema and RV hypertrophy, improved pulmonary haemodynamics, and reduced lung inflammatory infiltrates in guinea pigs that were chronically exposed to smoke (Paul et al., 2019). Analysis of transcriptomic changes in lung tissue from these animals suggested that down-regulation of the **perforin**/granzyme pathway might be the possible downstream mechanism mediating the described effects of sGC stimulation.

5.1.2 | PDE inhibition

Reinforcing the notion that sGC plays a prominent role in the pathology of COPD, another strategy for targeting the same downstream pathway supported this concept in preclinical studies. Namely, blockade of cGMP degradation by **PDE5** inhibitors, such as **sildenafil** (Dominguez-Fandos et al., 2015) or **tadalafil** (Seimetz et al., 2015), prevented the development of PH in smoke-exposed guinea pigs and mice, respectively. In addition, guinea pigs treated with sildenafil had a lower airspace size than the placebo group. Also, lung structure and function in tadalafil-treated mice after smoke exposure did not differ from non-exposed animals. Surprisingly, treatment with the **PDE4** inhibitor also had a significant protective effect on emphysema and PH development in mice, indicating that **cAMP** may play a role in COPD pathology as well (Seimetz et al., 2015). Regarding the transfer to the human disease, again, possible adverse effects on V/Q matching and oxygenation have to be taken into account (Blanco et al., 2010). Interestingly, these effects appeared to be less pronounced in severe COPD–PH (Vitulo et al., 2017).

5.2 | Therapies targeting oxidative and nitrosative stress

5.2.1 | iNOS inhibition

In an approach delineating the time course of emphysema and PH development in mice, Seimetz et al. (2011) also investigated the role of NO in COPD pathology, focusing on the **endothelial NOS** and iNOS signalling pathways. They discovered up-regulation of iNOS, predominantly in the pulmonary vasculature of COPD patients and smoke-exposed mice, and showed that deletion or inhibition of this enzyme protected mice against smoke-induced emphysema and PH. In contrast, endothelial NOS deletion had no effect on disease development. In the same study, pharmacological intervention with N^6-(1-iminoethyl)-L-lysine dihydrochloride (L-NIL), a selective iNOS inhibitor, even reversed fully established emphysema and PH. Surprisingly, bone marrow transplants and investigations on smoke-exposed chimeric animals revealed dichotomy of the underlying pathological mechanism. Expression of iNOS in bone marrow-derived cells was driving vascular remodelling, while chimeric animals lacking iNOS in non-bone marrow-derived cells were protected against emphysema. As the up-regulation of iNOS was seen primarily in vascular cells, a conclusion based on these findings indicated molecular alterations in lung vasculature, apparently unrelated to vascular remodelling, to be the underlying mechanism of the alveolar destruction—a hypothesis that still has to be substantiated. While one may find the described results contradictory to the above-mentioned beneficial effects of NO–sGC–cGMP axis stimulation, they obviously underline the dual role of NO in COPD and PH pathogenesis. On the one hand, NO can antagonize vasoconstriction and pulmonary vascular smooth muscle cell proliferation by stimulation of sGC activity (Ghofrani et al., 2017), while on the other, NO-driven mechanisms, suggested to act via peroxynitrite ($ONOO^-$) formation, can lead to the down-regulation of this pathway via nitration and inactivation of sGC (Weber, Lauer, Mulsch, & Kojda, 2001).

5.2.2 | Nuclear factor, erythroid 2-like 2 stimulation

In line with the proposed prominent role of oxidative and nitrosative stress in COPD pathology, **nuclear factor, erythroid 2-like 2 (Nrf2)** stimulation was shown to be protective against emphysema and PH in mice chronically exposed to smoke (Sussan et al., 2009). Nrf2 is a redox-sensitive transcription factor, orchestrating the antioxidant defence by up-regulation of antioxidative genes and cytoprotective proteins (Kim, Cha, & Surh, 2010). The deletion of Nrf2 in smoke-exposed mice aggravated airspace enlargement and the decline in RV function, whereas the stimulation of this pathway with 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im) attenuated smoke-induced emphysema and PH development and decrement of RV function in mice. Furthermore, treatment with CDDO-Im induced transcription of Nrf2-responsive cytoprotective genes and reduced apoptosis and oxidative damage in smoke-exposed animals. The resistance of Nrf2 knockout mice to this therapy reinforces the notion that CDDO-Im prevents smoke-induced pathological changes depending on Nrf2 activity. Importantly, since Nrf2 is a negative regulator of iNOS expression (Kim et al., 2010), the reported protective effects of its stimulation might be further confirmation of the important role of iNOS in smoke-induced pathophysiological changes. Another potential mechanism through which Nrf2 may exert protective effects against the elevation of PAP and alveolar destruction is the control of the inflammatory response, achieved via down-

regulation of pro-inflammatory cytokines, cell adhesion molecules, and some MMPs (Kim et al., 2010).

5.3 | Therapies targeting inflammation

5.3.1 | Myeloperoxidase inhibition

The abnormal inflammatory response has been the target of many other preclinical studies in the context of smoke-induced pathology, since its role in the pathogenesis of emphysema is well established (Macnee, 2007), and it is known to be critically involved in the development of different forms of PH (Pullamsetti et al., 2011). However, although ameliorating inflammation seems to be an intuitive way to simultaneously prevent emphysema and vascular remodelling, very few preclinical studies have evaluated the effects of anti-inflammatory therapies on both features of smoke-induced pathological changes. One of these studies reported that prophylactic as well as therapeutic intervention with AZ1 (3-[[(2*S*)-tetrahydrofuran-2-yl]methyl]-2-thioxo-7*H*-purin-6-one), 2-thioxanthine myeloperoxidase (MPO) inhibitor, completely reversed muscularization of small vessels and partially reversed PH in smoke-exposed guinea pigs (Churg et al., 2012). Furthermore, the treatment attenuated airspace enlargement and SAR in this model. MPO is an important antibacterial product of neutrophils and macrophages that generates powerful oxidants, including hypochlorous acid and reactive nitrogen species, and can potentiate inflammatory responses by activating cytokine release from macrophages and neutrophil degranulation (van der Veen, de Winther, & Heeringa, 2009). Indeed, in the described study, treatment with the MPO inhibitor prevented the smoke-induced increase in inflammatory cells (in broncho-alveolar lavage) and abolished NF-κB activation, dityrosine formation, and up-regulation of pro-inflammatory cytokines. These results underline the critical role of immune cell mediators in smoke-induced pathological changes, but, at the same time, they emphasize their connection to oxidative and nitrosative stress and their importance in COPD pathology.

5.3.2 | Statins

Targeting not only the pulmonary vascular compartment but also inflammation and oxidative stress with **hydroxymethylglutaryl-CoA reductase** inhibitors gave promising results in preclinical studies with smoke-exposed animals. This group of chemicals, collectively known as statins, was originally used as a cholesterol-lowering therapy in cardiovascular diseases, but their pleiotropic effects make them candidates for the treatment of COPD (Bonetti, Lerman, Napoli, & Lerman, 2003). In a study conducted by Lee et al. (2005), prophylactic treatment with **simvastatin** completely prevented emphysema development and PH in smoke-exposed rats. The authors further showed decreased perivascular and peribronchial inflammation, as well as reduced MMP9 activity in the lungs of the simvastatin-treated group. Late intervention with statins also proved to be efficient in reversing PH and preventing emphysema development but was unable to reverse SAR in guinea pigs exposed to smoke (Wright et al., 2011). Although the focus of their study was the physiological effects of statin treatment rather than molecular mechanisms of action, the authors speculated that statins ameliorated vascular remodelling by affecting proliferation and apoptosis rates of pulmonary vascular smooth muscle cells, as well as ET-1 expression and NO bioavailability (Bonetti et al., 2003), whereas the observed effects on emphysema were attributed to the inhibitory effects on the production of oxidants, pro-inflammatory cytokines, and MMPs. In contrast, a study employing an elastase model of emphysema in rats did not find an effect of **atorvastatin** treatment on lung parenchymal destruction or inflammation (Boiati et al., 2015). As in one earlier study the treatment with simvastatin was able to inhibit the development of elastase-induced pulmonary emphysema in mice (Takahashi et al., 2008), these findings highlight the diversity in the pleiotropic effects within this class of drugs. Differences between statins are also evident from the clinical trials, which are, nevertheless, showing reduced PH and improvement in lung function in COPD–PH patients treated with statins (Lu et al., 2019; Reed et al., 2011; Zhang et al., 2017). It is worth mentioning that even in those patients that benefited from the statin treatment, reduction in PAP was moderate compared with the complete reversal of PH seen in animal models. Taken together, preclinical and clinical studies demonstrate the potential usefulness of these drugs in the treatment of COPD–PH.

5.4 | Therapies targeting other pathways

5.4.1 | Mechanistic target of rapamycin kinase

Recent studies, employing primarily genetically modified animals as the model system, implicated the mechanistic target of rapamycin kinase (mTOR) as the important pathway in the pathology of COPD. In one of these studies, both mTOR complex 1 and 2 activities were found to be elevated in COPD patients and were associated with replicative cell senescence—a process thought to play an important role in the development of this disease (Houssaini et al., 2018). In line with that observation, an over-activation of mTOR signalling in endothelial or alveolar epithelial cells resulted in cell senescence and a COPD-like phenotype, including emphysema and PH. In contrast, an earlier study conducted by Yoshida et al. (2010) pointed towards Rtp801 (or DDIT4—DNA-damage-inducible transcript 4), a suppressor of mTOR signalling, as the important mediator of cigarette smoke-induced lung injury. Rtp801 was elevated in the lungs of COPD patients, and its overexpression or up-regulation upon smoke-exposure in mice led to the NF-κB activation in vitro and in vivo. Conversely, deletion of Rtp801 protected mice against acute cigarette smoke-induced lung injury and emphysema, partly via the activation of mTOR signalling. However, the same study showed that mTOR inhibition by rapamycin protected wild-type mice against cigarette smoke-induced lung inflammation, pointing towards the possible cell- and injury context-specific role of mTOR signalling, as well as

emphasizing the need for further studies tackling the role of this pathway in the pathology of COPD.

5.5 | Further perspectives for experimental preclinical therapy

It is important to mention further promising pharmacological strategies tested for the treatment of emphysema, with the hope that future studies will address their usefulness for the treatment of COPD–PH. For example, employing neutralizing antibodies is an option of major clinical relevance and proved to be efficient in the case of endothelial monocyte-activating protein 2, where it protected smoke-exposed mice against emphysema development (Clauss et al., 2011; Koike et al., 2019). Of interest is also the discovery that the balance between pro-apoptotic ceramide and its pro-survival metabolite, **sphingosine 1-phosphate (S1P)**, is important for the maintenance of septal integrity and that emphysema development can be prevented either by the inhibition of de novo ceramide synthesis or by the augmentation of S1P signalling (Diab et al., 2010; Petrache et al., 2005). However, S1P and **sphingosine kinase 1** are thought to be pathogenic factors involved in vascular remodelling in IPAH patients and hypoxic mice (Chen et al., 2014); therefore, it would be interesting to decipher whether this mediator of vascular remodelling is also implicated in COPD–PH. Promoting intermittent haematopoietic progenitor cell mobilization using **plerixafor (AMD3100)**, an antagonist of the chemokine receptor **CXCR4**, was also found to ameliorate cigarette smoke-induced emphysematous changes in mice (Barwinska et al., 2018). The same inhibitor was shown to decrease hypoxia-induced PH in rats (Yu & Hales, 2011), which makes the pharmacological inhibition of CXCR4 a strategy worth investigating for the treatment of COPD–PH. Loss of alveoli and airflow limitation could also be partially reversed by the application of **palifermin (N-terminally truncated recombinant human keratinocyte growth factor)** in the elastase mouse model of emphysema (Yildirim et al., 2010). Therapeutic application of this growth factor induced important alveolar maintenance programmes and had regenerative effects on interstitial tissue, which were linked to the up-regulation of epithelium-derived growth factors, including TGF-β. Yet another emerging target in the pathology of COPD could be elevated plasma **haem** levels, found in patients and in an inhalation injury mouse model, and suggested to be one of the factors inducing endoplasmic reticulum stress seen in this disease (Aggarwal et al., 2018). Since haem scavenging by haemopexin reduced endoplasmic reticulum stress and emphysema in this mouse model, it could represent an interesting treatment option for COPD patients. It should, however, still be investigated in other preclinical models and in the context of COPD–PH.

Further potential therapeutic targets tested in preclinical research, including MMPs, TNF-α, and components of the renin–angiotensin system, are discussed in detail in the Supporting Information.

5.6 | Transferability of findings from preclinical into clinical science

Preclinical studies with regard to pharmacological interventions in COPD found numerous pathological mechanisms that are shared between parenchymal destruction and vascular alterations, but also showed that some pathways and mediators can have different, sometimes opposing roles in the development of PH and emphysema. Pharmacological interventions targeting a dysregulated NO–sGC–GMP axis, iNOS, inflammation, proteases, oxidative stress, renin–angiotensin system, and mTOR signalling were effective in treating COPD-associated PH in animal models and may represent potential future strategies for ameliorating this devastating disease (Figure 1).

Of course, one has to be cautious when transferring findings in animal models to the situation in COPD patients. First, there are considerable differences between species in lung anatomy and responsiveness to injurious agents (Wright et al., 2008) that lead to the limited ability of animal models to reproduce some of the pathological changes seen in humans. For example, smoke induces only minimal changes in small airways of mice, which makes guinea pig the species of choice for studies focused on SAR. Moreover, the absence of

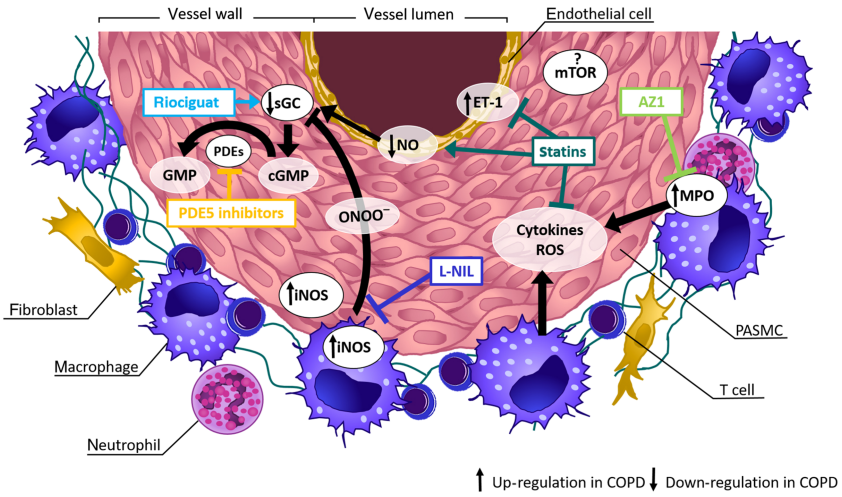

FIGURE 1 Current preclinical therapeutic approaches for the treatment of pulmonary hypertension in animal models of chronic obstructive pulmonary disease (COPD)/emphysema. ET-1, endothelin-1; iNOS, inducible NOS; L-NIL, N^6-(1-iminoethyl)-l-lysine dihydrochloride; MPO, myeloperoxidase; mTOR, mechanistic target of rapamycin kinase; PASMC, pulmonary arterial smooth muscle cell; sGC, soluble GC

bronchial glands in mice and their low numbers and small size in guinea pigs and rats make rodents a poor model for chronic bronchitis (Wright et al., 2008). In this regard, the use of large animals in later stages of preclinical research might help to bridge the gap between the rodents and humans.

Next, mouse lungs have much higher regenerative potential than human lungs (Fehrenbach et al., 2008), although it was shown in a recent case report that lung regeneration after pneumonectomy is also possible in humans (Butler et al., 2012). Importantly, as rodent lungs do not regenerate spontaneously after parenchymal destruction caused by long-term smoke exposure, identification of differences between smoke and non-smoke-exposed mice can help identifying mechanisms of lung regeneration.

However, it became clear that some of the findings in rodents are not readily transferrable to the human situation, as seen from the results with TNF-α antagonists (Barnes, 2007). However, disparity between the results from preclinical research and human situation has to be interpreted carefully for several reasons. First, the treatment period in humans can be too short to see clinically measurable improvement or to detect the effect on exacerbations and disease progression. Also, better selection of the patients that might profit from the treatment might be needed for successful translation of preclinical research to clinical practice (Barnes, 2007). Importantly, alternative or complementary outcome measures might be necessary for proper monitoring of the treatment effects in COPD patients. An example is the use of inhaled bronchodilators in COPD patients, where symptomatic improvement occurred despite only modest improvement in FEV_1. In this regard, hyperpolarized MRI has emerged as possible method for imaging lung microstructure and function (Coxson, Leipsic, Parraga, & Sin, 2014), as longitudinal worsening of MRI results was shown to be related to symptoms and exercise capacity in COPD patients in whom FEV_1 was not predictive (Kirby et al., 2015; Westcott, Capaldi, Ouriadov, McCormack, & Parraga, 2019).

Although not always directly transferable to clinical investigation, mechanistic studies in animals offer possible valuable insights into pathogenic mechanisms and help in identifying deregulated molecular pathways and potential new treatment approaches. Interestingly, current therapies approved for PH patients, such as sildenafil, riociguat, and inhaled iloprost, have been pre-evaluated in animal models. The success in this field gives hope that with right animal models (e.g., rodents chronically exposed to cigarette smoke), ongoing intensive preclinical research can help to identify new avenues for treatment of COPD, although transferability to humans is not finally predictable.

6 | CLINICAL STUDIES/TREATMENT OF COPD–PH IN HUMANS

Three approaches have been applied to treat PH associated with COPD: long-term oxygen administration, treatment with systemic vasodilators, and treatment with targeted PH therapy.

6.1 | Long-term oxygen therapy

In COPD, chronic hypoxemia is associated with PH. Therefore, correction of alveolar hypoxia with supplemental oxygen is a reasonable approach for treating PH in COPD. The acute administration of oxygen in patients with COPD generally has little effect on pulmonary haemodynamics (Barberà et al., 1996), although a subgroup of patients might show a significant decrease in PAP (Ashutosh, Mead, & Dunsky, 1983).

The classical Medical Research Council and Nocturnal Oxygen Therapy Trial studies showed that in COPD patients with PH and severe hypoxemia, long-term oxygen therapy (LTOT) at doses of 15 $hr{\cdot}day^{-1}$ prevented the progressive increase of mPAP (Stuart-Harris et al., 1981) and at doses of >18 $hr{\cdot}day^{-1}$ produced a slight decrease of mPAP (Barbera & Blanco, 2009; Timms, Khaja, & Williams, 1985; Weitzenblum, Sautegeau, Ehrhart, Mammosser, & Pelletier, 1985). In patients followed for a long period of time, before and after initiating LTOT (Weitzenblum et al., 1985), the progressive increase of PAP was reversed after initiating LTOT. The haemodynamic effect of LTOT is higher during the initial years of treatment, reaching a stabilization of PAP thereafter (Zielinski, Tobiasz, Hawrylkiewicz, Sliwinski, & Palasiewicz, 1998). The survival benefit achieved with LTOT does not relate to the long-term changes in pulmonary haemodynamics (Nocturnal Oxygen Therapy Trial Group, 1980; Stuart-Harris et al., 1981), although patients showing a significant decrease of PAP with the acute administration of oxygen show better survival than non-responders (Ashutosh et al., 1983). The beneficial effects of LTOT have been shown in COPD patients with severe hypoxemia; in those with moderate resting or exercise-induced desaturation, LTOT does not provide any benefit in terms of survival or hospitalizations (Albert et al., 2016).

6.2 | Systemic vasodilators

The use of systemic vasodilators in the treatment of COPD–PH has been disappointing. The acute administration of **nifedipine** reduces PAP and increases CO in COPD patients, both at rest and during exercise (Agusti et al., 1990; Simonneau, Escourrou, Duroux, & Lockhart, 1981). However, nifedipine also inhibits HPV (Naeije, Melot, Mols, & Hallemans, 1982) and worsens V/Q and arterial PO_2 (Agusti et al., 1990; Melot, Hallemans, Naeije, Mols, & Lejeune, 1984; Simonneau et al., 1981). Furthermore, long-term treatment with nifedipine in COPD patients did not provide any benefit on pulmonary haemodynamics or clinical status (Agostoni, Doria, Galli, Tamborini, & Guazzi, 1989; Saadjian, Philip-Joet, Vestri, & Arnaud, 1988). Accordingly, systemic vasodilators are not recommended for the treatment of PH associated with COPD.

6.3 | Targeted PH therapy

Several randomized controlled trials (RCTs), summarized in Table 1, and three meta-analyses have evaluated the safety and efficacy of

targeted therapy used in PAH in patients with COPD-associated PH (Chen et al., 2015; Park et al., 2013; Prins, Duval, Markowitz, Pritzker, & Thenappan, 2017). In the studies mentioned in Table 1, exclusion of patients with left-sided dysfunction was done by RH catheterization (with a wedge pressure lower than 15 mmHg as a mandatory criterion), or echocardiography was used, and a history of ischaemic or valve disease as well as decompensation of right or left HF was ruled out prior to inclusion.

6.3.1 | Effects on pulmonary haemodynamics

Targeted PH therapy improves pulmonary haemodynamics in patients with COPD and associated PH, as shown in two different meta-analyses (Chen et al., 2015; Prins et al., 2017). Haemodynamic improvement, assessed by RHC, has been shown with sildenafil (Vitulo et al., 2017), a PDE5 inhibitor, and with **bosentan** (Valerio, Bracciale, & Grazia, 2009), an antagonist of **ET_A** and **ET_B** receptors. One RCT also showed improvement of systolic PAP, assessed by Doppler echocardiography, with sildenafil (Rao, Singh, Sharma, Agarwal, & Singh, 2011), whereas an open-label study failed to show any effect of sildenafil (50 mg t.i.d.) on RV stroke volume, assessed by MRI, at rest or during exercise (Rietema et al., 2008). More recently, an open-label study also showed that riociguat, an sGC stimulator, improved PVR (Pichl et al., 2019).

6.3.2 | Effects on exercise tolerance

The effect of targeted PH therapy on exercise capacity in patients with COPD–PH is less apparent. Two meta-analyses failed to show significant improvement in the 6-min walking distance (6MWD; Park et al., 2013; Prins et al., 2017), whereas a third one reported a significant improvement in 6MWD but considering only two RCTs (Chen et al., 2015). Major RCTs involving more than 20 participants are shown in Table 1. Change in 6MWD was the primary endpoint in three RCTs (Goudie, Lipworth, Hopkinson, Wei, & Struthers, 2014; Rao et al., 2011; Stolz et al., 2008) and a secondary endpoint in another three (Blanco et al., 2013; Valerio et al., 2009; Vitulo et al., 2017). Two studies showed significant improvement in 6MWD, one using sildenafil (Rao et al., 2011) and the other using bosentan (Valerio et al., 2009), whereas in the other four studies, targeted PH therapy (bosentan, sildenafil, and tadalafil) failed to show significant differences in 6MWD compared with placebo (Blanco et al., 2013; Stolz et al., 2008; Vitulo et al., 2017). Furthermore, concomitant treatment with sildenafil did not improve the effects of a respiratory rehabilitation programme on exercise tolerance—assessed by endurance time and 6MWD—in COPD patients with moderate PH (Blanco et al., 2013). Taken together, the available evidence indicates that in COPD–PH, the effect of PAH targeted therapy on pulmonary haemodynamics does not translate into a clear improvement in exercise tolerance.

6.3.3 | Effects on symptoms and quality of life

The effect of targeted therapy on symptomatic burden in COPD–PH is also disappointing when evaluated in RCTs (Chen et al., 2015; Prins et al., 2017). Neither dyspnoea (Valerio et al., 2009) nor quality of life assessed by the St George's Respiratory Questionnaire (Blanco et al., 2013; Goudie et al., 2014; Valerio et al., 2009) improved significantly with targeted therapy (bosentan, sildenafil, and tadalafil) compared with placebo or usual care. Only one recent study conducted in COPD patients with severe PH showed that sildenafil significantly improved body mass, airflow obstruction, dyspnoea, exercise capacity index, modified Medical Research Council scale, and SF-36 general health domain (Vitulo et al., 2017).

6.3.4 | Effect on arterial oxygenation

As mentioned, in COPD, vasodilator treatment might impair V/Q matching due to the inhibition of HPV. Vasodilating agents used in targeted PH therapy may also inhibit HPV. Indeed, acute worsening of V/Q relationships has been shown with sildenafil (Blanco et al., 2010), aerosolized iloprost (Boeck, Tamm, Grendelmeier, & Stolz, 2012), and inhaled NO (Barberà et al., 1996). A non-significant decrease of PaO_2 has also been observed with the acute administration of riociguat (Ghofrani et al., 2015).

Contrasting with the acute detrimental effects on arterial oxygenation of targeted PH therapy, evidence on the long-term effects in COPD–PH is heterogeneous (Chen et al., 2015). Whereas deterioration of gas exchange was shown in some studies with the long-term use of bosentan (Stolz et al., 2008) or sildenafil (Lederer et al., 2012), no change was observed in others using sildenafil (Blanco et al., 2013; Vitulo et al., 2017), tadalafil (Goudie et al., 2014), or riociguat (Pichl et al., 2019). Observational studies on the use of targeted PH therapy in COPD patients with severe PH followed for 12 months indicate that moderate reduction of PaO_2 may occur but did not entail treatment withdrawal in any of the cases (Calcaianu et al., 2016).

6.3.5 | Effect on survival

The effects of targeted PH therapy on survival in COPD–PH have been assessed in retrospective studies, which included patients with different respiratory diseases (not only COPD) and usually with severe PH. Two studies showed longer survival in patients treated with targeted PH therapy (mostly PDE5 inhibitors), as compared with patients who did not receive PH treatment (Lange, Baron, Seiler, Arzt, & Pfeifer, 2014; Tanabe et al., 2015). In one of these studies, the survival benefit was apparent in patients with severe PH, whereas it was not significantly different in patients with mild-to-moderate PH (Lange et al., 2014).

In summary, although targeted PH therapy might improve pulmonary haemodynamics in patients with COPD-associated PH, no clear beneficial effects on clinically relevant outcomes, such as exercise

TABLE 1 Randomized controlled trials with PH targeted therapy in COPD

Author (year)	Number of patients	Inclusion criteria	Study design	Diagnosis of PH	Baseline haemodynamics	Baseline PFTs	Therapy	Duration	Primary endpoint, result	Other outcomes
Stolz et al. (2008)	30	GOLD 3–4, no haemodynamic requirement	RCT (2:1)	Echo	sPAP 32 (29–38) mmHg	Not reported	Bosentan 125 mg b.i.d.	12 weeks	6MWD, no change	Worsened hypoxemia and QOL
Valerio et al. (2009)	32	COPD with PH by RHC	RCT (open-label)	RHC	mPAP 37 ± 5 mmHg	FEV_1 37 ± 18% pred.	Bosentan 125 mg b.i.d.	18 months	No defined	Improved mPAP, PVR, BODE index, and 6MWD
Rao et al. (2011)	33	GOLD 3–4	RCT	Echo: sPAP > 40 mmHg	sPAP 52.7 ± 11.9 mmHg	FEV_1 32.5 ± 11.1	Sildenafil 20 mg t.i.d.	12 weeks	6MWD, +190 m	↓ sPAP
Blanco et al. (2013)	60	COPD with PH by RHC or Echo	RCT	RHC: mPAP ≥ 25 mmHg Echo: sPAP ≥ 35 mmHg	mPAP 31 ± 5 mmHg sPAP 42 ± 10 mmHg	FEV_1 32 ± 11% pred.	Sildenafil 20 mg t.i.d. and pulmonary rehabilitation	3 months	Exercise endurance time, no change	No change in 6MWD, maximal workload, peak VO_2, QOL, or oxygenation
Goudie et al. (2014)	120	COPD with PH by Echo	RCT	Echo: PAT < 120 ms or sPAP > 30 mmHg	Echo: sPAP 42 ± 10 mmHg	FEV_1 41 ± 16% pred.	Tadalafil 10 mg q.d.	12 weeks	6MWD, no change	↓ sPAP No change in QOL, BNP, or SaO_2
Vitulo et al. (2017)	28	COPD with severe PH by RHC	RCT (2:1)	RHC: mPAP > 35 mmHg if FEV_1 < 30% or ≥30 mmHg if FEV_1 ≥ 30%	mPAP 39 ± 8 mmHg CI 2.4 ± 0.5 $L{\cdot}min^{-1}{\cdot}m^{-2}$	FEV_1 54 ± 22% pred. DLCO 33 ± 12% pred.	Sildenafil 20 mg t.i.d.	16 weeks	PVR, −1.4 WU	Improved CI, BODE index, and QOL No change in oxygenation

Abbreviations: 6MWD, 6-min walking distance; BNP, brain natriuretic peptide; BODE, body mass, airflow obstruction, dyspnoea, exercise capacity; CI, cardiac index (reported as $L{\cdot}min^{-1}{\cdot}m^{-2}$); COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; Echo, echocardiogram; FEV_1, forced expired volume in the first 1 s; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; mPAP, mean pulmonary artery pressure; PAT, pulmonary acceleration time; PFTs, pulmonary function tests; PH, pulmonary hypertension; PVR, pulmonary vascular index (reported as Wood units [WU]); QOL, quality of life; RCT, randomized controlled trial; RHC, right heart catheterization; sPAP, estimated systolic pulmonary artery pressure.

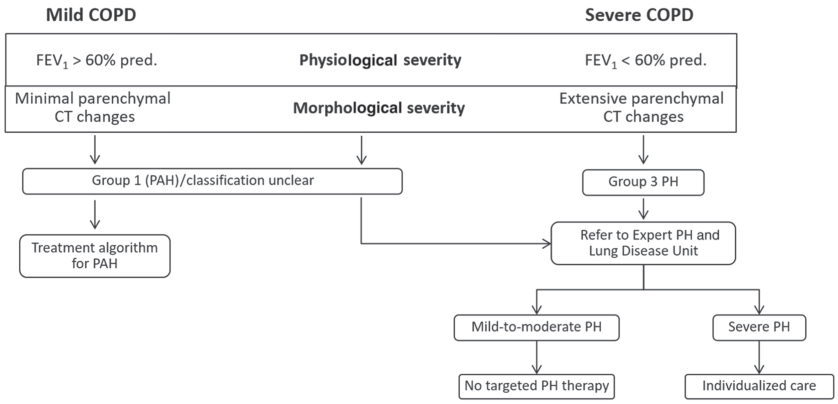

FIGURE 2 Treatment algorithm for chronic obstructive pulmonary disease (COPD)-associated pulmonary hypertension (PH), adapted from the Task Force on Pulmonary Hypertension in Chronic Lung Disease of the 6th World Symposium on Pulmonary Hypertension (Nathan et al., 2019). FEV_1, forced expiratory volume in 1 s; PAH, pulmonary arterial hypertension

tolerance or quality of life, have been substantiated in RCTs. Nevertheless, as most clinical trials have been conducted in COPD patients with mild-to-moderate PH, and there is some indirect signal suggesting that COPD patients with severe PH might have survival benefit, the Task Force on PH in Chronic Lung Disease of the 6th WSPH proposed a treatment algorithm for chronic lung diseases accompanied by PH, stratified by the clinical classification of PH (group 1 PH vs. group 3 PH) and its severity (Nathan et al., 2019; Figure 2).

7 | CONCLUSION

Pulmonary vascular remodelling and (mild) PH is an early common phenomenon in COPD patients. Despite the fact that even mild elevation of PAP is associated with increased mortality and morbidity in those patients, efficient treatment options are missing and may even be harmful when considered in non PAH-PH such as group 3. Preclinical research yielded a few promising targets that need to be further evaluated prior to routine clinical use.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos et al., 2019; Alexander, Fabbro, et al., 2019; Alexander, Kelly, et al., 2019).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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