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Pulmonary Hypertension in Chronic Respiratory Diseases

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Abstract **Original Research Article**

Pulmonary hypertension is a common complication of severe respiratory diseases, the prevalence of which remains unknown. The objective of the study is to determine the clinical, functional, etiological and evolutionary profile of patients followed for HTP associated with respiratory diseases. We report a retrospective study of 86 patients. The average age was 56 ± 8.2 years with male predominance of 62%. The most common underlying chronic respiratory pathology was COPD (46%). The main symptom was dyspnea. The majority of COPD patients (66%) had moderate to severe irreversible obstructive airway disease with a median FEV1 of 54% of theoretical and severe impairment of the alveolar-capillary diffusion capacity of CO (DLCO). Cardiac ultrasound revealed pulmonary hypertension with mean PAPS of 61mmHg. The mean value of the measured IT Vmax was 3.4 m/s. Pulmonary hypertension was more common in patients monitored for COPD groups C and D of the GOLD classification (p = 0.01). It was correlated with the severity of dyspnea according to the NYHA (r = 0.27). There was no correlation between the FEV1 value, the PaO2 value and the severity of PH. No correlation was found between the PAPS and the distance traveled during the 6MWT. Patients with severe HTP had more severe exacerbations requiring more frequent hospitalizations (p = 0.003) and a more severe BODE index (p = 0.002). Therapeutic management was based mainly on optimization of background treatment of the underlying respiratory disease, oxygen therapy and diuretics in case of right heart failure. The clinical course was marked by improvement of dyspnea and hypoxia in 68% of cases, twenty-four percent of patients had clinical and functional worsening. We deplore the death of eight patients following a severe exacerbation.

Keywords: Pulmonary hypertension, respiratory diseases, dyspnea, oxygen therapy.

INTRODUCTION

Pulmonary hypertension (PH) due to chronic respiratory disease is classified in group 3 of the World Symposium on Pulmonary Hypertension classification system [1]. It constitutes complication during the evolution of respiratory diseases and an indisputable aggravating prognostic factor.

Group 3 PH is the second most common form of pulmonary hypertension, all causes combined, after group 2 PH (secondary to left heart disease) [2]. Its prevalence is increasing worldwide and remains poorly understood. Only right heart catheterization can make a definitive diagnosis, but for technical and ethical reasons not all patients with CKD can benefit from this examination.

The pathophysiology of this condition is multifactorial and complex, while the predominant pathogenetic mechanisms include hypoxia, vasoconstriction, destruction of the pulmonary parenchyma (and vascular bed), vascular remodeling, and inflammation.

Non-invasive assessment is initially undertaken in suspected cases, referral to a specialist centre with haemodynamic assessment and right heart catheterisation remains indicated in patients with severe PH.

There is a lack of adequate therapeutic options for PH in respiratory diseases. Currently available therapies for group 1 pulmonary arterial hypertension (PAH) have been tested in group 3 PH with mixed results. This may reflect a lack of understanding of the mechanisms underlying group 3 PH as well as the heterogeneity of patients and diseases involved.

MATERIALS AND METHODS

This is a retrospective observational study, conducted between 2015 and 2024 and focusing on patients with PH associated with chronic respiratory diseases.

Echocardiography was performed in all patients to screen for HTP and assess its severity.

All patients underwent an etiological assessment to rule out other causes of PH and thoracic imaging, respiratory function tests, electrocardiogram, and BNP and / or proBNP measurement.

PH was classified in group 3 after multidisciplinary discussion. Right heart catheterization was performed in two patients with severe PH or hypoxemia disproportionate to the respiratory impairment.

We excluded incomplete records and records of patients with PH from other groups 1, 2, 4 or 5 and also records of PH whose mechanism is not clearly established.

We developed an operating sheet to collect sociodemographic data, level of education, lifestyle, occupation, associated comorbidities, toxic habits, characteristics of the underlying respiratory pathology (duration, severity), assessment of dyspnea according to the NYHA classification, nutritional status (BMI), thoracic imaging data, respiratory function data, cardiovascular assessment data (VmaxIT, estimation of PAPs , OD surface, TAPSE, presence or absence of pericardial effusion and paradoxical septum) and hemodynamic data (PAPm, PAPO, RVP, POD, Qc and IC) and quality of life assessment assessed by the George's Respiratory Questionnaire.

Data were collected and analyzed using Jamovi software version 1.6.7.0 Setup.

Descriptive statistics were described with percentages for qualitative variables, mean (±standard deviation) for normally distributed quantitative variables, and median (interquartile range) for skewedly distributed variables.

RESULTS

A total of 86 patients were included. The average age was 56 ± 8.2 years with male predominance of 62%.

Sixty-four percent of patients were smokers. 52% of participants had associated comorbidity, mainly hypertension 16%, gastroesophageal reflux 8% and 4% of patients had obstructive sleep apnea hypopnea syndrome.

The most common underlying chronic respiratory disease was COPD (46%), the majority of patients (76%) were classified as group D. Pulmonary fibrosis was the 2nd cause of PH in 18% of cases, sequelae of tuberculosis in 11% of cases, emphysema of the summits fibrosis of the bases syndrome in 9%, sequelae of tuberculosis in 8%, kyphoscoliosis 5%, obesity hypoventilation syndrome in 2%.

The main symptom was dyspnea, 42% of patients had NYHA class 2 dyspnea and 38% class 3.

Clinical examination found digital clubbing in 52% of cases, signs of right heart failure in 29% of cases and cyanosis in 27% of cases.

The median BMI was 28 kg/m², 36% of patients had BMI >25kg/m².

Chest CT showed emphysema bubbles in 66% of cases, pulmonary fibrosis lesions in 27% of cases, foci of bronchial dilation or sequelae lesions in 11% of cases and dilated pulmonary arteries in 46% of cases.

The majority of COPD patients (66%) presented with moderate to severe irreversible obstructive airway disorder with a median FEV1 = 54% of theoretical and severe impairment of the alveolar-capillary CO diffusion capacity (DLCO).

Hypercapnic respiratory failure in 32% of cases, isolated hypoxia in 45% of cases. The 6 minute walk test showed desaturation during exercise in 38% of cases with an average distance covered of 224m.

Median values of Brain Natriuretic Peptide (BNP) or N-Terminal pro- brain natriuretic peptide (NT-proBNP) levels were above normal values in 72% of cases. The electrocardiogram showed hypertrophy of the RA and/or RV in 49% of cases. Cardiac ultrasound revealed pulmonary hypertension with a mean PAPS of 61 mmHg. The mean value of the measured IT Vmax was 3.4m/s, pericardial effusion and paradoxical septum were observed in 6 patients.

Pulmonary hypertension was more frequent in patients followed for COPD group C and D of the GOLD classification (p = 0.01). It was correlated with the severity of dyspnea according to the NYHA (r = 0.27). There was no correlation between the FEV1 value, the PaO2 value and the severity of PH. No correlation was found between PAPS, PaO2 value and distance traveled during the 6MWT.

Patients with severe HTP had more severe exacerbations requiring more frequent hospitalizations (p = 0.003) and a more severe BODE index (p = 0.002).

Therapeutic management was essentially based on optimizing the basic treatment of the underlying respiratory disease and smoking cessation in patients who smoke.

Treatment of right heart failure and PH was based on oxygen therapy and diuretics, with digitalis

prescribed in only one patient with signs of rhythm disturbances.

Noninvasive ventilation was indicated in patients with chronic hypercapnic respiratory failure. Specific treatment for PAH was not prescribed in any of our patients.

The clinical course was marked by improvement of dyspnea and hypoxia in 68% of cases, twenty-four percent of patients presented a clinical and functional worsening. We deplore the death of eight patients following a severe exacerbation.

DISCUSSION

Many chronic respiratory diseases can be complicated by PH, the most frequently observed pathologies are COPD, idiopathic pulmonary fibrosis, apex emphysema-base fibrosis syndrome and hypoventilation syndromes.

Most patients with COPD will develop mild PH, characterized by mild elevations in pulmonary pressures. Approximately 1–5% of patients with COPD develop severe PH, with a mean pulmonary artery pressure (mPAP) > 35–40 mmHg at rest [3]

In idiopathic pulmonary fibrosis, 8–15% of patients had a mPAP ≥ 25 mmHg at initial assessment, with a higher prevalence in advanced stages [4, 5].

PH associated with chronic respiratory diseases is generally classified as non-severe, with mean PAP most often ranging from 20 to 35 mmHg at rest during a stable period of the disease. However, it should be noted that PH in chronic respiratory diseases, and mainly COPD, may become transiently more pronounced during exercise, sleep and episodes of disease exacerbation.

The presence of PH associated with lung disease is a powerful predictor of mortality. There is an inverse relationship between mPAP and pulmonary vascular resistance (PVR) and survival of patients with PH [5-7].

Regarding the pathophysiology of PH associated with lung disease, there is a disproportionate right ventricular dysfunction compared to PAH despite less severe hemodynamic alteration [9].

As in group 1 PAH, endothelial cell dysfunction and defective cell signaling are thought to cause uncontrolled proliferation of endothelial cells, fibroblasts, and smooth muscle cells with dysregulated angiogenesis contributing to the pathophysiology of group 3 PAH.

Transforming growth factor beta 1 (TGF- β1) is involved in the regulation of cell proliferation and differentiation, TGF- β1 expression is closely linked to hypoxia-inducible factor 1 alpha (HIF-1α), and both signaling pathways are well established in the development of pulmonary vascular disease [10-12].

Vascular endothelial growth factor A (VEGFA) is also induced by HIF-1α, its overexpression probably plays a protective role in hypoxic PH [13-15].

β (PDGF β) production is stimulated by TGF- β 1 and increases VEGFA expression, enhancing hypoxia-induced endothelial cell proliferation. Increased expression of angiogenesis mediators and growth factors such as VEGF and TGF- β receptor II (TGF- β RII) was observed in pulmonary arteries of COPD patients [16, 17].

Smoking is thought to play a central role in the vascular changes that lead to the development of PH in chronic respiratory diseases [18]. In vitro studies have confirmed this hypothesis, with exposure to cigarette smoke being responsible for a decrease in eNOS38 activity and protein expression and a decrease in prostacyclin synthase mRNA and protein expression [19].

Vascular remodeling due to cigarette exposure may precede the development of clinically detectable emphysema or airway obstruction, as observed in animal models [20, 21].

Recent studies have identified genetic variants that predispose to the development of group 3 PH in chronic respiratory diseases (variants of the KDR domain receptor that encodes VEGFR2) [22-24].

Functional signs, and in particular dyspnea, are the consequence of both the causal condition (COPD, fibrosis, etc.) and PH. Physical signs are late, clinical examination may find a burst of B2 at the pulmonary focus or a systolic murmur of tricuspid insufficiency. Signs of right heart failure may be present especially during severe exacerbations. The clinician may suspect PH in the event of dyspnea or hypoxemia poorly explained by the ventilatory disorder (disproportionate).

RV/RA hypertrophy or right heart axis deviation on the electrocardiogram, elevated BNP/NT-proBNP or increased pulmonary artery caliber suggest the diagnosis of PH.

Echocardiography remains the non-invasive diagnostic method used to assess PH, however, in more than 50% of patients with severe respiratory failure the TRV is not measurable with a risk of overestimating the PAPS [25, 26].

More recent data suggest that an echocardiographic score using other echocardiographic features, including RA area, RV/LV ratio, and LV eccentricity index, may be useful [27].

Right heart catheterization is indicated in patients who are candidates for lung transplantation, lung volume reduction surgery, in case of suspicion of PAH or CTEPH, and when additional information can help in phenotyping the disease and setting up a specific treatment. It should be performed in a stable patient after optimized management of his respiratory disease [28-30].

The development of severe PH does not depend on the severity of the ventilatory disorder on spirometry, but is usually accompanied by hypoxemia and a significant reduction in DLCO [31-33].

According to the 2015 ESC/ERS guidelines, PH is considered severe if mPAP >35 mmHg or mPAP ≥25 mmHg with CI <2.5 L/min/m2. However, two recent studies have shown that a PVR>5WU is a better threshold for predicting the severity of CKD-PH [34-36].

Among the phenotypes of PH associated with chronic respiratory diseases, a pulmonary vascular phenotype characterized by better preserved spirometry, low DLCO, hypoxemia and circulatory limitation to exercise has been proposed [37].

Management of PH associated with lung disease begins with optimization of basic treatment of the underlying respiratory pathology, including long-term oxygen therapy, noninvasive ventilation, diuretics in the presence of signs of right heart failure, and pulmonary rehabilitation.

OLD, used for more than 15 h/24 h in COPD patients with frank hypoxemia (PaO2 < 55-60 mm Hg), significantly improved their life expectancy. On the pulmonary hemodynamic level, OLD resulted in either stabilization or moderate regression of PH [38, 39].

For the establishment of a specific treatment for PH, the data from the studies carried out are insufficient and limited by the small number of patients, the short duration of evaluation and the insufficiency of hemodynamic data.

In COPD, PAH treatments are likely to impair gas exchange by vasodilation in areas with a low ventilation/perfusion ratio, and suppression of reflex vasoconstriction in hypoxic areas. This effect would be less marked with inhaled trepostinil [40, 41].

In a 16-week randomized controlled trial of 28 patients with COPD associated with severe PH confirmed by cardiac catheterization, sildenafil treatment resulted in statistically significant improvements in PVR and quality of life [42].

In the COMPERA registry launched in July 2007, currently 62 PH reference centers are involved. The exploitation of data from patients treated mainly with phosphodiesterase-5 inhibitors showed that patients with PH associated with COPD had a worse prognosis than patients with idiopathic PAH and that specific treatment of PH in patients with COPD and severe PH can improve exercise tolerance and dyspnea with a better prognosis in patients responding to treatment. These data remain to be confirmed by prospective, randomized and controlled clinical trials [43].

Numerous phase 2 and phase 3 trials have investigated the use of endothelin receptor antagonists to treat PH associated with ILD, with negative results [44-46]. In addition, ambrisentan was associated with an increased risk of clinical worsening in patients with ILD with or without PH [47, 48].

In a phase 2 trial, the combination of nintedanib and sildenafil did not provide a significant effect compared to nintedanib alone in patients followed for idiopathic pulmonary fibrosis with DlCO ≤35% of the predicted value [49].

Riociguat was associated with an increased risk of clinical worsening and possible excess mortality in patients with PH associated with idiopathic interstitial pneumonia [50].

In contrast, in a phase 3 randomized controlled trial (INCREASE), the use of inhaled treprostinil at a dose of 72 µg administered four times daily in 326 patients with PH associated with interstitial lung disease showed an improvement in the distance traveled at the 6MWT and NT- proBNP values. Further data are needed, particularly on long-term outcomes [51, 52].

To date, there are no official recommendations regarding the treatment of group 3 PH with vasodilators. This question therefore constitutes a real challenge for the future.

Patients with severe PH and/or severe RV dysfunction, or in case of uncertainty regarding PH treatment, referral to a PH center for further evaluation is recommended.

REFERENCES

1. Condon, D. F., Nickel, N. P., Anderson, R., Mirza, S., & de Jesus Perez, V. A. (2019). The 6th World Symposium on Pulmonary Hypertension: what's old is new. *F1000Research*, *8*.
2. Wijeratne, D. T., Lajkosz, K., Brogly, S. B., Lougheed, M. D., Jiang, L., Housin, A., ... & Archer, S. L. (2018). Increasing incidence and prevalence of World Health Organization groups 1 to 4 pulmonary hypertension: a population-based cohort study in Ontario, Canada. *Circulation: Cardiovascular Quality and Outcomes*, *11*(2), e003973.
3. Chaouat, A., Bugnet, A. S., Kadaoui, N., Schott, R., Enache, I., Ducoloné, A., ... & Weitzenblum, E. (2005). Severe pulmonary hypertension and chronic

obstructive pulmonary disease. *American journal of respiratory and critical care medicine*, *172*(2), 189-194.

4. Behr, J., & Ryu, J. H. (2008). Pulmonary hypertension in interstitial lung disease. *European Respiratory Journal*, *31*(6), 1357-1367.
5. Nathan, S. D., Shlobin, O. A., Ahmad, S., Koch, J., Barnett, S. D., Ad, N., ... & Leslie, K. (2008). Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Respiration*, *76*(3), 288-294.
6. Andersen, K. H., Iversen, M., Kjaergaard, J., Mortensen, J., Nielsen-Kudsk, J. E., Bendstrup, E., ... & Carlsen, J. (2012). Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. *The Journal of heart and lung transplantation*, *31*(4), 373-380.
7. Burrows, B., Kettel, L. J., Niden, A. H., Rabinowitz, M., & Diener, C. F. (1972). Patterns of cardiovascular dysfunction in chronic obstructive lung disease. *New England Journal of Medicine*, *286*(17), 912-918.
8. Oswald-Mammosser, M., Weitzenblum, E., Quoix, E., Moser, G., Chaouat, A., Charpentier, C., & Kessler, R. (1995). Prognostic factors in COPD patients receiving long-term oxygen therapy: importance of pulmonary artery pressure. *Chest*, *107*(5), 1193-1198.
9. Prins, K. W., Rose, L., Archer, S. L., Pritzker, M., Weir, E. K., Kazmirczak, F., ... & Thenappan, T. (2018). Disproportionate right ventricular dysfunction and poor survival in group 3 pulmonary hypertension. *American journal of respiratory and critical care medicine*, *197*(11), 1496-1499.
10. Lu, A., Zuo, C., He, Y., Chen, G., Piao, L., Zhang, J., ... & Yu, Y. (2015). EP3 receptor deficiency attenuates pulmonary hypertension through suppression of Rho/TGF-β1 signaling. *The Journal of clinical investigation*, *125*(3), 1228-1242.
11. Gilbane, A. J., Derrett-Smith, E., Trinder, S. L., Good, R. B., Pearce, A., Denton, C. P., & Holmes, A. M. (2015). Impaired bone morphogenetic protein receptor II signaling in a transforming growth factor-β–dependent mouse model of pulmonary hypertension and in systemic sclerosis. *American journal of respiratory and critical care medicine*, *191*(6), 665-677.
12. Tuder, R. M., Davis, L. A., & Graham, B. B. (2012). Targeting energetic metabolism: a new frontier in the pathogenesis and treatment of pulmonary hypertension. *American journal of respiratory and critical care medicine*, *185*(3), 260-266.
13. Voelkel, N. F., & Gomez-Arroyo, J. (2014). The role of vascular endothelial growth factor in pulmonary arterial hypertension. The angiogenesis paradox. *American journal of respiratory cell and molecular biology*, *51*(4), 474-484.
14. Christou, H., Yoshida, A., Arthur, V., Morita, T., & Kourembanas, S. (1998). Increased vascular endothelial growth factor production in the lungs of rats with hypoxia-induced pulmonary hypertension. *American journal of respiratory cell and molecular biology*, *18*(6), 768-776.
15. Tuder, R. M., Flook, B. E., & Voelkel, N. F. (1995). Increased gene expression for VEGF and the VEGF receptors KDR/Flk and Flt in lungs exposed to acute or to chronic hypoxia. Modulation of gene expression by nitric oxide. *The Journal of clinical investigation*, *95*(4), 1798-1807. [PubMed: 7706486]
16. Gore, B., Izikki, M., Mercier, O., Dewachter, L., Fadel, E., Humbert, M., ... & Eddahibi, S. (2014). Key role of the endothelial TGF-β/ALK1/endoglin signaling pathway in humans and rodents pulmonary hypertension. *PloS one*, *9*(6), e100310. [PubMed: 24956016]
17. Liang, S., Yu, H., Chen, X., Shen, T., Cui, Z., Si, G., ... & Yu, X. (2017). PDGF-BB/KLF4/VEGF signaling axis in pulmonary artery endothelial cell angiogenesis. *Cellular Physiology & Biochemistry (Karger AG)*, *41*(6), 2333–2349. [PubMed: 28478450]
18. Barbera, J. A., Peinado, V. I., & Santos, S. (2003). Pulmonary hypertension in chronic obstructive pulmonary disease. *European Respiratory Journal*, *21*(5), 892-905.
19. Nana-Sinkam, S. P., Lee, J. D., Sotto-Santiago, S., Stearman, R. S., Keith, R. L., Choudhury, Q., ... & Geraci, M. W. (2007). Prostacyclin prevents pulmonary endothelial cell apoptosis induced by cigarette smoke. *American journal of respiratory and critical care medicine*, *175*(7), 676-685. [PubMed: 17255567]
20. Weissmann, N., Lobo, B., Pichl, A., Parajuli, N., Seimetz, M., Puig-Pey, R., ... & Barberà, J. A. (2014). Stimulation of soluble guanylate cyclase prevents cigarette smoke–induced pulmonary hypertension and emphysema. *American journal of respiratory and critical care medicine*, *189*(11), 1359-1373. [PubMed: 24738736]
21. Wright, J. L., & Churg, A. (1991). Effect of long-term cigarette smoke exposure on pulmonary vascular structure and function in the guinea pig. *Experimental lung research*, *17*(6), 997-1009. [PubMed: 1769357]
22. Swietlik, E. M., Greene, D., Zhu, N., Megy, K., Cogliano, M., Rajaram, S., ... & Gräf, S. (2021). Bayesian inference associates rare KDR variants with specific phenotypes in pulmonary arterial hypertension. *Circulation: Genomic and Precision Medicine*, *14*(1), e003155.
23. Swietlik, E. M., Prapa, M., Martin, J. M., Pandya, D., Auckland, K., Morrell, N. W., & Gräf, S. (2020). 'There and back again'—forward genetics and reverse phenotyping in pulmonary arterial hypertension. *Genes*, *11*(12), 1408.
24. Eyries, M., Montani, D., Girerd, B., Favrolt, N., Riou, M., Faivre, L., ... & Soubrier, F. (2020). Familial pulmonary arterial hypertension by KDR

heterozygous loss of function. *European Respiratory Journal*, *55*(4).
25. Arcasoy, S. M., Christie, J. D., Ferrari, V. A., Sutton, M. S. J., Zisman, D. A., Blumenthal, N. P., ... & Kotloff, R. M. (2003). Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *American journal of respiratory and critical care medicine*, *167*(5), 735-740.
26. Fisher, M. R., Forfia, P. R., Chamera, E., Housten-Harris, T., Champion, H. C., Girgis, R. E., ... & Hassoun, P. M. (2009). Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *American journal of respiratory and critical care medicine*, *179*(7), 615-621.
27. Bax, S., Bredy, C., Kempny, A., Dimopoulos, K., Devaraj, A., Walsh, S., ... & Price, L. C. (2018). A stepwise composite echocardiographic score predicts severe pulmonary hypertension in patients with interstitial lung disease. *ERJ open research*, *4*(2), 124.
28. Zeder, K., Avian, A., Bachmaier, G., Douschan, P., Foris, V., Sassmann, T., ... & Kovacs, G. (2021). Elevated pulmonary vascular resistance predicts mortality in COPD patients. *European Respiratory Journal*, *58*(2), 2100944.
29. Vizza, C. D., Hoeper, M. M., Huscher, D., Pittrow, D., Benjamin, N., Olsson, K. M., ... & Grünig, E. (2021). Pulmonary hypertension in patients with COPD: results from the comparative, prospective registry of newly initiated therapies for pulmonary hypertension (COMPERA). *Chest*, *160*(2), 678-689.
30. Waxman, A., Restrepo-Jaramillo, R., Thenappan, T., Ravichandran, A., Engel, P., Bajwa, A., ... & Nathan, S. D. (2021). Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *New England Journal of Medicine*, *384*(4), 325-334.
31. Chaouat, A., Bugnet, A. S., Kadaoui, N., Schott, R., Enache, I., Ducoloné, A., ... & Weitzenblum, E. (2005). Severe pulmonary hypertension and chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine*, *172*(2), 189-194.
32. Vizza, C. D., Hoeper, M. M., Huscher, D., Pittrow, D., Benjamin, N., Olsson, K. M., ... & Grünig, E. (2021). Pulmonary hypertension in patients with COPD: results from the comparative, prospective registry of newly initiated therapies for pulmonary hypertension (COMPERA). *Chest*, *160*(2), 678-689.
33. Dauriat, G., Reynaud-Gaubert, M., Cottin, V., Lamia, B., Montani, D., Canuet, M., ... & Mal, H. (2021). Severe pulmonary hypertension associated with chronic obstructive pulmonary disease: a prospective French multicenter cohort. *The Journal of Heart and Lung Transplantation*, *40*(9), 1009-1018.
34. Galiè, N., Humbert, M., Vachiery, J. L., Gibbs, S., Lang, I., & Torbicki, A. (2015). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Pediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Euro Respir J*, 46, 903-975.
35. Zeder, K., Avian, A., Bachmaier, G., Douschan, P., Foris, V., Sassmann, T., ... & Kovacs, G. (2021). Elevated pulmonary vascular resistance predicts mortality in COPD patients. *European Respiratory Journal*, *58*(2), 2100944.
36. Olsson, K. M., Hoeper, M. M., Pausch, C., Grünig, E., Huscher, D., Pittrow, D., ... & Gall, H. (2021). Pulmonary vascular resistance predicts mortality in patients with pulmonary hypertension associated with interstitial lung disease: results from the COMPERA registry. *European Respiratory Journal*, *58*(2), 2101483.
37. Thabut, G., Dauriat, G., Stern, J. B., Logeart, D., Levy, A., Marrash-Chahla, R., & Mal, H. (2005). Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest*, *127*(5), 1531-1536.
38. TIMMS, R. M., KHAJA, F. U., & WILLIAMS, G. W. (1985). Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. *Annals of internal medicine*, *102*(1), 29-36.
39. Medical Research Council Working Party. (1981). Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet*, *1*(8222), 681-686.
40. Barberà, J. A., & Blanco, I. (2009). Pulmonary hypertension in patients with chronic obstructive pulmonary disease: advances in pathophysiology and management. *Drugs*, *69*, 1153-1171.
41. Boeck, L., Tamm, M., Grendelmeier, P., & Stolz, D. (2012). Acute effects of aerosolized iloprost in COPD related pulmonary hypertension-a randomized controlled crossover trial. *PloS one*, *7*(12), e52248.
42. Vitulo, P., Stanziola, A., Confalonieri, M., Libertucci, D., Oggionni, T., Rottoli, P., ... & Vizza, C. D. (2017). Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: a randomized controlled multicenter clinical trial. *The Journal of Heart and Lung Transplantation*, *36*(2), 166-174.
43. Vizza, C. D., Hoeper, M. M., Huscher, D., Pittrow, D., Benjamin, N., Olsson, K. M., ... & Grünig, E. (2021). Pulmonary hypertension in patients with COPD: results from the comparative, prospective registry of newly initiated therapies for pulmonary

hypertension (COMPERA). *Chest*, *160*(2), 678-689.

44. Raghu, G., Behr, J., Brown, K. K., Egan, J. J., Kawut, S. M., Flaherty, K. R., ... & ARTEMIS-IPF Investigators*. (2013). Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Annals of internal medicine*, *158*(9), 641-649.
45. King Jr, T. E., Behr, J., Brown, K. K., du Bois, R. M., Lancaster, L., de Andrade, J. A., ... & Raghu, G. (2008). BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*, *177*(1), 75-81.
46. King Jr, T. E., Brown, K. K., Raghu, G., Du Bois, R. M., Lynch, D. A., Martinez, F., ... & Behr, J. (2011). BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*, *184*(1), 92-99.
47. Raghu, G., Behr, J., Brown, K. K., Egan, J. J., Kawut, S. M., Flaherty, K. R., ... & ARTEMIS-IPF Investigators*. (2013). Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Annals of internal medicine*, *158*(9), 641-649.
48. Raghu, G., Nathan, S. D., Behr, J., Brown, K. K., Egan, J. J., Kawut, S. M., ... & O'Riordan, T. G. (2015). Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. *European Respiratory Journal*, *46*(5), 1370-1377.
49. Kolb, M., Raghu, G., Wells, A. U., Behr, J., Richeldi, L., Schinzel, B., ... & Martinez, F. J. (2018). Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. *New England Journal of Medicine*, *379*(18), 1722-1731.
50. Nathan, S. D., Behr, J., Collard, H. R., Cottin, V., Hoeper, M. M., Martinez, F. J., ... & Wells, A. U. (2019). Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. *The Lancet Respiratory Medicine*, *7*(9), 780-790.
51. Waxman, A., Restrepo-Jaramillo, R., Thenappan, T., Ravichandran, A., Engel, P., Bajwa, A., ... & Nathan, S. D. (2021). Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *New England Journal of Medicine*, *384*(4), 325-334.
52. Nathan, S. D., Tapson, V. F., Elwing, J., Rischard, F., Mehta, J., Shapiro, S., ... & Waxman, A. (2022). Efficacy of inhaled treprostinil on multiple disease progression events in patients with pulmonary hypertension due to parenchymal lung disease in the INCREASE trial. *American journal of respiratory and critical care medicine*, *205*(2), 198-207.