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EDITORIAL

Why there is a need to discuss pulmonary hypertension other than pulmonary arterial hypertension?

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Abstract

Pulmonary hypertension (PH) is a condition characterized by the elevation of the mean pulmonary artery pressure above 25 mmHg and the pulmonary vascular resistance above 3 wood units. Pulmonary arterial hypertension (PAH) is an uncommon condition with severe morbidity and mortality, needing early recognition and appropriate and specific treatment. PH is frequently associated with hypoxemia, mainly chronic obstructive pulmonary disease and DPLD and/or left heart diseases (LHD), mainly heart failure with reduced or preserved ejection fraction. Although in the majority of patients with PH the cause is not PAH, a significant number of published studies are still in regard to group Ⅰ PH, leading to a logical assumption that PH due to other causes is not such an important issue. So, is there a reason to discuss PH other than PAH? Chronic lung diseases, mainly chronic obstructive lung disease and DPLD, are associated with a high incidence of PH which is linked to exercise limitations and a worse prognosis. Although pathophysiological studies suggest that specific PAH therapy may benefit such patients, the results presented from small studies in regard to the safety and effectiveness of the specific PAH therapy are discouraging. PH is a common complication of left heart disease and is related to disease severity, especially in patients with reduced ejection fraction. There are two types of PH related to LHD based on diastolic pressure difference (DPD, defined as diastolic pulmonary artery pressure - mean PAWP): Isolated post-capillary PH, defined as PAWP > 15 mmHg and DPD < 7 mmHg, and combined post-capillary PH and pre-capillary PH, defined as PAWP > 15 mmHg and DPD ⩾ 7 mmHg. The potential use of PAH therapies in patients with PH related to left heart disease is based on a logical pathobiological rationale. In patients with heart failure, endothelial dysfunction has been proposed as a cause of PH and hence as a target for treatment, supported by the presence of increased endothelin-1 activity and impaired nitric oxide-dependent vasodilation. Unfortunately, so far, there is no evidence supporting the use of specific PAH therapies in patients with PH related to left heart disease. In conclusion, the presence of PH in patients with conditions other than PAH contributes to the severity of the disease, affecting the outcome and quality of life. The disappointing results regarding the effectiveness of specific PAH therapies in patients with

chronic lung diseases and LHD underline the need for seeking new underlying mechanisms and thus novel therapies targeting PH due to left heart disease and/or lung diseases.

Key words: Pulmonary hypertension; Pulmonary arterial hypertension; Chronic obstructive pulmonary disease; Heart failure; Treatment

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Core tip: Pulmonary arterial hypertension (PAH) is a rare disease that concerns a small population of patients. Recently, there has been a significant number of research, publications and novel therapies concerning PAH. However, pulmonary hypertension (PH), that concerns a much larger population of patients with common diseases such as lung and left heart diseases (LHD), is generally overlooked despite the fact that it significantly affects the prognosis of these patients. This editorial underlines the need for further research in regard to the pathogenesis and novel therapies for PH related to lung and LHD.

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TEXT

Pulmonary hypertension (PH) is a condition characterized by the elevation of mean pulmonary artery pressure (mPAP) above 25 mmHg and pulmonary vascular resistance (PVR) above 3 wood units[1]. Pulmonary arterial hypertension (PAH), *i.e.*, group Ⅰ according to the latest international guidelines[2], is a rather uncommon condition requiring specific treatment. In the majority of patients with PH, elevated pressures in pulmonary circulation are due to hypoxemia, mainly chronic obstructive pulmonary disease (COPD) and diffuse parenchymal lung diseases (DPLD including idiopathic pulmonary fibrosis and sarcoidosis), and/or due to left heart diseases (LHD), mainly heart failure with reduced or preserved ejection fraction. Furthermore, a small proportion of PH is due to chronic thromboembolic disease and other conditions. Definitions of the above mentioned subgroups of patients with PH are shown in Table 1.

Group Ⅰ PH, *i.e.*, PAH, is either familial, idiopathic or is associated with various well specified diseases[1]. In recent years, a large number of studies have shed light on the underlying pathophysiologic mechanisms for the development of PAH, eventually leading to targeted therapies that improved the morbidity and survival of these patients. Currently, there are three known pathways that play a part in cell proliferation and vasoconstriction in the pulmonary arteries of patients with PAH[3]. Treatments for PAH are aimed at these pathways[4]. The first one is the prostacyclin pathway. Prostacyclin is a potent vasodilator and drugs called epoprostanoids, *i.e.*, epoprostenol, treprostinil and iloprost, targeting this pathway, aim to increase the level of prostacylin in the body. The second pathway is the endothelin pathway. Endothelin is a known potent vasoconstrictor. The class of drugs that targets this pathway is called endothelin receptor antagonist, *i.e.*, bosentan, macitentan and ambrisentan. These drugs block the A and B endothelin receptors in the blood vessels from responding to endothelin. Finally, the third pathway is the nitric oxide pathway. Nitric oxide is a potent vasodilator. There are two classes of medications that target this pathway. Phosphodiesterase type 5 is a molecule in the body that interrupts the production of nitric oxide. The drugs that target this pathway are called phosphodiesterase type 5 inhibitors. Soluble guanylate cyclase stimulators work by stimulating an enzyme inside the cells called soluble guanylate cyclace. By increasing the activity of this enzyme, there is an increase in the production of cyclic GMP, which in turn leads to relaxation of the pulmonary arteries and improvements in PH. Currently, two phosphodiesterase type 5 inhibitors, sildenafil and tadalafil, and one soluble guanylate cyclase stimulator, riociguat, have been approved[4].

The majority of published studies concern PAH, thus leading to a logical assumption that PH due to other causes is not such an important issue. This is also enforced by the fact that published guidelines regarding PH groups Ⅱ, Ⅲ and Ⅳ cover only 26 out of 126 pages. So, is there a reason to discuss PH other than PAH?

COPD and DPLD, including idiopathic pulmonary fibrosis and sarcoidosis, are associated with a high incidence of PH, which is linked to exercise limitations and a worse prognosis[5]. Data showed that the prevalence of PH in COPD patients depends on the severity of the disease and the definition of PH. Accumulating data suggests that in approximately 90% of patients with severe disease, mPAP was more than 20 mmHg, with most ranging between 20 and 35 mmHg while 3% to 5% of the patients demonstrated "severe PH", *i.e.*, mPAP > 35 to 40 mmHg[6]. The "severe PH group" includes only a minority of chronic lung disease patients suspected of having significant vascular abnormalities (remodelling) accompanying the parenchymal disease[7]. For COPD, this corresponds to approximately 1% of the entire population[6].

Chronic hypoxia and fibroproliferation in DPLD lead to the remodelling of both the pulmonary arterial vascular wall and the pulmonary parenchyma due to common pathophysiological ways, while new data indicate that pathogenetic concepts that primarily relate to idiopathic pulmonary fibrosis may also take place in other forms of pulmonary fibrosis, including connective tissue diseases

Table 1 The definitions of pulmonary hypertension groups Ⅰ, Ⅱ, Ⅲ, Ⅳ[1,7,22]

Group	Definition
Group Ⅰ: Pulmonary arterial hypertension	Is defined as: Mean pulmonary artery pressure ⩾ 25 mmHg at rest, and end-expiratory pulmonary artery wedge pressure ⩽ 15 mmHg, and pulmonary vascular resistance > 3 Wood units
Group Ⅱ: PH due to left heart disease	Is defined as: mPAP ⩾ 25 mmHg, and PAWP > 15 mmHg, and normal or reduced CO
Group Ⅲ: PH due to chronic lung disease and/or hypoxia	Patients with confirmed COPD or DPLD, without chronic thromboembolic disease or left heart disease, who meet at least two of the following criteria: mPAP > 35 mmHg mPAP ⩾ 25 mmHg AND cardiac index < 2 lt/min per square pulmonary vascular resistance > 6 Wood units
Group Ⅳ: Chronic thromboembolic pulmonary hypertension	CTEPH is defined as pre-capillary PH as assessed by right heart catheterization (mean PAP ⩾ 25 mmHg, PCWP ⩽ 15 mmHg) in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least three months of effective anticoagulation

PH: Pulmonary hypertension; CO: Cardiac output; COPD: Chronic obstructive pulmonary disease; DPLD: Diffuse parenchymal lung diseases; PAP: Pulmonary artery pressure.

and granulomatous diseases such as sarcoidosis[8]. This leads to a rationale for evaluating the safety and effectiveness of the specific PAH therapy in such patients[5]. Data from such trials are discouraging. In COPD, pulmonary vasodilation without deterioration of gas exchange is more challenging than in lung fibrosis caused by the presence of low ventilation/perfusion ratio areas. Inhaled prostanoids may acutely reduce mPAP and PVR while largely maintaining gas exchange in COPD patients with PH[9].

However, long-term clinical trials have not been reported. In COPD patients with mild PH, bosentan, a nonselective endothelin-1 receptor antagonist, caused deterioration of gas exchange with a lack of improvement in peak oxygen uptake, exercise capacity and quality of life in a small randomized controlled trial[10]. On the other hand, another small trial reported an improvement in exercise capacity upon treatment of COPD patients with PH with bosentan[11].

Robust data on the effect of endothelin receptors antagonists on pulmonary hemodynamics and exercise tolerance in COPD patients are lacking[5].

PH is a common complication of LHD[12]. The presence of PH is often considered as a symptom of the underlying condition and often related to disease severity, especially in patients with reduced ejection fraction of the left ventricle[13]. The current hemodynamic definition of PH related to LHD combines a mPAP ⩾ 25 mmHg, a pulmonary artery wedge pressure (PAWP) > 15 mmHg and a normal or reduced cardiac output. There are also two types of PH related to LHD based on the diastolic pressure difference (DPD, defined as diastolic PAP - mean PAWP): Isolated post-capillary PH, defined as PAWP > 15 mmHg and DPD < 7 mmHg, and combined post-capillary PH and pre-capillary PH defined as PAWP > 15 mmHg and DPD ⩾ 7 mmHg[13].

The potential use of PAH therapies in patients with PH related to LHD is based on a logical pathobiological rationale, while in patients with heart failure, endothelial dysfunction has been proposed as a cause of PH and hence as a target for treatment, supported by the presence of increased endothelin-1 activity and impaired nitric oxide-dependent vasodilation[14]. Unfortunately, so far, there is no evidence supporting the use of specific PAH therapies in patients with PH related to LHD[13]. It must be pointed out that there are fundamental differences in the pathophysiologic pathways between patients with heart failure with reduced and preserved ejection fraction. These differences suggest that more pathophysiologically targeted drugs and therapies are needed for each case[15].

Therefore, it is anticipated that PAH therapies might have a different effect in patients with heart failure and preserved ejection fraction compared with other forms of heart failure. Data on the use of PAH therapies in the context of heart failure and reduced or preserved ejection fraction with or without PH are scarce; with sildenafil and riociguat the most studied medications in this setting[16-18].

Finally, specific PAH therapies may have a place in the treatment of acute PH. In one of our studies, we showed that the postoperative co-administration of inhaled nitric oxide and oral sildenafil, a phosphodiesterase-5 inhibitor, in patients with out-of-proportion PH undergoing cardiac surgery is safe and results in an additive favourable effect on pulmonary arterial pressure and PVR, without systemic hypotension and ventilation/perfusion mismatch[19].

Finally, left heart disease is a well-known but often underdiagnosed co-morbidity of COPD[20,21]. The presence of left heart disease in COPD patients may additionally contribute to the pathogenesis and severity of PH and thus the cause of moderate to severe PH in patients with COPD may be the result of multiple causal factors. Data regarding the incidence of HF in COPD patients are accumulating, but there is little known about the contribution of each condition to the presence and severity of PH in such patients.

In conclusion, the presence of PH in patients with conditions other than PAH contributes to the severity of the disease affecting the outcome and quality of life. Although these conditions affect a large proportion of patients with common diseases such as LHD and COPD/DPLD, there is a lack of data, pathophysiologic studies, and multicentre randomised trials addressing a target therapy for PH in such populations. The disappointing results for the effectiveness of specific PAH therapies in such populations underline the need to seek new

underlying mechanisms and thus novel therapies targeting PH due to LHD and/or lung diseases.

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