

Pulmonary hypertension inadequate to the clinical condition or hypoxemia disproportionate to the PH severity? (RCD code: II-1B.2)

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Abstract

We present four cases of patients with a history of a pulmonary hypertension (PH), who had a component of lung disease disproportionate to the PH severity. Detailed evaluation revealed pulmonary arterial hypertension (PAH) and patients were qualified to the targeted pharmacotherapy, however the treatment did not bring the significant improvement of patients' functional status. During follow-up, we observed deterioration of the clinical symptoms, that were not reflected in a significant progression of the right ventricle dysfunction. This article provides information regarding pathogenesis, clinical characteristics, diagnostic evaluation and treatment of patients with PAH and presents the basic knowledge of the contribution of lung disorders to the PH development. JRCD 2015; 2 (5): 150–155

Key words: pulmonary arterial hypertension, lung diseases, right heart catheterization, pulmonary artery pressure

Background

In recent years a large progress in the therapy of pulmonary arterial hypertension (PAH) was observed. The European Society of Cardiology (ESC) guidelines recommend several types of agents targeted on specific pathophysiological mechanisms of PAH including phosphodiesterase type 5 (PDE5) inhibitors, prostanoids or endothelin receptor antagonists. Further, according to the latest guidelines new drugs like guanylate cyclase stimulator riociguat or an orally available, selective prostacyclin IP receptor agonist selexipag can be used [1]. The PAH pharmacotherapy is based on monotherapy or a combination of the mentioned drug types.

PAH coexisting with chronic lung diseases often creates difficulties in identifying the main components of the patient's symptoms and making the correct diagnosis. A poor prognosis can thus be deepened by improper pharmacotherapy.

In this article we present four patients aged 61 – 77 years, who were suffering from a moderate PH and mild lung disease. The summarize of patients clinical parameters is shown in table 1.

Case presentation

Case 1.

77-year-old patient, male, a longtime smoker, with a stable coronary artery disease, hypertension and hypercholesterolemia was admitted to the hospital in 2013 due to progressive shortness of breath and exercise intolerance. History of cigarette smoking, dyspnea and low oxygen saturation (80%) might suggest chronic obstructive pulmonary disease (COPD), however spirometry did not confirm significant lower airway obstruction. Echocardiography showed enlargement of the right ventricle and elevated pulmonary artery pressure. Lung scintigraphy did not reveal ventilation or perfusion abnormalities. The right heart catheterization (RHC)

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Table 1. Characteristics of presented patients

	Case 1	Case 2	Case 3	Case 4
Age/ Gender	77/M	62/M	75/F	73/F
Background lung disease (COPD/ Asthma/other)	Yes			
WHO functional capacity	II -> IV	IV	III -> IV	III
BNP (pg/ml)	91 -> 673	160 -> 414	1720 -> 365 -> 616	143 -> 245
Spirometry	mild/no airflow obstruction			
V/Q	subsegmental defects			
HRCT	relatively mild fibrosis			
mPAP (mmHg)	41 -> 50	72	56 -> 45	33
PAWP (mmHg)	13	11	13	12
CO (l/min)	3,4 -> 6,5	4	2,5 -> 4,8	4,2
PVR (Wood units)	8,24 -> 5,54	5,2	18,4 -> 6,6	4,9
Treatment	Ilprost+sildenafil -> treprostiniil+sildenafil	ilprost -> sildenafil	dilitiazem -> +sildenafil -> +ambrisentan	sildenafil
mPAP Echo (mmHg)	27 -> 40	58,73 -> 61	60,56 -> 44	23,35 -> 37
Echo LVEF	35%	55%	55%	55%
DLCO	23%	45%	40%	24%
LTOT	Yes			
TLC	90%	85%	90%	75%
VO2 max (ml/kg/min)	10,6	13,3	no data	no data
pO2 (mmHg)	44	42,6	54	47
pCO2 (mmHg)	28	28	24	44
6MWT (m)	315 -> 240 -> 180	390	180	240 -> 180
ANA	negative			

F – female, M – male, COPD – chronic obstructive pulmonary disease, WHO – World Health Organization, BNP – brain natriuretic peptide, V/Q – ventilation / perfusion rate, HRCT – high resolution computed tomography, mPAP – mean pulmonary artery pressure, PAWP – pulmonary artery wedge pressure, CO – cardiac output, PVR – pulmonary vascular resistance, Echo – echocardiography, LVEF – left ventricular ejection fraction, LTOT – long-term oxygen therapy, DLCO – diffusing capacity for carbon monoxide, TLC – total lung capacity, VO2 max – maximum oxygen uptake, PO2 – partial pressure for oxygen, PCO2 – partial pressure for carbon dioxide, 6MWT – six-minute walk test, ANA – anti-nuclear antibodies

confirmed precapillary pulmonary hypertension (PH) (mean pulmonary artery pressure [mPAP] – 41 mm Hg, pulmonary wedge pressure [PWP] – 13 mm Hg, cardiac output [CO] – 3.4 l/min, cardiac index [CI] – 1.88 l/min*m²); an acute vasodilator challenge was negative. Diffusing capacity of the lungs for carbon monoxide (DLCO) was significantly decreased (23%), while total lung capacity (TLC) was normal (90%). Next, high resolution chest computed tomography (HRCT) showed generalized lung fibrosis in various stages (Figure 1), however the lung changes were not considered by external expert centers sufficient to cause such severe PH. Therefore, the PAH therapy with the use of iloprost was started. Despite the treatment with prostacyclin analogue, patient remained in World Health Organization (WHO) IV class. Tempo-

rary improvement was achieved by the intensification of diuretic therapy and adding of sildenafil.

In the following year the patient was hospitalized twice in serious condition due to severe dyspnea and cyanosis. Consecutive hemodynamic assessment revealed the similar mPAP with a decrease of CI to 1.55 l/min*m². The treatment was changed to a continuous subcutaneous infusion of treprostiniil – target dose was set at 15 mcg/kg/min. After a month patient was admitted because of cardiac decompensation with coexisting pneumonia. RHC was repeated and it revealed higher than the previous mPAP – 50 mm Hg with an increase of CI (3.5 l/min*m²) and a decrease of PVR (5.5 WU). We suspect that combined therapy of sildenafil and treprostiniil could be the cause of an imbalance of a ventilation-perfusion rate and decreased oxygen saturation. The increase



Figure 1. High resolution chest computed tomography (Case 1). Diffuse emphysematous changes with small blebs, ground-glass opacity



Figure 2. High resolution chest computed tomography (Case 2). Diffuse emphysematous changes

of the treprostinil dose could result in a better perfusion of poorly ventilated areas of lungs. We reduced treprostinil dose to 12 mcg/kg/min and continued therapy of heart failure (intensifying diuretic therapy), yielding gradual improvement of patient's condition. Since that decompensation, patient remains in stable but in WHO IV class condition.

Case 2.

A 62-year-old male, diagnosed with mild/moderate COPD treated with inhaled therapy and theophylline was admitted to the hospital in 2009 because of a recurrent chest pain, significant deterioration in exercise tolerance, dyspnea at rest and peripheral cyanosis. Coronary angiography revealed insignificant changes in the arteries. Based on echocardiographic assessment, a severe pulmonary hypertension was suspected. RHC confirmed PAH (mPAP – 72 mm Hg) with a negative acute vasodilator challenge. Patient was assigned to WHO IV functional class and started treatment with inhaled iloprost. This resulted in significant improvement of functional status.

In the following year the patient was hospitalized several times because of cardiac decompensation. Chest X-ray revealed increased interstitial lung markings and HRCT showed emphysema changes in lungs (Figure 2). Furthermore, an extensive inflammation of the oral mucosa was observed, which was probably the effect of inhaled steroids or iloprost, thus iloprost was switched to sildenafil. It resulted in a relief of these changes in the oral cavity. After next few months, due to clinical worsening, we decided to onset a subcutaneous treprostinil therapy replacing sildenafil. Unfortunately, patient died because of decompensated congestive heart failure before the start of the new therapy.

Case 3.

A 75-year-old woman, a longtime passive smoker with hypertension, type 2 diabetes and chronic kidney disease was admitted to the hospital due to increasing dyspnea on exertion over the past 6 months. During physical examination we observed facial cyanosis, peripheral edema, enlarged liver, varicose veins and post-thrombotic syndrome. The arterial blood gas analysis indicated deterioration of the pulmonary oxygenation (pO_2 47 mm Hg, pCO_2 44 mm Hg, pH 7.44). Echocardiography showed mild tricuspid regurgitation with PH (mPAP- 37mmHg), enlarged right ventricle (40 mm) and normal left ventricular systolic function, (LVEF 55%). Spirometry did not reveal a significant airflow obstruction (forced expiratory volume [FEV1]/forced vital capacity [FVC] 83%), however DLCO was severely impaired (24%) with TLC 75%. Thromboembolic events and interstitial lung diseases were excluded in computed tomography (CT) angiography and HRCT (Figure 3). RHC showed precapillary PH (mPAP – 33 mm Hg, PWP – 12 mm Hg), with normal CO (4.2 l/min), CI (2.87 l/min \cdot m 2) and increased PVR (4,9 WU); an acute vasodilator challenge with iloprost was negative.

The patient was diagnosed with PAH in WHO III class with a co-existing hypoxemic respiratory failure. A sildenafil therapy with oxygen supplementation was started that resulted in a slight clinical status improvement.

Case 4.

A 73-year-old woman diagnosed with an interstitial lung disease of unknown etiology (treated by prednisone) and insulin-dependent type 2 diabetes was admitted to the hospital in 2013 because of an acute pulmonary embolism. After a period of 3 month stabilization, attacks of breathlessness returned despite the antithrombotic therapy. The pulmonary function test did not show any ob-

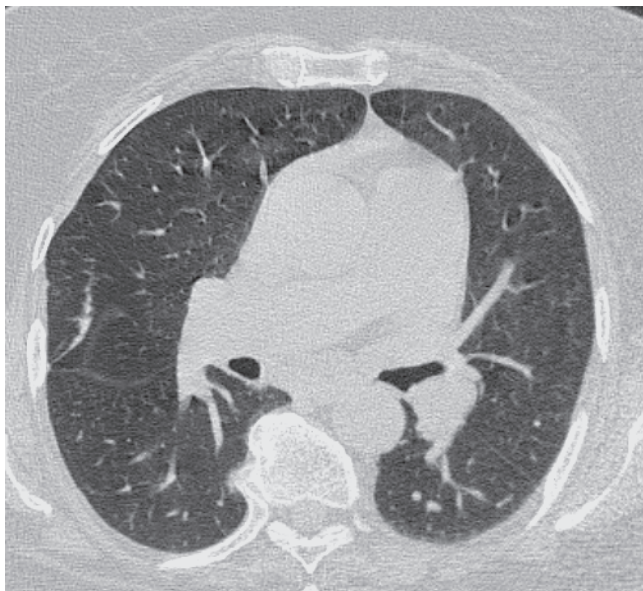


Figure 3. High resolution chest computed tomography (Case 3). Diffuse emphysematous changes

struction. Because of echocardiographic signs of right ventricular failure and a significant tricuspid regurgitation accompanied by high BNP levels (1720 pg/ml), RHC was performed. It showed a severe precapillary PH (mPAP – 56mmHg, CO – 2,5 l/min, CI – 1,48 l/min*m², PVR – 18 WU) with a positive acute vasodilator challenge. Lung scintigraphy and laboratory tests excluded a connective tissue disease and chronic thromboembolic PH. HRCT showed ground glass opacities (Figure 4). Moreover, normal TLC (90%) was combined with reduced DLCO (40%). On the basis of the overall clinical condition of the patient we diagnosed PAH with positive vasoreactive response. Therapy with calcium channel antagonist (diltiazem), glucocorticoids and anticoagulation resulted in a slight clinical improvement.

Two months later, the patient was referred to the hospital due to a dyspnea exacerbation and because of the absence of an adequate improvement, sildenafil was added to the PAH therapy. The subsequent RHC revealed a PVR reduction from 18.4 to 6.6 WU with slight mPAP decrease (45mmHg) and increase of CO – 4,8 l/min and CI – 3,11 l/min*m². This time, the acute vasodilator challenge was negative. Further hospitalizations were assigned to the respiratory decompensation due to the recurrent pneumonia caused by *Staphylococcus aureus*, however a satisfactory clinical improvement was not achieved. An overall assessment suggested PAH progression, so we decided to intensify the treatment with an endothelin receptor antagonist – ambrisentan. After few months the patient required hospitalization at the Pulmonology Department, where deterioration of the clinical status was assigned to progression of interstitial lung disease. Unfortunately, patient died because of the respiratory failure.

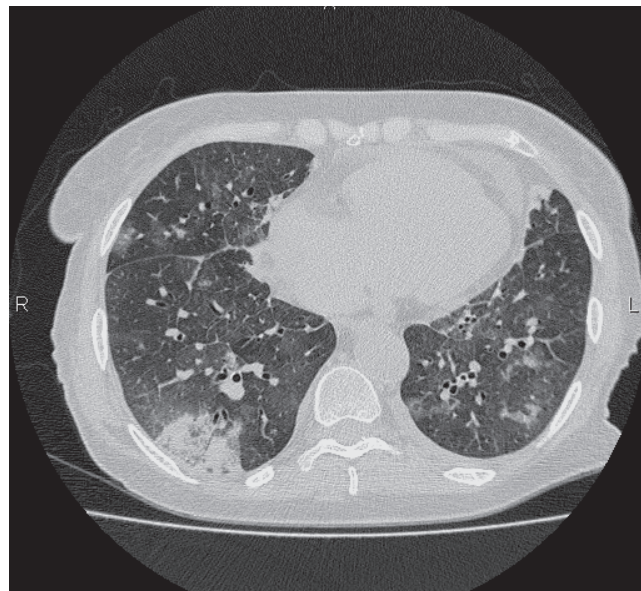


Figure 4. High resolution chest computed tomography (Case 4). Diffuse emphysematous changes; ground glass opacity

Review of literature

PH is a hemodynamic and pathophysiological condition that can accompany many cardiovascular and other system disorders. The PH therefore is divided into groups according to pathogenesis and clinical characteristics. Regardless of the group, PH is defined as an increase in mPAP over 25 mm Hg at rest as assessed by RHC [1, 2]. The diagnostic strategy in PH patients has to give information about disease severity but also should describe the potential secondary character of the disease. In the case of PAH, the diagnosis requires an exclusion of all other PH groups. In this article we focus on overlapping of the two groups: PAH and PH related to lung disorders.

PAH – a multifactorial disease

Recent data has described the epidemiology of PAH for 15–50 subjects per million population in Europe [3, 4]. The pathobiology of this disease involves different biochemical pathways and cell types, however the exact mechanism that onsets the unfavorable changes in PAH is still unknown. The main mechanism of the disease is an increase in PVR caused by a variety of processes, including vasoconstriction, proliferative and obstructive remodeling of the pulmonary arteries, thrombosis and inflammation. One of the basic causes underlying these processes is the dysfunction of endothelium that includes an impaired production of vasodilators and antiproliferative agents with overexpression of a proliferative substances. These multifactorial processes lead to right ventricular failure, decreased functional capacity, and ultimately death.

Therapeutic decisions should be based on parameters that reflect symptoms and have the ability to predict outcome. However, the well-established parameters, such as pulmonary artery pressure, may not reflect properly the disease advancement and patient's clinical status in all cases. It is important not to depend on

a single parameter because other parameters may provide divergent results. In addition, no clear-cut thresholds for any single parameter can be identified to divide patients into those with a good and poor prognosis [1].

PH associated to the lung diseases

The clinical classification of PH includes the lung disorders underlying the PH etiology [1]. In this group a number of diseases are mentioned, among which the most common is COPD, interstitial lung disease and chronic inflammation of the lung tissue [1]. In these cases the PH pathogenesis is based on progressive tissue destruction caused by a chronic inflammation and oxidative stress [2]. As a result of these factors overlap comes to the adverse pulmonary vascular remodeling that mostly affects the distal vessels. Ongoing processes include neovascularization and the proliferation of vascular smooth muscle cells, which normally could be overgrown in a small proportion. The major difference between PAH and PH due to lung diseases and/or hypoxia is the presence of plexiform lesions in PAH [3]. These processes lead to abnormal remodeling of the precapillary parts of the pulmonary vascular bed and ultimately to the PH development. Another important component is hypoxia, an effect of lowering the arterial blood oxygen saturation combined with the difficult excretion of carbon dioxide, what leads to hypercapnia. The oxygen deficiency results in the contraction of the pulmonary arteries and the redistribution of the blood to the better ventilated lung areas, that improves the ventilation to perfusion ratio (V/Q). Chronic hypoxia also promotes imbalance between the vasoconstrictors and vasodilators and stimulates endothelial cells to secrete cytokines. Thus the hypoxia-induced remodeling of the pulmonary circulation is a highly complex process where numerous interactive events promote cell proliferation in the vessel wall and lead to smooth muscle cells hypertrophy and thickening of the arteries [4]. Further, these processes translate into a mechanism of an adverse remodeling leading to an increase of the PVR and the PH fixation. The mechanism of hypoxia-induced pulmonary vasoconstriction is compounded by hypercapnia and acidosis. A concomitant inflammatory activation leads to remodeling of the pulmonary vasculature, but the exact mechanisms of these changes is not fully understood. Inflammatory mediators, such as C-reactive protein, interleukin 6 or tumor necrosis factor- α , are elevated in the case of PH as well as the blood pressure increase in the pulmonary artery in patients with COPD [5–7]. The undeniable role in the development of the disease (in pre-existing lung pathology) has reduced expression of nitric oxide synthase in pulmonary vascular endothelium, increased levels of VEGF and circulating endothelin, resulting in an intensification of the constriction mechanisms and pulmonary vessels remodeling [8].

The adaptive polycythemia may play the compensatory role in PH especially with a pulmonary component. In COPD it occurs secondary to hypoxia [9]. The increased viscosity of blood flow requires an increase in flow pressure, which results in increased pulmonary vascular tension [10].

Another aspect is the impact of shear stress, which also intensifies remodeling of the pulmonary vasculature. This mechanism particularly concerns the vessels, where the diameter is reduced,

for example as a result of contraction, and there is an increase of blood flow velocity. That leads to disruption of laminar and induction of turbulent flow. This process probably plays a role in the presence of hypoxia and its contractile influence on vessels, which is enhanced by an unfavorable vascular remodeling processes. In addition, shear stress promotes an increase of platelet activation and production of endothelin, pro-inflammatory cytokines, as well as reduction of the nitric oxide production [11, 12]. Currently there is no specific therapy for PH associated with lung diseases. Treatment with conventional vasodilators is not recommended because they may impair gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction [13]. The clinical benefit of PAH-specific vasodilators in lung disease-related PH is controversial. The data on the therapy is very limited and mainly concern the beneficial effect of PD-5 inhibitor – sildenafil [13, 14].

The treatment of choice for PH due to lung diseases and/or hypoxia (group 3) is long-term oxygen therapy (LTOT). LTOT may partly reverse hypoxic pulmonary vasoconstriction and stop the progression of PH but is not always effective in reducing PAP in COPD [15, 16, 17].

On the other side, patients diagnosed with ‘out of proportion’ PH due to lung diseases (characterized by dyspnea insufficiently explained by lung mechanical disturbances and mean PAP 40–45 mm Hg at rest) should be referred to expert centers and treated with PAH-specific drug therapy within the clinical trials [1]. However, the use of PAH drug therapy is not recommended in patients with PH due to lung diseases [1]. This fact highlights the need for proper patient evaluation, which is crucial for therapeutic decisions.

Summary

Four cases presented in this article demonstrate the complex problem of PH patients with coexisting lung disorders. Echocardiography and RHC excluded PH due to left heart diseases. Lung changes revealed in imaging and functional tests, albeit present, were not considered as sufficient to cause such severe PH and ventilation-perfusion scintigraphy ultimately excluded the thromboembolic etiology. Functional assessment of the respiratory system showed normal parameters or mild obstruction, which was disproportionate to the severity of pulmonary hypertension (out-of-proportion PH). In addition, those patients had a significantly reduced DLCO with preserved TLC, that is characteristic for patients with PAH.

Those cases with suspected ‘out of proportion’ PH show, how important is RHC evaluation and proper treatment decisions. The parameters obtained in the RHC, such as mPAP – 33–56 mm Hg, PCWP – 10–13 mm Hg, PVR – 5–18 WU revealed precapillary PH. The overall evaluation of these patients gave us the opportunity to recognize and implement pharmacotherapy of PAH, however the coexisting lung disorder cannot be omitted. We used vasodilators in the current four patients for several reasons. Firstly, all four patients noted progressive clinical symptoms of PH and right heart failure, with RHC measurements fulfilling the recent criteria of at least moderate PAH. Furthermore, the imaging and functional tests did not reveal lung abnormalities that may be responsible for

the deterioration of pulmonary hemodynamics and critically impaired functional capacity. However the applied pharmacotherapy did not have a satisfactory long-term effects and only temporarily reduced symptoms. The degree of hemodynamic improvement was noticed in three cases – in one of them mPAP decreased from 56mmHg to maximum 45mmHg, and CO increased from 2,8 l/min to 6,5 l/min. An important problem in hypoxic PAH patients is deterioration of hypoxia when using vasodilators. The underlying pathomechanism is that vasodilators may cause a dilatation of vessels in hyperinflated lung areas resulting in the ventilation-perfusion mismatch and hypoxia [1]. This phenomenon was observed in patient, who deteriorated after the increase of a treprostinil dose, despite an improvement of CO and a decrease of PVR.

This article also highlights a difficult problem of PAH coexistence with the hypoxic respiratory failure, that required LTOT. Oxygen administration has been demonstrated to reduce the PVR in patients with PAH [18], however there is a lack of randomized trials to confirm LTOT as beneficial. The majority of PAH patients, except those with CHD and pulmonary-to-systemic shunts, have minor degrees of arterial hypoxemia at rest [1]. The recommendations on oxygen therapy in patients with lung disease – COPD, suggest oxygen supplementation when arterial blood oxygen pressure is consistently less than 8 kPa (60 mm Hg), to achieve level of 8 kPa for at least 15 h/day [18]. Therefore LTOT should be considered when there is an evidence of a low arterial oxygen saturation at rest and possible benefits from this supportive therapy are expected.

The following cases illustrate how complex and ambiguous the image of PH may be and how difficult it is to determine the share of individual components in the etiology of disease, particularly lung disorders. The few months of observation showed, that the applied therapy allowed only for a slight reduction of symptoms without a significant improvement in functional and hemodynamic parameters. This suboptimal effect of the pharmacotherapy can be associated with the pulmonary component, but the main pathomechanism has still not been defined.

A limitation of the study was the small number of cases. Each of them presents different clinical manifestation of PH as well as various treatment of the lung disease component. Another aspect is the lack of histopathological analysis, that is crucial for proper diagnosis.

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