VIA MEDICA

INVITED REVIEW

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# Pulmonary hypertension in the course of diffuse parenchymal lung diseases — state of art and future considerations

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## Abstract

Lung diseases are one of the most frequent causes of pulmonary hypertension (PH). The development of PH influences the course of lung disease, worsening the clinical symptoms and prognosis. According to the most recent publications, PH in the course of lung diseases develops as a result of both "parenchymal" and vascular pathology, in the patients with genetic predisposition. Prolonged infection (especially viral one) may be an additional promoting factor. Right heart catheterization (RHC), which is an invasive procedure, is the only objective method of diagnosing PH. According to the latest recommendations, the management algorithm of PH and coexisting interstitial lung disease is based on RHC and the results of pulmonary function tests. Majority of the patients develop mild PH in the course of advanced lung disease. Best treatment of underlying lung pathology combined with long term oxygen treatment is recommended in this group. In case of severe PH (mean resting pulmonary artery pressure (mPAP) $\geq$ 35 mm Hg) the alternate cause of PH has to be sought. PAH-specific drugs use should be limited to patients with severe PH participating in clinical trials.
In this review, the value of various non-invasive methods (echocardiography, radiological examination, exercise capacity and brain natriuretic peptides assessment) in the process of screening for PH is presented, and the results of recent randomized clinical trials with PAH-specific drugs in patients with diffuse parenchymal lung diseases are discussed.

**Key words:** pulmonary hypertension, idiopathic pulmonary fibrosis, diffuse parenchymal lung diseases, diagnosis, treatment

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## Introduction

Lung diseases are one of the most frequent causes of pulmonary hypertension (PH). The development of PH influences the course of lung disease, worsening the clinical symptoms and prognosis [1]. Despite much progress in the recognition, differential diagnosis and treatment of PH, there are still many doubts concerning the optimal diagnostic and therapeutic algorithms in PH due to lung pathology. In the present review we try to summarize the present status of knowledge and discuss future directions of research in this field.

## Classification of PH in the course of diffuse parenchymal lung diseases

The latest classification of PH was published in JACC after the Fifth World Symposium on Pulmonary Hypertension held in Nice in February 2013 [2]. The causes of PH were classified, as previously, into 5 groups: 1 — pulmonary arterial hypertension (PAH), 2 — PH due to left heart disease (venous, postcapillary PH), 3 — PH due to lung diseases and/or hypoxia, 4 — chronic thromboembolic pulmonary hypertension (CTEPH) and 5 — PH with unclear, multifactorial mechanisms (Table 1). The group 1' consisting of

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**Table 1. Current classification of pulmonary hypertension [2]**

| |
|---|
| 1. Pulmonary arterial hypertension |
| 1.1. Idiopathic PAH |
| 1.2. Heritable PAH |
| 1.2.1. BMPR2 |
| 1.2.2. ALK-1, ENG, SMAD 9, CAV1, KCNK3 |
| 1.2.3. Unknown |
| 1.3. Drug and toxin induced |
| 1.4. Associated with: |
| 1.4.1. Connective tissue disease |
| 1.4.2. HIV infection |
| 1.4.3. Portal hypertension |
| 1.4.4. Congenital heart diseases |
| 1.4.5. Schistosomiasis |
| 1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis |
| 1″ Persistent pulmonary hypertension of the newborn (PPHN) |
| 2. Pulmonary hypertension due to left heart disease |
| 2.1. Left ventricular systolic dysfunction |
| 2.2. Left ventricular diastolic dysfunction |
| 2.3. Valvular disease |
| 2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies |
| 3. Pulmonary hypertension due to lung diseases and/or hypoxia |
| 3.1. Chronic obstructive pulmonary disease |
| 3.2. Interstitial lung disease |
| 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern |
| 3.4. Sleep-disordered breathing |
| 3.5. Alveolar hypoventilation disorders |
| 3.6. Chronic exposure to high altitude |
| 3.7. Developmental lung diseases |
| 4. Chronic thromboembolic pulmonary hypertension (CTEPH) |
| 5. Pulmonary hypertension with unclear multifactorial mechanisms |
| 5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy |
| 5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis |
| 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders, |
| 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH |

BMPR — bone morphogenic protein receptor type II; CAV1 — caveolin-1; ENG — endoglin; HIV — human immunodeficiency virus; PAH — pulmonary arterial hypertension

pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH) remained unchanged, and group 1" including persistent PH of the newborn was additionally listed.

According to this classification, PH in the course of various diffuse parenchymal lung diseases (DPLD) is still listed in different groups: due to idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), other types of interstitial pneumonia, hypersensitivity pneumonitis (HP), eosinophilic pneumonitis, and pulmonary alveolar proteinosis — in the group 3, due to sarcoidosis, pulmonary Langerhans cells histiocytosis (PLCH), lymphangioleiomyomatosis (LAM) and vasculitis — in the group 5, due to connective tissue diseases with predominant vascular involvement — in the group 1. Such classification was a consequence of the belief that distinct pathophysiological mechanisms were responsible for PH development in different nosological types of lung disease, but in the light of new experimental data this way of thinking may be out of date.

## Pathobiology of PH in the course of DPLD

The established model of PH in the course of DPLD was the one related to vascular remodeling due to interstitial pathology and/or hypoxia [3]. Nevertheless, the presence of vascular pathology in the areas of minor interstitial lung disease, and the occurrence of PH in the early stage of disease in patients without substantial hypoxemia, indicate the more complex pathogenesis. Recent studies suggest the role of alveolar epithelial cells, fibroblasts, and vascular cells in PH development [4]. In IPF the process is initiated by fibrocytes bearing CD34 or CD45 markers, derived from the bone marrow or from the population of pulmonary steam cells, responsible for inducing collagen production and recruitment of profibrogenic inflammatory mediators [5–7]. The process seems to be regulated by a large variety of angiogenesis promoters and inhibitors as well as growth factors.

The animal model of progressive interstitial pulmonary fibrosis and associated pulmonary hypertension was described recently by Jarman et al. as a result of increased activity of TGF$\beta$ signaling pathway [8]. The fibrotic foci adjacent to areas of alveolar injury and vascular remodeling were combined with profibrotic microenvironment with elevated levels of matrix metalloproteinases (MMP2, MMP7 and MMP12), PDGF$\beta$ and chemokines (CCL2, CXCL12), resulting in secondary recruitment of macrophages, mast cells and fibrocytes [8].

**Table 2. Prevalence of pulmonary hypertension in different interstitial lung diseases (based on RHC evaluation)**

| Type of ILD | Sample size | mPAP > 25 mm Hg(%) | mPAP > 40 mm Hg(%) | Author [ref] |
|---|---|---|---|---|
| Sarcoidosis | 130 | 54% (venous in 15%) | | Baughman [27] |
| Sarcoidosis | 50 | 6% | | Rizatto [25] |
| Sarcoidosis end-stage | 363 | 73.8% | 36% | Shorr [26] |
| IPF early-stage | 61 | 8% | | Hamada [17] |
| IPF early-stage | 232 | 11% | | Raghu [18] |
| IPF end-stage | 2525 | 46% | 9% | Shorr [20] |
| IPF end-stage | 626 | 43% | | Modrykamien [21] |
| IPF end-stage | 72 | 32% | 2% | Lettieri [19] |
| SSc | 3818 | 9% | | Avouac [28] |
| SSc | 1483 | 15–18% | | Hunzelman [29] |

ILD — interstitial lung disease; IPF — idiopathic pulmonary fibrosis; SSc — systemic sclerosis; mPAP — mean pulmonary artery pressure

The pathomorphological signs of lung injury in humans, with different type and degree of concomitant vessels remodeling, depend among others, on individual predisposition, probably related to genetic or epigenetic changes. Hoffman et al. described recently the altered genes belonging to retinol metabolism pathway or extracellular matrix receptor pathway in the lungs explanted due to pulmonary hypertension in the course of IPF [9].

Viral antigens could play a role in promoting vascular changes. Such model of PH was previously described in HIV patients [10]. Calabrese et al. demonstrated lately the presence of herpes virus genetic material in lungs of patients with IPF, and the correlation between the presence of viral material and degree of PH [11].

The pathomorphological analysis of material obtained from postmortem examination or from explanted lungs of the patients with PH revealed the presence of both vascular and parenchymal pathology in IPF, sarcoidosis, PLCH and connective tissue diseases (CTD) [12–15]. The vascular changes disproportionate to parenchymal lung disease were frequently found in the course of CTD [12] and occasionally in sarcoidosis and PLCH [14, 15]. On such circumstance, the clinical picture may be more similar to that found in PAH, with severe PH and mild lung disease only. Moreover, fibrous remodeling of the pulmonary veins mimicking PVOD has been frequently found in systemic sclerosis (SSc) and PLCH [12, 16] and occasionally in IPF and sarcoidosis [13, 14].

On the other hand, an extensive fibrotic process in the course of IPF may be responsible for mild PH only, observed in the end-stage disease. The recognition of different phenotypes of PH within the population of patients with lung diseases will be an important task for the future, enabling the classification of PH according to dominating pathogenic process in lungs, and not according to nosological type of disease.

## Epidemiology of PH in the course of DPLD

The published data concerning the frequency of PH on right heart catheterization regarded mostly patients with end stage DPLDs, and only occasionally with an early stage (Table 2). In IPF, PH was found in 8–11% of patients with early stage disease [17, 18], 32–46% of those with advanced disease [19–21], and even in 86% of patients at the time of referral for lung transplantation [22]. In majority of the patients mPAP was within 25–40 mm Hg, mPAP, exceeding 40 mm Hg was found in only 2–9% of the patients [19, 20]. The prevalence of PH is probably the highest (approaching 50% of the patients) in the distinct IPF phenotype — combined pulmonary fibrosis and emphysema (CPFE) [23, 24].

In sarcoidosis, overall prevalence of PH according to Rizatto et al. was 6% [25], in stage IV disease — 38–51% [26, 27], in the patients referred for lung transplantation — 73,8% [26].

In PLCH, PH was very common in late stages of the disease (92–100%) [15, 16], nevertheless there is not much data concerning its early stage.

Among CTD, scleroderma is the one with the highest predisposition to PH development. The overall prevalence of PAH diagnosed on RHC is 8–18% [28, 29].

## Diagnostic algorithm and differential diagnosis of PH in the course of DPLD

### Screening for PH in DPLDs

The only indication for screening for pulmonary hypertension in the patients without the symptoms of PH concerns scleroderma patients [30]. The rationale of this approach is combined with the possibility of active treatment of PAH in this group of patients. The indications for screening, established during the Nice Conference, concern SSc spectrum of diseases (SSc, mixed connective tissue disease) with diffusion capacity for carbon monoxide (DLCO) ≤ 60% pred. and the disease duration exceeding 3 years [30]. The proposed algorithm was similar to the one published by Coghlan et al. in DETECT study [31]. The first step included assessment of the presence of: telangiectasia, anticentromere antibodies, righ-axis deviation on ECG, low DLCO, elevated serum of uric acid and increased brain natriuretic propeptide (NT-proBNP) concentrations. The second step included echocardiographic examination, and finally the diagnosis of PH was verified by RHC. This algorithm allowed for much lower rate of missed PAH cases (4%) comparing to the algorithm proposed by European Society of Cardiology (ESC) based on echocardiography alone (29%) [31]. The value of this approach is not known in other CTDs and in patients with DLCO > 60% pred.

### Early recognition of PH in DPLD

The rationale for the early recognition of PH in the course of DPLD is based on several facts:

1. The risk of bleeding during diagnostic lung biopsies is higher in PH patients.
2. The presence of PH in the patient with hypoxemia is a strong indication for the long term oxygen therapy (LTOT).
3. PH significantly worsens the prognosis of DPLD and should be taken into account as an additional indication for lung transplantation in end-stage DPLD in otherwise suitable patients.
4. The patients with documented severe PH in the course of DPLDs have the possibility to enter randomized clinical trials with PAH -specific treatment.

PH in the course of DPLD develops in majority of patients in advanced disease stage. Most patients complain of worsening dyspnea and limited exercise tolerance. Such symptoms are non-specific and may be caused by the progression of DPLD. The signs of right ventricular insufficiency, which are more specific for PH, indicate the advanced pulmonary hypertension. Thus the attempts of predicting PH based on the results of pulmonary function tests (PFT), exercise capacity and radiological presentation have been made by many authors. Most published data concern the diagnostic value of: plethysmography and DLCO, blood gas analysis, exercise capacity, radiological presentation.

*Plethysmography and DLCO*

The pattern of disturbances in PFT depends on the type of DPLD. In sarcoidosis, significant PFT abnormalities appear usually in advanced stage of the disease (stages III and IV) and concern 60% of patients [32]. The most typical is a restrictive PFT pattern ( TLC< lower limit of normal — LLN), occasionally with coexisting bronchial obstruction ($FEV_1$/FVC< LLN) [32]. An obstructive pattern is caused by either bronchial hyperreactivity or extrinsic compression of large bronchi by enlarged lymph nodes. In the latter situation, the obstruction is usually irreversible. DLCO is lowered proportionally to PFT disturbances. In HP, a restrictive pattern is predominating; nevertheless, large proportion of patients present with bronchial obstruction and hyperinflation due to air-trapping. Decreased DLCO is a sensitive marker of the lung disease. In IPF, the plethysmography reveals a restrictive pattern with concomitant DLCO lowering in most cases.

According to many published data, the development of PH should be suspected in patients with DLCO decreased disproportionally to the degree of PFT disturbances [17–20, 33]. The criterion of low DLCO used for PH prediction was the value below 40% pred. [17].

The other possibility of predicting PH was based on carbon monoxide transfer coefficient (Kco) value. Kco is diffusing capacity corrected for alveolar volume (VA). In patients in whom low DLCO is caused mostly by interstitial lung disease, DLCO and VA are usually proportionally decreased. If vascular pathology predominates, the decrease of DLCO is greater than the decrease of VA. Thus, in the patients with PH in the course of DPLDs, Kco should theoretically be lower than in the patients with ILDs without PH. Nevertheless, Zisman et al. didn't find significant difference of Kco between the IPF patients with PH confirmed by RHC and those without PH [33].

The best strategy in everyday practice would be close PFT monitoring in DPLD and early identification of cases with DLCO decreasing disproportionally to volume parameters.

*Resting blood gases analysis and exercise capacity*

Most patients with severe PH demonstrate low partial oxygen tension of arterialized capillary blood ($PaO_2$), with oxygen hemoglobin saturation ($SaO_2$) lower than 90% [20]. Hypoxemia is very sensitive but nonspecific sign of PH, as most of the patients with advanced DPLDs present with low $PaO_2$ irrespective of the presence or absence of PH.

In patients with PH due to DPLD, decreased exercise capacity expressed as shortened 6-min walk distance and deep desaturation on exertion is observed [19, 34]. The exercise capacity strongly depends on the age, thus the actual distance covered should be expressed as % predicted rather than absolute value.

*Radiological examination*

Pulmonary hypertension may be suspected on base of both conventional chest X-ray examination and chest computed tomography with angiography. Conventional chest X-ray demonstrates the enlarged cardiac silhouette, wide pulmonary artery trunk and main pulmonary arteries with vessels narrowing in distal parts of the lungs. The typical X-ray presentation of PAH is showed in Figure 1A, B. The diagnostic value of chest X-ray in patients with DPLDs is, however, low due to interstitial lung disease and/or lymphadenopathy (Fig. 2).

The criteria of PH recognition on chest CT angiography are composed of: widening of pulmonary artery (PA) (> 29 mm), with PA to ascending aorta (AA) size ratio > 1 [35, 36]. Spruijt et al. found recently the utility of joint radiological criteria: PA/AA ≥ 1 and right to left ventricular dimension ≥ 1.2 in predicting precapillary PH [37]. The radiological features of PH on chest CT angiography in the patient with PAH are presented on Figure 3A, B. Nevertheless, in the patients with DPLDs, the radiological features of PH are usually less expressed than in PAH, and thus they are less sensitive in PH diagnosing [33, 38] (Fig. 4A–C).

*Brain natriuretic peptides*

Brain natriuretic peptides (BNP, NT-proBNP) are frequently implemented in the diagnostic algorithm of PH. The increased serum concentration of NT-proBNP indicates the presence of circulatory insufficiency, but doesn't differentiate between left or right heart failure. Handa et. et. found that in sarcoidosis patients NT-proBNP correlated better with the presence of cardiac sarcoidosis than with the presence of PH [39]. Wiliams et al. found NT-proBNP exceeding 395

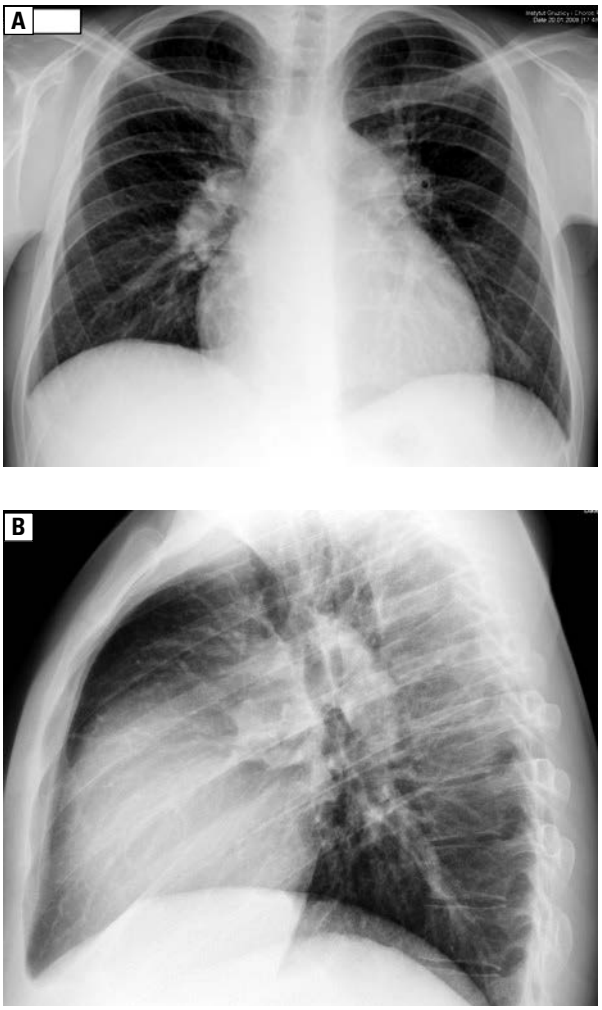


**Figure 1.** Chest X-ray of a patient with idiopathic pulmonary arterial hypertension: **A** — PA, **B** — lateral. Main pulmonary artery and bilateral pulmonary arteries dilatation. Enlarged right ventricle

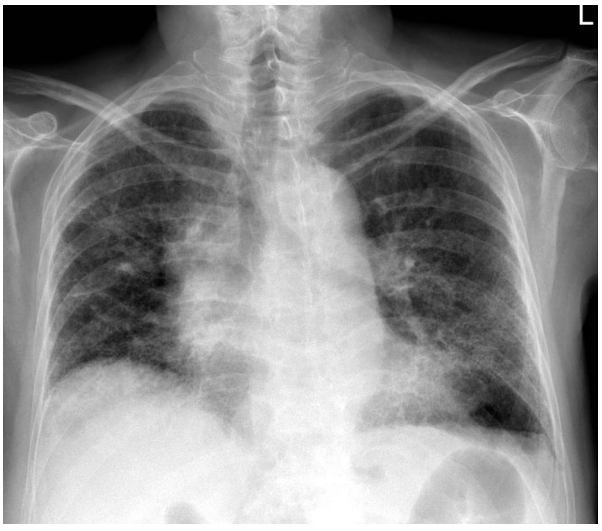


**Figure 2.** Chest X-ray of a patient with usual interstitial pneumonia, PA. Reduced lung volume. Bilateral reticular pattern predominantly involving the lower lung zones. Enlarged hila

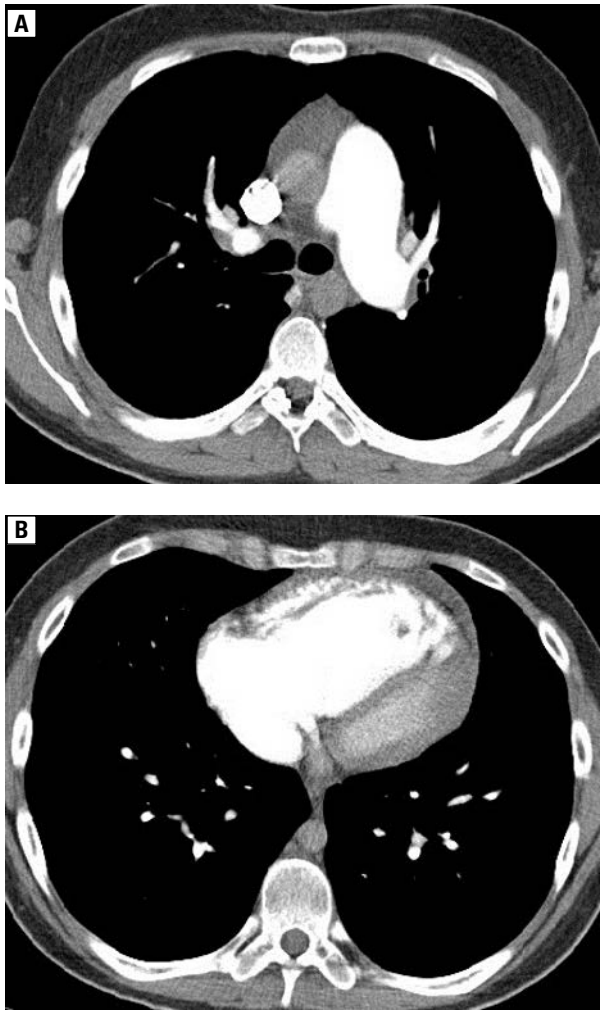


**Figure 3.** Contrast enhanced chest CT of a patient with idiopathic pulmonary arterial hypertension, mediastinal window. Enlarged main pulmonary artery (**A**) and right ventricle (**B**)

pg/ml to be a specific marker of PH in scleroderma patients (95%); unfortunately, the sensitivity of this cut off value was only 56% [40].

Palazzuoli et al. showed that BNP > 50 pg/ml had 77% of sensitivity and 81% of specificity in recognition of PH in the patients with DPLDs participating in ARTEMIS-IPF study [41]

Allanore et al. tried to combine NT-proBNP with Kco %pred for prediction of PAH in SSc. NT-proBNP > 97$^{th}$ percentile of normal and Kco < 60% pred. were independent predictors of PH [42]. The authors concluded that universal NT-proBNP cut off is impossible to establish due to its age and sex dependence [42]. Nevertheless, Thakkar et. al. found that NT-proBNP ≥ 209.8 pg/ml and/or DLCO < 70% pred. and FVC/DLCO ≥ 1.82 were the sensitive (100%) and specific (78%) indicators of PAH in SSc [43].

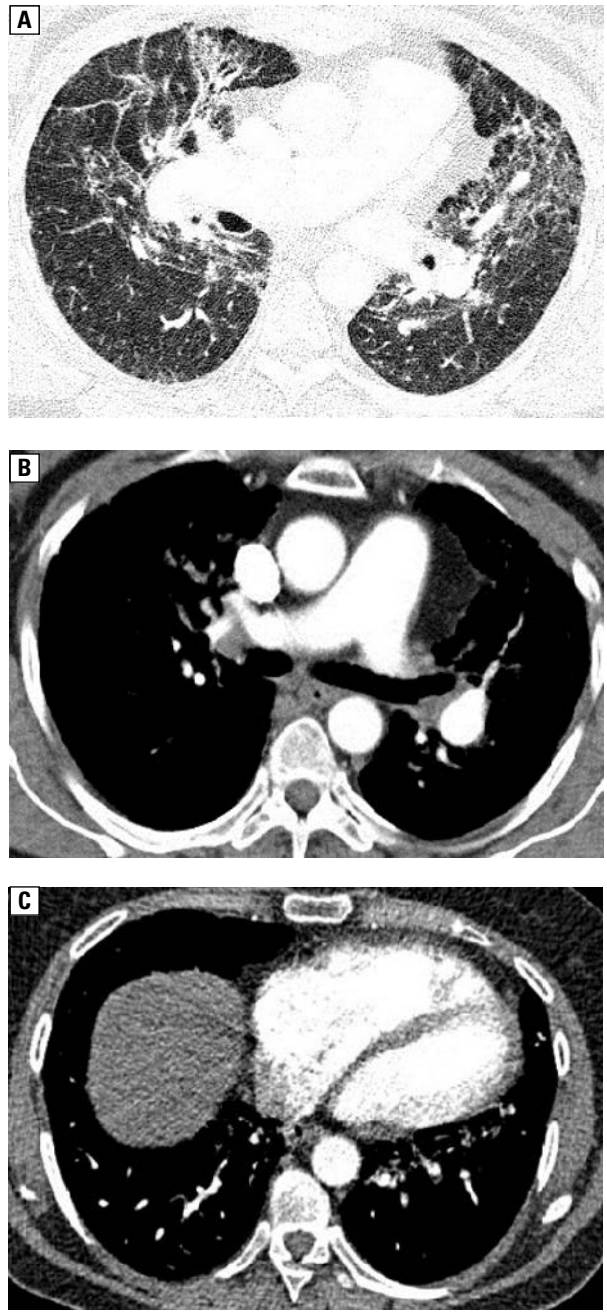


**Figure 4.** Contrast enhanced chest CT of a patient with sarcoidosis with lung fibrosis, lung window (**A** — retraction of the hilar due to irregular reticular and linear opacities; traction bronchiectasis) and mediastital window (**B, C** — features of pulmonary hypertension: dilatation of central pulmonary arteries and right ventricle; enlargement of hilar lymph nodes)

*Echocardiographic examination*

Echocardiography is the most frequently used noninvasive modality for the recognition of PH in DPLDs. Right ventricle systolic pressure (RVSP) and pulmonary artery systolic pressure (PASP) are calculated using the maximal velocity of tricuspid regurgitation jet [44]. The probability of PH based on PASP, according to ESC guidelines, is presented in table 3 [44]. Greiner et al. found

**Table 3. Criteria for pulmonary hypertension based on echocardiography according to ESC [44]**

| TRV [m/sec] | PASP [mm Hg] | Additional PH variables suggestive of PH* | Probability |
|---|---|---|---|
| ≤ 2.8 | ≤ 36 | Lacking | PH unlikely |
| ≤ 2.8 | ≤ 36 | Present | PH possible |
| 2.9–3.4 | 37–50 | Lacking | |
| > 3.4 | >50 | Present or lacking | PH likely |

*Increased velocity of pulmonary vave regurgitation, short acceleration time of RV ejection into the PA, increased dimensions of right heart chambers, abnormal shape and movement of interventricular septum, increased RV wall thickness, dilated main PA; TRV — tricuspid regurgitation velocity; PASP — pulmonary artery systolic pressure; PH — pulmonary hypertension; PA — pulmonary artery; RV — right ventricle

SPAP > 36 mm Hg indicative of PAH on RHC with 87% sensitivity, 79% of specificity, 91.5% of PPV and 70% of NPV in 99 PAH patients [45]. Nevertheless, the diagnostic value of echocardiography in DPLDs is uncertain. The comparison between echocardiographic measures and the parameters obtained on RHC in the patients with lung diseases revealed the discordant results (both underestimation and overestimation) in 50–60% of patients [46, 47]. The optimal RVSP cut off value predictive for PH could not be found by Nathan et. al. in IPF patients; RVSP > 50 mm Hg had 50% sensitivity, 68% specificity, 45% PPV and 72% NPV for the recognition of PH [47].

*Right heart catheterization*

Right heart catheterization (RHC) is the only objective method of diagnosing PH. PH in the course of lung diseases belongs to the category of precapillary pulmonary hypertension, which is defined as mPAP equal or higher than 25 mm Hg, pulmonary artery occlusion pressure (PAOP) not exceeding 15 mm Hg, and pulmonary vascular resistance (PVR) higher than 3 Wood units [1].

RHC is mandatory in the differential diagnosis of PAH; nevertheless, in patients with PH due to lung diseases the indications for RHC should take into account the possible therapeutic gain for a patient. Taking this into consideration RHC is recommended:

1. In end stage lung diseases during the procedure of listing for lung transplantation, especially in the cases with the suspicion of concomitant left heart insufficiency.
2. In patients with echocardiographic suspicion of severe pulmonary hypertension in the course of lung diseases, to exclude the possible influence of left heart insufficiency.
3. In patients who are candidates to randomized clinical trials with PH-specific drugs.

In Nice, the experts decided to abandon the term 'out of proportion PH' in the course of lung diseases and replaced it with the term 'severe PH'[1], which was defined as:

— mPAP equal or higher than 35 mm Hg or
— mPAP equal or higher than 25 mm Hg with CI < 2 l/min/$m^2$.

The document covering this issue was dedicated to COPD, IPF and CPFE. Severe PH in respiratory diseases listed in the group 3 of PH classification was characterized recently as separate phenotype of PH in the Official Statement of American Thoracic Society [48].

It remains uncertain whether the same classification of PH should be applied for the DPLD listed in the group 5 (sarcoidosis, PLCH, LAM, vasculitis).

Severe pulmonary hypertension has been diagnosed in 2-9% of patients with end-stage DPLDs [19, 20]. In such situation, the possible influence of other factors such as venous thromboembolic disease and left heart failure should be excluded.

Recently, Dalleywater et al. found the probability of pulmonary embolism (PE) six times higher and the probability of deep vein thrombosis doubled during 1.7 years of observation in 3211 IPF patients compared to controls adjusted for age, sex, and smoking habit [49]. Swigris et al. found that PE as the cause of death was significantly more frequent in sarcoidosis patients comparing to others (2.54% and 1.13% respectively) [50]. Vorselaars et al. found PE in 6.2% of the patients with severe sarcoidosis requiring immunosuppressive therapy other than corticosteroids [51].

There is no consensus regarding the diagnostic algorithm of VTE in DPLDs , but it seems reasonable to use chest CT with angiography as initial modality. The utility of ventilation-perfusion scintigraphy in the patients with DPLDs is uncertain.

The frequent clinical problem is the exclusion of left heart insufficiency (especially the one with preserved left ventricular ejection fraction on echocardiographic examination) as the

**Table 4. Various causes of PH in the patients with interstitial lung diseases**

| Type of ILD | Lung disease and/ /or hypoxia | VTE | Left heart disease | PAH phenotype | PVOD phenotype |
|---|---|---|---|---|---|
| IPF | +++ | + | ++ | + | + |
| Sarcoidosis | +++ | + | ++ | ++ | + |
| Sysytemic sclerosis | ++ | + | ++ | +++ | ++ |
| PLCH | ++ | ? | ? | ++ | + |
| LAM | ++ | ? | ? | ++ | ? |

+++ most probable; ++ probable; + possible

IPF — idiopathic pulmonary fibrosis; PLCH — pulmonary Langerhans cells histiocytosis; LAM — lymphangioleiomyomatosis; VTE — venous thromboembolism; PAH pulmonary arterial hypertension; PVOD — pulmonary veno-occlusive disease

**Table 5. Differential diagnosis between group 1 (PAH) and group 3 (PH due to lung diseases) [1]**

| Criteria suggestive of PAH | Parameter | Criteria suggestive of PH due to lung disease |
|---|---|---|
| Normal or mildly impaired<br>$FEV_1 > 60\%$ pred. (COPD)<br>FVC > 70% pred. (IPF) | Pulmonary function tests | Moderate to very severly impaired<br>$FEV_1 \leq 60\%$ pred. (COPD)<br>FVC ≤ 70% pred. (IPF) |
| Absence of or only modest abnormalities | HRCT | Characteristic airway and/or parenchymal abnormalities |
| Features of exhausted circulatory reserve, preserved breathing reserve<br>Reduced oxygen pulse<br>Low $CO/VO_2$ slope<br>Mixed venous oxygen saturation at lower limit<br>No change or decrease in $PaCO_2$ during exercise | Exercise cardiopulmonary test and right heart catheterization | Features of exhausted ventilatory reserve, reduced breathing reserve,<br>Normal oxygen pulse,<br>Normal $CO/VO_2$ slope<br>Mixed venous oxygen saturation above lower limit<br>Increase in $PaCO_2$ during exercise |

CO — cardiac output; $VO_2$ — oxygen consumption ratio; $PaCO_2$ — partial pressure of carbon dioxide in arterial blood; HRCT — high resolution CT scan; $FEV_1$ — forced expiratory volume in 1 sec; FVC — forced vital capacity; IPF — idiopathic pulmonary fibrosis; COPD — chronic obstructive pulmonary disease; PAH — pulmonary arterial hypertension; PH — pulmonary hypertension

coexisting cause of PH in the patients with DPLDs [52]. The gold standard is the PAOP measurement on RHC, the values exceeding 15 mm Hg indicate the presence of postcapillary PH. The role of fluid loading or exercise testing in diagnosis of occult left heart disease requires further standardization and validation [52].

The factors possibly influencing PH in the patients with various DPLDs are presented in Table 4.

As mentioned before, the most difficult diagnostic challenge is to differentiate between the PAH with coexisting lung disease and severe PH in the course of lung disease. Badesch et al. found COPD as coexisting pathology in 25% of the PAH patients in REVEAL registry [53]. The radiological signs of DPLD in PAH patients is the common clinical problem. Trip et al. found mild or moderate fibrosis on HRCT in 12% of the patients with IPAH [54].

The algorithm of differential diagnosis proposed during the PH Conference in Nice is based on PFT results, HRCT, cardiopulmonary exercise test and RHC (Table 5) [1]. The phenotype suggestive of pulmonary arterial hypertension in a patient with DPLD includes following features: mild disturbances on PFT (in IPF — FVC higher that 70% pred.), absence or only modest parenchymal abnormalities in HRCT, signs of exhausted circulatory reserve at the end of exercise (low mixed venous oxygen saturation and reduced slope of cardiac output/oxygen consumption ratio) with breathing reserve maintained (low arterial $PaCO_2$) [1].

## Treatment considerations of PH in the course of DPLDs

According to previous ESC guidelines, patients with PH in the course of DPLDs should receive the best treatment for underlying lung disease [44]. Long term oxygen therapy is indicated in case of hypoxemic respiratory insufficiency; nevertheless, there is no proof that such treatment results in the prolongation of life in the patients with PH in the course of DPLD [44]. The patients with end-stage DPLDs who are suitable for lung transplantation should be referred to transplan-

**Table 6. Recommendations concerning management of PH in the patients with lung diseases [1]**

| Clinical characteristics | mPAP < 25 mm Hg | mPAP 25–34 mm Hg | mPAP ≥ 35 mm Hg |
|---|---|---|---|
| $FEV_1 \geq 60\%$ pred. (COPD)<br>FVC ≥ 70% pred. (IPF)<br>HRCT: absence of or modest abnormalities | No PH,<br>No PAH specific treatment recommended | PH classification uncertain<br>No data supporting treatment with PAH specific drugs | PH classification uncertain: discrimination between PAH with concomitant lung disease (group 1) or PH caused by lung disease (group 3)<br>Refer to a center with expertise in both PH and chronic lung disease |
| $FEV_1 < 60\%$pred. (COPD)<br>FVC < 70% pred. (IPF)<br>HRCT: Combined pulmonary fibrosis and emphysema | No PH<br>No PAH specific treatment recommended | PH-COPD, PH-IPF,<br>PH- CPFE<br>No data currently suport treatment with PAH-specific drugs | Severe PH-COPD, severe PH-IPF, severe PH-CPFE<br>Refer to a center with expertise in both PH and chronic lung disease for individualized patient care because of poor prognosis: randomized controlled trials required |

mPAP — mean pulmonary artery pressure; HRCT — high resolution computed tomography; $FEV_1$ — forced expiratory volume in 1 sec; FVC — forced vital capacity; IPF — idiopathic pulmonary fibrosis; COPD — chronic obstructive pulmonary disease; CPFE — combined pulmonary fibrosis and emphysema; PAH — pulmonary arterial hypertension; PH — pulmonary hypertension

**Table 7. Randomized clinical trials concerning the use of PAH-specific drugs in the patients with interstitial lung diseases**

| Author [ref] | Type of ILD | Type of treatment | RCT duration | No of pts | RHC | Primary end-point | Result |
|---|---|---|---|---|---|---|---|
| King [55] | IPF | Bosentan | 12 months | 154 | No data | 6MWT | neg |
| Zisman [57] | IPF | Sildenafil | 12 weeks | 180 | No data | Increase of 6MWD > 20% | neg |
| King [56] | IPF | Bosentan | 12 months | 616 | No data | Time to progression | neg |
| Raghu [18] | IPF | Ambrisentan | 35 weeks | 492 | 11%PH | Time to progression | closed |
| Raghu [59] | IPF | Macitentan | 12 months | 178 | No data | Change of FVC | neg |
| Han [58] | IPF | Sildenafil | 12 weeks | 119 | Echo: RVSD in 19% | 6MWD | In RVSD +99 meters p = 0.04 |
| Corte [61] | fNSIP IPF | Bosentan | 16 weeks | 60 | mPAP > 25 mm Hg | PVR | neg |
| Baughman [60] | Sarcoidosis | Bosentan | 12 months | 35 | mPAP > 25 mm Hg | mPAP | −4 mm Hg < 0.02 |

ILD — interstitial lung disease; RCT — randomized clinical trial; IPF — idiopathic pulmonary fibrosis; fNSIP — fibrotic non-specific interstitial pneumonia; RVSD — right ventricle systolic dysfunction; mPAP — mean pulmonary artery pressure; PVR — pulmonary vascular resistance

tation centers. The presence of severe PH in the course of end-stage lung disease substantially worsens the survival, especially in the patients with IPF and CPFE, thus they should be referred for lung transplantation without any delay.

The recommendations from Nice Conference concerning treatment of PH in lung diseases are summarized in table 6 [1]. PAH-specific treatment is not recommended in the patients with mild PH at rest (mPAP 25–34 mm Hg). The patients with severe PH (mPAP ≥ 35 mm Hg) should be referred to the centers with expertise in both PH and chronic lung diseases. In patients with mild restriction (FVC > 70% pred.), the alternative factor influencing PH should be searched. In those with FVC < 70% pred., the personalized treatment decisions are required. According to published recommendations, the subsets of patients with FVC < 70% and low or normal cardiac output, not adequately increasing on exercise, should be preferably included in randomized clinical trials (RCT) with PAH specific drugs [1].

The overview of RCT with PAH-specific drugs, published between 2008 and 2014, indicates that the patients participating in many trials were not the proper candidates for PAH-specific treatment (Table 7).

The largest RCT trials, Build 1 and Build 3, investigated the efficacy of one year bosentan therapy in IPF patients [55, 56]. Unfortunately, neither echocardiographic assessment of PH nor RHC was performed. The primary end point of the first study (improvement of 6 minutes walking distance) was not achieved [55]. The second study used as a primary end-point time to IPF worsening, defined as IPF acute exacerbation, death,

decrease of FVC ≥ 10% or DLCO ≥ 15% [56]. This study was also negative. The subgroup analysis revealed that bosentan was more effective in the patients with less PFT compromise [56].

Zisman et al. investigated the effect of Sildenafil in the end-stage IPF patients with DLCO < 35% pred (STEP-IPF study) [57]. This study was also lacking RHC. The primary end point (6MWD ≥ 20% improvement) was not achieved, either [57]. In 2013, Han et al. published the results of sub-study of STEP-IPF that included 119 patients in whom echocardiography was available [58]. In 19% of them the signs of right ventricle systolic failure was present. This group achieved a significant improvement in the course of sildenafil treatment, with less decrease of 6MWD compared to placebo, p = 0.01 [58].

Another negative study was published by Rhagu et al., who investigated the effect of macitentan in IPF patients (Music Trial) [59]. The primary endpoint (FVC change) was not achieved.

The inclusion criteria of recently published trials applied hemodynamic assessment ( with PH defined as mPAP > 25 mm Hg). Baughman et al. investigated the effect of bosentan in sarcoidosis patients with PH confirmed on RHC [60]. The primary end point was mPAP assessed after 16 week of treatment. The trial was positive, mPAP in the treatment group decreased by mean of 4 mm Hg compared to placebo group, p = 0.01 [60].

Corte et al. assessed the effect of bosentan in fibrotic NSIP and IPF with PH confirmed on RHC. The primary outcome was the fall of pulmonary vascular resistance by 20% or more over 16 weeks. The study was negative [61].

According to recent recommendations, the candidates to PAH specific treatment should be recruited from the population with severe PH (mPAP p ≥ 35 mm Hg) [1]. There is no data about such trial in DPLDs , nevertheless Saggar et al,. who used intravenous treprostinil in 15 patients with end-stage IPF and severe PH, as a bridging to transplantation, observed the positive effect on RHC [62].

The most important adverse effect of PAH-specific treatment in the patients with lung diseases was hypoxemia, resulting from the inhibition of hypoxic pulmonary vasoconstriction in the poorly ventilated lung areas [63].

Hoeper et al. reported the decrease of $SaO_2$ by 1–2% from baseline in the patients with PH (mPAP > 30 mm Hg) in the course of DPLDs treated with Riociguat in the observational study [64]. Nevertheless, mixed venous oxygen saturation slightly increased.

Corte et al. didn't observe any significant difference in the oxygen saturation and oxygen requirement between bosentan and placebo groups in the patients with IPF and fibrotic NSIP [61]. Zisman et al. found improved oxygenation in the group of IPF patients treated with Sildenafil in the STEP-IPF study [57].

These data indicate that the oxygenation may behave differently during treatment of DPLDs with PAH-specific drugs. Probably the largest desaturation occurs in the patients with the most severe pulmonary disease. On the other hand, in the patients with severe PH and less severe lung disease, the improvement of cardiac output in the course of PAH-specific treatment may balance the saturation decrease due to vasodilatation. Thus, in our opinion, the candidates for the future RCT of PAH-specific treatment should be rather recruited from the population with PAH-like phenotype (mild respiratory disease but severe PH).

Another important issue is the duration of studies and the projected end-points [65]. Taking into consideration the results obtained in the group of PAH patients, the hemodynamic indices and the walking distance may not be the sufficient indicators of the treatment success. The objective end-points of RCT in the patients with PH due to DPLDs, should be the survival time without clinical worsening combined with overall survival and transplantation rate.

The patients with PH coexisting with end-stage lung disease are probably heterogeneous population. Those in whom the decreased life expectancy is caused by exhausted circulatory reserve could benefit from the PAH-specific treatment in the future.

## Conflict of interest

The authors declare no conflict of interest.

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