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# Pulmonary veno-occlusive disease: pathogenesis, risk factors, clinical features and diagnostic algorithm — state of the art

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## Abstract

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) are rare disorders, with the estimated prevalence of less than 1 case per million inhabitants. The vascular pathology in PVOD/PCH involves pre-septal and septal veins, alveolar capillaries and small pulmonary arteries. According to the ERS/ESC classification of pulmonary hypertension (PH) from 2015, PVOD/PCH have been included in the subgroup 1' of pulmonary arterial hypertension (PAH). Recent data indicate, however, the possibility of PVOD/PCH pathology in the patients diagnosed in the group 1. The problem may concern PAH associated with scleroderma, drug-induced PAH, PAH due to HIV infection and up to 10% of patients with idiopathic PAH (IPAH). Recently, bi-allelic *EIF2AK4* mutations were found in the cases with heritable form of PVOD/PCH and in about 9% of sporadic cases. Moreover, an association between occupational exposure to organic solvents and PVOD/PCH was proved. The present review is an attempt to summarise the current data on pathogenesis, risk factors, clinical features and diagnostic algorithm for PVOD/PCH.

**Key words:** pulmonary venoocclusive disease; risk factors; genetic dependence

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## Introduction

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) constitute the subgroup 1' of pulmonary arterial hypertension (PAH) in the clinical classification of pulmonary hypertension (PH) (Table 1) [1]. PVOD and PCH were first described as two distinct diseases; recently, it has been suggested that PCH could be a secondary process in the course of PVOD [2]. Histological examination of a lung specimen remains the gold standard for a definitive diagnosis of PVOD/PCH, but it may be obtained only in the end-stage disease (from explanted lungs) or post-mortem, as lung biopsy is contraindicated in the setting of clinically significant PH, due to high bleeding risk.

The pathological data documented PVOD/PCH in PAH associated with CTD (mainly scleroderma) and with drug induced PAH. Moreover, PVOD/PCH is believed to be an unrecognised cause of pulmonary hypertension in up to 10% of patients diagnosed with idiopathic PAH (IPAH) [1, 3]. The clinical course of disease in such patients may be different from typical group 1 patients: the response to PAH-specific drugs may be worse, occasionally lung oedema in the course of PAH-specific therapy is noted. Due to poor life expectancy, such patients should be promptly qualified for lung transplantation.

Therefore, an urgent need for a non-invasive diagnostic approach to PVOD/PCH recognition is required. Such approach, based on genetic counselling and the results of clinical, pathophysio-

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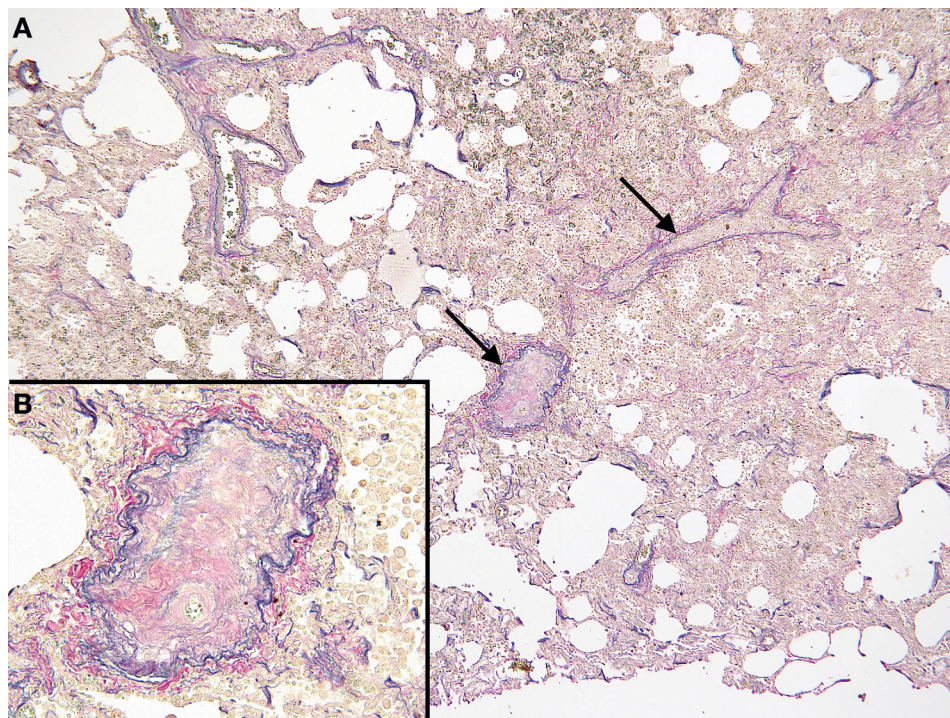
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**Figure 1 A, B.** Pulmonary veno-occlusive disease. **A** — almost totally occluded veins are seen within interlobular septa (arrows) at low magnification. Surrounding alveolar spaces show hemorrhage; **B** — medium-power magnification of one of the veins: the lumen of the vessel (a space inferiorly to the black stained elastic fiber layer) is clearly narrowed and filled with a fibrotic tissue (Elastic van Gieson stain, magn.  $\times 40$  (A) and 200 (B))

logical, radiological, and bronchoalveolar lavage examinations, has been proposed recently [4, 5]. The present review is an attempt to summarise the data on pathogenesis, risk factors, clinical features and diagnostic algorithm for PVOD/PCH.

### Pathology of PVOD/PCH

The vascular pathology in PVOD/PCH involves pre-septal and septal veins, alveolar capillaries and small pulmonary arteries (Figs 1, 2). Small pulmonary veins and venules become narrow or obliterated as a result of thrombosis, usually organised and seen as intensive intimal fibrosis. The veins become arterialised, i.e., the normal single layer of elastic fibres in vein walls is doubled or even tripled, mimicking pulmonary arteries. Sometimes elastic fibres can be encrusted with iron and calcium deposits. Reactive granulomas formed by multinucleated giant cells often surround such deposits [3]. Alveolar capillaries are changed due to downstream obstruction, with their dilatation and proliferation. This angioproliferative process is called PCH [2]. Pulmonary haemorrhages due to venous obstruction result in the accumulation of haemosiderin — laden macrophages. The inter-

stitial oedema or mild fibrosis of the interlobular septa is also seen [2].

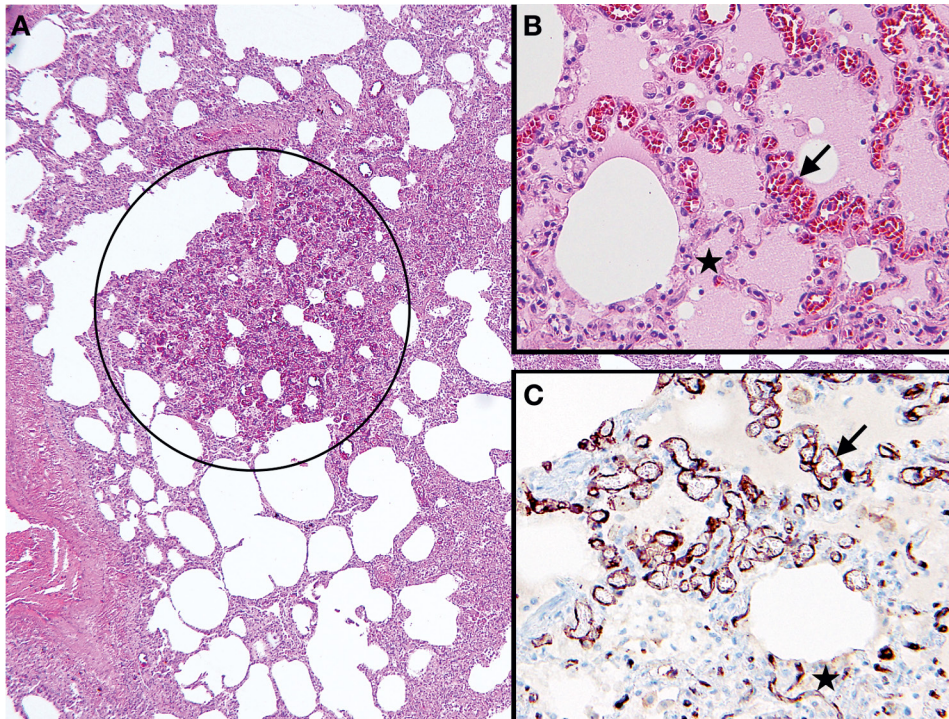
Arterial lesions in PVOD/PCH are similar to PAH and include intimal fibrosis, medial hypertrophy and thrombotic occlusion; however, plexiform lesions typical of PAH are not present [2, 3].

PVOD/PCH pathology described above has been found either in the patients with isolated pulmonary vascular disease or in connection with other conditions such as: scleroderma [6], pulmonary Langerhans cell histiocytosis (PLCH) [7] or rarely — sarcoidosis [8, 9]. Recently, PVOD/PCH was also reported in a patient with diffuse lung emphysema and severe pulmonary hypertension [10].

### Genetic alterations in PVOD/PCH

In 2014, bi-allelic, autosomal recessive mutations of the eukaryotic translation initiation factor 2alpha kinase 4 (*EIF2AK4*) gene were identified in the families with heritable PVOD by Eyries *et al.* [11]. *EIF2AK4* mutation has been confirmed in all patients with heritable form of PVOD and in about 9% of sporadic cases [12]. Moreover, this type of genetic alteration was absent in the control group of PAH patients. Best *et al.* [13] also found *EIF2AK4* mutation in the patients with





**Figure 2 A–C.** Pulmonary capillary hemangiomas. **A** — at low power, one of multiple foci of “hyperemia-like area” can be noted (circle); **B** — at higher power, the lesion is composed of irregular in shape, dilated capillary structures (arrow) filled with blood that clearly differ from normal interalveolar septa (asterisk); **C** — the same area as in B — immunohistochemical reaction to CD34 highlights the endothelium (arrow) and normal capillaries (asterisk) (A: hematoxylin and eosin staining, magn.  $\times 40$ ; B: hematoxylin and eosin staining, magn.  $\times 200$ ; C: anti-CD34 immunohistochemical reaction, magn.  $\times 200$ )

familial occurrence of PCH [13]. The same type of mutation was identified by Tenorio *et al.* [14] in 5 Iberian Gypsy families with an aggressive form of PAH that developed in a young age [14]. These families were of Gypsy-Romantic ethnicity, with high rate of co-sanguinity due to endogamy. The authors have not found any genetic alterations in TGF beta family in the above mentioned ethnic group [14].

Best *et al.* [15] found bi-allelic *EIF2AK4* mutations in 1 out of 9 hereditary PAH (hPAH) patients, and none of 72 IPAH patients.

Recently, Hadinnapola *et al.* [16] performed whole genome sequencing in 808 patients with IPAH, 56 with hPAH and 16 patients with PVOD/PCH. Bi-allelic mutations of *EIF2AK4* were identified in 5 PVOD/PCH patients and in 9 IPAH patients (1%). Interestingly, *EIF2AK4* positive IPAH patients, investigated both by Best *et al.* [15] and by Hadinnapola *et al.* [16], exhibited clinical symptoms that might be indicative of PVOD/PCH.

Woerner *et al.* [17] reported on 9 cases of histologically confirmed PVOD in children (mean age 13.5 years, range 8–16 years). Unfortunately, mutation status was not investigated in them. Recently, Levy *et al.* [18] found *EIF2AK4* mutation

in 2 out of 3 children with PVOD presenting as severe refractory pulmonary precapillary hypertension.

### Occupational dependence of PVOD/PCH

In 2015, Montani *et al.* reported on the association between occupational exposure to organic solvents and PVOD [5]. A case control study conducted among 33 consecutive PVOD patients and 65 PAH patients as controls revealed significantly higher prevalence of occupational exposure to organic solvents in PVOD patients, compared to PAH patients (72.7% vs 27.7%, respectively). Exposure to trichloroethylene was significantly more frequent in PVOD compared to PAH (42% vs 3%, respectively) [5]. The trichloroethylene use was reported mostly by: metal workers, mechanics and repairers, building painters and cleaners. Other exposures included degreasing agents, paints and varnish/glue. Occupational exposure to organic solvents was more frequent in men and in the older age group. The questionnaire also revealed a significantly higher tobacco exposure in PVOD compared to PAH patients (total pack-years  $33 \pm 24.7$  vs  $8.0 \pm 14.3$  respectively) [5].

## PVOD/PCH in the course of other pathologies

PVOD/PCH may also be induced by chemotherapeutic agents and/or radiation. Ranchoux *et al.* [19] presented the summary of clinical findings in chemotherapy-induced, histologically confirmed PVOD. It was based on 10 cases from the French PH network and 27 cases published in the literature. PVOD occurred in the course of chemotherapy of both solid tumours (breast, lung, brain) and haematologic malignancies (Hodgkin and non-Hodgkin lymphoma, acute lymphoblastic and myeloid leukaemia). Most patients received the regimens composed of several drugs, with alkylating agents use in 83.8% of cases, antimetabolites in 40.5%, plant alkaloids and other naturally occurring molecules in 45.9%, as well as cytotoxic antibiotics in 43.2% [19]. Alkylating drugs, most frequently related to PVOD development included the following: cyclophosphamide, mitomycin C (MMC) and cisplatin, especially when combined with additional radiotherapy or allogeneic stem cell transplantation [19]. The ability of cyclophosphamide to induce PH was confirmed by the authors in animal models [19]. Subsequently, the same group of authors reported on 7 cases of chemotherapy-induced PVOD in patients with squamous cell anal carcinoma, who received MMC alone or in combination with 5-fluorouracil [20].

Another causes of PVOD/PCH are HIV infection and connective tissue diseases [1]. Dorf-muller *et al.* analysed lung samples obtained post-mortem or from the explanted lungs of 8 patients with PAH associated with CTD and 29 IPAH patients [6]. Fibrous remodelling of pulmonary venules was found in 75% of cases of PAH associated with CTD and 17% of IPAH specimens. Scleroderma was the most frequent CTD linked with PAH.

The group of conditions that can be associated with PVOD/PCH also includes interstitial lung diseases — PLCH [7] and sarcoidosis [8, 9], autoimmune diseases such as Hashimoto's thyroiditis [21], haematopoietic stem cells transplantation [4] and other haematologic malignancies (polycythemia vera) [22].

## Epidemiology

PVOD/PCH is a rare disease, with the estimated incidence rate of 0.2–0.5 cases per million inhabitants per year [1]. Nevertheless, the true incidence is possibly higher as 3–12% of cases classified as idiopathic PAH exhibit various

clinical features suggestive of PVOD/PCH [1, 3]. In addition, the cases associated with other conditions or drugs/toxins-induced are also missing in the statistics.

## Diagnosis of PVOD/PCH

### Age and sex

Distribution of age at PVOD/PCH diagnosis is bimodal. The first peak is observed at the age of 20–30, and it probably reflects the genetic dependence of the disease. Montani *et al.* [23] compared phenotypes of PVOD with and without *EIF2AK4* mutation. The mutation carriers were significantly younger compared to non-carriers (median age 26 vs 60 years, respectively) [23]. The second peak is observed at the age of 70–80, which is more typical of all the secondary causes of PVOD/PCH. The heritable cases are diagnosed with the same frequency among men and women, the occurrences associated with occupational exposures are more frequent in males than in females [23].

### Clinical presentation

Clinical presentation of PVOD/PCH is in many aspects similar to PAH. Dyspnoea on exertion, syncope and heart palpitations are common. Digital clubbing is more frequent in PVOD/PCH compared to PAH [1]. On auscultation, bi-basal crackles may be heard due to lung congestion, while they are unusual in PAH [1, 24].

### Lung function, gas exchange and exercise testing

The presence of lung congestion in addition to pulmonary hypertension in PVOD/PCH worsens the gas exchange in the lungs. Thus, PVOD/PCH patients present with more profound resting hypoxaemia, deeper exercise desaturation and lower lung diffusion capacity for carbon monoxide compared to PAH patients [1,24].

### Radiological features of PVOD/PCH

The chest X-ray is of limited value, in the diagnostic algorithm for PVOD/PCH. High resolution computed tomography of the chest (HRCT) is the study of choice. It reveals the presence of three characteristic features of PVOD/PCH: smooth thickening of interlobular septa, ill-defined centrilobular ground glass opacities and mediastinal lymph nodes enlargement [1] (Fig. 3A, B).

Resten *et al.* [25] compared HRCT findings of 15 patients with confirmed PVOD and 15 IPAH patients. They found ground glass opacifications



**Figure 3A, B.** PVOD in 35-year old man, computed tomography of the chest (CT); **A** — high resolution CT image (lung window level) shows interlobular septal thickening and diffuse bilateral patchy ground glass opacities. There is no pleural effusion noted; **B** — angio CT image (mediastinal window level) shows dilated pulmonary trunk and proximal central pulmonary arteries — signs of pulmonary hypertension

in 87% vs 33% cases, septal lines in 93% vs 13% of cases, and enlarged mediastinal lymph nodes in 80% vs 0%, respectively [25]. All the differences were statistically significant.

Gunther *et al.* [26] analysed retrospectively HRCT data from 26 systemic sclerosis (SSc) patients with precapillary PH and compared them to 28 SSc patients without PH or interstitial lung disease. They found lymph node enlargement in 57.7% vs 3.6%, centrilobular ground glass opacities in 46.6% vs 10.7% and septal lines in 88.5% vs 7.1% of the patients in these two groups respectively [26]. All the differences were statistically significant. Moreover, in 61.5% of SSc patients with precapillary PH, at least two of radiologic features coexisted [26]. At present, the thickening of interlobular septa in HRCT is considered the most specific radiological feature of PVOD/PCH.

Ill-defined centrilobular ground glass opacifications are probably most frequent, although less specific, because they are also occasionally observed in IPAH. In our own group of IPAH patients, centrilobular nodules as the only parenchymal lung abnormality on HRCT were found in 19% of the cases [27]. Their presence was related to the lower mean age, lack of the persistent foramen ovale, and the higher mean right atrial pressure compared to IPAH patients with no centrilobular nodules [27]. There is no consensus on the pathogenesis of centrilobular ground glass opacifications. Some authors state that they may be caused by the presence of cholesterol granulomas due to occult pulmonary haemorrhage [28]. In PCH, centrilobular nodules may be dominating over other radiological signs [29]. Miura *et al.* [30] found that the centrilobular nodules in PCH are significantly larger than in PVOD [30].

Enlarged mediastinal lymph nodes develop as a result of venous lung congestion, veno-lymphatic shunts and angiogenic factors [31]. They are usually observed in combination with other radiological features of PVOD/PCH [26]. De Montpreville *et al.* [31] reviewed pulmonary and mediastinal lymph nodes resected during lung transplantation in 19 PVOD/PCH patients and found lymphatic congestion, vascular transformation of the sinuses, intra-sinusal haemorrhage and lymphoid follicular hyperplasia [31].

The presence of at least two from the above mentioned features on HRCT study of the lungs rises suspicion of PVOD/PCH, and the existence of all three findings has 100% specificity and 66% sensitivity for PVOD/PCH in cases of PAH [1].

#### *Lung scintigraphy as diagnostic tool in PVOD/PCH*

The guidelines recommend the use of ventilation-perfusion lung scintigraphy in the differential workup of PH to differentiate between PAH and chronic thromboembolic pulmonary hypertension (CTEPH) [1]. The presence of unmatched segmental perfusion defects is typical of CTEPH, but not of PAH. According to some authors, multiple unmatched segmental perfusion defects may be also found in PVOD patients [32]. Nevertheless, recent retrospective double blind analysis performed in 70 IPAH/hPAH and 56 PVOD patients, documented unmatched perfusion defects in 10% of IPAH and 7% of PVOD patients [33]. Thus, according to the present state of knowledge, the ventilation-perfusion scans are not helpful in distinguishing PAH from PVOD/PCH, although they are still very important to distinguish CTEPH from PAH [1].

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

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 disease
    - 1.4.5. Schistosomiasis
- 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
  - 1'.1. Idiopathic
  - 1'.2. Heritable
    - 1'.2.1. EIF2AK4 mutation
    - 1'.2.2. Other mutations
  - 1'.3. Drugs, toxins and radiation induced
  - 1'.4. Associated with:
    - 1'.4.1. Connective tissue disease
    - 1'.4.2. HIV infection
- 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) and other pulmonary artery obstructions
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; EIF2AK4: eukaryotic translation initiation factor 2 alpha kinase 4; HIV: human immunodeficiency virus; PAH: pulmonary arterial hypertension

### *Bronchoalveolar lavage*

Occult alveolar haemorrhage may happen in PVOD/PCH due to capillary pathology and lung congestion. The proof of this concept was published by Rabiller *et al.* [34] who found the increased percentage of haemosiderin — laden macrophages in bronchoalveolar lavage fluid (BALF) of PVOD patients compared to PAH patients ( $40 \pm 37\%$  vs  $3 \pm 6\%$ ) [34]. The intensity of haemosiderin staining per 100 macrophages (Golde score) was calculated as  $81 \pm 88$  in PVOD and  $4 \pm 10\%$  in PAH [34].

The induced sputum Golde score was also found to be diagnostic tool in the patients with

PVOD suspicion by Lederer *et al.* [35]. The authors proposed the Golde score of 200 as the cut off value indicating the possibility of occult alveolar haemorrhage [35]. The validation of this method in PVOD diagnosis has not been provided yet; nevertheless, it is promising in the patients with severe hypoxaemia, who are at high risk of bronchoscopy complications.

### *Haemodynamic evaluation*

Right heart catheterisation (RHC) is mandatory for the recognition of PAH. As PVOD/PCH involves small pulmonary veins, pulmonary artery wedge pressure remains usually below

15 mm Hg. Thus, PVOD/PCH patients fulfil the criteria of precapillary PH [3]. Nevertheless, due to increased pressure in small pulmonary veins and capillaries, lung oedema may develop in the course of acute vasoreactivity testing on RHC or after the introduction of PAH-specific therapy [1, 3]. In a case-series published by Montani *et al.*, lung oedema in the course of PAH-specific therapy was observed in 21–23% of patients with PVOD/PCH [23].

### Recommended PVOD diagnostic criteria

New PVOD diagnostic algorithm was proposed recently by Montani *et al.* [5]. The authors introduced subsequent definitions:

#### Confirmed PVOD

1. The presence of characteristic pathological features in the lung tissue obtained from the explanted lung or on post-mortem examination.
2. The presence of a bi-allelic *EIF2AK4* mutation in the patients with pulmonary arterial hypertension.
3. Pulmonary oedema following the introduction of PAH-specific therapy in the patient with clinical signs of highly probable PVOD.

### Highly probable PVOD

The patients fulfilling at least two of the following criteria:

1. Two or more characteristic radiological signs of PVOD described on HRCT (septal lines, centrilobular ground glass opacities, enlarged mediastinal lymph nodes).
2. Diffusing capacity of the lung for carbon monoxide to alveolar volume ratio DLCO/VA < 55% or resting arterial oxygen tension (PaO<sub>2</sub>) < 65 mm Hg.
3. The presence of alveolar haemorrhage on BALF with the Golde score > 80% or hemosiderin-laden macrophages > 30%.

### Differential diagnosis

Taking into account previously described difficulties in distinguishing between PAH and PVOD as well as potential overlap within both conditions, it is justifiable that all patients diagnosed with PAH should be carefully screened for the possibility of PVOD.

The differences between PAH and PVOD are summarised in Table 2.

**Table 2. Differential diagnosis between pulmonary veno-occlusive disease (PVOD) and pulmonary arterial hypertension (PAH), based on Montani *et al.* [3]**

Factor	PVOD	PAH
Genetics	<i>EIF2AK4</i> Autosomal recessive	<i>BMPR2, ACVRL1, ENG, KCNK3, CAV-1, SMAD 9</i> Autosomal dominant
Sex	No sex predominance in familial PVOD, males predominance in occupationally induced PVOD	Females predominance
Smoking	Frequent	Not frequent
Occupational exposure	Organic solvents	None
Other risk factors	Alkylating agents, radiotherapy	Anorexigens, toxic rapeseed oil, dasatinib, selective serotonin re-uptake inhibitors
Other associated conditions	CTD, Hashimoto thyroiditis	CTD, HIV, CHD, portal PAH
Auscultatory crackles	present	Absent (in IPAH)
DLCO	Often severe reduction	Mild reduction
Resting PaO <sub>2</sub>	Often severe reduction	Mild reduction
Desaturation on 6MWT	Often significant	Usually mild
Chest CT	Centrilobular ground glass opacities, septal lines, mediastinal lymph nodes enlargement	Usually no parenchymal abnormalities (IPAH)
BALF	Possible hemosiderin laden macrophages	Normal
Targeted PAH therapy	Risk of pulmonary oedema	Improved FC and haemodynamics
Prognosis	Poor	Dependent on FC and haemodynamics

EIF2AK4: eukaryotic translation initiation factor 2alpha kinase 4; BMPR2: bone morphogenetic protein receptor type II; ACVRL1: activin receptor-like kinase 1; ENG: endoglin; KCNK3: potassium channel subfamily K member 3; CAV-1: caveolin 1; SMAD 9: mothers against decapentaplegic homolog 9; CTD: connective tissue disease; HIV: human immunodeficiency virus; CHD: congenital heart disease; DLCO: diffusing capacity of the lung for carbon monoxide; PaO<sub>2</sub>: arterial oxygen partial pressure; 6MWT: 6-minute walk test; CT: computed tomography; IPAH: idiopathic pulmonary arterial hypertension; BALF: bronchoalveolar lavage fluid; FC: functional class

**Table 3. Differential diagnosis between pulmonary venoocclusive disease (PVOD), hypersensitivity pneumonitis (HP) and sarcoidosis (BBS)**

Factors	PVOD	HP	BBS
Factors involved in pathogenesis	Exposure to organic solvents, alkylating agents, radiotherapy	Recurrent exposure to overt or occult environmental antigens	Not known (mycobacterial, bacterial antigens?)
Clinical picture	Lung disease	Lung disease	Possible multi-organ disease
Auscultation			
bi-basal crackles	Present	Present	Sometimes present
wheezing	Absent	Sometimes present	Possible
Plethysmography	Normal	Restrictive lung pattern, occasionally hyperinflation and/or obstruction	Restrictive lung pattern, occasionally obstruction
DLCO	Severe reduction	Reduced	Reduced
Chest CT	Centrilobular ground-glass opacities, septal lines, mediastinal lymph nodes enlargement	Diffuse centrilobular micronodular pattern, ground glass opacification, air-trapping, fibrosis, occasionally mediastinal lymphadenopathy	Micronodular pattern, localisation along the broncho-vascular bundles, mediastinal and hilar lymph nodes enlargement
BALF	Possible hemosiderin-laden macrophages	Lymphocytosis > 25% (usually higher)	Lymphocytosis > 25%
Serum markers	None	Specific IgG antibodies (precipitins) to environmental antigens	ACE
Pulmonary hypertension on RHC	Severe precapillary	Mild precapillary — in end-stage disease	Mild precapillary — mostly in stage IV Possibility of post-capillary PH due to heart involvement or mediastinal fibrosis
Prognosis	Poor	Dependent on the possibility of elimination of responsible antigen	Dependent on disease stage, presence of PH and type of organ involved

DLCO: diffusing capacity of the lung for carbon monoxide; CT: computed tomography; BALF: bronchoalveolar lavage fluid; IgG: immunoglobulin G; ACE: angiotensin-converting enzyme; PH: pulmonary hypertension

Findings on lung HRCT in PVOD/PCH have to be differentiated from interstitial lung disease. The morphology of centrilobular ground glass opacities seen in PVOD/PCH in HRCT is similar to that seen in hypersensitivity pneumonitis (HP) [29, 36]. However, HP has other typical radiological features not seen in PVOD/PCH such as mosaic lung attenuation, air trapping or lung fibrosis [37, 38]. Moreover, in most cases HP may be excluded basing on the lack of characteristic elements such as: a history of exposure to organic dusts, restrictive pattern on body plethysmography, and lymphocytosis in BALF [37, 38]. The details of differential diagnosis between HP and PVOD/PCH are listed in Table 3. Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and PLCH have to be also taken into account in the patients with centrilobular ground glass nodules [39].

The thickening of the interlobular septa and lymphadenopathy seen in PVOD/PCH may require the differential diagnosis with sarcoidosis;

nevertheless, in PVOD/PCH the septa thickening is smooth and localised in subpleural region, while in sarcoidosis the thickening is nodular due to the accumulation of nodules along the bronchovascular bundles [40]. The details of differential diagnosis are listed in Table 3.

### Therapy and prognosis

The introduction of PAH-specific therapy in PVOD/PCH patient may result in the acute clinical worsening due to lung congestion. Such complications have been observed in 20–50% of PVOD/PCH patients undergoing PAH-specific therapy [3, 23, 41], and even in 75% of PVOD/PCH patients receiving calcium channel blockers [3]. The development of lung oedema is caused by the vasodilatation of pulmonary arterioles, with an increase of trans-capillary hydrostatic pressure due to augmented blood flow in fibrotic post-capillary venules.



Resten *et al.* [42] evaluated the results of epoprostenol therapy in 73 patients with severe PH. In 12 patients with radiological picture that might be suggestive of PVOD/PCH, the adverse clinical response to epoprostenol was observed. In 6 of them PVOD was confirmed on pathologic examination.

Nevertheless, the use of epoprostenol at a low dose, with slow up-titration and with a high dose of loop diuretics to prevent pulmonary oedema resulted in mild clinical improvement or stabilisation of the disease in 12 patients with severe PVOD, listed for lung transplantation [43]. Similar observation was published by Ogawa *et al.* [44] who treated 8 PVOD/PCH patients with epoprostenol (maximum dose  $55.3 \pm 10.7$  ng/kg/min). The therapy significantly decreased brain natriuretic peptide (BNP) level, improved 6-min walk distance as well as cardiac index; nevertheless, pulmonary artery pressure and pulmonary vascular resistance did not change significantly.

An interesting case report concerning different efficacy of several PAH-specific drugs in the patient with MMC-induced PVOD/PCH (in the course of the treatment of peritoneal cancer) was reported by Koyama *et al.* [45]. The introduction of sildenafil (20 mg/day) caused pulmonary oedema, but a subsequent use of bosentan, at a low dose at the beginning and then increasing up to 250 mg/day, with tadalafil (20 mg) as add-on therapy, brought clinical improvement. The patient died of disseminated neoplastic disease after several months and post-mortem examination confirmed PVOD/PCH.

Thus, even if stabilisation of the disease or mild clinical improvement are observed in the course of the first line therapy in PVOD/PCH, the treatment goals are usually not achieved. On the other hand, life-threatening lung oedema may be observed in the patients listed for sequential add-on therapy with PAH-specific drugs after inadequate response to first-line drug [46].

In accordance with a general opinion of experts, a cautious use of specific PAH therapy could be proposed to patients with suspected PVOD and careful monitoring must be implemented, but only at centres with extensive experience in the management of PH. The patients should be fully informed about the risks. Due to lack of effectiveness of PAH-specific treatment in PVOD/PCH, several authors tried to investigate the role of anti-proliferative therapy in this group of patients.

The most scrutinised drug in refractory PAH was tyrosine-kinase inhibitor — imatinib [47,

48]. The use of imatinib as an add-on therapy in advanced PAH treated with at least two PAH-specific drugs was associated with the occurrence of fatal subdural haematomas, and the drug was not approved for refractory PAH therapy [47, 48].

Recently, Ogawa *et al.* [49] reported on imatinib as add-on therapy, at a dose of 100–400 mg/day, in 9 PVOD/PCH patients, and compared the results with 7 PVOD/PCH patients who did not receive the drug [49]. Imatinib resulted in the significant improvement of the World Health Organisation (WHO) functional class and serum BNP concentration, as well as in the decrease of mean pulmonary artery pressure and prolonged survival [49]. The authors did not observe the development of subdural haematomas, but two patients in the imatinib-treated group died of infective complications. Nevertheless, median survival in the group treated with imatinib was over 4 years, which is unusual for PVOD/PCH patients [49].

The prognosis of PVOD/PCH patients is poor, due to relative unresponsiveness to treatment and fast progression of the disease. Rapid development of the condition is observed especially in the patients with two or more radiological signs of PVOD/PCH [26, 50].

The only proved effective mode of therapy is bilateral lung transplantation [1]. Wille *et al.* [51] compared 6-month survival of PVOD/PCH patients and PAH patients remaining on the lung transplantation waiting list [51]. The death rate was 22.6% vs 11.0% respectively, indicating that patients with PVOD/PCH are at higher risk of death while on the transplant waiting list [51]. Thus, current guidelines recommend early listing for lung transplantation of the patients with newly recognised or highly probable PVOD/PCH [1].

## Conclusions

PVOD/PCH is a rare disease causing severe PH. It may be an idiopathic as well as related to other conditions disease. Genetic and environmental factors connected to the development of the disease have been identified. Diagnosis should be based on a combination of clinical observations, physical examination, bronchoscopy and radiological findings. In heritable cases, the presence of a bi-allelic *EIF2AK4* mutation is enough to confirm the diagnosis. The prognosis in PVOD/PCH is very poor. The patients should be cared for in experienced PH centres. Bilateral lung transplantation is the only effective therapy, and all eligible PVOD/PCH patients should be

referred to a transplant centre for evaluation as soon as the diagnosis is made.

### Conflict of interest

The authors declare no conflict of interest.

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