REGULAR ARTICLE

Pulmonary Veno-Occlusive Disease

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Pulmonary veno-occlusive disease (PVOD) represents a rare yet severe etiology of pulmonary arterial hypertension (PAH). Classified within the spectrum of PAH as Group 1.5 PAH with features of venous/capillary involvement, PVOD is distinguished by its progressive fibrotic obliteration of pulmonary venules and capillary hemangiomatosis. The etiology of PVOD is multifactorial, encompassing idiopathic cases, associations with solvent or chemotherapy exposure, and heritable forms linked to biallelic mutations in the *EIF2AK4* gene. Clinically, PVOD is marked by pronounced impairment in gas exchange, notably reduced diffusing capacity of the lungs for carbon monoxide (DLCO), distinctive radiological features on chest computed tomography, and a potential risk of pulmonary edema when PAH-approved drugs are initiated. Currently, no established evidence-based medical treatment is available, and lung transplantation remains the preferred therapy for eligible patients.

Pulmonary veno-occlusive disease (PVOD) is a rare and devastating cause of pulmonary artery hypertension (PAH). PVOD is characterized by the involvement of all 3 compartments of the pulmonary microcirculation. This includes predominant venular involvement (intimal fibrosis of small preseptal venules) and capillary lesions (capillary hemangiomatosis), as well as pulmonary arterial remodeling without plexiform lesions (Figure 1). Such obstruction of the pulmonary vascular bed leads to elevated pulmonary arterial pressure and subsequent right heart failure.[1–3] PVOD can manifest as a sporadic condition (typically associated with exposure to solvent or chemotherapy) or as a heritable disorder resulting from biallelic mutations in the eukaryotic translation initiation factor 2 α kinase 4 (*EIF2AK4*) gene. A notable clinical feature of PVOD is severe impairment of gas exchange and the potential development of pulmonary edema when PAH-specific therapies are introduced.[4] Currently, no established evidence-based medical treatment is available, and for eligible patients, lung transplantation remains the preferred and definitive therapy.

Key Words—pulmonary veno-occlusive disease, pulmonary hypertension, *EIF2AK4*, chemotherapy, solvents, pulmonary edema, transplantation
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CLASSIFICATION, RISK FACTORS, AND NATURAL EVOLUTION OF PVOD

Classification of Pulmonary Hypertension

Following the recently updated guidelines from the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) on pulmonary hypertension (PH), the group "PAH with features of PVOD involvement" is now incorporated into Group 1 PH (Table 1). PVOD is further divided into various subtypes, including idiopathic, heritable, and drug- or toxin-induced forms. It is noteworthy that venous and capillary involvement can also manifest in conditions like connective tissue disease, chronic respiratory disease, pulmonary Langerhans histiocytosis, and sarcoidosis, which are also poorly responsive or refractory to PAH-approved drugs. However, they are not classified as PVOD in the current

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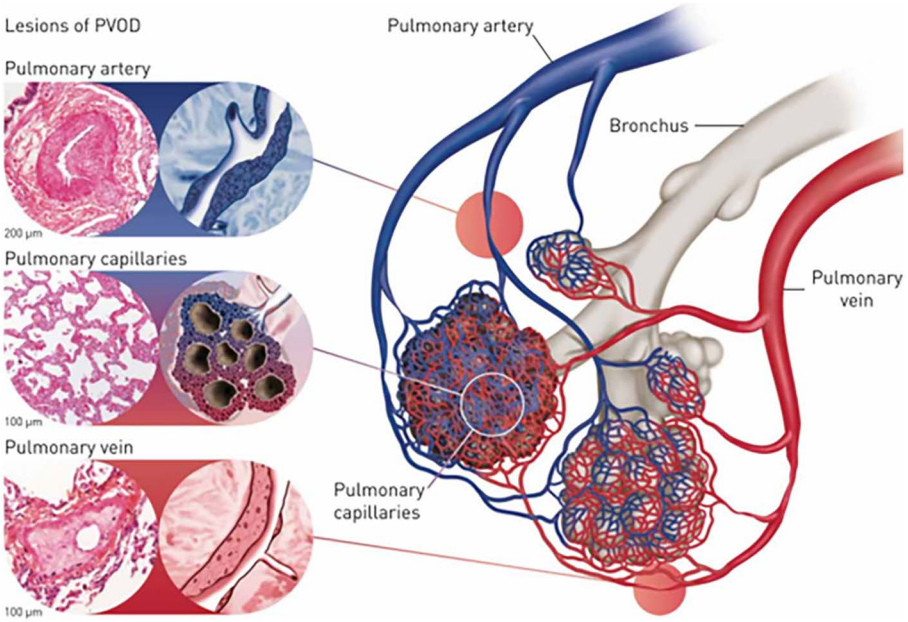

Figure 1: Pathological features of pulmonary veno-occlusive disease (reproduced from Ref. 33). All 3 compartments of the pulmonary microcirculation are affected in PVOD, although preferential involvement of the pulmonary venous system exists. Venular lesions include intimal fibrosis of small preseptal venules. Capillary lesions are characterized by exuberant proliferation of endothelial cells (capillary hemangiomatosis). Arterial lesions resemble those of pulmonary arterial h+ypertension with intimal fibrosis and medial hypertrophy, but complex plexiform lesions are absent. Reproduced with permission of the © ERS 2023: *European Respiratory Journal.* 47(5):1518–1534. https://doi.org/10.1183/13993003.00026-2016. Published 30 April 2016.

classification but within their respective groups.

Epidemiology

The precise incidence of PVOD remains uncertain, primarily due to the likelihood of many cases being misclassified as idiopathic PAH, given the similarity in clinical and hemodynamic features between these 2 conditions. PVOD's estimated annual incidence rate is 0.1–0.5 cases per million.[1,5] PVOD cases were reported across all age groups, including children. Unlike idiopathic PAH, PVOD appears to predominantly affect men, especially in instances of occupational exposure. However, because of its mode of transmission, both men and women are equally affected by heritable forms of PVOD.[4,6–10]

Pathogenesis and Risk Factors

Genetics: Autosomal recessive biallelic mutations in the *EIF2AK4* gene, coding for the general control nonderepressible 2 (GCN2) protein, was identified as the primary genetic cause of PVOD,[10,11] although the exact mechanism of how this deletion leads to PVOD remains largely unknown.[12,13] It is passed down with a complete or nearly complete penetrance; consanguinity and a family history of PH in siblings should thus raise the suspicion of heritable PVOD. Genetic counseling and testing are now integral to managing PAH, and *EIF2AK4* mutation screening should be offered to all patients with idiopathic PAH or suspected PVOD.[14,15] Indeed, it was demonstrated that genetic testing may correct the diagnosis of PAH for PVOD.[16]

While no specific guidelines for screening relatives with biallelic *EIF2AK4* mutations exist, a yearly, noninvasive evaluation may be considered. This evaluation could include symptom assessment, electrocardiogram, NT-proBNP levels, diffusing capacity of the lung for carbon monoxide (DLCO), echocardiography, cardiopulmonary exercise testing (CPET), and high-resolution computed tomography (HRCT).[6] Current evidence suggests that relatives carrying a single *EIF2AK4* mutation are not at an increased risk for PVOD.[17]

Chemotherapy: Various drugs, especially chemotherapeutic agents, were described as potential triggers for PVOD with various levels of evidence. Alkylating or alkylating-like agents were particularly implicated in chemotherapy-induced PVOD, and the most reported causal agents were cyclophosphamide (43.2%), mitomycin-C (MMC) (24.3%), and cisplatin (21.6%).[18,19]

Organic Solvent Exposure: PVOD is significantly associated with occupational exposure to organic solvents, especially trichloroethylene (TCE).[4,5] The latter, a chlorinated solvent,[4,5] is mainly used in the mechanical, textile, and plastic industries. Organic solvents have also been used in pesticides and herbicides, with potential exposures among farmers. In a rat model exposed to TCE, it was demonstrated that the latter causes a breakdown of the endothelial barrier, which is responsible for increased endothelial permeability and subsequent pulmonary perivascular edema.[20]

Tobacco Exposure: Cumulative tobacco exposure was reported to be higher in PVOD compared with idiopathic PAH.[6] This increased risk could be explained by the alteration of vascular permeability and endothelial barrier dysfunction described after cigarette smoke exposure.[21] In a case-control study comparing PVOD patients and patients with PAH, all patients with significant exposure to trichloroethylene had concurrent tobacco exposure.[8]

Other Forms of PH Associated With Venous and Capillary Involvement: It is increasingly recognized that significant venular involvement is often found in connective tissue disease-associated PAH, particularly systemic sclerosis,[22,23] and that they are often less responsive or even refractory to PAH-approved drugs, like patients with PVOD. Significant venous/capillary involvement was also reported to complicate other inflammatory disorders such as sarcoidosis, pulmonary Langerhans cell granulomatosis, or interstitial lung diseases.[24–27] Regarding their categorization, it is more appropriate to classify them according to the group of the underlying disease regardless of venular or capillary involvement.

Table 1. Classification of Pulmonary hypertension ESC/ERS guidelines on PH[3]

GROUP 1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.1.1 Nonresponders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable
1.3 Associated with drugs and toxins
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
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
GROUP 2 PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to postcapillary PH
GROUP 3 PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease
3.6 Developmental lung disorders
GROUP 4 PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
GROUP 5 PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1
5.3 Metabolic disorders
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

Abbreviations: HF, heart failure; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

EVALUATION AND APPROACH TO CLINICAL DIAGNOSIS OF PVOD

Several distinctive features distinguish PVOD from PAH: resting hypoxemia with severe desaturation on exertion, very low DLCO, radiological signs on HRCT, and occult alveolar hemorrhage if bronchoalveolar lavage is performed. Since histological confirmation of PVOD is not feasible, a noninvasive diagnostic approach using clinical, functional, CT, hemodynamic, and genetic findings is to be adopted.

Clinical Features

PVOD and PAH share a joint clinical presentation characterized by

progressive dyspnea, fatigue, palpitations, chest pain on exertion, hemoptysis, or syncope. Notably, PVOD patients often experience more severe dyspnea and impaired exercise capacity than those with PAH with similar hemodynamic parameters.[28,29] Physical signs include typical signs of PH and right heart failure. Cyanosis is more frequently observed in PVOD due to frequent concomitant hypoxemia, whereas clubbing or Raynaud's phenomenon occur in both PVOD and PAH in similar proportions.[4] Other signs suggestive of PVOD may include pulmonary edema and pleural effusions.[30,31] Pulmonary edema after the initiation of PAH-approved drugs strongly suggests a diagnosis of PVOD.

Right Heart Catheterization

PH is diagnosed through right heart catheterization (RHC), with a mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest. In the case of PVOD, pulmonary hemodynamics are characterized by a pattern of precapillary PH (mPAP ≥ 20 mmHg, normal pulmonary arterial wedge pressure [PAWP] ≤ 15 mmHg, and pulmonary vascular resistance [PVR] ≥ 2 WU). Despite the primary anatomical involvement of postcapillary venules in PVOD, the PAWP typically remains within the normal range.[4,7,32,33] Normal PAWP is explained by the predominant impact on small venules and capillaries, with relatively spared larger veins.[33] PAWP, in this case, is thus not a reflection of pulmonary capillary pressure. Acute vasoreactivity testing, usually performed systematically in the workup of PH before PVOD is suspected, is not very helpful in the management of PVOD patients. It does not predict long-term response to calcium channel blockers, even if it yields a positive result,[34] nor is it indicative of the potential development of pulmonary edema under PAH-specific therapy. Furthermore, the initiation of a calcium channel blocker may lead to life-threatening pulmonary edema.

Doppler Echocardiography

Transthoracic echocardiography is a valuable diagnostic tool for assessing patients with suspected PH.[3] In the context of PVOD, typically associated with hypoxemia and radiological abnormalities, echocardiography can be particularly useful for ruling out intracardiac or intrapulmonary shunts as well as for diagnosing left-sided heart disease.

Radiographic Findings

HRCT of the chest has become a fundamental component in the noninvasive diagnostic approach of PVOD specifically, in addition to revealing more general signs of PH. The triad of findings suggestive of PVOD is centrilobular ground-glass opacities, smooth bilateral interlobular septal thickening, and mediastinal lymphadenopathy (Figure 2).[6,31] For patients suspected of having PVOD, ventilation-perfusion lung scans do not reveal abnormalities specific to PVOD: segmental or subsegmental defects or, occasionally, diffuse and patchy perfusion defects are observed in the same proportion as in idiopathic PAH.[35] It is important to note that radiological abnormalities may be absent or mild at diagnosis in approximately 25% of PVOD patients.[6] When the diagnosis is uncertain, HRCT should be repeated, as it can reveal a worsening of radiological signs over time or after the initiation of PAH-approved drugs.

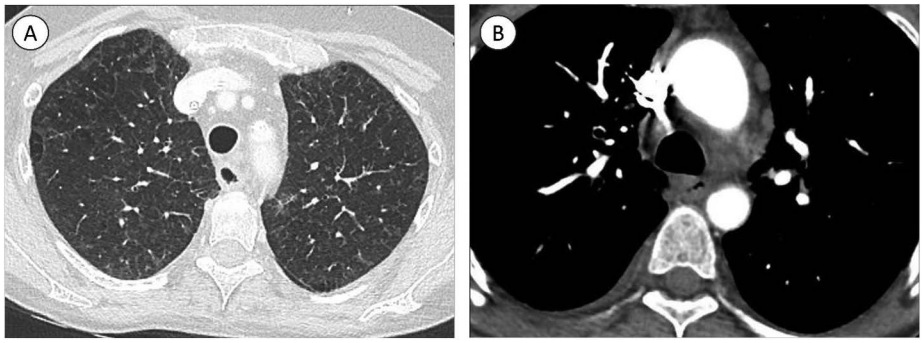

Figure 2: High-resolution CT scan of the chest in patients with PVOD. (**A**) Centrilobular ground-glass opacities and septal lines. (**B**) Mediastinal lymph node enlargement.

Pulmonary Function Test, Gas Exchange, and Exercise Testing

While spirometry and lung volume tests generally yield normal results, PVOD patients typically exhibit a reduced DLCO compared with the relatively preserved DLCO in patients with idiopathic or heritable PAH.[6,7] This can be explained by a reduced capillary blood volume due to a compromised pulmonary vascular bed and a poorer membrane diffusion due to interstitial edema. Arterial blood gas also reveals significant resting hypoxemia in PVOD.[4] Data on the 6-minute walk distance (6MWD) are limited, but they usually show severe impairment accompanied by significant desaturation.[4] Compared with other PAH patients, patients with PVOD exhibit greater ventilatory inefficiency (as demonstrated by higher minute ventilation to carbon dioxide output slope) and more severe functional impairment (revealed by lower peak oxygen consumption and earlier anaerobic ventilatory threshold).[29,36]

Bronchoalveolar Lavage

Bronchoalveolar lavage is not recommended as part of the diagnostic workup of PH and may pose a significant risk in PVOD patients who are frequently hypoxemic. Nonetheless, when it is conducted, occult alveolar hemorrhage with a significantly increased percentage of hemosiderin-laden macrophages can be found.[37] This can be explained by the increased transmural capillary pressure secondary to the remodeling of the postcapillary vasculature. However, with this finding, PVOD can only be suggested after having ruled out left-sided cardiac pathology, such as mitral valve stenosis.

Histopathological Diagnosis

A histological diagnosis before autopsy or lung transplantation should not be pursued, given the substantial risk of performing lung or transbronchial

biopsy in the setting of significant PH with compromised hemodynamics and low functional capacity, associated with the risk of bleeding. Therefore, it is recommended to follow a diagnostic approach based on clinical features and noninvasive tests alone.

When histological information is accessible, notably on lung explants or postmortem analysis, PVOD patients showcase extensive constrictive remodeling by intimal fibrotic thickening of postcapillary venules and small veins, capillary hemangiomatosis, and significant muscularization of precapillary arterioles with no plexiform lesions (Figure 1).[13] The unique histopathological pattern of PVOD parallels the radiological findings on HRCT: subpleural basal lines on HRCT align with increased collagen deposition in septal veins. Centrilobular ground-glass opacities correlate with the centrilobular distribution of capillary angioproliferation, the accumulation of intra-alveolar hemosiderin-laden macrophages, and edematous fluid. Finally, histological examination of lymphadenopathy reveals a vascular transformation of the sinus, characterized by increased wall thickness of the sinuses.[38]

MANAGEMENT AND EVOLUTION OF PVOD

General and Supportive Measures

Hypoxemia should be addressed by administering oxygen to prevent further worsening of PH from hypoxic pulmonary vasoconstriction. Diuretics can help optimize patients' fluid status. In line with the most recent ESC/ERS guidelines, anticoagulation is not systematically recommended in PAH patients.[3] Since PVOD patients may be at an increased risk of alveolar hemorrhage, and no known benefit of anticoagulation was demonstrated to date, it seems reasonable to avoid routine anticoagulation.

PAH-Approved Therapies

Several therapeutic classes are currently used to treat PAH: prostacyclin and prostacyclin-receptor agonists, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 inhibitors/soluble guanylate cyclase stimulators. In patients with PVOD, the effectiveness and safety of PAH-approved drugs remain controversial. Some improvements were reported in the 6MWD and PVR.[28] However, considerable concern about the potential development of life-threatening pulmonary edema exists. Additionally, for a significant proportion of PVOD patients, the initiation of PAH-approved drugs leads to a deterioration of gas exchange.[6,28,39,40] The initiation of PAH-approved drugs should, therefore, be undertaken at expert centers, preferring a monotherapy regimen for selected patients, accompanied by very close monitoring.[3]

Other Therapies

While current guidelines do not endorse the use of immunosuppressive therapy in PAH, evidence indicates the participation of inflammation in the pathophysiology of both PVOD and PAH.[5,41,42] It was suggested in isolated cases that mycophenolate and prednisolone helped stabilize symptoms, enhance oxygenation, and improve gas exchange and hemodynamic parameters in PVOD, possibly by downregulating the underlying inflammatory process[43] Immunosuppression was notably suggested in systemic lupus erythematosus and mixed connective tissue disease, with a possibly improved clinical outcome. However, it is not effective for systemic sclerosis-associated PAH. Therefore, currently, the use of immunosuppressive therapy in PVOD without substantial confirmatory data cannot be encouraged. In addition, *EIF2AK4* loss-of-function mutations, which lead to an absence of GCN2, a protein that participates in the integrative stress response,[12,44] may represent a potential target for future innovative therapies.

Lung Transplantation

The only definitive treatment for PVOD is a bilateral lung or heart-lung transplantation. Posttransplant survival in PVOD cases seems to be comparable with that of idiopathic PAH. Due to the difference in epidemiological characteristics, patients with heritable forms are more often eligible for transplantation than those with sporadic forms, who are older and often have comorbidities.[4] Overall, the prognosis of PVOD is poor, and the disease inevitably progresses with an event-free survival rate (considering death or transplantation) estimated to be around 65% at 1 year and 35% at 3 years.[4] Given the risk of rapid deterioration and the absence of effective treatment, it is recommended to discuss early listing for transplantation at the time of diagnosis, particularly when no program for urgent listing transplantation exists.

CONCLUSION

PVOD stands as a rare and intricate form of PAH, marked by its association with genetic and environmental risk factors and a notably grim prognosis. Diagnosing PVOD can be challenging, but high diagnostic certainty can be attained through a battery of noninvasive tests. Given the disease's progressive and ultimately fatal course, along with the absence of established and effective medical treatments, an expeditious referral for lung transplantation remains the sole definitive therapeutic option. Ongoing research to understand the role of the *EIF2AK4*/GCN2 pathway in maintaining pulmonary vascular homeostasis may hold promise for uncovering innovative strategies for managing PVOD.

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