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SERIES "PULMONARY HYPERTENSION: BASIC CONCEPTS FOR PRACTICAL MANAGEMENT"
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Pulmonary veno-occlusive disease

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ABSTRACT: Pulmonary veno-occlusive disease (PVOD) is currently classified as a subgroup of pulmonary arterial hypertension (PAH) and accounts for 5–10% of cases initially considered to be idiopathic PAH. PVOD has been described as idiopathic or complicating other conditions, including connective tissue diseases, HIV infection, bone marrow transplantation, sarcoidosis and pulmonary Langerhans cell granulomatosis. PVOD shares broadly similar clinical presentation, genetic background and haemodynamic characteristics with PAH. Compared to PAH, PVOD is characterised by a higher male/female ratio, higher tobacco exposure, lower arterial oxygen tension at rest, lower diffusing capacity of the lung for carbon monoxide, and lower oxygen saturation nadir during the 6-min walk test. High-resolution computed tomography (HRCT) of the chest can be suggestive of PVOD in the presence of centrilobular ground-glass opacities, septal lines and lymph node enlargement. Similarly, occult alveolar haemorrhage is associated with PVOD. A noninvasive diagnostic approach using HRCT of the chest, arterial blood gases, pulmonary function tests and bronchoalveolar lavage could be helpful for the detection of PVOD patients and in avoiding high-risk surgical lung biopsy for histological confirmation. PVOD is characterised by a poor prognosis and the possibility of developing severe pulmonary oedema with specific PAH therapy. Lung transplantation is the treatment of choice. Cautious use of specific PAH therapy can, however, be helpful in some patients.

KEYWORDS: Alveolar haemorrhage, BMPR2, computed tomography, diffusing capacity of the lung for carbon monoxide, pulmonary arterial hypertension, pulmonary veno-occlusive disease

Pulmonary arterial hypertension (PAH) is a severe condition characterised by elevated pulmonary artery pressure leading to right heart failure and death [1, 2]. Pulmonary veno-occlusive disease (PVOD) is classified as a subgroup of PAH and accounts for 5–10% of histological forms of cases initially considered to be idiopathic PAH. Even though the first well-documented case of PVOD was described >70 yrs ago, the characteristics and pathophysiology of this disease remain poorly understood [3, 4]. While pulmonary vascular pathology of idiopathic or familial PAH is characterised by a major remodelling of small pre-capillary pulmonary arteries with typical plexiform and/or thrombotic lesions, PVOD preferentially affects the post-capillary venous pulmonary vessels [5, 6]. Despite this anatomical histological difference, PVOD has a very similar clinical presentation to PAH but is characterised by a worse prognosis and the possibility that severe pulmonary oedema can develop with specific PAH therapy, justifying the importance of diagnosing this disease. A definitive diagnosis of PVOD requires histological analysis of a lung sample [7, 8]; however, surgical lung biopsy is a high-risk procedure in these patients and the development of a less invasive diagnostic approach would be preferable [9–11]. The present manuscript will summarise the current knowledge of PVOD.

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None declared.

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CLASSIFICATION AND DEFINITION

Although pulmonary hypertension can be screened for by Doppler echocardiography, a definite diagnosis of PAH requires right heart catheterisation showing a mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg during exercise and normal pulmonary capillary wedge pressure (P_{pcw}) [1, 2]. PAH has been divided into several subcategories according to the clinical classification of pulmonary hypertension (World Conference in Pulmonary Hypertension, Venice, Italy, 2003): idiopathic PAH; familial PAH; PAH associated with different conditions (connective tissue diseases, congenital heart diseases, HIV, portal hypertension and exposure to drugs and/or toxins); and PAH associated with significant venous or capillary involvement [2, 12]. The latter group mainly corresponds to PVOD and, to a lesser extent, pulmonary capillary haemangiomatosis (PCH), two uncommon causes of PAH. It has been hypothesised that PAH and PVOD might represent two parts of the spectrum of the same disease, with lesions in the different components of the vascular tree (predominant arteriolar, capillary or venous lesions). Because of its histopathological characteristics, its poor response to specific PAH therapy and its dismal prognosis, PVOD is now clearly identified as a particular subgroup of pulmonary hypertensive disease. In addition, occlusive venopathy could also occur in severe PAH associated with different conditions and it has been recently demonstrated to be relatively frequent in PAH associated with connective tissue diseases, such as systemic sclerosis [13, 14]. PVOD may also be described with virtually all conditions associated with PAH, including HIV infection. However, PVOD shares numerous similarities with idiopathic PAH and may, therefore, be difficult to diagnose, especially in cases with incomplete clinical and radiological initial presentation. Such cases may deteriorate with time, especially when vasodilator therapy is prescribed without precautions, with the risk of pulmonary vasodilator-induced pulmonary oedema. In these circumstances, dyspnoea, hypoxaemia, exercise limitation and pulmonary infiltrates may progress dramatically within hours, days or weeks.

PATHOLOGICAL ASSESSMENT

In PVOD, vascular lesions predominate on the post-capillary level of pulmonary vasculature. However, lesions frequently involve veins, capillaries and arteries in lungs of PVOD patients. In PVOD, the observed post-capillary lesions of septal veins and pre-septal venules frequently consist of loose, fibrous remodelling of the intima that may totally occlude the lumen (fig. 1a). The involvement of pre-septal venules should be considered necessary for the histological diagnosis of PVOD. Indeed, fibrous occlusion of large septal veins may be seen in many forms of pulmonary venous hypertension, which do not correspond to the clinical entity of PVOD. While septal veins usually display a pauci-cellular, cushion-like fibrous obstruction, intimal thickening of pre-septal venules can present with a dense pattern and increased cellularity. Anti-α-actin staining may reveal involvement of smooth muscle cells and/or myofibroblasts within such venous lesions. Also, thrombotic occlusion of small post-capillary microvessels has been observed, corresponding to ''colander-like'' lesions, which can be seen otherwise in small pulmonary arteries. The tunica media may be muscularised in both septal veins and pre-septal venules. Pleural and pulmonary lymphatic vessels are usually dilated [15]. The presence of calcium encrusting elastic fibres in the vessel wall or the perivascular space, and consecutive inflammatory activation through a foreign body giant cell response is considered as an argument in favour of PVOD rather than more common forms of pulmonary venous hypertension [5]. Importantly, occult pulmonary haemorrhage regularly occurs in patients displaying PVOD (fig. 1b). This particularity, which is certainly due to the post-capillary block, is of diagnostic importance, as bronchoalveolar lavage (BAL) can reveal an occult haemorrhage [9]. The degree of haemorrhage can be evaluated semi-quantitatively and qualitatively using the Golde score, which takes number of intra-alveolar siderin-laden macrophages, and the degree of staining of these macrophages by Perl's Prussian blue into consideration [9]. In addition to an increased number of siderophages, large amounts of haemosiderin can be found in type-II pneumocytes, as well as within the interstitial space. Arterial lesions of patients displaying PVOD mainly consist of concentric and eccentric intimal thickening, as well as medial hypertrophy (fig. 1c). Complex lesions do not usually occur in the context of PVOD. Moreover, post-capillary obstruction may frequently lead to capillary angiectasia and even capillary angioproliferation; in PVOD cases, doubling and trebling of the alveolar septal capillary layers may be focally present (fig. 1d). Recently, this histological peculiarity has raised questions concerning a possible overlap between PVOD and cases of PCH, a disease classically characterised by an aggressive patch-like capillary angioproliferation. LANTUEJOUL *et al.* [6] have recently reported 35 cases of PVOD and PCH with more or less similar pattern, suggesting the possibility of a same disease entity. After histological review of 30 patients originally classified as PVOD and five as PCH, PCH-like lesions were found in 24 PVOD patients. Most PVOD patients displayed pulmonary arterial lesions, as seen in PAH. Conversely, four out of five former PCH patients, after review, presented with pulmonary arterial and venous lesions. These findings suggest an individual morphological emphasis of the same disease entity [6]. This is consistent with similar clinical and radiological presentation [2, 10, 16]. Recent studies are drawing attention to PAH subgroups with clinical particularities, suggesting other than pure arterial involvement in connective tissue diseases (such as systemic sclerosis and systemic lupus erythematosus) can be complicated by severe PAH [13]. Until recently, lesions of the pulmonary arterial component, more or less similar to those occurring in idiopathic PAH, have been thought to be responsible for pulmonary hypertension in these patients [2]. DORFMULLER *et al.* [13] have recently reported frequent involvement of pulmonary veins and venules in a PVOD-like pattern in patients displaying connective tissue diseases associated PAH, suggesting a clinically relevant effect of post-capillary occlusion in this subset of PAH. This peculiarity might explain, at least in part, why these patients are less prone to responding to specific PAH treatment, compared with idiopathic PAH patients.

In conclusion, these latest insights into the pathology of PVOD may indicate a new approach to the disease with a less rigid perception of pre-, post- and capillary lesions in patients with pulmonary hypertension. The most clinically relevant information is the presence of post-capillary involvement, which may lead to a very different clinical outcome (as discussed below).

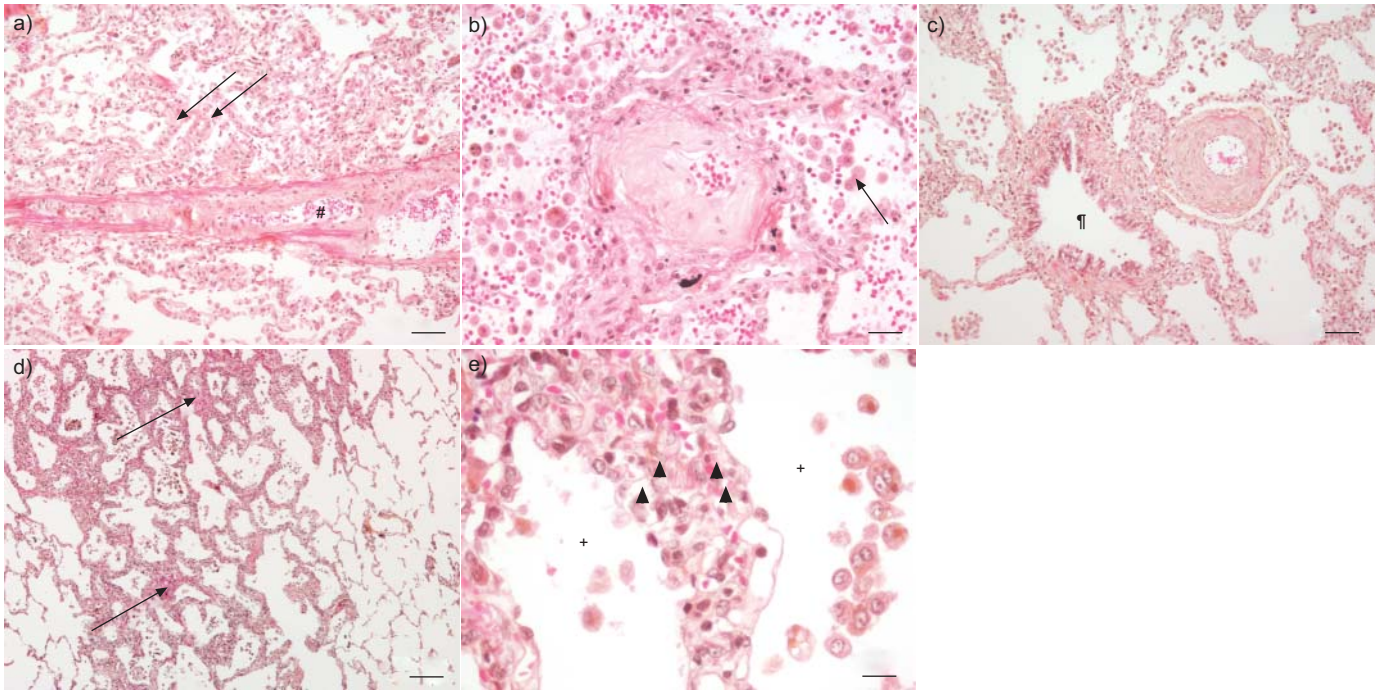

FIGURE 1. Pulmonary vascular lesions in a patient suffering from pulmonary veno-occlusive disease (haematoxylin–eosin–saffron staining). a) Fibrous obstruction of a septal vein (#) and pre-septal venules (arrows). b) Pre-septal venule with occlusive remodelling. Note the intra-alveolar haemorrhage and siderin-laden macrophages (arrow). c) Muscular artery presenting with marked intimal fibrosis and adjacent bronchiole (¶). d) Patchy thickening of alveolar septa in the presence of occlusive microvessels (arrows). e) Alveolar septum displaying capillary proliferation. Note the multi-layered lumen (arrowheads) separating two alveoli (+). a) and c) Scale bar=100 μm; b) scale bar=50 μm; d) scale bar=200 μm; e) scale bar=25 μm.

EPIDEMIOLOGY AND RISK FACTORS

PVOD represents a difficult-to-diagnose subgroup of a rare disease, leading to challenges in evaluating its true prevalence and incidence. Until recently, no large cohort had precisely defined the characteristics of this population, and the need for a pathological confirmation of vascular lesions has limited the number and quality of clinical studies in the field. Furthermore, the true incidence of PVOD is probably underestimated because many cases may be classified as idiopathic PAH. The recent publication of national cohorts of PAH patients could help to evaluate the prevalence and incidence of this disease. Using the French national registry, HUMBERT *et al.* [17] have estimated that the prevalence and incidence of PAH in France were 15.0 cases per million adult inhabitants and 2.4 cases per million adult inhabitants per year, respectively. Usually, PVOD is considered to account for 5–10% of histological forms of cases initially thought to be ''idiopathic'' [8]. Application of this frequency to the incidence rate of idiopathic PAH yields an estimated incidence rate of ''idiopathic'' PVOD of 0.1–0.2 cases per million [17, 18]. However, PVOD can also occur in patients with associated diseases, including HIV infection [19–21], bone marrow transplant [22–28], connective tissue diseases [13, 14, 29], sarcoidosis [30] or pulmonary Langerhans cell granulomatosis [8, 31, 32], suggesting that PVOD could have a much higher prevalence than indicated by these registries.

Case reports have reported a very wide range for age at diagnosis of PVOD, from the first weeks to the seventh decade of life [8]. In the series of MONTANI *et al.* [4], the age at diagnosis of the 24 ''idiopathic'' PVOD cases confirmed by histology ranged 7–74 yrs (median 39 yrs) with no significant difference compared with idiopathic PAH patients. In contrast with idiopathic PAH, which has a clear female predominance, PVOD occurred equally in men and women [4, 7].

Genetic factors

A genetic risk factor in the development of PVOD has been previously suggested by several reports of PVOD occurring in siblings [33, 34]. Several cases of *BMPR2* (the gene for bone morphogenetic protein receptor type II) mutation have now been reported in PVOD (table 1) [4, 35–37]. These reports demonstrate a possible role of the *BMPR2* pathway in the development of PVOD and further emphasise the similarities between PVOD and PAH. These results support systematic screening for a possible familial history of pulmonary vascular disease and similar genetic counselling in both PAH and PVOD patients.

Autoimmune diseases

In national registries, PAH associated with connective tissue diseases represents 15–30% of PAH patients [17, 18]. JOHNSON *et al.* [14] described a series of four patients with probable PVOD with scleroderma associated PAH. However, the real prevalence of PVOD in connective tissue diseases associated PAH is difficult to estimate because no systematic assessment of venous involvement was available in PAH patients, and in particular in PAH associated with connective disorders. DORFMULLER *et al.* [13] studied lung samples from eight patients with end-stage PAH associated with connective tissue disease (four limited systemic sclerosis, two systemic lupus

TABLE 1 *BMPR2* mutations in patients with pulmonary veno-occlusive disease

Mutation location	Nucleotide change	Amino acid change	Reference
Exon 1	c.44delC	p.Pl5fsX31	Runo *et al.* [35]
Exon 2	c.77-?_247+?del	p.A26_Q82del	Aldred *et al.* [36]
Exon 2	c.120T>G	p.Y40X	Machado *et al.* [37]
Exon 8	c.1120delA	p.I374fsX	
Exon 5	c.604A>T	p.Asn202Tyr	Montani *et al.* [4]
Exon 5	c.583G>T	p.Glu195X	

The mutation nomenclature follows current guidelines as recommended by the Human Genome Variation Society [38].

erythematosus, one mixed connective tissue diseases and one rheumatoid arthritis) and showed that significant obstructive pulmonary vascular lesions predominating in veins or pre-septal venules were more frequent in PAH associated with connective tissue disease (75%) compared with idiopathic PAH (17.2%). It can be hypothesised that the poor prognosis and the lack of response to specific PAH therapies observed in PAH associated with connective tissue diseases could be due, at least in part, to the high prevalence of venous involvement. As previously described in idiopathic PAH, Montani *et al.* [4] have shown that PVOD shares a similar autoimmune background with idiopathic PAH.

Toxic and tobacco exposure

It has been clearly demonstrated that the risk of developing PAH is increased after exposure to anorexigens, such as aminorex and fenfluramine derivatives [12, 39–42]. For example, Souza *et al.* [40] have shown that fenfluramine-associated PAH shares similar clinical, functional, haemodynamic and genetic characteristics with idiopathic PAH. Fenfluramine exposure is considered to be a potent trigger for PAH but, until recently, PVOD had not been reported following anorexigen use. The current authors have recently reported a case of PVOD in a patient with a history of fenfluramine exposure, suggesting a possible association between anorexigen exposure and PVOD as previously described in PAH [4].

Chemical exposures have previously been proposed to play a role in the development of the disease, but this association has only been reported in isolated case reports. The two largest series of PVOD found no significant association with chemical exposure, but they did not include a specific exposure questionnaire [4, 7]. However, PVOD shares some pathological characteristics with hepatic veno-occlusive disease, which is a well-recognised complication of antineoplastic chemotherapy and ''pyrrolizidine alkaloid'' exposure (bush teas) [43]. PVOD has been reported in association with various chemotherapy regimens, including bleomycin, BCNU and mitomycin [44–47] and after bone marrow transplantation [22–28, 48].

The present authors have recently reported a higher tobacco exposure and an increased proportion of smokers in PVOD compared with PAH [4]. This difference was not explained by the difference in the male/female ratio, since the increased tobacco exposure was observed in both sexes. Interestingly, this association has been suggested by the series of Rabiller *et al.* [9] with a nonsignificant predominance of tobacco smokers in the PVOD patients. Even if it has been previously demonstrated that tobacco exposure may contribute to pulmonary vascular injury [49, 50], it is not clear why tobacco exposure would be a specific risk factor for PVOD and why it was not found in idiopathic PAH [39]. This relationship is also supported by the described association between PVOD and pulmonary Langerhans cell granulomatosis, a pulmonary disease occurring almost exclusively in smokers [31, 32, 49, 50]. Further studies should attempt to confirm a link between tobacco exposure and PVOD, as well as the mechanism that would explain this association.

CLINICAL FEATURES

PVOD and idiopathic PAH share the same clinical presentation and clinical examination is unhelpful in distinguishing them. As in PAH, progressive dyspnoea on exertion is the most frequent symptom, although it is often neglected by the patients, leading to frequent delay in establishing the diagnosis. As observed in PAH, most of the patients have severe exertional dyspnoea with a New York Heart Association (NYHA) functional class III or IV at the time of the diagnosis [4, 7]. Signs of right heart failure occur in the late phase of the disease when the right ventricle is unable to tolerate the pressure overload. Cardiac auscultation shows a prominent P2 component of the second heart sound and a systolic murmur of tricuspid regurgitation [7]. Auscultatory crackles may occur in PVOD patients with predominant pulmonary infiltrates and have been reported in six out of the 11 PVOD patients of the series published by Holcomb *et al.* [7]. Clubbing and Raynauld's phenomenon have been reported in PVOD but the current authors' recent series indicated it can also be found in idiopathic PAH (16% of PVOD and 8% of idiopathic PAH patients) [4]. Haemoptysis has been reported in both diseases but one could suggest that it would occur more frequently in PVOD because of the possible presence of alveolar haemorrhage in this condition [9]. However, in the recent study by Montani *et al.* [4], haemoptysis was reported in a similar proportion in both PAH and PVOD, which gives further support to the finding that alveolar haemorrhage in PVOD is usually occult [9]. Pleural effusions may be present but data available from high-resolution computed tomography (HRCT) chest scans demonstrated that pleural effusions were observed in the same proportion in both end-stage diseases [4, 7, 10, 16].

HAEMODYNAMIC CHARACTERISTICS

All patients with PVOD have evidence of severe pre-capillary PAH and, ultimately, right ventricular dysfunction. A large recent series comparing a group of patients with biopsy-proven idiopathic PAH with a group with biopsy-proven PVOD indicated similar haemodynamic characteristics, except that those with PVOD had a lower mean systemic arterial pressure and right atrial pressure [4].

P_{pcw}

Until recently, a widely accepted belief was that P_{pcw} could be of interest in the diagnostic approach of PVOD; indeed, elevated P_{pcw} in the setting of severe PAH with radiographic

evidence of pulmonary oedema was believed to suggest PVOD. However, case reports [11] and case series [4, 7, 9] have shown that P_{pcw} is, in fact, usually normal in PVOD patients. A ''wedged'' trace has been reported as difficult to obtain in PVOD but no difference was observed in the proportion of measurable P_{pcw} between PVOD and idiopathic PAH in the current authors' recent series [4], in which P_{pcw} usually appears normal (<15 mmHg). It has been reported that even if P_{pcw} is elevated following pulmonary occlusion, it will progressively normalise in time, with a slow fall thought to reflect trapping of blood in fibrotic and narrowed pulmonary veins on its way to the left atrium [8]. In patients with PAH, an elevated P_{pcw} implies raised pressure in the column of blood distal to the wedged catheter or inflated balloon (fig. 2). Following equilibration, this reflects the pressure in a pulmonary vein of similar diameter to the occluded pulmonary arterial branch. The diameter of this vein would be larger than that of the small veins and venules affected by PVOD, where patency in the large veins is usually well preserved [5]. The pressure measured by P_{pcw} is, therefore, distal to the site affected by the PVOD process, and explains the usually normal P_{pcw} in these patients [4, 5]. The usual causes of an elevation in P_{pcw} are any cause of elevated left atrial pressure, such as mitral stenosis, or pathology affecting large-diameter pulmonary veins, such as fibrosing mediastinitis or obstruction of the large pulmonary veins after catheter ablation for cardiac atrial fibrillation or left heart failure [2, 51]. If marked pulmonary vein stenosis is present, the P_{pcw} trace may be damped, but the ''absolute'' value should be normal [52]. Patients with PVOD differ from the patients with idiopathic PAH with isolated pre-capillary pulmonary hypertension in that they have obstruction to blood flow in the pulmonary veins leading to an elevated true capillary pressure (P_c) [53, 54], although not P_{pcw}, as described. Estimation of the true P_c or microvascular pressure might theoretically be useful in PVOD, both in order to conceive a diagnostic strategy and to predict those who may develop pulmonary oedema with the use of pulmonary vasodilators. The principle of P_c pressure measurement is extrapolated from a canine model, whereby the pressure decay following balloon occlusion is mathematically analysed to represent the emptying of the capillary compartment [55]. Interestingly, patients with PAH may also have elevated P_c pressure using this method [56, 57], with one explanation for this being more extensive venous involvement in patients previously labelled with ''pre-capillary'' idiopathic PAH. More study is needed in this area before applying P_c measurements clinically.

Acute vasodilator testing

In patients with PAH, a positive vasoreactivity test can predict the response to calcium channel blockers, with this group of ''responders'' having a better long-term prognosis compared with nonresponders [58, 59]. An acute vasodilator response has been reported in some PVOD cases. In a recent series, one patient with PVOD responded to nitric oxide; however, within 24 h of initiation of calcium channel blocker therapy, pulmonary oedema developed [4]. This suggests that an acute vasodilator response in PVOD may not be predictive of a better prognosis and that calcium channel blockers should not be used in PVOD, even in the context of a positive acute test. One of the main concerns in PVOD is the risk of pulmonary oedema with continuous intravenous epoprostenol and other specific PAH therapies [4, 7, 60]. Pulmonary oedema has been described both following vasodilator testing [7, 60] and at varying intervals after initiation of specific PAH therapies [4]. The development of pulmonary oedema is extremely suggestive of PVOD in a context of PAH. It may occur during vasodilator testing with any of the agents used, including calcium channel blockers, prostacyclin, nitric oxide or adenosine. However, in a recent series of 24 histologically confirmed PVOD patients given 10 ppm nitric oxide for a short period (5–10 min), none developed pulmonary oedema acutely, and this regimen of nitric oxide administration is thought to be safe in patients with suspected PVOD [4]. The acute vasodilator test in the same series was, however, unable to predict those patients who later developed pulmonary oedema following initiation of

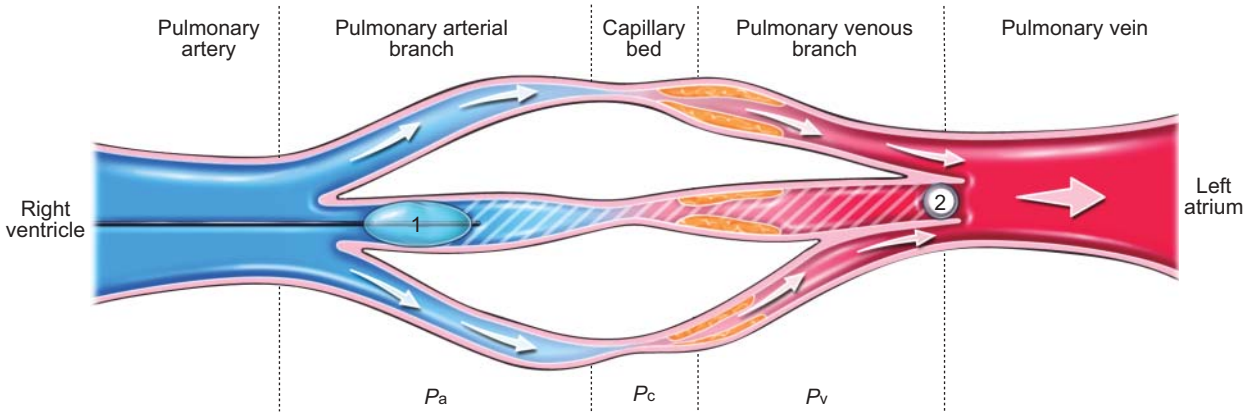

FIGURE 2. Diagram explaining why pulmonary capillary wedge pressure (P_{pcw}) is usually normal in pulmonary veno-occlusive disease (PVOD). PVOD mostly affects small pulmonary veins, leading to an elevation of pressure in this region (P_v), as well as to an elevation in true pulmonary capillary pressure (P_c) and pre-capillary pulmonary arterial pressure (P_a). Larger pulmonary veins are usually not affected by PVOD, and it is in fact the pressure here that is reflected by P_{pcw}: the static column of blood (hatched) occluded by pulmonary arterial catheter wedging or balloon inflation of a pulmonary arterial branch (balloon 1) reflects the pressure in a vein of similar diameter (balloon 2), usually of a larger size than those vessels affected by PVOD. Therefore, this measurement technique does not reflect the important elevation of pressure in the smaller diameter vessels associated with PVOD.

a PAH-specific therapy. Therefore, it can be argued that vasoreactivity testing plays no real role in the investigation of PVOD patients, as none of them are calcium channel blocker responders and it will not predict those patients at risk of developing pulmonary oedema with specific PAH therapy.

NONINVASIVE DIAGNOSTIC TOOLS

Histological analysis of a lung sample is still considered to be the ''gold standard'' for a definite diagnosis of PVOD. However, surgical lung biopsy is too invasive for these frail patients, emphasising the importance of developing less invasive tools to obtain the diagnosis. In this context, recent data have shown that HRCT of the chest, BAL, arterial blood gas measurements and pulmonary function tests could be helpful in defining a subgroup of PAH with high probability of PVOD.

Pulmonary function tests

Pulmonary function tests may be helpful in the diagnostic approach of PVOD. Previous reports have suggested that mild restrictive or obstructive ventilatory defects could be observed [7]. However, in a large series of ''idiopathic'' PVOD patients, MONTANI *et al.* [4] have found normal mean values of forced expiratory volume in one second (FEV1), FEV1/forced vital capacity ratio and total lung capacity in these patients, and no difference was observed in pulmonary function tests analysed during spirometry and plethysmography compared with idiopathic PAH [4]. Reports of low diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) in patients with PAH have previously been published. A low $D_{L,CO}$ has also been described in PVOD patients, with possible severe reductions (<50%) in some patients [7, 61]. It could be hypothesised that $D_{L,CO}$ may be normal or increased in PVOD because of the frequent occult alveolar haemorrhage [9]. MONTANI *et al.* [4] compared $D_{L,CO}$ and $D_{L,CO}$/alveolar volume (V_A) ratio between PVOD and PAH patients, and showed that they were in fact both significantly reduced in PVOD compared with idiopathic PAH, suggesting that this characteristic may help identify patients with PVOD (fig. 3a) [4]. In the series studied by MONTANI *et al.* [4], a $D_{L,CO}$ <55% had a sensitivity of 64.3% and a specificity of 89.5% for the detection of PVOD in patients with presumed PAH.

Oxygenation parameters

In one series, HOLCOMB *et al.* [7] reported varying degrees of hypoxaemia in PVOD patients. MONTANI *et al.* [4] have shown that mean±SD baseline partial pressure of arterial oxygen (P_{a,O_2}) at rest is significantly lower in PVOD patients than in idiopathic PAH patients (61.3±17.3 mmHg (8.15±2.30 kPa) and 75.4±13.8 mmHg (10.0±1.84 kPa), respectively; fig. 3b). In the latter study, partial pressure of arterial carbon dioxide was decreased in a similar pattern in both PVOD and PAH patients. The pathophysiological mechanism of exaggerated hypoxaemia compared with patients with non-PVOD PAH is likely to be a combination of pulmonary oedema, alveolar haemorrhage and overall more extensive obliteration of the pulmonary vascular bed, leading to severe ventilation–perfusion mismatching and diffusion limitation. This latter feature is also suggested by the reduced $D_{L,CO}$ observed in these patients. Furthermore, the 6-min walk distance (6MWD) is a reproducible test used as a measure of baseline severity and a surrogate marker of response to treatment in PAH. It correlates with functional status and survival in PAH, although there are few data available in patients with PVOD. In one series comparing PAH and PVOD patients there was a significantly lower 6MWD in the PVOD group [9]. In a recent case series, MONTANI *et al.* [4] compared biopsy-confirmed PVOD and idiopathic PAH. It was shown that, even though PVOD patients also had lower P_{a,O_2} and $D_{L,CO}/V_A$, 6MWD was similar to that of the PAH patients [4]. The PVOD patients had, however, lower nadir arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) during the test. Further observational and follow-up data are required to demonstrate whether 6MWD measurements could help guide therapy in patients with PVOD.

BAL

Bronchoscopy is not usually a routine investigation in patients with PAH, and transbronchial biopsy is considered contra-indicated [62]. Patients with PAH and associated parenchymal

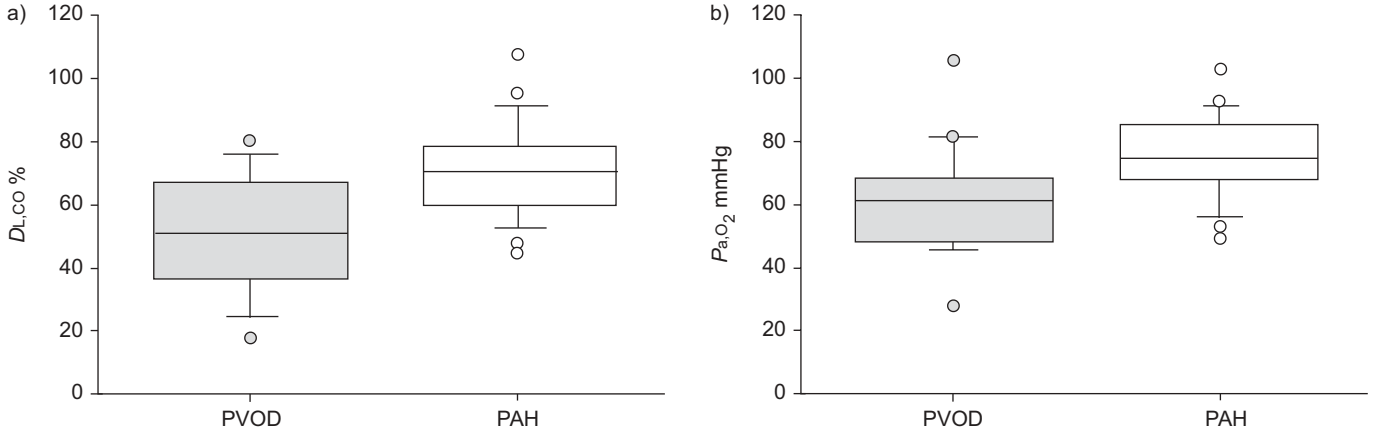

FIGURE 3. Pulmonary function tests a) diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) and b) arterial oxygen tension (P_{a,O_2}) at rest in patients with pulmonary veno-occlusive disease (PVOD) and pulmonary arterial hypertension (PAH). a) $D_{L,CO}$ was significantly lower in patients with PVOD (■) compared with idiopathic or familial PAH (□). b) P_{a,O_2} was significantly lower in patients with PVOD (■) compared with idiopathic or familial PAH (□). Boxes represent the median and interquartile range, whiskers represent the 10th and 90th percentiles, and circles represent observations outside this range. 1 mmHg=0.133 kPa.

lung disease may, however, undergo BAL as part of routine investigation, and there may be a role for BAL in patients with suspected PVOD [9]. This procedure appears to be safe in stable PAH patients [9]. Bronchoscopic airway inspection may show hyperaemia of the lobar and segmental bronchi due to vascular engorgement [63]. The appearance could be compared to that in cardiac disease, such as mitral stenosis, where chronic pulmonary venous hypertension leads to engorgement and dilatation of the bronchial venous plexuses and veins [64]. RABILLER *et al.* [9] have compared results of BAL from eight PVOD patients and 11 idiopathic PAH patients. There was a nonsignificant trend towards elevated alveolar cell counts in the PVOD group with a significantly elevated percentage of haemosiderin-laden macrophages and a higher Golde score, in keeping with the hypothesis that PVOD is associated with occult alveolar haemorrhage [9]. Given the difficulty in obtaining a histological diagnosis in patients with suspected PVOD, there may be a case for performing BAL to detect occult alveolar haemorrhage as part of the diagnostic work-up.

HRCT of the chest

Chest radiographs and HRCT of the chest may show Kerley B lines or pleural effusions when pulmonary oedema occurs in the setting of severe PVOD, most frequently after initiation of vasodilatator therapy [4, 7, 16, 60, 65]. With the exception of this particular situation, HRCT of the chest could help physicians to discriminate between PVOD and PAH [4, 7, 10, 16]. RESTEN *et al.* [10] showed that, in 15 histologically confirmed cases of PVOD, HRCT was characterised by higher frequency of centrilobular ground-glass opacities, septal lines and mediastinal lymph node enlargement compared with idiopathic PAH (fig. 4). Neither pleural effusion nor any other abnormal parenchymal findings correlated with the presence of PVOD [10]. MONTANI *et al.* [4] have confirmed these results and shown that the presence of two or three radiological abnormalities (including lymph node enlargement, septal lines and centrilobular ground-glass opacities) had a sensitivity of 75% and a specificity of 84.6% for the detection of PVOD. In contrast, the absence or presence of only one radiological abnormality could not rule out PVOD, highlighting the importance of a diagnostic approach using several tools, including HRCT of the chest, arterial blood gases, pulmonary function tests and BAL whenever possible [4].

These findings suggest that noninvasive tests could be helpful in suggesting the diagnosis of PVOD in PAH patients. A low resting P_{a,O_2}, low S_{p,O_2} during 6-min walk test, low $D_{L,CO}$, occult alveolar haemorrhage (BAL) and the presence of centrilobular ground-glass opacities, septal lines and lymph node enlargement on HRCT of the chest may determine a subgroup of patients with high probability of PVOD and, therefore, avoid hazardous surgical invasive procedures in these frail patients.

PROGNOSIS AND TREATMENTS

Prognosis

Treatment options other than lung transplantation are unfortunately limited in PVOD, and survival is far worse than in other forms of PAH. This is the reason why early diagnosis and consideration for lung transplantation in this subset of patients is crucial. Data suggests that the 1-yr mortality rate may be as high as 72% in PVOD [7], and the most recent series of a group of 24 histologically confirmed severe PVOD patients found a mean$\pm$SD time from first symptoms (or diagnosis) to death or lung transplantation of 24.4$\pm$22.2 (or 11.8$\pm$16.4) months, compared with 57.9$\pm$38.2 (or 42.3$\pm$29.9) months in patients with idiopathic PAH [4]. It appears obvious that, even if baseline haemodynamic, NYHA and 6MWD parameters are similar to those observed in PAH patients, PVOD patients have a worse outcome, highlighting the relevance of early diagnosis of PVOD. This dismal prognosis is probably related to the development of pulmonary oedema, either in the course of the natural history of the disease or as precipitated by specific pulmonary vasodilator therapies. Based on these considerations, the worse outcome of patients with connective tissue disease-associated PAH is likely to be limited at least to a venous component of the pulmonary vascular disease [13].

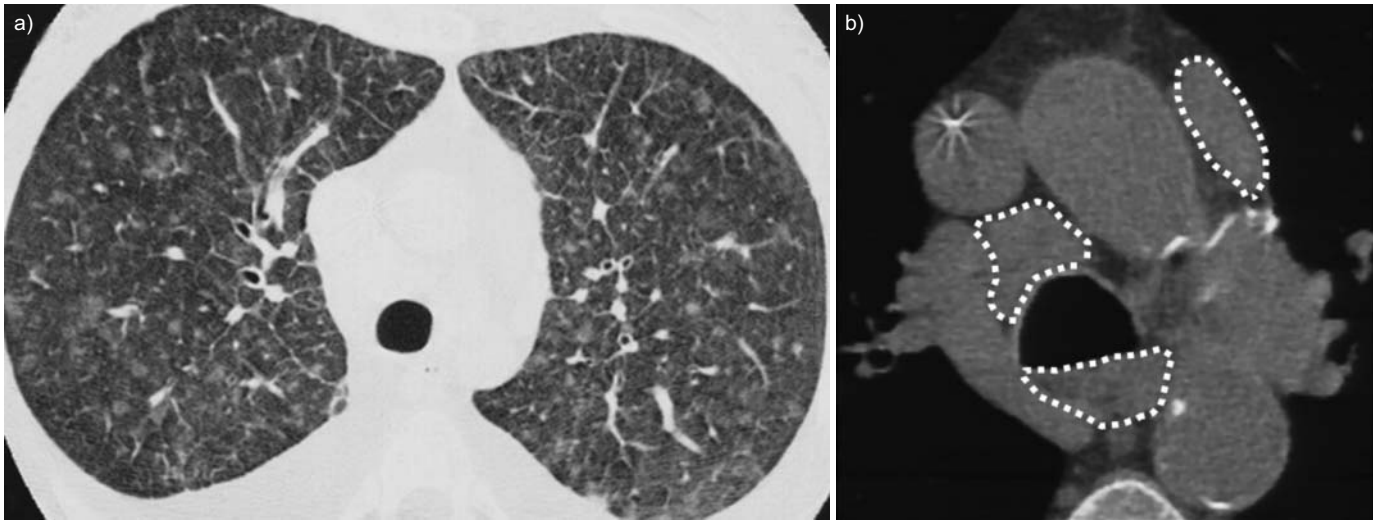

FIGURE 4. High-resolution computed tomography (HRCT) of the chest in pulmonary veno-occlusive disease. a) HRCT of the chest showing marked ground-glass opacities with centrilobular pattern, poorly defined nodular opacities, septal lines and minimal right pleural effusion. b) HRCT of the chest showing mediastinal lymph node enlargement (white dotted lines).

Conventional therapy

PVOD patients have lower P_{a,O_2} at rest than idiopathic PAH [4]. As hypoxic vasoconstriction is an aggravating factor in PAH, oxygen therapy should be considered for patients with chronic hypoxia for symptomatic purposes as well as to avoid PAH deterioration. Nevertheless, its usefulness in the event of a true shunt is debatable. The current authors recommend maintaining oxygen saturation >90% in these patients, as well as any PAH patients [59].

Warfarin therapy improves outcome in patients with idiopathic PAH and, although there are no data specific to PVOD, the rationale is sensible as organising thrombi [66] and subsequent *in situ* thrombosis contribute to both conditions [67]. Current recommendations propose warfarin therapy with an international normalised ratio of 1.5–2.5 in idiopathic PAH. Although the evidence is derived exclusively from idiopathic PAH, anticoagulation has been generalised to all patient groups with the absence of contraindications. Special care in the application of anticoagulation is required in PVOD because of the frequency of occult alveolar haemorrhage, and anticoagulation is not indicated if there is a history of severe haemoptysis.

The increased prevalence of smokers in PVOD compared with other types of PAH suggests an aetiological link. Although this is currently unconfirmed, the authors advise their patients not to smoke and recommend a smoking cessation programme to smokers.

Immunosuppressive therapy

The basis for the use of immunosuppressive agents in some selected PAH patients was initially anecdotal, with rare reports of clinical and haemodynamic improvements in PAH and PVOD patients, suggesting the use of corticosteroids, cyclophosphamide and azathioprine [19, 27, 68–71]. PVOD is also thought to be present in some cases of pulmonary hypertension patients displaying sarcoidosis. However, in these patients, the pulmonary vascular component may be less responsive to treatment with glucocorticoids than the parenchymal lung disease [30]. There has been mounting evidence that PAH has a significant inflammatory component [72], and that PAH seen in some connective tissue diseases responds well to immunosuppressive therapy [70, 71, 73]. Specific patients who may improve with immunosuppression include those with mixed connective tissue disease and systemic lupus erythematosus, but not in scleroderma-associated PAH [70, 71]. A full histopathological assessment has shown that severe connective tissue disease-associated PAH has a major venous pathological component in 75% of cases [13]. In cases where such venous occlusion was observed, there was also an association with local inflammatory infiltrates [13]. The reason why this subset of connective tissue disease-associated PAH patients do not improve with pulmonary vasodilator therapy might be due, at least in part, to venous involvement. More studies are needed to understand whether PVOD, either idiopathic or associated with other conditions such as connective tissue diseases, are responsive to immunosuppressive therapies. Currently, corticosteroids or immunosuppressive therapy should only be considered in the context of sarcoidosis or connective tissue disease (except scleroderma).

Specific PAH therapy

Data on specific PAH therapies in PVOD are weak and conflicting. One of the main concerns is the risk of pulmonary oedema with specific PAH therapy in PVOD. Recently, MONTANI *et al.* [4] have reported the occurrence of pulmonary oedema with different specific PAH therapies (epoprostenol, bosentan and calcium channel blocker) highlighting that pulmonary oedema is not a therapeutic class effect and can occur with all specific PAH therapies [4]. Similar cases have occurred with long-term sildenafil therapy (D. Montani and co-workers, Centre National de Référence de l'Hypertension Artérielle Pulmonaire, Clamart, France; unpublished observation). The mechanism is thought to be due to the increased vasodilatation of the pre-capillary resistance relative to the pulmonary capillaries and veins, which is associated with an increased blood flow, resulting in an increase in transcapillary hydrostatic pressure and transudation of fluid into the pulmonary interstitium and alveoli. In the current authors' recent cohort of histologically confirmed PVOD patients, seven out of 16 patients who received specific PAH therapy developed pulmonary oedema. None had developed pulmonary oedema during acute testing with nitric oxide and none of the clinical, functional or haemodynamic characteristics were predictive of the development of pulmonary oedema after initiation of therapy with epoprostenol, bosentan or calcium channel blockers [4]. Unlike in pre-capillary PAH, there remains no clear-cut evidence of the value of PAH specific therapy in PVOD because of the small numbers of patients and the possibility of severe adverse effects [4]. However, clinical improvement or at least stabilisation has been observed in some patients with continuous intravenous prostacyclin [7, 74–76], oral sildenafil monotherapy [77, 78], bosentan [79] and even chronic inhaled nitric oxide or iloprost therapy [80, 81]. Combination therapy with sildenafil as an adjunct to high-dose prostacyclin has been shown to improve haemodynamics and clinical course in one case [82]. Selective pulmonary venodilatory properties are likely to be most useful in addition to arterial effects. Indeed, prostacyclin seems to have veinodilatory effects in animal models and humans [76, 83]. Other agents such as sildenafil also have venodilating properties, and there are cases of long-term clinical improvement on sildenafil monotherapy in PVOD patients [77]. However, as with other PAH-specific therapies, pulmonary oedema may occur with sildenafil in PVOD patients (D. Montani and co-workers; unpublished data). While pulmonary vasodilators such as intravenous prostacyclin have established efficacy in treatment of PAH [84, 85], benefits of these treatments in patients with PVOD are still unclear. However, even if there is a risk of pulmonary oedema, continuous intravenous epoprostenol therapy has been shown to improve haemodynamics in some cases of PVOD [7, 74–76] and should be considered in these patients because of their very poor prognosis [4]. As described above, cautious use of PAH specific therapy may be of interest in PVOD as a bridge to lung transplantation.

Lung transplantation

Lung transplantation was historically the treatment of choice for severe PAH and still offers the only real possibility of cure for the disease [59, 86, 87]. Notably, there has been one reported case of PVOD recurrence 3 months following transplantation with similar symptoms, worsening PAH and radiographic

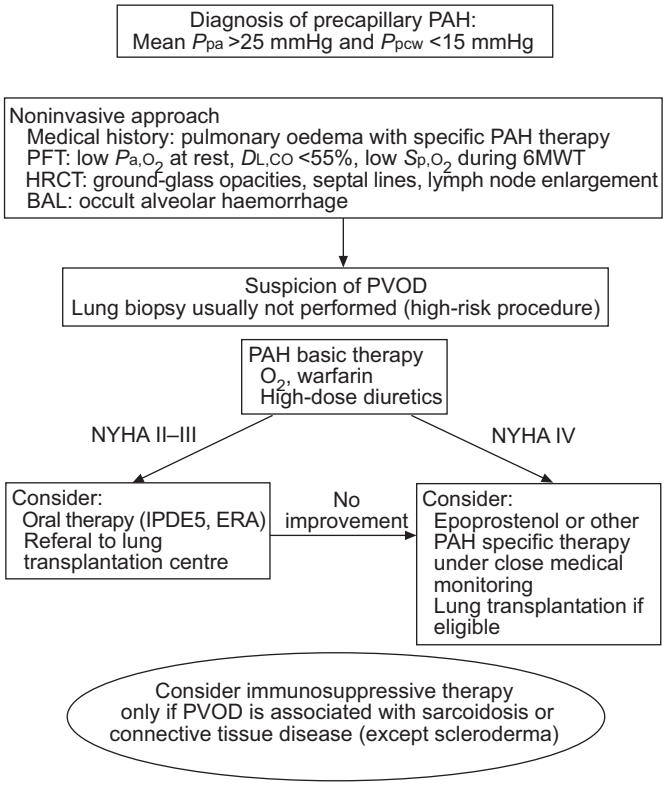

FIGURE 5. Management of pulmonary veno-occlusive disease (PVOD) at the French Reference Center for Pulmonary Hypertension. A noninvasive diagnostic approach is taken, including arterial blood gas measurements, pulmonary function tests (PFT), arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) during 6-min walk test (6MWT), high-resolution chest tomography (HRCT) of the chest and bronchoalveolar lavage (BAL) when possible. Lung biopsy is not usually performed. Patients with suspected PVOD receive basic pulmonary arterial hypertension (PAH) therapy including warfarin, diuretics and oxygen if needed. Cautious use of specific PAH therapies is required in these patients because of the risk of pulmonary oedema. Oral therapy is considered for PVOD patients in New York Heart Association (NYHA) functional class II and III. Because of the poor prognosis, patients in NYHA functional class IV are treated with continuous intravenous epoprostenol and are referred at time of diagnosis for lung transplantation, if eligible. P_{pa}: pulmonary artery pressure; P_{pcw}: pulmonary capillary wedge pressure; P_{a,O_2}: arterial oxygen tension; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; IPDE5: phosphodiesterase type-5 inhibitor; ERA: endothelin receptor antagonist.

pulmonary congestion [88]. However, lung transplantation can only be considered in a minority of patients with end-stage pulmonary diseases and long-term benefits remain disappointing, with ~50% survival at 5 yrs [89, 90]. Mono-pulmonary transplantation has good long-term results [91, 92] but most centres currently prefer bi-pulmonary or cardiopulmonary transplantation, which have fewer post-operative complications [90, 93]. Because of the worse prognosis of PVOD patients, it may be necessary to discuss lung transplantation early in the course of PVOD. In these patients, PAH-specific therapies may be a bridge to lung transplantation.

Experience of the French National PAH Centre

Since 2003, the current authors have used a noninvasive multiple approach for the detection of patients with a high probability of PVOD in the French National PAH Centre (Clamart, France), including chest radiograph, HRCT of the chest, blood gas measurements, pulmonary functional tests and BAL (fig. 5). This approach has led to an important decrease in surgical biopsies during this period. The majority of the referred PVOD patients are in NYHA functional class III or IV and have a poor prognosis [4, 9]. In French National PAH Centre, eligible PVOD patients in functional class III or IV are now listed for lung transplantation at the time of diagnosis. Conventional therapy is used, including oxygen if needed, diuretics in order to decrease the risk of pulmonary oedema, and warfarin, if not contraindicated. At the same time, continuous intravenous epoprostenol is initiated in the most severe patients with a slowly increasing dose and high-dose diuretics under close medical monitoring (fig. 5). Since 2003, the current authors have proposed this approach as a bridge therapy to lung transplantation in several severe highly probable PVOD patients (later confirmed by histology after lung transplantation). In these patients, intravenous epoprostenol may improve haemodynamics without major adverse complications (D. Montani and co-workers; unpublished data). In patients with less severe disease, oral or inhaled agents associated with high-dose diuretics may be considered as bridge therapy to lung transplantation.

CONCLUSION

Pulmonary veno-occlusive disease is a rare subgroup of pulmonary arterial hypertension characterised by specific pathological changes of post-capillary venous pulmonary vessels. Pulmonary veno-occlusive disease shares a broadly similar clinical presentation with pulmonary arterial hypertension, including possible heritable pulmonary veno-occlusive disease with *BMPR2* mutations. Patients with pulmonary veno-occlusive disease have poor prognosis and are susceptible to the development of pulmonary oedema with specific pulmonary arterial hypertension therapy. Haemodynamic parameters, including pulmonary capillary wedge pressure, do not help discriminate between these two diseases. However, history of tobacco exposure, arterial blood gases (low arterial oxygen tension at rest), pulmonary function tests (low diffusing capacity of the lung for carbon monoxide or diffusing capacity of the lung for carbon monoxide/alveolar volume), low arterial oxygen saturation measured by pulse oximetry during 6-min walk test, occult alveolar haemorrhage in bronchoalveolar lavage, high-resolution computed tomography of the chest (centrilobular ground-glass opacities, septal lines, lymph node enlargement) could help clinicians to diagnose patients with high-risk of pulmonary veno-occlusive disease. Cautious use of specific pulmonary arterial hypertension therapy could be proposed to pulmonary veno-occlusive disease patients, but lung transplantation remains the major treatment of the disease. Further studies are needed to improve understanding of the pathophysiology of this subgroup of pulmonary arterial hypertension and whether new therapeutic approaches with antiproliferative therapies might be helpful in pulmonary veno-occlusive disease.

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