Pulmonary veno-occlusive disease: The bête noire of pulmonary hypertension in connective tissue diseases?

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Summary

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension that may develop in patients with connective tissue diseases (CTD). Most cases have been reported in patients with systemic sclerosis, though associations with systemic lupus erythematosus and mixed connective tissue disease have also been described. PVOD is characterised by progressive obstruction of small pulmonary veins and venules that leads to increased pulmonary vascular resistance, right heart failure and premature death. Distinguishing PVOD from pulmonary arterial hypertension (PAH) is often difficult, though use of a diagnostic algorithm may improve diagnostic accuracy and preclude recourse to lung biopsy. The finding of normal left-heart filling pressures in the context of radiological studies suggestive of pulmonary oedema is an important diagnostic clue, particularly if this clinical scenario coincides with the introduction of vasodilator therapy. There are no approved treatments for the disorder, though cautious use of PAH specific therapy may improve short-term outcomes in selected idiopathic PVOD cases. This review summarises the epidemiologic, clinico-pathologic and imaging characteristics of PVOD in the setting of CTD and discusses potential management approaches.

Pulmonary arterial hypertension (PAH) represents a frequently lethal complication of several connective tissue diseases (CTD). PAH is defined haemodynamically as a resting mean pulmonary arterial pressure (mPAP) of at least 25 mmHg with a normal (< 15 mmHg) pulmonary capillary
wedge pressure (PCWP) at right heart catheterization [1,2]. Pulmonary veno-occlusive disease (PVOD) is an uncommon form of vasculopathy that shares many of the clinicopathological characteristics of PAH [3]. Significant improvement have been made over the last quarter of a century with regards to the diagnostic and therapeutic approaches in PAH. By contrast, PVOD remains a poorly understood clinical entity that is often diagnosed late, is difficult to manage and is associated with a uniformly poor outcome. The pathological hallmarks of PVOD, irrespective of its underlying cause, are an obliterator fibrotic vasculopathy that principally involves the smaller branches of the pulmonary venous circulation [4,5]. Prognosis most closely relates to the degree of impairment of right ventricular function that is the inevitable consequence of chronically abnormally elevated pulmonary vascular resistance. It has also long been known that patients demonstrating a veno-occlusive pattern on lung biopsy have a worse prognosis than other forms of PAH [6]. Even though PAH and PVOD share many similarities, the consensus following the Fourth World Symposium on PAH held in 2008 at Dana Point, California, was to separate PVOD from other forms of PAH [1,2]. As a result, PVOD is now classified, together with pulmonary capillary hemangiomatosis (PCH) in a distinct but related group, referred to as Group 1. Pleuro-pulmonary complications frequently develop in patients with CTD. Furthermore, different components of the respiratory system may be simultaneously affected in a given individual, whether as a result of the underlying disease or its treatment. Whereas pulmonary complications are generally identified in those with a known CTD, lung disease may occasionally precede the onset of more typical CTD manifestations. When PVOD occurs in the setting of CTD, its clinicopathological characteristics are often indistinguishable from when the disease occurs in an idiopathic form. Furthermore, distinguishing PVOD from other disorders such as CTD-associated PAH or interstitial lung disease can be extremely challenging, even for experienced clinicians. The past decade has witnessed considerable advances in the sphere of PAH therapeutics and a host of different target agents are now available for this disease. Despite these developments, however, the prognosis for PVOD remains dismal and novel treatments are urgently needed. This is even more so the case in CTD, in which context PVOD can truly be considered a “bête noire”. This review will focus on the current concepts with respect to the pathogenesis of PVOD in the setting of CTD and will discuss potential therapeutic strategies.

**Epidemiology and risk factors**

Systemic sclerosis (SSc) is an autoimmune disease of unknown cause characterised by a progressive fibrosis of the skin and internal organs that leads to organ dysfunction and premature death [7]. Antinuclear antibodies (ANAs) are detected in 90% of SSc patients. Disease-specific autoantibodies including anti-centromere, anti-topoisomerase 1 or anti-RNA polymerase III antibodies are present in approximately two thirds of the cases. Patients with SSc are classified according to the extent of skin involvement: limited cutaneous SSc (lcSSc), with skin involvement essentially limited to the hands and face; and diffuse SSc (dSSc), with skin involvement in a distribution that is proximal to the elbows and knees. In patients with lcSSc, visceral involvement is relatively rare, whereas patients with dSSc commonly experience visceral involvement, which are responsible for reduced life expectancy. Although other visceral manifestations such as gastrointestinal, renal and left heart involvement contribute significantly to the burden of disease, interstitial lung disease and PAH contribute most to patient mortality in SSc [8,9]. In addition, severe pulmonary hypertension may develop as a consequence of interstitial pulmonary fibrosis or left ventricular dysfunction. Both the limited or diffuse forms of SSc confer increased risk of PAH, though the disorder is most commonly seen in the limited subtype and is associated with the presence of anti-centromere antibodies [10,11]. By contrast, PVOD remains underrecognized as a complication of SSc and is often unmasked only after introduction of specific PAH therapy (see below). The overall prevalence of SSc is approximately 100-250 cases per million inhabitants, depending on the region studied [12,13]. Data from a multicentre French epidemiological study has estimated that the prevalence and incidence of PAH in SSc patients are approximately 7.85% and 0.6 cases per 100 patients-years, respectively [14,15]. Although PVOD may complicate both forms of SSc, the preponderance of cases has been described in those with the limited form of the disease [16]. The overall incidence rates of PVOD in SSc are, however, not known. Furthermore, the
frequent co-existence of both pulmonary arterial and venous involvement in part accounts for difficulties in previous attempts to generate reliable estimates [17].

Systemic lupus erythematosus (SLE) is a chronic relapsing systemic autoimmune disease that predominantly involves the skin, joints, pericardium, pleura, kidneys and nervous system. Lung parenchymal involvement, though described, is an uncommon complication of SLE. Anti-nuclear antibodies (ANAs) are uniformly positive in affected patients; anti-double stranded DNA antibodies are also present in most cases and correlate with the disease course. Pulmonary vasculopathy in SLE may be attributable to any of the five distinct WHO pulmonary hypertension categories [18].

In addition, anti-phospholipid syndrome may develop in SLE patients and is an important risk factor for chronic thromboembolic pulmonary hypertension (CTEPH). Thus, more than in other forms of CTD, more than one mechanism may underlie to development of PAH in SLE patients. In Northern Europe, the prevalence rate for SLE is approximately 40 per 100,000 of population [19]. The overall prevalence of pulmonary hypertension in this disease, reported to be between 5 and 30% is probably an overestimation, due to the absence of confirmation of PAH, as established by right heart catherization, in published studies. Similarly, reliable estimation of the frequency with which PVOD occurs in SLE patients is also difficult as its description in the medical literature is mostly limited to case reports and small series [20–22].

Mixed connective-tissue disease (MCTD) is an uncommon multisystem disorder in which clinical features of SSc, SLE and polymyositis can coexist and overlap. Considerable debate remains as to whether MCTD in fact represents a distinct clinical entity [23]. MCTD is characterized by the presence of high titers of antibodies directed against U1-ribonucleoprotein (U1-RNP) and the absence of antibodies specific for other autoimmune diseases. In a study of 47 MCTD patients, PAH was found to be the most common cause of death. Typical autopsy findings from this series included intimal proliferation with medial hypertrophy of the arteries, plexiform lesions and arteritis, and in situ thrombosis [24]. In contrast, the development of PVOD as a complication has been only rarely described [25].

Based on data from the French National PAH Registry, the annual incidence of idiopathic PVOD is estimated to be approximately 0.1 to 0.2 cases per million in the general population [26,27]. However, this figure is likely an underestimation of the true incidence of PVOD, as many cases are misclassified as having PAH. Gathering reliable data regarding the incidence of PVOD in CTD is even more difficult, particularly given the frequency with which co-existing pulmonary complications are observed [17].

**Pathogenesis**

The precise aetiology of PVOD is unknown. Given its rarity, defining potential causes (as opposed to disease associations) is challenging and it is likely that disease pathogenesis is multifactorial. Nonetheless, an exaggerated response to endothelial injury is believed an early inciting event, leading to activation of aberrant repair mechanisms and ultimately a widespread fibrosis of the lung microvasculature [28]. A number of anecdotal reports have linked development of PVOD to different forms of malignancy or exposure to various cytotoxic agents [29–34]. Peripheral blood stem cell transplantation [28], autologous and allogenic bone marrow transplantation [35,36], solid organ transplantation [37] and radiotherapy [32] have additionally been described as potential risk factors.

It is well established that dysregulation of host immunity is a common mechanism in the pathogenesis of CTDs. This fact forms the basis for the hypothesis that the development PVOD may have, at least in part, an immunologic basis. In addition to cases of PVOD that develop in patients with CTDs, a number of cases have also been reported in patients with other inflammatory diseases, including sarcoidosis [38], Langerhans’ cell granulomatosis [39], chronic active hepatitis [40], celiac disease [40] and Hashimoto’s thyroiditis [41]. A number of potential mechanisms to explain the development of PVOD in patients with these various inflammatory disorders have been postulated, though these remain largely speculative. Given the heterogeneous nature of these different conditions, it seems likely that involvement of several distinct pathophysiological factors may be necessary to trigger the disease.

Genetic predisposition is known to be an important determinant of risk for the development of idiopathic PAH. Germline mutations within the coding region of the type-II bone morphogenetic protein receptor gene (BMPR2) are present in 50% of familial cases and at least 25% of sporadic cases of the disease. Interestingly, mutations in several loci of the BMPR2 gene have also been reported in idiopathic PVOD, suggesting a similar pattern [42–45]. These genetic similarities lend support to the notion that PAH and PVOD may in fact represent merely different patterns of lung vasculopathy, with the former predominantly involving the pulmonary arterial vasculature and the latter a variant that preferentially affects the venous side of the lung circulation [46]. It has also been demonstrated that SSC-associated PAH develops more frequently in those demonstrating the genetic markers HLA-DRW6 and HLA-DRW52 [47] and that anti-U1 RNP antibodies promote pulmonary artery endothelial expression of intercellular adhesion molecule-1, leukocyte adhesion molecule-1 and major histocompatibility complex class II [48]. Whether similar mechanisms might be of pathological relevance in CTD-associated PVOD requires additional study.

**Histopathological characteristics**

The defining histopathological hallmark of PVOD is an extensive obstruction by collagen-rich fibrous tissue of the venules and
small-sized veins of the lung [21] (figure 1). Whereas extramural fibrous obstruction of larger pulmonary veins is a non-specific finding that may be seen in a variety of disorders that lead to pulmonary venous hypertension, involvement of the preseptal venous tributaries is the typical histomorphological appearance in PVOD. Affected pulmonary veins display marked smooth muscle hypertrophy and increased deposition of extracellular matrix. This results in a characteristic thickening of affected vessels that progressively obliterates the vascular lumina. In situ thrombosis is another common finding, often accompanied by evidence of recanalization of occluded venous branches. In PVOD, chronically increased downstream pressure cause veins to develop an arterialized appearance over time, leading to diagnostic confusion with pulmonary arteries. Use of movat elastic or orcein stains in order to distinguish between internal and external elastic laminae can be useful in determining whether affected vessels are venous or arterial in nature. Depending on how advanced is the stage of the disease, the pattern of involvement may be either patchy of diffuse. In some cases, affected veins display loose, oedematous and hypocellular fibro-myxoid remodeling while a dense, collagen-rich and sclerotic destruction of the pulmonary venous circulation is observed in others. However, tissue sampling and geographical heterogeneity may account for some of the variation in histological appearance [49].

In addition to venous involvement, histopathological examination usually reveals evidence of significant remodeling that also involves the capillaries, arterioles and small arteries of the lung. Medial hypertrophy and intimal thickening of pulmonary arteries, as well as so called colander-like lesions that are the result of organized thrombi within small pulmonary artery branches may be observed, while progressive microvascular engorgement may produce characteristic capillary lesions with patchy capillary multiplication, leading to a hemangioma-like appearance [49]. By contrast, plexiform lesions, which are classically described in PAH, are not typical in PVOD [50]. Excessive haemosiderin is commonly detected in the pulmonary interstitium and within the cytoplasm of alveolar macro-

**Figure 1**

Lung histology (haematoxylin-eosin staining) from a patient with scleroderma-associated PAH.

**A.** Small pulmonary artery displaying pronounced intimal fibrosis, as typically seen in PAH (Group 1). Note alveolar hemorrhage and numerous intra-alveolar macrophages (star). Magnification ×200. **B.** Thickened alveolar septa with exuberant capillary multiplication. Alveolae are filled with siderophages, erythrocytes and desquamated epithelial cells. Magnification ×200. **C.** Septal veins with fibrotic remodeling and narrowed lumina filled with erythrocytes (arrows). Magnification ×100. **D.** Small preseptal venule with collagen-rich dense fibroitic occlusion (arrows). Magnification ×200.
phages, the result of chronic venous congestion and occult pulmonary haemorrhage [51]. Dilatation and congestion of lymphatic vessels and lymphoid follicular hyperplasia is also frequently observed, and so-called vascular transformation of the sinus has been described in lymph nodes from affected patients [52].

Interestingly, pathological changes of another rare pulmonary vascular disease, pulmonary capillary hemangiomatosis (PCH), may also be observed in PVOD patients. PCH is distinguished histologically by abundant but well-circumscribed capillary proliferation [53]. Lantuejoul et al. showed that there is considerable overlap in the pathologic findings of these two disorders, such that patients with PVOD frequently also demonstrate features characteristic of PCH and vice versa [21]. Furthermore, clinical presentation and therapeutic responses of PVOD and PCH are similar, leading these investigators to speculate that the two disorders may in fact represent variants of the same disease.

**Clinical presentation**

Progressive dyspnoea, fatigue, dizziness, palpitations, and chest discomfort, particularly if worsened by exercise, are the cardinal symptoms of PVOD. However, these presenting clinical features are also characteristic of PAH and are similarly associated with other pulmonary complications of CTDs [27]. Indeed, given its relative rarity, patients are frequently misdiagnosed with (and treated for) other, more common disorders prior to the diagnosis of PVOD being established. Moreover, by the time such symptoms are apparent and the diagnosis of PVOD is made, the disease is generally at an advanced stage and affected persons are most commonly in New York Heart Association (NYHA) functional class III or IV. In the majority of cases, therefore, significant haemodynamic and morphological changes will have already developed within the pulmonary vasculature long before the onset of clinical manifestations.

The diagnostic evaluation of suspected PVOD in the setting of CTD is most commonly undertaken in patients in whom a diagnosis of CTD has previously been established. However, patients presenting with features suggestive of PVOD (and PAH in general) should be carefully assessed for a possible underlying CTD. For example, the presence of new onset or worsening Raynaud’s phenomenon, puffy fingers or sclerodactyly, telangiectasias and/or reflux symptoms may indicate possible SSc. By contrast, patients without Raynaud’s phenomenon are highly unlikely to have the diffuse form of SSc. A history of arthralgias, malar rash, photosensitivity, oral and/or nasal ulceration, alopecia or previous venous thromboembolic events should alert the clinician to the possibility of SLE. Arthralgia and synovitis also represent key features of rheumatoid arthritis (RA), though PVOD is very rarely observed in this disease. Sjögren’s syndrome may be suspected in patients reporting progressive oral and/or ocular dryness, sometimes in association with parotiditis. Progressive dysphagia, proximal muscle weakness or classic heliotrope periorbital rash may point to an underlying inflammatory myopathy such as polymyositis or dermatomyositis, especially if there is a history of associated malignancy.

Physical examination should focus on detection of typical signs of pulmonary hypertension and may also reveal typical CTD features. An accentuated pulmonic component to the second heart sound is a key finding and indicative of increased pulmonary arterial pressure. The sequelae of such an increase in pressure, including a pansystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary regurgitation and a right ventricular additional third or fourth sound, may also be detectable by cardiac auscultation. In advanced disease, there may also be evidence of right ventricular decompensation (cyanosis, elevation of the jugular venous pulse, hepatomegaly, ascites and oedema of the lower limbs), which portends a worse prognosis. Digital clubbing may also be seen in some patients. One of the most important physical signs that helps distinguish PVOD from other forms of PAH is the presence of auscultatory fine inspiratory crackles that develop in the context of acute pulmonary oedema, particularly after initiation of specific PAH therapy (see below) and if there is no evidence of associated parenchymal lung involvement. However, the absence of crackles does not exclude the diagnosis. Pleural effusions may also occur and similarly reflect elevated post-capillary pulmonary vascular pressures, though pleural effusions are not uncommon in patients with CTD that is not complicated by pulmonary hypertension A careful assessment for classic features of SSc (sclerodactyly, tapering of the finger tips, calcinosis, telangiectasias, narrowed oral aperture, or healed ulcerations), SLE (malar rash, livedo reticularis, palpable purpura, or an erythematous rash between the MCP andPIP joints) and early possible RA (symmetrical synovial distension, warmth or erythema) is mandatory.

**Diagnostic evaluation**

The diagnosis of CTD-associated PVOD requires not only the clinical appreciation of the associated symptoms but also the use of screening tools and the confirmation of the diagnosis by independent diagnostic procedures. In order to definitively establish the diagnosis of PVOD in SSc, formal histopathological evidence of pulmonary venous involvement is required. However, lung biopsy in patients with pulmonary hypertension is associated with significant risk and is thus usually contraindicated [54]. We have previously shown that by combining data from a range of routine investigative modalities it is generally possible to make the diagnosis of idiopathic PVOD with reasonable certainty [27]. However, the validity of this approach has not been validated for the diagnosis of PVOD in CTD. Furthermore, there are a number of disorders that share clinical and/or
Differential diagnoses to consider in PVOD

- Pulmonary arterial hypertension
- Pulmonary capillary hemangiomatosis
- Post-capillary pulmonary hypertension due to left heart disease
- Chronic thromboembolic pulmonary hypertension
- Pulmonary thrombotic microangiopathy
- Pulmonary vasculitis
- Alveolar hemorrhage
- Hypersensitivity pneumonitis/drug-induced lung toxicity
- Chronic interstitial lung disease
- Fibrosing mediastinitis

Radiological features with PVOD that can be difficult to differentiate (Box 1). In particular, distinguishing PVOD from left ventricular dysfunction that complicates CTD can be difficult since both entities share overlapping findings on physical examination and may have show an identical radiological abnormalities. Even so, making this distinction is of critical importance, since the management approaches for the different forms of PH that may complicate CTD are dictated by the underlying mechanism (see below).

Transthoracic echocardiography

Transthoracic echocardiography is now established as an invaluable non-invasive diagnostic adjunct for the evaluation of breathless CTD patients. Furthermore, it is becoming increasingly employed as part of routine screening programs for at-risk groups, particularly SSc patients [15]. Detection of a systolic pulmonary artery pressure of greater than 40 mmHg, as estimated by the velocity of the regurgitant jet of flow through the tricuspid valve, is suggestive of pulmonary hypertension. However, echocardiography is neither specific nor sensitive enough to confirm the diagnosis of pulmonary hypertension and additional testing by right heart catheterization is mandatory in suspected cases. In particular, finding of an elevated systolic PAP cannot be considered as confirmatory of PAH, and it is important to stress that therapeutic decisions should not be made on the basis of echocardiographic findings in isolation. Nonetheless, echocardiography remains a useful tool to help exclude associated valvular heart disease, diastolic heart failure and intracardiac shunts, which are important differential diagnoses to exclude in this patient population.

Invasive hemodynamic assessment

As is the case for all forms of suspected pulmonary hypertension, investigation for possible PVOD requires invasive hemodynamic assessment by right heart catheterisation in order to confirm the diagnosis and to ascertain the severity of disease [1,2]. Although the pattern of vascular obstruction in PVOD is post-capillary in nature, pulmonary hemodynamics are indistinguishable from those of precapillary PAH, which is defined by a mean PAP greater than 25 mmHg at rest and a PCWP of 15 mmHg or less than 15 mmHg. This is despite an increase in right ventricular afterload that is predominantly due to an obliterative vasculopathy within upstream pulmonary venules and smaller branches of the pulmonary veins. This apparent hemodynamic contradiction is explained by the fact that the term PCWP is somewhat misleading. Measurements of the PCWP are taken when an inflated catheter balloon tip is wedged in a large proximal pulmonary artery branch and in fact reflect the corresponding pressures in similarly sized pulmonary veins (figure 2). However, these larger vein branches are characterised by a normal intravascular pressure, being distal to the site of venous obstruction and uninvolved in the disease process. Thus, the true value for the pulmonary capillary pressure is underestimated using the wedge technique in PVOD cases and does not reflect the important elevation of pressure in the smaller diameter venous tributaries.

As already discussed, a high index of suspicion for subclinical left heart disease is also important when assessing CTD-associated PH and post-capillary pulmonary hypertension should form part of the differential diagnosis for this patient population [15]. In particular, diastolic heart failure with preserved left ventricular (LV) ejection fraction may present a very similar clinical picture. Patients with diastolic heart failure tend to have modestly increased values for PCWP, though pseudonormalization of PCWP and LV end-diastolic pressure (LVEDP) is not uncommon in patients treated with diuretics. In this regard, crystalloid fluid challenge performed during right heart catheterisation may unmask co-existent pulmonary hypertension that is predominantly post-capillary in origin [55]. Where suspicion of associated left ventricular disease remains, it may be necessary to perform left heart catheterisation so that LVEDP can be directly measured.

In patients in whom precapillary pulmonary hypertension is confirmed, international guidelines recommend performing acute vasodilator testing with short acting vasodilators such as inhaled nitric oxide (NO), intravenous epoprostenol or adenosine during right heart catheterization in order to identify those patients that may potentially benefit from treatment with oral calcium channel blocker (CCBs) Such patients are characterised by a decrease in mPAP of at least 10 mmHg that results in a mPAP of less than 40 mmHg, without associated decrease in cardiac output.

In a recent study from the French National Pulmonary Hypertension Reference Centre, positive acute vasodilator responses rates for idiopathic- and CTD-associated PAH were comparable [56]. A high proportion of CTD-associated PAH and idiopathic PVOD/PCH patients demonstrated an acute vasodilator response during acute testing (10.1 and 12.2% respectively). However, only one of the 168 CTD-associated PAH patients who showed an initial acute vasodilator response was considered a
long-term CCB responder (defined as a marked hemodynamic improvement after 3–4 months and NYHA functional class I or II after 1 year of therapy). There were no patients with SSc or SLE who demonstrated a long-term response, and discontinuation of CCBs was deemed necessary for nearly all CTD patients due to subsequent clinical and/or hemodynamic worsening. Likewise, no patients with idiopathic PVOD were classified as long-term responders and all such patients treated with CCBs developed at least mild pulmonary oedema during follow up [56]. Given these observations, we consider use of CCBs to be contra-indicated in idiopathic and CTD-associated PVOD, even in the presence of an acute vasodilator response. It is important to stress that even though there were no episodes of acute pulmonary oedema during acute vasodilator testing in our study group, its absence during testing does not exclude a diagnosis. In general, for CTD-associated PAH patients there appears to be little merit in systemically performing acute vasodilator testing even though it appears safe, since an acute response is not predictive of a favourable outcome with long-term CCB treatment. This is especially the case particularly where there is a strong clinical suspicion of CTD-associated PVOD.

Radiological studies
Chest imaging is a central component of the diagnostic algorithm when PVOD is suspected. In typical cases, the plain chest radiograph demonstrates pulmonary arterial enlargement and features consistent with post-capillary congestion (Kerley B lines and pleural effusions) but a normal sized left atrium. However, these classically described findings are not universal and the chest radiograph may be unremarkable. Frank pulmonary oedema may be apparent in the setting of acute clinical deterioration, particularly after introduction of specific PAH therapy (see below). High resolution computed tomography (HRCT) is a particularly important investigative tool. The triad of mediastinal lymph node enlargement, septal thickening and diffuse ground-glass opacities, particularly in a centrilobular distribution, is classically described (figure 3). However a similar radiological appearances may also be identified in idiopathic PAH cases [57]. Moreover, one quarter of pathologically confirmed PVOD cases have one or none of these tomographical features [27]. Thus, the absence of typical radiological abnormalities does not exclude the diagnosis. Additional HRCT findings include pericardial effusions, diffuse pulmonary nodules, and other features common to all forms of PAH (central pulmonary arterial enlargement, right ventricular hypertrophy and dilatation and bowing of the interventricular septum). Pleural effusions have been reported but are uncommon. The presence of diffuse bilateral patchy infiltrates in an alveolar filling pattern may indicate the presence of intrapulmonary hemorrhage, particularly if associated with anaemia and hypoxemia and an associated elevated alveolar-to-arterial oxygen gradient.

HRCT is also an important investigation to help exclude other more common pulmonary complications of CTD and disorders that may mimic PVOD (Box 1). Therefore, the absence of the
hallmarks of interstitial lung disease (early fibrosis with or without honeycombing) or bronchiolitis obliterans (air trapping and bronchial wall thickening) is of equal diagnostic relevance. In certain cases, it may be difficult to differentiate with certainty between CTD-associated PVOD and early interstitial fibrosis [58]. Contrast-enhanced chest CT is an important tool for the exclusion of CTEPH, which is reported with increased frequency in SLE patients. However, mosaic perfusion patterns associated with CTEPH may mimic ground glass opacities that may be found in PVOD cases, leading to potential diagnostic confusion [59]. There are no large series specifically reporting the radiological characteristics of CTD-associated PVOD, though HRCT findings appear broadly similar to those commonly identified in PVOD that is idiopathic in nature [58]. Although ventilation perfusion lung scintigraphy is integral to the diagnostic evaluation of pulmonary hypertension in general, this technique is of limited usefulness in PVOD as most scans are either normal or non-specifically abnormal. However, as is observed in idiopathic PAH, multiple mismatched perfusion defects may also be observed, which may lead to diagnostic confusion with chronic thromboembolic disease [60]. Where diagnostic uncertainty remains, pulmonary angiography should be performed in order to exclude CTEPH and is considered the gold standard investigative modality [59].

**Bronchoalveolar lavage**

Flexible bronchoscopy is another potentially useful tool to help distinguish PVOD from PAH in CTD patients. A study by Rabiller et al. showed that bronchoalveolar lavage (BAL) samples from PVOD patients consistently demonstrated increased numbers of haemosiderin-laden macrophages and higher average Golde score compared to idiopathic PAH [61], indicating a high rate of subclinical alveolar hemorrhage in PVOD. However, subclinical alveolar hemorrhage may develop in CTD patients in the absence of this complication [62]. No study has been undertaken to specifically examine the diagnostic potential of BAL in CTD-associated PVOD. It is therefore not possible to extrapolate data regarding its utility in idiopathic PVOD to the CTD population. Transbronchial biopsy should be avoided when suspicion of PVOD or PAH is high as it affords little additional diagnostic value and is associated with a high rate of complications [42]. In the majority of cases of PVOD, lung spirometry is either normal or shows a mild restrictive ventilatory defect, though an obstructive pattern may occasionally be demonstrated [27,63]. Lung volumes are usually maintained. In contrast, measurements of the single-breath diffusing capacity for carbon monoxide (DLCO) are significantly lower in idiopathic PVOD compared to idiopathic PAH and this technique has been used proposed as useful to screen for PVOD cases among patients with suspected idiopathic PAH [27]. In the setting of CTD, however, the finding of a reduced DLCO may be multifactorial (interstitial or pleural disease, neuromuscular involvement, anaemia etc.) and the measure has a much lower discriminatory value for PVOD in this setting. In addition, values for DLCO in the normal range do not exclude the diagnosis, as overestimations may occur in the context of occult alveolar haemorrhage. Nonetheless, a decrease in DLCO that is significantly out of proportion to any degree of restrictive or obstructive abnormality should alert clinicians to the possibility of PVOD. Idiopathic PVOD patients are characterised by a lower PaO₂ at rest and lower SpO₂ during 6 min walk test. Whether the same characteristics apply to CTD-associated PVOD has not been determined.

Other important investigations generally performed to assess the severity of disease include arterial blood gas analysis and quantification of circulating N-terminal pro-brain natriuretic
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Supportive measures and therapies

A number of general lifestyle modifications, therapeutic interventions and relatively simple precautions are generally advocated for all PVOD patients. Though these measures are mostly based on expert recommendations and not on robust clinical trial data, their application is biologically plausible in this patient population and thus broadly advocated [68]. Avoidance of strenuous exercise to reduce the risk of syncope, particularly in those with advanced disease, is important. Pregnancy should be avoided because the additional haemodynamic stress placed on the mother confers a significant risk of clinical deterioration and even death. Female patients of childbearing age should therefore be advised on effective contraceptive measures. Since hypoxemia is potent pulmonary vasconstrictor, use of supplemental oxygen in order to maintain a target oxygen saturation of at least 90% is recommended, and may also confer symptomatic improvement. Annual pneumococcal and influenza vaccinations should be encouraged.

Reduction of right ventricular preload with the use of loop diuretics, aldosterone antagonists or both is warranted for those with symptomatic volume overload. Indeed, in our experience, high-dose diuretics are generally necessary because of the tendency for these patients to develop pulmonary oedema. This is particularly the case when specific PAH therapy is introduced (see below).

There is evidence to suggest that long-term oral anticoagulation with vitamin K antagonist therapy improves prognosis in idiopathic PAH through prevention of in situ thrombosis and venous thromboembolism. In this setting, an international normalized ratio (INR) range of 1.5 to 2.5 is usually recommended. Although there are no specific data to support this strategy in PVOD, the therapeutic rationale is the same. A higher target INR is appropriate in patients with known associated antiphospholipid syndrome, particularly in the context of recurrent thromboembolic events. However, anticoagulants should be administered with caution in CTD-associated PVOD given the significant risk of occult alveolar haemorrhage [61]. Furthermore, their use should probably be avoided in those at high risk for or previous episodes of significant gastrointestinal hemorrhage. Particular care should be taken when considering anticoagulation in cases of angiodysplasia. Clearly, the benefits and risks of this strategy should be evaluated on an individual basis in the context of the patient’s clinical status, associated thromboembolic tendency and history of thrombotic and/or bleeding events.

Pulmonary arterial hypertension specific therapy

The last two decades have witnessed remarkable progress with respect to the therapeutic options available for the treatment of PAH [69]. Regulatory approval has now been granted for a number of drug therapies that produce meaningful and sustained clinical improvements as a result of associated pulmonary-specific vasodilatory and antiproliferative activities. In contrast, there is a distinct lack of prospective clinical trial data in support of these various treatments options in the context of CTD-associated PVOD. Indeed, patients with PVOD are generally excluded as a matter of course from trials of novel pulmonary
hypertension therapies. As a result, there is no established medical treatment recommended for the disease [1,2]. Furthermore, given its rarity, it is highly unlikely that randomised studies of existing or novel agents will ever be realised. Instead, treatment decisions are therefore based on clinical experience, case reports and data extrapolated from trials of PAH-specific therapies involving different forms of PAH. It is also important to note that pathological confirmation is rare and treatment decisions are usually based on clinico-radiological grounds alone.

Idiopathic PAH patients treated by chronic intravenous epoprostenol therapy show improvements in symptoms, exercise capacity, quality of life, pulmonary haemodynamics and survival. [70,71]. Recently published data suggest that in SSc-associated PAH, long-term continuous epoprostenol therapy may confer a survival advantage [72]. There is also in vitro evidence that this agent may reverse increased vasomotor tone in pulmonary venules [73]. However, exposure to pulmonary vasodilators, including epoprostenol, may result in severe and even fatal acute pulmonary oedema in PVOD [27,74]. In one series, nearly half of patients studied developed this complication after initiation of vasodilators, with epoprostenol the most commonly used agent [27]. Indeed, the development of acute dyspnoea and hypoxemia after initiation of specific PAH therapy for presumed CTD associated-PAH is one of the classic modes of presentation of PVOD. The likely mechanism is a selective dilatation of the small pulmonary arteries without associated pulmonary venodilatation, resulting in an abrupt increase in transcapillary hydrostatic pressure and transudation of fluid across into the interstitium and alveolar spaces. There are no clinical or hemodynamic characteristics that are predictive of this complication. Despite concerns that treatment with prostanoids may be associated with dramatic clinical worsening, descriptions of successful outcomes with this class of agent have also been reported. In one retrospective study of 12 patients with advanced idiopathic PVOD listed for lung transplantation, continuous intravenous epoprostenol conferred significant improvements in NYHA functional class and haemodynamic indices in most patients after 3–4 months of therapy [75]. Treatment was well tolerated, and mild pulmonary oedema was observed in only one patient. However, in comparison to the standard approach adopted for idiopathic PAH patients, a slower dose augmentation strategy was undertaken and target doses of epoprostenol were lower in this study (median maximal dose was 13 ng/kg/min). In addition, high doses of diuretic therapy were co-administered. Ten patients were subsequently transplanted in this study suggesting epoprostenol may be considered as a therapeutic bridge to transplantation. However, there are several difficulties in considering this approach for CTD-associated PVOD. Firstly, durable treatment effects with epoprostenol are unusual and eventual clinical deterioration is inevitable for the majority. Secondly, lung transplantation is rarely proposed in these patients due to the high rate of associated comorbidities. Lastly, and perhaps most importantly, there are no published data, even from retrospective series, that support this strategy in CTD patients that develop PVOD.

Over the last decade, a number of orally active PAH-specific therapies that demonstrate both vasodilatory and antiproliferative properties have become available for use in PAH of different aetiologies. However, there is limited clinical experience with the use of such agents in the setting of PVOD. Isolated incidences of clinical improvements following introduction of the non-selective endothelin antagonist bosentan [76] and the phosphodiesterase type-5 inhibitor sildenafil have been published [77,78]. In contrast, other investigators have reported that treatment with bosentan confers no benefit in SSc-associated PVOD [58]. Use of inhaled iloprost has also been successfully attempted, suggesting a potential application in advanced disease [79]. Beneficial effects with the tyrosine kinase inhibitor imatinib were reported in one patient with PVOD refractory to other therapies, though this approach is also highly experimental and not recommended [80]. It is important to emphasize that there is no data to support the use of long-term calcium antagonist therapy in CTD-associated PVOD, even among those who demonstrate a positive acute vasodilator response, and given the risk of pulmonary oedema, we consider such an approach to be contraindicated [27,56].

A consistent observation in clinical studies of novel PAH-specific agents is that patients with CTD, in particular SSC, frequently have poorer therapeutic responses than do their idiopathic PAH counterparts [81–83]. One possible explanation for this discrepancy is that pulmonary venous remodeling may be more common in CTD than previously recognised, and there is some evidence from histopathological series to support this hypothesis. Overbeek et al. compared lung specimens from eight SSc-associated PAH patients to tissue samples from 11 patients deemed to have the idiopathic form the disease [84]. Interestingly, the investigators observed evidence of remodeling of both the arterial and venous pulmonary microvasculature in all SSC cases and a typical pattern of PVOD in half of these individuals. By contrast, venous involvement was present in less than a third of the idiopathic PAH group. This high rate of post-capillary involvement in CTD-associated PAH was also documented by Dorfmuller et al., who identified significant obstructive vasculopathy predominantly involving the veins and pre-septal venules in six out of eight CTD patients (four SSc, two SLE, one MCTD and one RA), and all four SSC-PAH patients, but only five out of 29 control PAH patients [4]. Adopting a combination treatment approach in a ‘goal-oriented’ strategy has become the norm for patients with PAH that do not meet therapeutic targets with monotherapy [85,86]. However, combining PAH-specific treatments in SSc-associated PVOD should be undertaken with extreme caution.
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even if first-line monotherapy is not complicated by pulmonary oedema and not attempted outside of specialized centres [87]. A supervised setting is necessary in order to closely monitor for the development of worsening oxygenation or acute pulmonary oedema. In our centre, patients with PVOD commencing vasodilator therapy are routinely hospitalized in the intensive care unit for continuous monitoring, and only after discussion of the potential risks and benefits of this approach.

It is important to stress that patients with CTD are at increased risk of developing PH that results from mechanisms other than PAH. This is of particular relevance in the context of therapeutic decision-making with respect to PAH-specific treatments. In this regard, there are no data to support the administration of such agents in patients with PH due to left ventricular systolic or diastolic failure or advanced interstitial lung disease. Indeed, such an approach may result in dramatic clinical worsening and is contraindicated.

Immunomodulatory agents

There is strong evidence to support the notion that inflammation plays a key pathogenic role in PAH [88]. The observation of transmural venous inflammatory infiltration in some patients with SSC-associated pulmonary vasculopathy suggests that similar mechanisms may also be important in PVOD [84]. There are also some data to suggest that immunosuppressive therapy may have a limited role in selected cases of CTD-associated pulmonary hypertension. Clinical improvements associated with the use of pulsed or continuous corticosteroids and cyclophosphamide, either alone or in combination, for PAH complicating SLE, primary Sjögren’s syndrome, PM and MCTD have been described [89–94]. In contrast, no benefit with this approach has been demonstrated to date in SSC patients. In some cases, immunosuppressive therapy resulted in apparent complete disease regression [92]. However, a significant treatment effect on coexistent parenchymal lung disease, a frequent complication of CTD, cannot be confidently excluded in some of these studies. Moreover, introduction of upfront immunosuppressive therapy in PAH associated with scleroderma was shown to have no significant effect on either NYHA functional class or pulmonary haemodynamics [95]. Despite these occasional observations, there remains a scarcity of robust long-term outcome data. The role of these agents in the treatment in CTD-associated PVOD is even less well-defined. In the absence of controlled clinical data, routine use of immunosuppressive therapy for this indication is not recommended [1,2] and should be reserved instead for those patients with definite evidence for active interstitial lung disease.

If vasodilatory or immunosuppressive therapies are initiated, the impact of such treatment needs to be carefully monitored at regular intervals. Ideally this should be in a multidisciplinary clinical setting with input from respiratory physicians, rheumatologists, cardiologists, radiologists and pathologists with experience in pulmonary vascular disease, as well as specialised nurses and paramedical health staff as appropriate. Serial evaluations (e.g. 3–6 monthly) of patient symptoms, physical exam, 6 min walk test, chest radiograph, blood testing, pulmonary function testing and echocardiography is advisable. Repeat right heart catheterisation should also be considered if there is clinical, laboratory or echocardiographic evidence of disease progression or to formally evaluate the hemodynamic effect of any therapeutic modifications.

Lung transplantation

Orthotopic lung transplantation (OLT) remains a potentially life-saving intervention for end-stage lung disease. However OLT remains controversial in CTD, in particular SSC, and is less frequently considered as a therapeutic approach in this context because of the high incidence of comorbidities. Nevertheless, in highly selected individuals, lung transplantation may represent a viable alternative [96]. Although there appears to be an increased risk of post-operative death among SSC patients undergoing OLT, two-year survival rates for this population are nonetheless comparable to those of IPAH and idiopathic pulmonary fibrosis patients [97]. Because PVOD is associated with an extremely poor prognosis and limited therapeutic alternatives, lung transplantation is recommended in idiopathic cases [1,2,42]. However, there are no published reports of success with this approach in the case of CTD-associated PVOD specifically. Further data are needed in order to establish whether OLT is associated with improved outcomes for this population.

Conclusion

Whereas the advent of novel targeted therapies has improved the outlook for PAH patients, the same cannot be said for PVOD, particularly when this disorder arises in the setting of CTD. Survival rates remain dismal, even with treatment. Currently, transplantation (lung or combined heart-lung) is deemed the only effective intervention for the disease [98]. However, many CTD patients, in particularly those with SSC, are either not considered for listing because of comorbidities or die while waiting for transplantation. For most patients the possibility of an effective treatment is therefore remote. Effective new approaches are urgently needed in order to improve outcomes for those with this devastating disease.

Conflicts of interest: Xavier Jais, Olivier Sitbon, Gerald Simonneau, Marc Humbert and David Montani have relationships with drug companies including Actelion, Bayer-Schering, GSK, Novartis, Pfizer and United Therapeutics. In addition to being investigators in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards.

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