Pulmonary vascular and cardiac impairment in interstitial lung disease

Marios Panagiotou, Alistair C. Church, Martin K. Johnson and Andrew J. Peacock

Affiliation: Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Glasgow, UK.

Correspondence: Andrew J. Peacock, Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Agamemnon Street, Glasgow G81 4DY, UK. E-mail: apeacock@udcf.gla.ac.uk

ABSTRACT   Pulmonary vascular and cardiac impairment is increasingly appreciated as a major adverse factor in the natural history of interstitial lung disease. This clinically orientated review focuses on the current concepts in the pathogenesis, pathophysiology and implications of the detrimental sequence of increased pulmonary vascular resistance, pre-capillary pulmonary hypertension and right heart failure in interstitial lung disease, and provides guidance on its management.

Introduction

Several pathophysiological abnormalities exist in patients with interstitial lung disease (ILD), with respiratory impairment traditionally being the focus of attention. Cardiovascular impairment, dominated by the detrimental sequence of increased pulmonary vascular resistance (PVR), pulmonary hypertension and right heart failure, is increasingly appreciated as a significant contributing factor to the disease burden. Pulmonary hypertension due to ILD is classified under group 3 (pulmonary hypertension due to lung diseases and/or hypoxia) in the updated clinical classification of pulmonary hypertension [1]. Idiopathic pulmonary fibrosis (IPF) has been the archetype and the source of most of the current knowledge on this phenomenon [2, 3], but patients with ILD secondary to systemic disease, primarily connective tissue disease and sarcoidosis, are also commonly affected [4]. Several case reports and series also confirm the development of pulmonary hypertension in rarer conditions such as pulmonary Langerhans cell histiocytosis (PLCH) [5–7] and lymphangioleiomyomatosis [8].

Examining the spectrum of ILD as a whole is inherently challenging. More than 300 different conditions with variable pathophysiology and natural history are encompassed under the umbrella term of ILD. Therefore, findings in certain populations may not always be extrapolated to all types of ILD. Also, the variable combination of lung parenchymal involvement and pulmonary vascular impairment in ILD makes this patient population a difficult target for study. The issue of what degree of pulmonary hypertension can be expected within the context of lung disease is of paramount importance, since lung disease may not always be the only cause of pulmonary hypertension [9]. Not uncommonly, further diagnostic procedures are necessary to rule out causative comorbidities such as left heart disease, liver disease and chronic thromboembolic pulmonary disease. In some cases, it is even possible that the

pulmonary hypertension is a "true" pulmonary arterial hypertension (PAH; group 1 pulmonary hypertension [1]) with a coexisting lung disease and no causal significance. This has major therapeutic and prognostic implications [4, 9].

With the above facts in mind, this brief review attempts to examine the current concepts on the pathogenesis, pathophysiology and implications of the pulmonary vascular and cardiac impairment in ILD. Emphasis is put on the adverse physiological and clinical impact of coexistent pulmonary hypertension. Although the right heart, pulmonary circulation and left heart represent a pathophysiological continuum, they are examined separately for the purpose of simplicity.

The pulmonary circulation

The principal cardiovascular abnormality in ILD is the increased vascular resistance in the pre-capillary pulmonary circulation that leads to increased pulmonary arterial pressure (PAP) and the development of pulmonary hypertension. Current guidelines define pulmonary hypertension as an increase in mean PAP (mPAP) $\geqslant$25 mmHg and severe pulmonary hypertension as mPAP $\geqslant$35 mmHg, or $\geqslant$25 mmHg with a low cardiac index ($<$2.0 L·min^{-1}·m^{-2}), measured at rest during right heart catheterisation (RHC) [2].

Hypoxic pulmonary vasoconstriction and obliteration of the vascular bed by progressive parenchymal fibrosis are considered major culprits for the increased PVR in ILD [2, 10]. A significant reduction in the mean capillary surface and vascular density with a shift of interstitial vessels away from airspaces occurs in fibrotic lung compared with normal lung [11, 12]. Additionally, fixed microscopic anatomical changes (remodelling) of the pulmonary vasculature, including medial hypertrophy and intimal obstructive proliferation and fibrosis, result in narrowing of the pulmonary vascular bed and further increase in PVR [3, 13, 14]. An intrinsic vasculopathy caused by primary granulomatous invasion and remodelling at all levels from large elastic pulmonary arteries to venules, vasa vasorum and lymphatic capillaries has been described in sarcoidosis [15]. Additional mechanisms that have been implicated in the development of severe pulmonary hypertension in sarcoidosis include extrinsic compression of large pulmonary arteries by fibrotic mediastinitis or mediastinal or hilar adenopathy, pulmonary vasoconstriction by vasoactive factors, pulmonary veno-occlusive disease and (rarely) portopulmonary hypertension secondary to liver sarcoidosis [16]. In patients with PLCH and pulmonary hypertension, a widespread, proliferative vasculopathy with medial hypertrophy and intimal fibrosis of small pulmonary arteries and pulmonary veno-occlusive disease patterns have been identified in lung samples [6].

Possible mediators of the vascular remodelling include chronic hypoxia and the inflammatory response within the pulmonary vasculature specific to the underlying disease [10, 17]. Evidence from patients with IPF suggests that these effects are mediated by complex abnormalities in endothelial function with disruption to the normal homeostasis in apoptosis, angiogenesis, growth factor and cytokine expression, and coagulation cascade [13, 17]. Underexpression of several angiogenic factors (e.g. vascular endothelial growth factor and platelet endothelial cell adhesion molecule) as well as factors affecting vascular tone (e.g. angiotensin-converting enzyme and endothelin-1) have been identified in IPF patients with pulmonary hypertension when compared with patients without pulmonary hypertension [18]. In contrast, inflammatory (e.g. phospholipase A2) and remodelling genes are overexpressed, suggesting a fundamental alteration in the vascular cell phenotype that may contribute to the development of pulmonary hypertension in IPF [18].

The low operating lung volumes in ILD can also raise PVR [19]. As the lung volume falls from functional residual capacity towards residual volume the extra-alveolar vessels become increasingly tortuous and tend to collapse. Similarly, terminal airways tend to collapse in low lung volumes, which can aggravate alveolar hypoxia and propagate hypoxic pulmonary vasoconstriction [20]. Finally, even after age adjustment, ILD patients appear to be unusually predisposed to a number of comorbidities that can independently provoke pulmonary hypertension, such as emphysema, obstructive sleep apnoea and pulmonary thromboembolism [21].

The prevalence of pulmonary hypertension in ILD varies depending on the type of ILD, disease severity and diagnostic modality. Although RHC is mandatory to establish the diagnosis, transthoracic echocardiography remains the most important screening tool to suggest the possibility of pulmonary hypertension [22]. Overall, studies using RHC report a higher prevalence of pulmonary hypertension, which may reflect the higher sensitivity of RHC in the diagnosis of pulmonary hypertension. However, a confounding selection bias cannot be excluded, since RHC is generally reserved for the most compromised patients. In lung transplant candidates with IPF, the prevalence of RHC-detected pulmonary hypertension has been reported to be in the range 20–46% [23–25]. Combined pulmonary fibrosis and emphysema (CPFE) syndrome has been associated with an even higher prevalence, up to 55% [26]. In a meta-analysis of five studies, the prevalence of RHC-confirmed pre-capillary pulmonary hypertension in 3818 European Caucasians with systemic sclerosis was 9% [27]. In a subanalysis of two of those studies with available data, the prevalence of PAH and pulmonary hypertension secondary to ILD (defined by forced vital capacity <70% predicted in

addition to significant changes on high-resolution computed tomography (HRCT)) among those with pulmonary hypertension was 63% and 36% (1.9% of the total population), respectively [27]. In a retrospective analysis of 363 lung transplant candidates with sarcoidosis who had RHC, the prevalence of pulmonary hypertension was 74% [28]. In a cohort of 212 subjects with ILD due to mixed aetiologies including IPF, nonspecific pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis and connective tissue disease, the prevalence of echocardiography-determined pulmonary hypertension (systolic PAP >40 mmHg with right ventricular dilatation or tricuspid annular plane systolic excursion <1.8) was 14% [29]. Thus, there is a wide spectrum of reported prevalence of pulmonary hypertension in ILD that may have resulted from the different selection criteria used in the published studies.

The degree of pulmonary hypertension in ILD is most often mild-to-moderate (resting mPAP ⩾25 mmHg, but <35 mmHg). In this setting, the degree of pulmonary hypertension can generally be explained by the extent of pulmonary fibrosis and the degree of the expected hypoxia [30]. However, a subset of patients across the spectrum of ILD display severe pulmonary hypertension (previously termed "out of proportion pulmonary hypertension") that cannot be fully accounted for by the degree of hypoxia and restrictive ventilatory defect as indicated by the poor or absent correlation with arterial oxygen tension and lung volumes [6, 8, 10, 16, 23, 25, 28, 29, 31–33]. This apparent disconnect is thought to be accounted for by pulmonary artery remodelling accompanying the parenchymal disease [2, 9, 13, 14]. In contrast, the prevalence and severity of pulmonary hypertension in several types of ILD, such as IPF [23, 24, 34, 35], scleroderma [27, 36, 37] and sarcoidosis [23, 28, 38], correlate significantly with low diffusing capacity of the lung for carbon monoxide (especially with values <40% of predicted) reflecting perfusion impairment.

Evidence on the natural history of pulmonary hypertension in ILD is limited. In the majority of IPF subjects with mild-to-moderate restriction (n=117), PAP remained stable over 1 year [34]. In contrast, transplant candidates with severe IPF [39] and scleroderma [37] showed haemodynamic progression of pulmonary hypertension. Also, a clear histological progression of pulmonary vessel involvement was observed in few patients with PLCH despite the absence of progression of parenchymal bronchiolar lesions [6]. Overall, it remains unclear whether pulmonary hypertension in ILD may be progressive because of vasculocentric events or whether the increases in PAP are a mere surrogate for progression of the parenchymal disease and chronic respiratory failure [21].

The right heart

Retrograde transmission of the elevated PAP raises the intraluminal pressure and increases the wall stress of the right ventricle. Since an increase in wall stress increases myocardial oxygen demand and impedes myocardial perfusion, an important adaptation of the right ventricle is to increase wall thickness by accumulating muscle mass (hypertrophy) and to assume a more rounded shape [40]. However, the right ventricle is not capable of sustaining long-term pressure overload. Eventually, myocardial contractile force declines and the right ventricle dilates. This establishes a vicious circle with further increase in the right ventricular wall tension, greater oxygen demand and impaired myocardial perfusion [40], resulting in right ventricular failure, significant exercise limitation and increased mortality [24, 41]. In reality, of course, the right ventricular flow output is limited well before right ventricular dilatation occurs as right ventricular failure in pulmonary hypertension is a continuum from insufficient systolic function to increased ventricular dimensions [42]. Theoretically, the function of the right heart may also be compromised by the stiff lung parenchyma *via* restriction of the right ventricular diastolic filling and, in turn, prevention of a compensatory increase in stroke volume by the Starling mechanism [43]. Collectively, these effects are increasingly recognised as leading to right ventricular–pulmonary arterial uncoupling where the relationship between the right ventricular contractility and the afterload present in the pulmonary circulation becomes dysfunctional [44].

The left heart

In the presence of pulmonary hypertension, biventricular dysfunction ensues with increasing frequency and severity. As right ventricular function declines, underfilling of the left ventricle develops as result of the decreasing stroke volume and increasing contraction time of the right ventricle. The prolonged right ventricular contraction leads to ventricular dyssynchrony and a leftward bowing of the interventricular septum that impairs the left ventricular filling volume during early diastole [45].

In contrast, in the absence of pulmonary hypertension or separate comorbidities, left ventricular dysfunction is not common in ILD. Accordingly, pulmonary capillary wedge pressure most usually remains within the normal range [46]. Individual studies in IPF patients reported a low prevalence of elevated pulmonary capillary wedge pressure during RHC between 9% [34] and 16% [47]. However, as most haemodynamic evaluations during RHC were performed at rest, a more frequent and significant impairment in cardiac performance during exercise cannot be ruled out.

Direct cardiac involvement that may occur in some types of ILD may account for the development of left ventricular dysfunction and subsequent post-capillary pulmonary hypertension (pulmonary hypertension due to left heart disease; group 2 pulmonary hypertension [1]) in a subset of patients with ILD. In systemic sclerosis, for example, ischaemic, fibrotic and inflammatory cardiac lesions occur commonly, and may lead to subclinical or clinical diastolic left ventricular dysfunction. Less frequently, systolic dysfunction, arrhythmias, conduction system defects, pericardial and valvular disease as well as overt heart failure can also develop [4, 48, 49]. When clinically manifested, direct cardiac involvement in systemic sclerosis is of adverse prognostic significance [49]. Patients with sarcoidosis are also at risk of direct myocardial involvement that may result in left ventricular dysfunction [38]. In a retrospective analysis of 363 patients with sarcoidosis listed for lung transplantation, resting pulmonary capillary wedge pressure was concomitantly higher in the setting of pulmonary hypertension (n=268); however, it remained within the normal range (<15 mmHg) even in the subset of patients with severe pulmonary hypertension (n=131) [28]. Sarcoid granulomatous infiltration of the myocardium and sinus node might have been the basis for the exertional dyspnoea, increased heart rates and exercise limitation observed in patients with sarcoidosis compared with healthy subjects [50].

The response to exercise

The response of the pulmonary vasculature to exercise in ILD is abnormal. The naturally occurring increase in PAP during exercise is commonly exaggerated in patients with ILD. The correlation between rise in mPAP and fall in systemic oxygenation in exercising IPF patients suggests that this may be in part due to amplified hypoxic vasoconstriction during exercise [51]. Additionally, parenchymal lung abnormalities may impair the mechanisms of pulmonary vascular recruitment and distension that normally prevent disproportionate surges in PAP during exercise [52]. Eventually, increased filling pressure in the pulmonary vasculature, right heart and central veins is thought to affect the breathing pattern and exaggerate dyspnoea [53]. The right heart most likely contributes to the sensation of dyspnoea *via* mechanoreceptors situated in the right atrium and ventricle that relay details of filling pressure and volume and the amount of work performed by the right ventricle, *via* afferent sympathetic pathways, to the central nervous system [54–56].

As a result of the relatively reduced stroke volume, patients with ILD typically have heart rate values higher than normal (compensating tachycardia) [52] that allow for a preserved cardiac output at submaximal levels of exercise [57]. Tachycardia may also be independently triggered by arterial hypoxaemia. However, the deleterious effect of the reduced left ventricular pre-load becomes pronounced at higher work intensities where cardiac output is impaired compared with age-matched healthy individuals despite an exaggerated heart rate response [52, 53].

Ultimately, the increase in the right ventricular stroke volume in response to exercise often becomes inadequate to match the increase in oxygen requirements of the peripheral muscles, resulting in exercise limitation. Indeed, interceding pulmonary hypertension resulted in significantly impaired 6-min walking distance (6MWD) in patients with IPF [24] and decreased peak oxygen uptake in patients with ILD [58]. GLASER et al. [59] reported a significant reduction in exercise capacity in IPF patients with systolic PAP >50 mmHg compared with those with moderate pulmonary hypertension, and a strong inverse correlation between systolic PAP at rest and maximal exercise performance. In the study by BOUTOU et al. [60], maximum work rate, peak oxygen uptake, anaerobic threshold, peak oxygen pulse and ventilatory equivalent for carbon dioxide were significantly lower in IPF patients with severe pulmonary hypertension (systolic PAP >50 mmHg) compared with matched patients with mild pulmonary hypertension (systolic PAP 36–50 mmHg) or those without pulmonary hypertension. Also, systolic PAP at rest correlated with indices of gas exchange and circulatory status (peak oxygen uptake, anaerobic threshold, peak oxygen pulse and end-tidal oxygen at anaerobic threshold), but not with defective lung mechanics [60].

A stress test such as cardiopulmonary exercise testing (CPET) may unmask pulmonary vascular pathology which is silent at rest. Recently, DEGANI-COSTA et al. [61] reported on exercise haemodynamics in 27 patients with ILD and normal or near-normal mPAP at rest and 11 matched controls. 15 patients had an abnormally steep mPAP−cardiac output slope $\geqslant 3$ mmHg·min·L^{-1}, indicating an abnormal pulmonary vascular response to exercise. These subjects did not differ from the patients with lower mPAP−cardiac output slope in terms of age, sex, body mass index, pulmonary function testing or degree of exercise oxygen desaturation, but had decreased peak oxygen uptake and increased minute ventilation. These results suggest that exercise-induced abnormal pulmonary vascular response is relevant in ILD [62]. However, due to the lack of suitable definition and reliable data that define which levels of exercise-induced changes in mPAP or PVR have prognostic value and therapeutic consequences, a disease entity "pulmonary hypertension on exercise" cannot be defined and current guidelines do not support its use [3, 22].

Pulmonary hypertension adds to the respiratory burden in ILD. Exercising ILD subjects with pulmonary hypertension (but not matched ILD subjects without pulmonary hypertension) showed significantly

pronounced ventilatory inefficiency (expressed as increased slope of minute ventilation to carbon dioxide output) both at the anaerobic threshold and during peak exercise [63]. Also, the ventilatory inefficiency in patients with ILD correlated with systolic PAP [59, 60], predicted independently the presence of pulmonary hypertension [60], and associated strongly with dyspnoea and exercise limitation [59]. The increased ventilatory requirements relative to the metabolic rate in the presence of pulmonary hypertension can be attributed to 1) dead space ventilation due to hypoperfusion of ventilated alveoli, 2) increased lactic acid ventilatory drive resulting from hypoperfusion of exercising skeletal muscles and 3) increased hypoxic ventilatory drive. Subjects with ILD and pulmonary hypertension show generally higher levels of resting and exercise hypoxaemia compared with matched subjects without pulmonary hypertension [34, 60]. An abrupt hypoxaemic effect may develop due to intracardiac right-to-left shunting across a patent foramen ovale when right atrial pressure exceeds left atrial pressure [64], whereas functional intrapulmonary right-to-left shunt might be another hypoxaemic mechanism [65]. Indeed, abnormal anastomoses between the pulmonary and systemic circulation exist in patients with diffuse pulmonary fibrosis with or without pulmonary hypertension [66]. Finally, an abnormally low cardiac output in the presence of ventilation–perfusion inequality may also cause hypoxaemia due to mixed venous hypoxaemia [67].

Cardiovascular impairment may not simply add to the effect of the restrictive ventilatory impairment on exercise capacity in ILD; it may actually be the primary determinant of exercise limitation in ILD. A retrospective review of 42 ILD patients who underwent CPET reported that physiological indices of cardiovascular dysfunction (including early anaerobic threshold and low oxygen pulse) correlated with exercise limitation more closely than ventilatory mechanics (breathing reserve: maximum voluntary ventilation minus the peak ventilation) or gas exchange impairment (partial pressure of oxygen, dead space ventilation) [58]. In fact, patients with reduced peak oxygen uptake values often had a normal breathing reserve, whereas cardiovascular dysfunction was correlated with the severity of the underlying lung disease [58]. Circulatory impairment, as determined by low oxygen pulse and low oxygen uptake at anaerobic threshold, was also the primary limitation to exercise in most patients with systemic sclerosis [68]. Finally, patients with IPF were more likely to be circulatory limited than those with scleroderma [64], which suggests that the pathophysiological abnormalities in patients with ILD depend on the specific aetiologies.

Therapy

Currently there is no specific therapy for pulmonary hypertension due to ILD [3]. The treatment of the underlying lung disease should be optimised. Patients who are hypoxemic should receive long-term oxygen therapy adapting the general recommendations for chronic obstructive pulmonary disease (COPD) [3]. Long-term oxygen therapy has been shown to partially reduce the progression of pulmonary hypertension in COPD, although PAP rarely returns to normal values and the structural abnormalities of pulmonary vessels remain unaltered [69].

The use of drugs approved for PAH is not recommended for patients with pulmonary hypertension due to lung disease [3]. Conventional vasodilators such as calcium channel blockers are not recommended because of their interference with hypoxic vasoconstriction, which diverts pulmonary blood flow from more seriously to less seriously affected lung segments and lack of efficacy after long-term use [2]. Sufficient evidence is lacking on the long-term use of vasodilators such as inhaled prostanoids or nitric oxide that may preferentially access the better ventilated/oxygenated areas of the fibrotic lung due to their advantageous mode of distribution [70, 71]. However, a 16-week monotherapy trial with inhaled iloprost was associated with improvement in baseline PVR, mPAP and activity in some patients with sarcoidosis-associated pulmonary hypertension [72]. Retrospective, small case series of patients with sarcoidosis-associated pulmonary hypertension also reported an acute reduction in PVR and sustainable clinical improvement to long-term intravenous epoprostenol (mean follow-up of 29 months) [73], and improvement in PVR and cardiac output/index with parenteral prostacyclin as monotherapy or in combination with oral vasodilators (mean follow-up of 12.7 months) [74]. Finally, 12-week treatment with parenteral treprostinil improved right heart haemodynamics and echocardiographic parameters in a small group of patients with pulmonary fibrosis with severe pulmonary hypertension (mPAP $\geqslant$35 mmHg) [75].

Although the value of 6MWD as a surrogate end-point in IPF-associated pulmonary hypertension has recently been questioned [76], 6MWD was improved by the phosphodiesterase-5 inhibitor sildenafil in a small open-label study of IPF patients with pulmonary hypertension [77]. Sildenafil also preserved the 6MWD and improved the St George's Respiratory Questionnaire score compared with placebo in the subgroup of 22 patients with right ventricular systolic dysfunction in a controlled trial of 180 patients with advanced IPF [78]. A phase II trial missed the primary end-point (reduction in PAP), but demonstrated efficacy of the soluble guanylate cyclase stimulator riociguat in decreasing pulmonary and systemic vascular resistance and increasing cardiac output and 6MWD in patients with pulmonary hypertension due to ILD [79]. However, a recent randomised controlled trial (www.ClinicalTrials.gov: NCT02138825) of riociguat

versus placebo in pulmonary hypertension due to IPF was discontinued prematurely due to increased rates of death and serious adverse effects in the riociguat study arm. Negative randomised trial results have already been reported in IPF for nonselective (bosentan [80]) and selective (ambrisentan [81], macitentan [82]) endothelin receptor antagonists. Ambrisentan has actually been contraindicated in IPF patients, regardless of the presence of pulmonary hypertension, due to its association with increased rate of disease progression and respiratory hospitalisation [81]. In summary, published experience with targeted PAH drug therapy is limited and so far there is no adequate evidence to suggest that PAH drugs result in improved symptoms or outcomes in ILD [3]. Finally, evidence is missing on the safety and efficacy of antifibrotic agents such as pirfenidone and nintedanib in patients with IPF-associated pulmonary hypertension.

Referral of patients with ILD to a unit with expertise in pulmonary hypertension should be considered on an individual basis. We advise referral for assessment if echocardiographic pressures seem excessive (systolic PAP >60 mmHg) for the measured abnormalities in lung function or there are other pulmonary hypertension-associated conditions. A comprehensive diagnostic workup including HRCT, ventilation/perfusion scan, complete lung function testing, CPET, sleep study and RHC (with or without and pulmonary angiogram) may be considered if therapeutic consequences are to be expected. The latter includes lung transplantation, alternative diagnoses such as PAH or chronic thromboembolic pulmonary hypertension or potential enrolment in a clinical trial. Of note, chance association of pulmonary hypertension is much less likely in IPF than in COPD [2]. Patients with suspected PAH in addition to their ILD (characterised by mild lung parenchymal abnormalities, symptoms insufficiently explained by lung mechanical disturbances and a haemodynamic "PAH phenotype", *i.e.* severe pulmonary hypertension with high PVR and low cardiac output) may be treated according to the recommendations for PAH, keeping in mind the potential implications of the coexisting lung disease on symptoms and response to therapy [3]. Patients with more severe ILD and severe pulmonary hypertension should preferably be included in randomised controlled trials if available [2].

Prognosis

Eventually, pulmonary hypertension develops into a negative prognostic factor for several types of ILD including IPF [24, 83], systemic sclerosis [84], sarcoidosis [16, 28], CPFE syndrome [85], PLCH [5] and lymphangioleiomyomatosis [8]. In a prospective study of patients with IPF, mPAP >17 mmHg was already
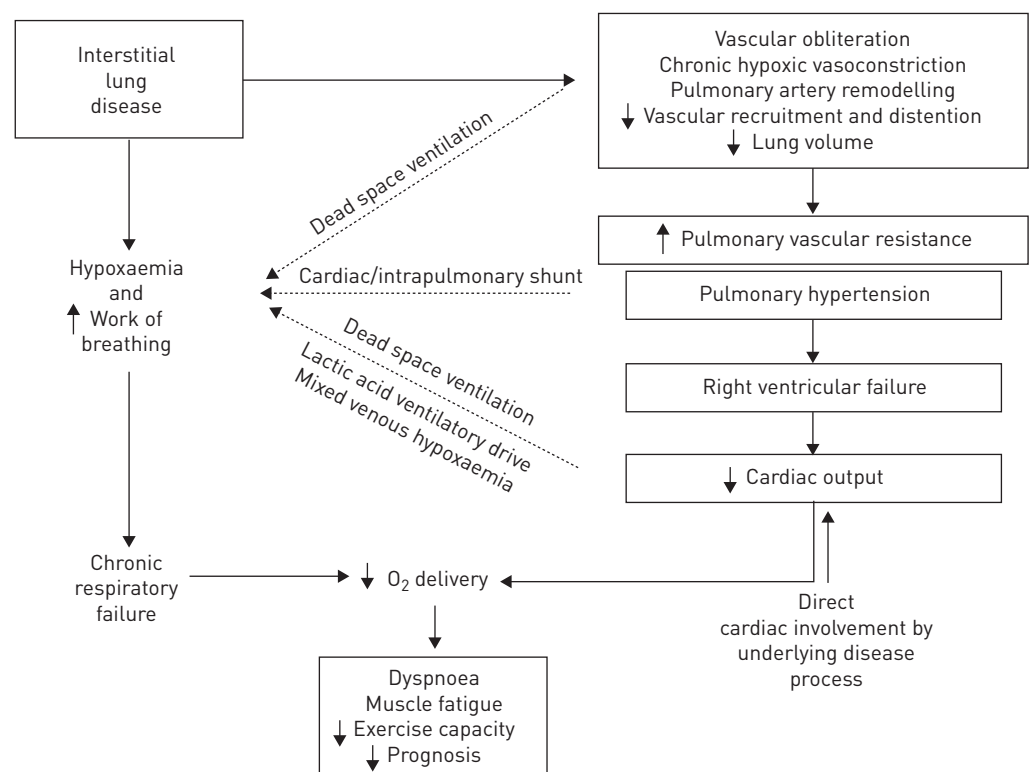

FIGURE 1 A summary of the pathogenesis, pathophysiology and clinical implications of the pulmonary vascular and cardiac abnormalities in interstitial lung disease. The dashed arrows denote the additive effect of the pulmonary vascular and cardiac impairment to the respiratory burden of interstitial lung disease.

linked to a poorer prognosis [35]. In systemic sclerosis, ILD-associated pulmonary hypertension was associated with a significantly poorer survival than systemic sclerosis-associated PAH, despite similar pulmonary haemodynamics [84, 86].

The pathogenesis, pathophysiology and clinical implications of the pulmonary vascular and cardiac impairment in ILD are summarised in figure 1.

Conclusions

Allowing for the heterogeneity of ILD, pulmonary vascular impairment with resulting pulmonary hypertension and right ventricular failure is the predominant cardiovascular abnormality. In a subset of patients, the degree of pulmonary hypertension is disproportional to the degree of the restrictive ventilatory defect and hypoxaemia due to remodelling of pulmonary vasculature. The development of pulmonary hypertension, especially mPAP ⩾35 mmHg, alters the natural history of ILD, resulting in increased morbidity and mortality. Unravelling the underlying mechanisms of this complex phenomenon will enable a better understanding of the natural history of ILD, differentiation between physiological limitations and assessment of the clinical manifestations of the disease; it may also enable effective therapeutic interventions which are currently missing.

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