Physiology of the lung in idiopathic pulmonary fibrosis

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Physiological impairment in IPF is complex and involves all compartments of the respiratory system
http://ow.ly/gyao30hdHUb

Cite this article as: Plantier L, Cazes A, Dinh-Xuan A-T, *et al*. Physiology of the lung in idiopathic pulmonary fibrosis. *Eur Respir Rev* 2018; 27: 170062 [https://doi.org/10.1183/16000617.0062-2017].

ABSTRACT The clinical expression of idiopathic pulmonary fibrosis (IPF) is directly related to multiple alterations in lung function. These alterations derive from a complex disease process affecting all compartments of the lower respiratory system, from the conducting airways to the lung vasculature. In this article we review the profound alterations in lung mechanics (reduced lung compliance and lung volumes), pulmonary gas exchange (reduced diffusing capacity, increased dead space ventilation, chronic arterial hypoxaemia) and airway physiology (increased cough reflex and increased airway volume), as well as pulmonary haemodynamics related to IPF. The relative contribution of these alterations to exertional limitation and dyspnoea in IPF is discussed.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia and one of the most frequently diagnosed interstitial lung diseases (ILDs). Although the novel antifibrotic agents pirfenidone and nintedanib attenuate the progressive decline in lung function characteristic of IPF [1], reduce the risk of hospitalisation or exacerbation [2, 3], and reduce the risk of death [3–5], IPF is a very severe disease where clinical decline is common. IPF is of particular interest to the lung physiologist because its clinical expression, which ranges from exertional dyspnoea occurring early in the disease to end-stage respiratory failure, is directly related to alterations in lung physiology. The aim of the present article is to review the multiple alterations in lung function in IPF. The diagnosis of IPF relies on high-resolution computed tomography (HRCT) scanning and pathological studies [6, 7], and is not discussed here. The role of lung function studies for prognostication and clinical decision making has been the focus of recent reviews [8–10]. Few data are available regarding the additional physiological derangements occurring during IPF exacerbations, so the present review focuses on stable or progressive IPF.

Received: May 22 2017 | Accepted after revision: Oct 15 2017

Conflict of interest: None declared.

Provenance: Submitted article, peer reviewed.

Pathobiology and pathology of IPF

The factors driving the course of IPF are not definitively identified. Current concepts implicate chronic and/or repetitive microinjuries of the alveolar epithelium as triggers of the disease. Such microinjuries may include environmental pollutants such as cigarette smoke, acid aspiration due to gastro-oesophageal reflux, and viral infections. Epithelial damage is followed by injury and/or activation of cells lining the vascular (capillary endothelial cells, pericytes) and interstitial (resident mesenchymal cells including alveolar fibroblasts) compartments of the lung, as well as the epithelium of distal airways and resident macrophages. Eventually, lung mesenchymal cells accumulate, undergo glycolytic reprogramming [11], and differentiate to myofibroblasts, which are considered the effector cells of fibrogenesis. Whether the epithelial-to-mesenchymal transition or the recruitment of circulating fibrocytes participates in the increase in myofibroblast numbers in IPF is subject to debate. Myofibroblasts synthetise an abnormally stiff extracellular matrix [12] that further drives mesenchymal cell activation through mechano-transduced signals [13].

The contribution of genetic factors to IPF is suggested by the occurrence of IPF-like disease in patients with rare genetic disorders [14] and by cases of familial idiopathic interstitial pneumonia [15]. Analysis of genetic factors provides valuable insight into IPF pathogenesis. The development of acute and chronic fibrotic lung disease in patients with mutations in the pulmonary surfactant apoproteins *SFTPA2* and *SFTPC* [15], or lipid transport genes such as *ABCA3* [16], suggests that alterations in surfactant composition or metabolism play important roles in IPF. The occurrence of IPF-like disease in patients with mutations in components of the telomerase complex (*TERT*, *TERC*) or other telomere-associated proteins (*DKC1*, *TINF2*, *RTEL1*) suggests the contribution of genomic instability, defective cell homeostasis and/or cell senescence to IPF [14, 17]. A gain-of-function mutant allele in the promoter regions of the gene coding the secreted mucin MUC5B is found in ~40% of patients with sporadic idiopathic interstitial pneumonia, including patients with IPF, *versus* 9–10% of control subjects [18, 19], although the mechanisms by which increased mucin production relates to alveolar fibrosis are not known.

IPF is associated with multiple pathological alterations involving most compartments of the lower respiratory system (figure 1). Lung fibrosis is defined by the replacement of the normal, compliant lung extracellular matrix, which is rich in elastin, with an abnormal matrix that is rich in fibrillar collagen [20]. Alveolar lesions conform to the usual interstitial pneumonia (UIP) pattern. The UIP pattern is defined by: 1) spatial heterogeneity, as lesions alternate with areas of normal lung; 2) temporal heterogeneity, with the concomitant presence of discrete lesions in lung tissue that appears otherwise normal (called fibroblastic foci) and fibrotic areas composed mainly of dense acellular collagen; and 3) the presence of honeycomb lesions, which are abnormal dilated airspaces with walls composed of fibrotic tissue, lined by an epithelium that shares characteristics with the airway epithelium [21, 22]. Tissular alterations are also present in other parts of the respiratory system in IPF. Expression of Ki67, a marker of cell proliferation, is detected in conducting airway epithelial cells [23, 24].

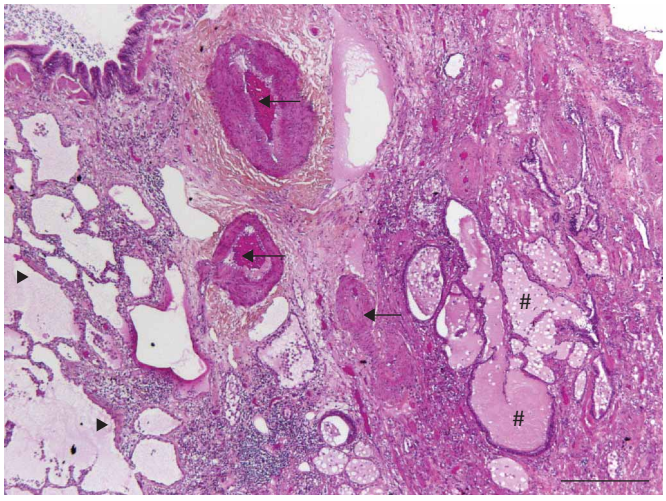

FIGURE 1 Pathological alterations in idiopathic pulmonary fibrosis (IPF). Lung biopsy of a patient with IPF showing the usual interstitial pneumonia pattern (haematoxylin–eosin–saffron stain; ×10 magnification; scale bar=500 µm). Fibrotic lung with microscopic honeycomb change (#) and remodelled arteries (arrows) is visible on the right, adjacent to preserved alveolar parenchyma on the left. Fibroblastic foci (arrowheads) are visible in between. A bronchiole is visible in the upper left corner of the micrograph.

Distinct vascular alterations are observed in the fibrotic regions and the more preserved regions of IPF lungs. In areas of dense fibrosis, sharp decreases in vessel density are observed [25, 26]. The walls of pulmonary arteries show intimal fibrosis and medial hypertrophy, and are thickened [27, 28]. Pulmonary veins and venules present loose and intimal fibrosis with reduced calibre [28]. In the histologically preserved areas, occlusion of pulmonary venules is frequent (65% of patients) and is associated with alveolar capillary multiplication [26] and/or muscularisation of arterioles, whereas arterial lesions are rare [28]. Capillary density is increased in regions bordering fibroblastic foci and honeycomb cysts [25].

Alterations in the mechanical properties of the lung

Reduction in lung compliance

Lung compliance describes the ability of the lung to expand and is key to describing the lung from a mechanical point of view. It is defined as the change in lung volumes divided by the change in transpulmonary pressure. IPF results in profound reductions in lung compliance. This reduction in lung compliance is driven both by reductions in the compliance of the lung extracellular matrix and by alterations in the pulmonary surfactant. In patients with IPF, lung surfactant shows alterations in its lipid profile (reduced phosphatidyl glycerol, increased phosphatidylinositol and increased sphingomyelin levels, alterations in fatty acid composition) [29, 30], leading to severely impaired surface activity compared to controls [29]. The association of IPF with mutations in genes associated with surfactant metabolism [15, 16] or with mutations in the telomerase complex [14, 17] driving accelerated epithelial cell senescence suggests that surfactant alterations may contribute to the progress of IPF.

Lung compliance is typically measured under quasi-static conditions during lung deflation, when flow is interrupted at several points during slow exhalation from total lung capacity (TLC). Transpulmonary pressure is defined as the difference between mouth pressure and oesophageal pressure in the absence of flow, under the assumption that mouth pressure approximates alveolar pressure and that oesophageal pressure approximates pleural pressure. Lung compliance measurements thus require placement of an oesophageal pressure probe. This invasive measurement is not routinely done in the clinic. Normal static lung compliance is 328±102 $mL{\cdot}cmH_2O^{-1}$ and normal dynamic compliance is 285±105 $mL{\cdot}cmH_2O^{-1}$ in Swedish men, with little impact of age [31].

Reductions in lung compliance occur early in IPF. In one series, static lung compliance was reduced in all but one out of 25 patients with IPF [32]. Among 31 IPF patients with a mean vital capacity (VC) of 79±17% predicted values, static lung compliance was constantly and strikingly reduced (44±6% pred) [33]. In another series of 14 IPF patients, none had normal static lung compliance [34]. Anecdotally, lung compliance was markedly reduced in a patient with biopsy-proven IPF but a normal chest HRCT scan [35]. Altogether, these data suggest that measurements of lung compliance may be helpful for the early diagnosis of IPF.

Reductions in lung compliance may be tightly correlated with the degree of lung fibrosis. Among 23 patients with biopsy-proven IPF, static lung compliance correlated with VC and TLC, but not with the diffusing capacity of the lung for carbon monoxide (D_{LCO}) [36]. Importantly, although no correlation was observed between standard physiological studies (VC, TLC, D_{LCO}) and pathological severity, static lung compliance was strongly correlated with the degree of fibrosis assessed by scoring of lung biopsies. Such an association between lung compliance and the extent of fibrosis was not replicated in another study [34]. Reduction in lung compliance appears to progress with disease. In seven patients with end-stage IPF requiring mechanical ventilation, dynamic lung compliance was considerably reduced (19±2.4 $mL{\cdot}cmH_2O^{-1}$) [37]. Reductions in dynamic compliance occur to the same extent as reductions in static compliance in subjects with ILD [38]. The forced oscillation technique allows noninvasive approximation of the dynamic compliance of the respiratory system in the absence of airway obstruction and may be of interest in IPF [39]. However, in an earlier study [40], no correlation was observed in five patients between lung compliance and either respiratory system resistance or reactance.

It remains to be defined how reductions in lung compliance relate to clinical features such as dyspnoea. Such an association is highly likely, considering that lung compliance is a major determinant of the load of the respiratory muscles and thus of the work of breathing [41]. The distribution of lesions is heterogeneous in IPF. It is therefore expected that the compliance of the lung is uneven among lung regions, as was shown in a sheep model of lung fibrosis [42], and consequently that convective ventilation predominantly occurs in the less affected regions of the lungs. In support of this hypothesis, the distribution of radiolabelled aerosols predominates in the upper regions of the lungs in IPF, whereas lesions predominate in the basal regions [43]. The distribution of ventilation to the less affected regions is an obstacle to the development of inhaled therapeutics for IPF.

Reduction of lung volumes

A restrictive ventilatory defect, defined by a reduction in static (TLC) and/or operating (VC) lung volumes, is typical in patients with IPF as in other ILDs [9]. Reduction of lung compliance is key to restriction because both chest wall compliance [37] and respiratory muscle strength, as assessed by measurements of transdiaphragmatic pressure [44] and maximal inspiratory pressure at the mouth [45], are mostly preserved.

Restriction is often absent at the time of diagnosis. In 96 patients with biopsy-confirmed IPF, forced vital capacity (FVC) ranged from 26% to 112% pred, while TLC ranged from 42% to 125% pred [46]. In recent clinical trials, mean FVC was close to 80% pred, consistent with half of patients having normal operating volumes [47]. These elements indicate poor sensitivity of lung volume measurements for the diagnosis of IPF. Although restriction of operating lung volumes is consistently associated with an increased risk of death [9], it correlates weakly with dyspnoea or an altered quality of life in IPF [48], consistent with other physiological alterations also playing key roles in clinical expression of the disease.

It is not known whether the lack of restriction in some patients reflects the natural history of IPF, or illustrates a limitation of population-based reference values. For instance, IPF subjects who had better than average lung function when healthy may present with apparently normal lung volumes before disease reaches a severe stage. The confounding effect of smoking could explain the preservation of static lung volumes in a fraction of patients, due to the effects of comorbid pulmonary emphysema on lung compliance [49]. Patients with the combined pulmonary fibrosis and emphysema (CPFE) syndrome have higher residual volume and TLC than patients with IPF [50].

Alterations in pulmonary gas exchange

IPF is associated with multiple alterations in the lung vasculature. In concert with alterations of the alveolar–capillary membrane, these lesions impair both gas diffusion and ventilation/perfusion (V'/Q') relationships in the lung, leading to reduced diffusing capacity of the lung, increased dead space ventilation, and increases in the alveolar–arterial oxygen tension difference (P_{A-aO_2}) and chronic arterial hypoxaemia.

Reduced diffusing capacity of the lung

Lung diffusing capacity is almost always reduced in patients with IPF. The D_{LCO} was reduced in 98% of IPF patients at the time of initial evaluation, although 27% of these patients had normal TLC and 56% had normal FVC [51]. Reduction of D_{LCO} results from parenchymal and vascular lesions, as described by the Roughton–Forster model where gas diffusion across the alveolar barrier depends on membrane conductance (D_{mCO}) and vascular conductance, the latter being mostly dependent on the pulmonary capillary volume [41].

D_{LCO} is usually measured by a single-breath test where the subject inhales a gas mix comprising an insoluble gas such as helium (He) or methane (CH_4) along with carbon monoxide. The volume where gas exchange occurs (alveolar volume (V_A)) and the transfer constant of carbon monoxide (K_{CO}) are calculated based on the reduction of He/CH_4 and carbon monoxide concentrations in exhaled breath. D_{LCO} is calculated by multiplying V_A and K_{CO} [52]. K_{CO} can also be referred to as D_{LCO}/V_A, although this term is misleading as it implies that D_{LCO} is the primary measurement from which D_{LCO}/V_A is then calculated, when the opposite is actually correct. Overall, D_{LCO} reflects the general gas-exchanging function of the whole lungs, while K_{CO} reflects gas exchange per unit of lung volume. Reference values for D_{LCO}, V_A and K_{CO} were obtained in healthy subjects at full lung inflation [53]. When the lungs are inflated below TLC (*i.e.* low V_A), D_{LCO} slightly decreases while K_{CO} increases [54]. The increase in K_{CO} at low lung volume in normal individuals is due to the incomplete expansion (unfolding) of alveolar walls resulting in increased mass of gas-exchanging tissue per unit of volume.

Both V_A and K_{CO} are reduced to varying degrees in IPF. Of note, K_{CO} is in the normal range in up to 30% of patients with IPF [55], particularly in patients with moderately altered D_{LCO} [56]. It is important not to misinterpret this finding as being indicative of a preservation of gas exchange units, as it can be surmised that full lung inflation may not be attainable in IPF where subpleural fibrosis impairs lung inflation. In normal subjects, K_{CO} increases at low lung volumes, so predicted values are inadequate to interpret K_{CO} in patients with restrictive disease [57]. In addition, the spatial heterogeneity of lesions in IPF may influence K_{CO} as relatively preserved areas of the lung are preferentially ventilated [43]. Our opinion is that a normal K_{CO} value in IPF patients does not indicate that pulmonary gas exchange is normal. D_{LCO} correlates more strongly than K_{CO} with exertional increases in P_{A-aO_2} in IPF [58]. D_{LCO} and K_{CO} both strongly correlate with the extent of disease as determined by scoring of computed tomography scans [59]. In support of the importance of D_{LCO} measurements to the clinical appraisal of IPF, D_{LCO} is highly correlated both with dyspnoea [60] and survival [61].

It is unclear whether alterations in the alveolar–capillary membrane or the lung vasculature are the predominant mechanism of D_{LCO} reductions in IPF. K_{CO} is inversely correlated both with oxygen diffusion limitation and with alveolar ventilation (V'_A)/Q' mismatch, as shown by the multiple inert gas elimination technique (MIGET) [62]. Simultaneous carbon monoxide and nitric oxide diffusion measurements can help to dissect to what extent alterations in the alveolar–capillary membrane or the lung vasculature contribute to reductions in D_{LCO}. Nitric oxide reacts almost immediately with haemoglobin, so the diffusing capacity of the lung for nitric oxide (D_{LNO}) is mostly independent of vascular conductance and is equal to the conductance of the alveolar–capillary membrane to nitric oxide (D_{mNO}). Because D_{mNO}/D_{mCO} is fixed, both D_{mCO} and vascular conductance can be calculated with the D_{LCO}/D_{LNO} technique [63]. Such studies show severe and similar decreases in both membrane conductance and lung capillary volume in IPF patients [64], indicating that alterations in the alveolar membrane and the lung vasculature both contribute to the impairment of gas diffusion in IPF [65]. However, it is worth noting that in one study, the capillary volume was in the normal range for half of 30 patients with IPF [66]. It is unclear whether discrepancies between these studies reflect differences in patient selection or are due to differences in data acquisition, as different equipment and procedures were used for carbon monoxide and nitric oxide measurements. Interestingly, in one study, the D_{LNO} correlated better than D_{LCO} with the extent of fibrotic lesions as assessed by HRCT [66]. Recent approaches based on hyperpolarised ^{129}Xe magnetic resonance imaging suggest that both impaired membrane conductance and transfer to red blood cells participate in the reduced pulmonary gas exchange in IPF [67].

Dead space ventilation

Patients with IPF have increased physiological dead space ventilation (increased ratio of dead space volume to tidal volume (V_D/V_T)) at rest and at exercise [62, 68]. This feature results from both increased anatomical dead space due to the increased volume of conducting airways [69], and from regional increases in V'/Q' ratios, *i.e.* alveolar dead space. V'/Q' lung scans demonstrate that fibrotic lesions, and honeycomb lesions in particular, are very poorly perfused although they still receive some ventilation [70].

Interestingly, severe dead space ventilation may be a peculiar feature of IPF in comparison with other ILDs, as patients with IPF fail to reduce V_D/V_T at exercise [62], in contrast with patients with asbestosis [71]. V_D/V_T at exercise is strongly correlated with D_{LCO} in IPF [55]. It is not known whether direct or indirect measures of V_D/V_T at rest and exercise provide additional information in comparison with resting measurements of gas diffusion in the lung, although experience acquired in the context of pulmonary hypertension (PH) [72] or heart failure [73] suggests this may be so.

Chronic arterial hypoxaemia

Alterations in the mechanical properties of the lungs, abnormalities of the lung vasculature and diffusion impairment lead to early-onset exertional chronic arterial hypoxaemia and later-onset resting chronic arterial hypoxaemia in IPF. Alveolar hypoventilation (hypercapnia) while awake is not common in IPF and is considered a feature of end-stage disease [74], when respiratory muscles fail in the face of a highly increased mechanical load (strongly reduced lung compliance). Alveolar hypoventilation is frequent during sleep in IPF [75]. An increase in P_{A-aO_2} is the main mechanism driving hypoxaemia in IPF [62]. P_{A-aO_2}, which is calculated from arterial oxygen tension (P_{aO_2}) and arterial carbon dioxide tension (P_{aCO_2}) using the ideal alveolar gas equation [41], can be increased because of reduced V'/Q' ratios, right-to-left shunting, or impairment of oxygen diffusion *per se* (referred to in the past as "alveolar–capillary block"). In a series of 15 patients, MIGET demonstrated that V'/Q' mismatch and diffusion impairment contributed to chronic arterial hypoxaemia in IPF [62]. In that study, 2% and 4% of cardiac output perfused areas with absent (shunting) or altered (low V'/Q') ventilation, respectively, while breathing room air at rest, suggesting that right-to-left shunting was in the physiological range in these patients. MIGET allows the calculation of a predicted P_{aO_2} value based on the observed V'_A/Q' mismatch, under the assumption that diffusion limitation does not occur. In IPF, the observed P_{aO_2} was lower than the predicted value, allowing the attribution of 19% of P_{A-aO_2} to diffusion limitation [62] at rest. At exercise, V'/Q' and shunt accounted for 60% of P_{A-aO_2} and diffusion limitation for 40% [62]. These data are consistent with a more recent MIGET study [76]. It is not known whether exaggerated decreases in central venous oxygen tension contribute to hypoxaemia in IPF at rest. At submaximal exercise, the oxygen tension of mixed venous blood was 29 mmHg in IPF patients [62], similar to healthy subjects [77].

Although V'/Q' mismatch and diffusion limitation are the main contributors to increased P_{A-aO_2} in IPF, anatomical right-to-left shunting may contribute in a fraction of patients. In a study of 15 IPF patients breathing 100% oxygen, mean P_{aO_2} and P_{aCO_2} were 481 mmHg and 38 mmHg [62], which translate to a shunt fraction of 12% according to the shunt equation. At variance with earlier reports [62, 78], brain imaging following intravenous injection of ^{99m}Tc-labelled albumin aggregates demonstrated right-to-left shunting in two out of 22 patients with IPF [79]. It was not reported whether contrast echocardiography

confirmed the existence of anatomical shunting, and it is unclear whether shunting resulted from the IPF disease process or was incidental in these patients. Identifying the few patients with anatomical shunting may be clinically important. It is reported that closure of the abnormal communication partially corrected chronic arterial hypoxaemia in a patient with IPF [80]. However, the benefit of shunt closure should be precisely evaluated because shunt could be life-preserving if the patient had concomitant PH.

Alterations in the structure and function of the conducting airways

IPF is understood to primarily involve the alveolar regions. Several lines of evidence, however, suggest that IPF also affects the airways. IPF lungs show evidence of airway epithelial cell proliferation [23] and differentiation [69], along with increased numbers of bronchioles in the distal regions [24]. In line with these observations, alterations in the function of conducting airways have been observed.

Elevation of nerve growth factor levels in induced sputum, which preferentially samples proximal airways, raises the hypothesis that the proximal airways may be involved in IPF [81]. Patients with IPF have an increased cough reflex to inhaled capsaicin. The inhalation of substance P induces cough in some IPF patients, which does not occur in normal subjects [59]. These data suggest functional upregulation of airway sensory neurons in IPF. Cough, however, may not be related to alterations in conducting airways only, as direct stimulation of the chest wall suffices to induce cough in IPF patients [82].

Multiple data suggest reduced resistance of the conducting airways in IPF. Among 55 IPF patients with a mean age of 71 years, the mean ratio of the forced expiratory volume in 1 s (FEV_1) to FVC (FEV_1/FVC) was 0.83 [56], which is higher than expected (0.74 for males, 0.75 for females according to European Respiratory Society reference equations) [83]. The ratio of the forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) to FVC ($FEF_{25–75\%}$/FVC) correlates positively with HRCT indices of IPF [39], suggesting that airway dilation occurs as part of the disease process. The increase in FEV_1/FVC and $FEF_{25–75\%}$/FVC is consistent with data obtained with aerosol-derived morphometry, which show increased airway dimensions at all lung depths in IPF [84]. Recently, we measured the volume of conducting airways by volumetric capnography in patients with IPF, other ILDs and healthy controls. Interestingly, airway volume was higher in IPF than in controls and non-IPF ILDs, suggesting that increased airway volume may be somewhat IPF-specific [69]. Anecdotal evidence indicates reduced distensibility of the proximal airways in IPF, although it is not clear whether this is related to either reduced compliance of the airway wall or to changes in airway transmural pressure due to increased lung recoil [85].

Alterations in pulmonary haemodynamics

Vascular lesions lead to disproportionate increases in pulmonary vascular resistance (PVR) and PH in a subset of patients with IPF. Right heart catheterisation is the gold standard for the diagnosis of PH, which is defined as a mean pulmonary artery pressure (mPAP) $\geqslant$25 mmHg at rest [86].

PH associated with IPF may represent a specific phenotype of IPF. In a series of 488 IPF patients with minimal honeycomb changes (<5% of the lung) and mild-to-moderate restriction (mean FVC between 67% and 69% pred), right-heart catheterisation showed PH without elevated capillary wedge pressure in 14% of patients, PH with elevated wedge pressure in 5%, and isolated elevated wedge pressure in 4% [87]. Patients with PH and normal capillary wedge pressure had lower D_{LCO} and increased haemoglobin desaturation at exercise. Interestingly, PH does not seem to progress rapidly in these patients, as repeat catheterisation at 48 weeks yielded levels quite similar to baseline [87].

The prevalence of PH is 46.1% in patients with severe IPF listed for transplantation [88]. Severe PH correlates with elevated capillary wedge pressure, suggesting the participation of left-sided ventricular dysfunction to PH in IPF patients [88]. The prevalence of PH appears to be lower in IPF compared to connective tissue disease-associated ILD of similar severity [89]. PH is associated with increased mortality in IPF. In a series of 135 patients, there was a 2.4 increase in the hazard ratio (HR) for death per 10 mmHg increase in mPAP, while an increase in PVR of 1 Wood unit was associated with a 1.4 increase in the HR for mortality [90].

The precise nature of lesions driving PH in IPF is not well understood. There is no correlation between mPAP and operating lung volumes [87, 91]. Anatomical–functional correlation analysis in 26 explanted lungs showed that mPAP is significantly correlated with the extent of fibrosis in damaged regions, but no correlation exists between mPAP and the extent of venous lesions in less-damaged areas [28]. It is probable that the rarefaction of vessels in fibrotic areas contributes to PH in IPF, as suggested by the presence of major defects on V'/Q' lung scans [92]. It is possible that the discrepancy between global vascular rarefaction [93] and the higher density of capillary vessels in alveolar septa of IPF lungs [94] pertains to variation in the sites of biopsy.

Impairment of pulmonary haemodynamics at rest is detected late in IPF, although early alterations may be detected at exercise. Increases in mPAP are observed in IPF patients during exercise at 60% of the maximal workload, while PVR does not decrease as observed in normal subjects [62]. In favour of the early onset of vascular damage in IPF, mPAP increased from 20 mmHg to 40 mmHg in seven patients with mild-to-moderate IPF [76]. The increase in oxygen diffusion impairment at exercise, documented by MIGET, is consistent with decrease of the alveolar–capillary contact time subsequent to the increase in cardiac output, most probably indicating reduced recruitment of the lung vasculature in IPF [62].

Measurements of systolic pulmonary artery pressure by echocardiography lack sensitivity and specificity for the diagnosis of PH in IPF [75]. Other echocardiographic indices may be useful for the identification of right ventricle dysfunction and PH. A right ventricle to left ventricle diameter ratio >1 is associated with a 5.4 increase in the HR for mortality in IPF [90], while moderate-to-severe right ventricle dysfunction, identified by tricuspid annular plane systolic excursion <1.6 cm, is associated with a 7.5 increase, suggesting that echocardiography may indeed have a role for the identification of IPF patients with clinically significant pulmonary vascular impairment [90]. HRCT measurements of the diameter of the pulmonary artery do not accurately indicate PH in IPF, possibly due to the confounding effect of reduced pleural pressure causing the dilation of cavitary intrathoracic organs [76]. Noninvasive measurements of pulmonary blood flow using rebreathing of sulfur hexafluoride may be an interesting tool for the exploration of haemodynamic limitation in IPF [77].

Central control of ventilation

Alterations in lung mechanics and gas exchange drive persistent activation of the central command of ventilation in IPF. An elevated ventilatory drive, detected by a rise in the 100 ms occlusion pressure ($P_{0.1}$), was reported in patients with ILD, at rest and under carbon dioxide rebreathing [44, 95]. Correlations between $P_{0.1}$ and both lung compliance and VC were observed in IPF, suggesting that the increased ventilatory drive reflects the mechanical load imposed by fibrosis [96, 97]. An association was also observed between $P_{0.1}$ and K_{CO} in patients with ILD, suggesting that impaired gas exchange contributes to ventilatory drive [98]. Diaphragm activation is increased in IPF in comparison with healthy subjects, both during carbon dioxide rebreathing [99] and at exercise [38], consistent with the preservation of the command of ventilation in this disease.

Impact of comorbidities on lung function in IPF

Because IPF typically affects older patients and smokers, multiple comorbidities can affect patients with IPF [100, 101]. In particular, chronic obstructive pulmonary disease (COPD) and pulmonary emphysema are common. The prevalence of emphysema in patients with IPF, which defines the CPFE syndrome, ranges from 6% to 67% [100]. Emphysema is associated with higher FVC and TLC at diagnosis in patients with IPF [102]. CPFE is associated with markedly lower D_{LCO}, especially when emphysema is present in lung areas not affected by fibrosis [103]. Of note, the pattern of lung function impairment in CPFE is quite distinct from COPD. Some, but not all, patients with CPFE present with airway obstruction and hyperinflation [104]. Impulse oscillometry showed that the expiratory increase in the reactance of the respiratory system at low frequency (5 Hz), which indicates expiratory collapse of the distal airways, was much lower in CPFE than in COPD [104], consistent with the lack of dynamic hyperinflation in CPFE [104]. It is not known whether lung compliance is affected in CPFE to the same extent as in IPF without emphysema. 9.1% of IPF patients show reversible airflow obstruction as indicated by a 200 mL and 12% increase in either FVC or FEV_1 after inhalation of a bronchodilator, although it is not clear whether this reflects comorbid asthma or COPD, or an intrinsic feature of IPF [105].

Heart disease is a common occurrence in patients with IPF. The prevalence of coronary heart disease has been reported to range from 3.2% to 68% [100]. 9% of patients with mild to moderate IPF and left ventricle ejection fraction ⩾40% have increased pulmonary artery wedge pressure, indicating occult heart failure [87]. In terms of lung function, heart failure can be associated with restriction, obstruction, reduced D_{LCO} [106, 107] and PH [108]. Heart failure with preserved ejection fraction is associated with reduced D_{LCO} [109]. Venous thromboembolism may also contribute to low D_{LCO} in a fraction of IPF patients. Venous thrombosis is twice as frequent in IPF patients as in the control population [110], while the incidence of pulmonary embolism is 6.4-fold higher in IPF than in the general population.

Lung function indices as indicators of prognosis and outcomes in clinical trials

The severity of lung function impairment at the time of diagnosis and the decline of lung function over time are both tightly associated with survival in IPF. Impairment of operating lung volumes, static lung volumes and carbon monoxide transfer are associated with worse prognosis in IPF, with the strongest associations observed with FVC, TLC and D_{LCO}, respectively [111]. In a large cohort (n=1156), FVC <80% pred and D_{LCO} ⩽45% pred were associated with increased mortality [112]. Since a >5% absolute

decline in FVC (% pred) and a ⩾15% decline in D_{LCO} (% pred) over 6 months are also highly associated with mortality [112], follow-up investigations are critical to determine prognosis in patients with IPF. The prognostic impact of lung function may be assessed using composite indices such as the Composite Physiological Index, which combines FVC, FEV_1 and D_{LCO} [113], or the Gender Age Physiology score, which combines FVC and D_{LCO} with gender and age [114].

The rate of decline in FVC was the most common primary outcome end-point in recent clinical trials in IPF, expressed either in millilitres per year [47] or as percentage of the predicted value [115–117]. It is currently debated whether change in FVC over time is the optimal outcome for clinical trials in IPF. The presence of emphysema affects the rate of FVC decline in IPF. Patients with more emphysema show less decrease in FVC, while D_{LCO} does decline, raising the hypothesis that FVC may not be the best end-point in patients with emphysema [118]. In a series of 32 patients with IPF and moderate to severe emphysema, a 10% decline in FVC also failed to predict mortality [119]. In addition, although decline in both FVC (10%) and D_{LCO} (15%) do predict mortality in the subsequent year, neither predicts change in lung function in the subsequent year [120]. These limitations to the use of FVC decline have led to the use of progression-free survival, defined as time to all-cause death or a categorical decrease from baseline in FVC % pred, in a recent trial of LOXL2 antibodies [121].

How do physiological alterations integrate in IPF? Exercise limitation and dyspnoea

The multiple alterations of lung physiology in IPF translate into profound alterations in exercise capacity and dyspnoea. Oxygen uptake, power, tidal volume and P_{aO_2} are reduced at exercise in IPF patients compared with healthy controls [38, 68], while P_{A-aO_2} and V_D/V_T are increased.

It is not clear whether reduced lung compliance, haemodynamic dysfunction, hypoxaemia or increased V_D/V_T are the prime determinants of dyspnoea and exertional limitation in IPF. Short-term therapeutic intervention studies addressed this question. Alleviation of the load of the respiratory muscles by noninvasive ventilation during submaximal exercise leads to increases in endurance time and arterial haemoglobin saturation, and reductions in breathlessness [122]. These data clearly indicate that alterations in the mechanical properties of the respiratory system play an important role in exercise limitation in IPF patients, and are consistent with both the reduction in operating lung volumes and increased diaphragmatic activity at exercise [38].

PH may play key roles in a subset of patients. When PH is present, it is associated with reduced oxygen pulse at exercise, consistent with haemodynamic limitation [123], with more severe arterial haemoglobin desaturation at exercise [87] and with increased V_D/V_T, as suggested by an increase in the ratio of minute ventilation (V'_E) to carbon dioxide elimination (V'_{CO_2}) at the ventilatory threshold [124]. Likewise, correlations exist between the 6-min walk distance and both mPAP and PVR [125]. It is unclear whether these associations reflect a causative relationship between the alteration of pulmonary haemodynamics and exertional limitation in IPF patients without severe PH. In seven patients with IPF (mean FVC 60% pred, D_{LCO} 52% pred), two of whom had mPAP slightly over 25 mmHg at rest, the inhalation of nitric oxide during submaximal exercise reduced the increase in mPAP and reduced PVR, but did not increase cardiac output or P_{aO_2} and did not reduce V_D/V_T [76]. However, a 12-week course of oral sildenafil, which potentiates the effect of endogenous nitric oxide, yielded clinically significant benefits in terms of dyspnoea and quality of life in patients with advanced IPF [126].

Gas exchange abnormalities during exercise are highly prevalent in IPF. Patients with mild-to-moderate IPF and normal or near-normal resting P_{aO_2} have a significant decline in arterial haemoglobin saturation after a 6-min walk [127]. Multiple factors contribute to exertional arterial hypoxaemia in IPF, with alterations of both V'/Q' ratios [128] and diffusion [129] playing key roles. Uncontrolled retrospective [130, 131] and prospective [132] studies show increased walk performance, better quality of life and reduced dyspnoea in IPF patients treated with supplemental oxygen. This effect was observed both in patients with resting arterial hypoxaemia and in patients without resting arterial hypoxaemia [131, 132]. Whether the effect of oxygen therapy is related to a placebo effect remains subject to debate. In a controlled study, supplemental oxygen given at exercise in IPF patients with exertional arterial hypoxaemia but without resting arterial hypoxaemia failed to improve the 6-min walk distance and dyspnoea in comparison with placebo (air), despite improvements in arterial haemoglobin saturation [133], while another study reported beneficial effects with regard to endurance time and dyspnoea [134]. Indirect evidence suggests key roles of dead space ventilation in the genesis of dyspnoea, although the lack of a possibility to experimentally amend the V_D/V_T ratio precludes definitive demonstration. In a series of 25 IPF patients, the V'_E/V'_{CO_2} slope, which is tightly correlated with V_D/V_T, was the physiological parameter most strongly correlated with patient-reported exertional dyspnoea [135]. In addition to alterations in pulmonary anatomy and physiology, anaemia may occasionally contribute to gas exchange abnormalities

in patients with IPF. This condition may be more prevalent in patients bearing mutations of the telomerase complex [136].

Dyspnoea is the main complaint in patients with IPF. Exertional dyspnoea correlates with markers of both reduced lung compliance and altered pulmonary gas exchange [98, 137]. It is conceivable that the increased V'_E required to maintain P_{aCO_2} at normal levels in the face of high V_D/V_T, in combination with the reduced lung compliance requiring higher effort to increase ventilation and a small-volume/high-respiratory-rate breathing pattern [38], are responsible for increased ventilatory drive and dyspnoea in IPF. Strong correlations exist between increases in diaphragm activation and dyspnoea at exercise [38], as well as between $P_{0.1}$ at rest and patient-reported exertional dyspnoea [98]. Increased respiratory drive, secondary both to the increased elastic load and the higher ventilation levels required by abnormal pulmonary gas exchange, is a key contributor to dyspnoea in patients with IPF [138].

The role of physiological tests in the diagnostic workup of IPF patients presenting with an increase in dyspnoea remains to be defined. A key aim in this context is to determine whether clinical worsening relates to the natural history of IPF, or to other conditions. Exacerbations of IPF and comorbidities such as infection or heart failure would probably result in worsening of restriction, diffusion impairment and hypoxaemia. Because physiological alterations are nonspecific, it is unclear whether such tests would bring additional diagnostic information to clinical, biological and imaging studies in the context of acute or subacute dyspnoea, although pulmonary embolism may be associated with an isolated decrease in D_{LCO} [139]. Occasionally, specific physiological tests may help to recognise differential diagnoses of IPF. For example, respiratory muscle studies may help with recognising polymyositis-associated ILD [140].

TABLE 1 Alterations of lung function tests in idiopathic pulmonary fibrosis (IPF)

	Mild IPF	Moderate to severe IPF
Spirometry		
FVC	Normal	Decreased
FEV_1/FVC	Normal or increased	Normal or increased
Static lung volumes		
TLC	Normal	Decreased
FRC	Normal	Decreased
Blood gases at rest		
P_{aO_2}	Normal	Decreased
P_{aCO_2}	Normal	Decreased
Carbon monoxide transfer		
D_{LCO}	Decreased	Decreased
V_A	May be normal	Decreased
K_{CO}	May be normal	Decreased
Airways		
Cough reflex	Increased	Increased
Airway resistance	Decreased	Decreased
Pulmonary haemodynamics at rest		
PAP	May be increased	Frequently increased
PCWP	Normal	May be increased
Ventilatory drive		
$P_{0.1}$	May be normal	Increased
Ventilatory response to CO_2 rebreathing	Normal	Normal
Exercise physiology		
Peak V'_{O_2}	May be normal	Decreased
V_D/V_T	Increased	Increased
V'_E/V'_{CO_2}	Increased	Increased
PAP at exercise	Increased	Increased
P_{A-aO_2} at exercise	Increased	Increased

FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; FRC: functional residual capacity; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; K_{CO}: transfer constant of carbon monoxide; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; $P_{0.1}$: 100 ms occlusion pressure; V'_{O_2}: oxygen uptake; V_D/V_T: ratio of dead space volume to tidal volume; V'_E/V'_{CO_2}: ratio of minute ventilation to carbon dioxide elimination; P_{A-aO_2}: alveolar–arterial oxygen tension difference.

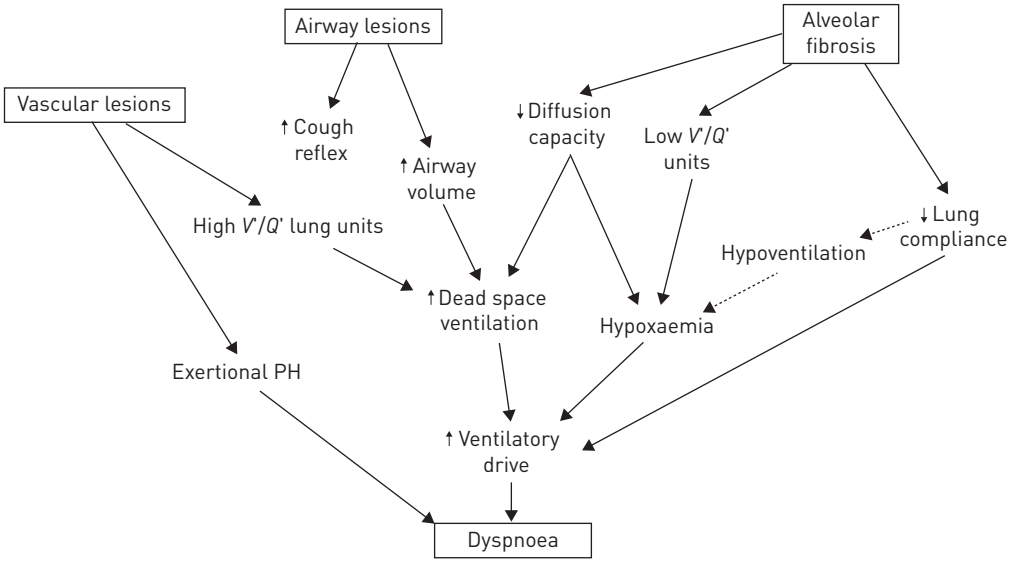

FIGURE 2 Model for the association between pathological features, physiological alterations and their association with pathological and clinical features. Filled arrows represent strong and/or demonstrated associations; dotted arrows represent associations seen in end-stage disease. V'/Q': ventilation/perfusion ratio; PH: pulmonary hypertension.

Conclusion

In IPF, pathological processes affect not only alveoli but also other regions of the respiratory system, such as the lung vasculature and conducting airways. As a result, patients with IPF show multiple alterations in lung physiology (summarised in table 1 and figure 2) that combine to a different degree in each individual patient, along with infrequent or rare alterations such as severe PH or right-to-left shunting. We advocate that, although spirometry and D_{LCO} measurements provide critical information and remain the backbone of the functional evaluation of IPF patients, physiological testing may not be limited to these tests when questions remain as to the explanation of the clinical picture in a given patient. In such a context, measurements of lung compliance, blood gas analysis while breathing 100% oxygen, assessment of pulmonary haemodynamics and exploration of the ventilatory drive, as well as exercise testing with quantification of dead space ventilation, may provide useful information when relevant comorbidities such as heart failure or anaemia have been ruled out. This aspect may be of particular importance for the definition of clinical–physiological disease phenotypes, analogous with other fields such as severe asthma [141]. Future studies will inform us about the respective roles of select physiological tests in the general IPF care strategy.

Acknowledgements

The authors thank Benoit Wallaert (University of Lille, Lille, France) for advice.

Authors contributions were as follows. L. Plantier prepared the first draft of the manuscript. C. Bancal, A. Cazes, A-T. Dinh-Xuan, S. Marchand-Adam and B. Crestani made important intellectual input and revised the manuscript. All authors have agreed to the final content.

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