**Alterations in the mechanical properties of the lung**

**Reduction in lung compliance**

{plantier2018physiology}

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) \citep{gunther1999surfactant, schmidt2002altered}, leading to severely impaired surface activity compared to controls \citep{gunther1999surfactant}. The association of IPF with mutations in genes associated with surfactant metabolism \citep{borie2012familial, campo2014large} or with mutations in the telomerase complex \citep{spagnolo2016genetics, borie2016prevalence} driving accelerated epithelial cell senescence suggests that surfactant alterations may contribute to the progress of IPF.

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 \citep{radwan1999functional}. 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) \citep{zielonka2010angiogenic}. In another series of 14 IPF patients, none had normal static lung compliance \citep{sansores1996correlation}. Anecdotally, lung compliance was markedly reduced in a patient with biopsy-proven IPF but a normal chest HRCT scan \citep{orens1995sensitivity}. 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 ) \citep{fulmer1979morphologic}. 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 \citep{sansores1996correlation }. 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·cmH 2 O −1 ) citep{nava1999lung}. Reductions in dynamic compliance occur to the same extent as reductions in static compliance in subjects with ILD \citep{faisal2016common}. 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 \citep{lopes2007correlation}. However, in an earlier study \citep{van1989total}, 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. 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 \citep{organ2015structural}, 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 \citep{kanazawa1993assessment}. The distribution of ventilation to the less affected regions is an obstacle to the development of inhaled therapeutics for IPF.

**Reduction of lung volumes**

{plantier2018physiology}

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 \citep{martinez2006pulmonary }. Reduction of lung compliance is key to restriction because both chest wall compliance \citep{nava1999lung } and respiratory muscle strength, as assessed by measurements of transdiaphragmatic pressure \citep{dimarco1983occlusion} and maximal inspiratory pressure at the mouth \citep{jastrzkebski2008pulmonary}, 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 \citep{cherniack1995correlation}. In recent clinical trials, mean FVC was close to 80% pred, consistent with half of patients having normal operating volumes \citep{richeldi2014efficacy}. 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 \citep{martinez2006pulmonary}, it correlates weakly with dyspnoea or an altered quality of life in IPF \citep{du2011ascertainment }, 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 \citep{doherty1997cryptogenic}. Patients with the combined pulmonary fibrosis and emphysema (CPFE) syndrome have higher residual volume and TLC than patients with IPF \citep{mura2006presence }.

{american2000idiopathic}

The lung volumes (TLC, functional residual capacity [FRC], and residual volume [RV]) are reduced at some point in the course of disease in all patients with IPF. Early on, or more commonly in patients with superimposed chronic obstructive pulmonary disease, the lung volumes may be normal. Lung volumes are higher in smokers compared with never-smokers with IPF \citep{hanley1991impact}.

**Small airway**

{crystal1976idiopathic}

This physiologic evidence of small airway disease correlates well with the morphologic observations that the small airways in idiopathic pulmonary fibrosis have peribronchiolar fibrosis and inflammation and that 70% of the patients with this disease show narrowed airways (Table 3). The clear association of abnormal physiologic function of small airways with the morphologic evidence of disease of these airways suggests that at least part of the ventilation abnormalities, and hence hypoxemia, of idiopathic pulmonary fibrosis may be due to small airways disease.

**Alterations in pulmonary gas exchange**

{plantier2018physiology}

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.

{american2000idiopathic}

The D CO (corrected for hemoglobin level) is reduced and may actually precede the reduction of lung volume. The reduction in the DLCO is probably caused both by a contraction of the pulmonary capillary volume and by ventilation and perfusion abnormalities. The resting arterial blood gases may be normal initially or may reveal mild hypoxemia and respiratory alkalosis. The major cause of resting hypoxemia is ventilation and perfusion mismatching and is not due to either impaired oxygen diffusion, as was originally suspected, or by anatomic shunts. With exercise, the alveolar–arterial O2 gradient (AaPO2) widens, and the arterial O2 pressure (PaO2) and arterial O2 saturation (SaO2) fall. During exercise, 20 to 30% of the exercise-induced widening of the AaPO2 may be caused by some impairment of oxygen diffusion. Importantly, the abnormalities identified at rest do not accurately predict the magnitude of the abnormalities that may be seen with exercise. Although these abnormalities can be assessed by oximetry saturation, it has been demonstrated that this method may not yield as dramatic or significant a change as that obtained by arterial blood gases. Thus, formal cardiopulmonary exercise testing is more sensitive than resting physiologic testing in the detection of abnormalities in O2 transfer, and exercise gas exchange has been demonstrated to be a sensitive parameter for monitoring the clinical course \citep{fulmer1979morphologic}.

**Reduced diffusing capacity of the lung**

{plantier2018physiology}

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 \citep{cortes2014idiopathic }. 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.

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 \citep{rosenberg19961995}. 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 \citep{macintyre2005standardisation}. When the lungs are inflated below TLC (i.e. low V A), D LCO slightly decreases while K CO increases \citep{johnson2000importance}. 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 \citep{wallaert2012we}, particularly in patients with moderately altered D LCO \citep{pastre2015different}. 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 \citep{frans1997effect}. In addition, the spatial heterogeneity of lesions in IPF may influence K CO as relatively preserved areas of the lung are preferentially ventilated \citep{kanazawa1993assessment }. 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 \citep{agusti1994clinical}. D LCO and K CO both strongly correlate with the extent of disease as determined by scoring of computed tomography scans \citep{wells1997lone}. In support of the importance of D LCO measurements to the clinical appraisal of IPF, D LCO is highly correlated both with dyspnoea \citep{swigris2012ucsd} and survival \citep{hamada2007significance}.

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) \citep{agusti1991mechanisms}.

**Dead space ventilation**

{plantier2018physiology}

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 \citep{agusti1991mechanisms, miki2009acidosis}. This feature results from both increased anatomical dead space due to the increased volume of conducting airways \citep{plantier2016increased}, 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 \citep{strickland1993cause}.

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 \citep{agusti1991mechanisms}, in contrast with patients with asbestosis \citep{agusti1988different}. V D /V T at exercise is strongly correlated with D LCO in IPF \citep{wallaert2012we}. 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) \citep{paolillo2012exercise} or heart failure \citep{poggio2010prediction} suggests this may be so.

{crystal1976idiopathic}

Another characteristic of idiopathic pulmonary fibrosis is the increased physiologic dead space found in 60% of the patients even at rest \citep{ holland1960physiologic, herbert1962pathophysiology, fulmer1976diffuse}. Whereas normal persons waste (that is, ventilate nonfunctional regions of lung) less than one third of their total ventilation, patients with idiopathic pulmonary fibrosis will often have dead space to tidal volume ratios (VD/VT) of greater than 0.4. In normal individuals the efficiency of ventilation improves with exercise (that is, the VD/VT falls) \citep{jones1966physiological, wasserman1975exercise}; in more than 90% of patients with idiopathic pulmonary fibrosis it stays constant or may increase (Figure 1, bottom).

**Arterial hypoxaemia**

{plantier2018physiology}

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 \citep{bennett2015mortality}, 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 \citep{milioli2016sleep}. An increase in P A–aO 2 is the main mechanism driving hypoxaemia in IPF \citep{agusti1991mechanisms}. 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, 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 \citep{agusti1991mechanisms}. 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 \citep{agusti1991mechanisms} at rest. At exercise, V′/Q′ and shunt accounted for 60% of P A–aO 2 and diffusion limitation for 40% \citep{agusti1991mechanisms}. These data are consistent with a more recent MIGET study \citep{blanco2010effects}. 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 \citep{agusti1991mechanisms}, similar to healthy subjects \citep{stringer1997cardiac}.

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 \citep{agusti1991mechanisms}, which translate to a shunt fraction of 12% according to the shunt equation. At variance with earlier reports \citep{agusti1991mechanisms, miller1986anatomical}, brain imaging following intravenous injection of 99m Tc-labelled albumin aggregates demonstrated right-to-left shunting in two out of 22 patients with IPF \citep{graves2003scintigraphic}. 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 \citep{nguyen2007idiopathic}. However, the benefit of shunt closure should be precisely evaluated because shunt could be life-preserving if the patient had concomitant PH.

{crystal1976idiopathic}

These investigators coined the term "alveolar-capillary block," suggesting that the hypoxemia of idiopathic pulmonary fibrosis was secondary to an anatomic barrier to oxygen due to a thickened alveolar interstitium \citep{ austrian1951clinical}. This term was popular in the literature until 1962, when Finley, Swenson, and Comroe \citep{ finley1962cause} presented data suggesting that the major cause of hypoxemia in these patients was not a diffusion barrier to oxygen, but rather was secondary to ventilation- perfusion mismatching. Clinicians had only recently adjusted to this new concept when it was challenged. Using sophisticated methods, Wagner and associates \citep{ wagner1976distribution} showed that most of the hypoxemia in idiopathic pulmonary fibrosis is indeed secondary to ventilation-perfusion imbalance. With exercise, however, ap proximately 20% is due to a diffusion barrier to oxygen. Thus, our understanding of this phenomenon has come full circle. We will see later that, although ventilation-perfusion mismatching is critically important in idiopathic pulmonary fibrosis, we are just beginning to understand what causes it.

Most patients with idiopathic pulmonary fibrosis have resting arterial hypoxemia that worsens with exercise. Polycythemia, however, is almost never seen \citep{ livingstone1964diffuse}, in marked contrast to other hypoxic states such as chronic obstructive lung disease or congenital heart disease \citep{ balcerzak1975secondary}.

The average patient with idiopathic pulmonary fibrosis had a total lung capacity of 62.9% predicted and a diffusing capacity of 46.8% predicted. However, two patients had normal lung volumes and one patient a normal diffusing capacity, even though they had morphologic evidence of mild to moderate fibrosis. Thus, although a reduced total lung capacity and diffusing capacity are the physiologic hallmarks of the disease, it is not mandatory that both be abnormal. Likewise, the average patient with idiopathic pulmonary fibrosis has resting arterial hypoxemia (69.3 mm Hg), but four of our patients have normal resting arterial oxygen tension (Pao2). It is important to point out that a decreased diffusing capacity does not implicate a defect in oxygen diffusion but rather signifies a reduction of available alveolar-capillary bed \citep{ hamer1964cause}.

**Alterations in the structure and function of the conducting airways**

{plantier2018physiology}

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 \citep{vuorinen2008peroxiredoxin} and differentiation \citep{plantier2016increased}, along with increased numbers of bronchioles in the distal regions \citep{chilosi2002abnormal}. In line with these observations, alterations in the function of conducting airways have been observed.

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 \citep{jones2011mechanical}.

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 \citep{pastre2015different}, which is higher than expected (0.74 for males, 0.75 for females according to European Respiratory Society reference equations) \citep{quajer1993lung}. 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 \citep{lopes2007correlation}, 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 \citep{brand1999aerosol}. 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 \citep{plantier2016increased}. 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 \citep{baier1981influence}.

{plantier2016increased}

Conducting airway volume was higher in subjects with IPF in comparison with controls and in

comparison with subjects with non-IPF ILD.

Airway volume was not associated with the severity of alveolar lesions in IPF

Airway volume was not associated with dyspnea, cough or quality of life

The main results of this study are that the volume of conducting airways was higher in subjects with IPF in comparison with control subjects and in comparison with subjects with non-IPF ILD, and that this increase was independent of the severity of alveolar lesions.

It may speculated that the increased airway volume in IPF patients reflects developmental abnormalities of the respiratory tree associated with either deleterious events in early life or gene variants that predispose to lung fibrosis, consistent with the lack of an association between VDaw and IPF severity in our study.

Increases in airway volume in IPF may reflect dilation of airways consistent with the characteristic extent of bronchiectasis in this disease. Supported by the observation that ground-glass opacities predate airspace enlargement \citep{akira1993idiopathic}, a commonly held view is that bronchiectasis in IPF may be caused by fibrotic retraction of peribronchiolar alveolar attachments and subsequent airway dilation, hence the frequently-employed term ‘traction bronchiectasis’ \citep{sumikawa2008computed}. Interestingly, we did not observe any relationship between airway volume and the severity of fibrosis assessed either by physiological measurements or imaging, while higher airway volume was present even in patients with moderate/ early IPF. This result is in line with recent data showing the lack of a relationship between bronchiectasis and total disease extent as assessed by CT scanning in IPF patients \citep{walsh2015relationship}. Put together, these observations suggest that the development of conducting airways lesions in IPF may be dissociated from alveolar fibrosis, and thus that retraction forces may not play critical roles in the development of bronchiectasis in this disease.

**Airway mechanics**

{american2000idiopathic}

Patients with IPF are tachypneic; they develop more rapid shallow breaths as the disease progresses, and therefore the work of breathing is increased \citep{ kornbluth1980respiratory, renzi1982pattern}. This rapid respiratory rate is felt to be secondary to altered mechanical reflexes, because of the increased elastic load and/or vagal mechanisms, since no defined chemical basis for the hyperventilation has been identified \citep{lourencco1965regulation, patton1972ventilatory, bradley1976regulation, van1981respiratory, savoy1981role, dimarco1983occlusion, renzi1986breathing}. Expiratory flow rates, forced expiratory volume in 1 s (FEV1), and forced vital capacity (FVC) are often decreased because of the reduction in lung volume, but the FEV1-to-FVC ratio is maintained or increased in IPF. However, because of the increased static elastic recoil found in these patients, flow rates when compared with lung volumes are often increased. Functional and pathologic alterations consistent with small airways disease have been described in patients with various interstitial pulmonary diseases, including IPF \citep{ ostrow1973resistance, Yernault1975Pulmonary, Fulmer1977Small, Schofield1976Small}. However, chronic airflow obstruction has been reported exclusively among smokers with IPF \citep{ kornbluth1980respiratory, renzi1982pattern, Mccarthy1980Chronic}.

**Alterations in pulmonary vasculature**

{plantier2018physiology}

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) ⩾25 mmHg at rest \citep{caminati2013pulmonary}.

{Puxeddu2017Impact}

Linkage between fibrosis and alterations in pulmonary vessel density in IPF is not a new observation. The histopathological evaluation of surgical lung biopsy samples performed by E BINA et al. \citep{ Ebina2012Heterogeneous} established that tissue surrounding regions of fibrosis in IPF is characterised by an increase in vessel profusion, whilst the fibrotic tissue itself demonstrates a reduced number of vessels. In line with these findings, fibroblastic foci, a pathological hallmark of IPF \citep{Raghu2011An}, have been shown to be relatively avascular \citep{Lappi1999Intraluminal} yet have a network of capillaries at the base of the lesion. Furthermore, within fibrotic regions of histopathological IPF samples, the normal reduction in vessel profusion with increasing distance from the alveoli spaces has been shown to be disrupted \citep{ Renzoni2003Interstitial}.

{Jacob2016Evaluation}

To further evaluate the PVV variable, relationships with markers of interstitial disease and pulmonary vascular disease were explored. On linear regression analyses, PVV demonstrated strong linkages with CALIPER ILD extent (R 2 =0.73, P <0.0001) and visual ILD extent (R 2 = 0.39, P <0.0001) but only weak associations with RVSP (R 2 = 0.09, P=0.002) and Kco (R 2 =0.05, P=0.002).

On univariate mortality analysis, predictors of mortality included CALIPER and visual measures of fibrosis including reticular pattern, honeycombing, and ILD and fibrosis extents as well as visual traction bronchiectasis and CALIPER PVV (Table 2). Of the pulmonary function indices, DLco, Kco, and the CPI were strong univariate predictors of mortality (Table 2). Patient age and a positive smoking history were also strongly linked to mortality. Univariate mortality analyses were also performed for the continuous scores (prior to their categorization into indices) of the three models: ILD-GAP, Stratified CT, and Stratified CT-GAP models (Table 2).

Our study has demonstrated for the first time, that, across the range of CTD-ILD diagnoses, a computer-derived CT parameter, the pulmonary vessel volume, is an independent predictor of mortality. Furthermore, the PVV is a stronger predictor of mortality than all other CT and pulmonary function variables following correction for age and gender.

{Jacob2016Mortality}

CALIPER-derived parameters, in particular PVV, are more accurate prognostically than traditional visual CT scores. Quantitative tools such as CALIPER have the potential to improve staging systems in IPF.

The pulmonary vessel volume (PVV) score quantified the volumes of pulmonary arteries and veins excluding vessels at the lung hilum as a percentage of lung volume.

Total extent of ILD represented the sum of ground glass, reticular and honeycomb percentages. The sum of grade 2 and 3 decreased lung attenuation represented emphysema \citep{ Jacob2016Automated}.

Blood perfusion in areas of fibrosis has been shown to be reduced \citep{ Renzoni2003Interstitial}, but conversely increased in spared lung adjacent to areas of fibrosis \citep{ Ebina2012Heterogeneous, Cosgrove2004Pigment}. It follows that the strong correlations between ILD extent and vessels may reflect regional, subclinically elevated local pulmonary arterial pressures within mildly fibrotic lung, or capillary bed destruction in more advanced disease, which may produce a preferential diversion of blood flow to relatively spared or nonfibrotic lung. The vascular capacitance of spared lung (the upper and middle lobes in patients with IPF, a predominantly basal disease) may result in an increase in vessel volume in more advanced disease. The identification of greater numbers of vessels, of a size that could be detected by CALIPER, could therefore act as a surrogate marker for the extent and severity of parenchymal disease in IPF.

Another possible explanation for the relationship between PVV and ILD extent relates to the increased negative intrathoracic pressure that noncompliant fibrotic lungs need to generate during inspiration. The transmission of high negative pressures through the pleural space into the parenchyma could in turn be exerted on the vasculature, resulting in dilatation throughout the lung and an increase in capacitance. A third possible mechanism relates to pleuroparenchymal and/or bronchial-pulmonary artery anastomoses described histopathologically in patients with fibrosing lung disease \citep{ Turnerwarwick1963Precapillary}. While the clinical importance of shunting within the lungs is yet to be established \citep{ miller1986anatomical}, the development of shunts could theoretically increase the PVV as fibrosis progresses.

{Hamada2007Significance}

D LCO was a critical factor for evaluating disease status and prognosis, and PAP status provided feasible information in the initial workup of IPF patients.

The main focus in this study was to evaluate the influence of elevated PAP on the prognosis of IPF.

Among the 70 patients who underwent RHC during their initial workup, the prevalence of PAH based on standard criterion (mPAP > 25 mm Hg) was 8.1% (6 patients). Lettieri et al 26 reported a markedly higher prevalence of 31.6% among IPF patients who underwent the evaluation while waiting for lung transplantation. In estimations of PAP by Nadrous et al 25 using the USCG method, systolic PAP was > 50 mm Hg in 30.7% of patients. Differences in the populations and measuring methods in these three studies make it difficult to directly compare the prevalence of PAH. It is possible that the lower prevalence of PAH in our current study could be due to the fact that our patients as a whole were in relatively early stages of IPF when they underwent their initial workup.

**How do physiological alterations integrate in IPF**

{plantier2018physiology}

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.

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 \citep{boutou2011exercise}, with more severe arterial haemoglobin desaturation at exercise \citep{raghu2015pulmonary} 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 \citep{van2014pulmonary}.

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 \citep{nishiyama2007dyspnoea}. Multiple factors contribute to exertional arterial hypoxaemia in IPF, with alterations of both V′/Q′ ratios \citep{hempleman1991estimating} and diffusion \citep{hughes1991dlco} playing key roles.

Dyspnoea is the main complaint in patients with IPF. Exertional dyspnoea correlates with markers of both reduced lung compliance and altered pulmonary gas exchange \citep{londner2014cross, swigris2014assessing}.

**Summary**

{plantier2018physiology}

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.

{crystal1976idiopathic}

In general, patients have reduced lung volumes, reduced diffusing capacity, a normal forced expiratory volume in 1 sec/forced vital capacity (FEVi%), and arterial hypoxemia that worsens with exercise.

{cortes2014idiopathic}

On diagnosis, 73% of patients with IPF had a restrictive pattern, with a mean TLC of 72% of predicted. Mean forced vital capacity (FVC) was 71% and 44% of patients had an FVC <95th percentile. Mean diffusing capacity for carbon monoxide (DLCO) was 60% and DLCO / alveolar volume (VA) 92% of predicted. Increased severity of restriction–based on TLC – was associated with lower DLCO (74% of predicted in mild restriction and 39% of predicted in severe restriction) and higher forced expiratory volume in 1 s (FEV 1 )/FVC ratio (82% of predicted in mild restriction and 90% of predicted in severe restriction) but not with age (76 years in mild restriction and 69 years in severe restriction). Regardless of severity of restriction, the average DLCO /VA (≥86% of predicted) remained within normal limits.

One in four patients with IPF had normal TLC and more than one-half had a normal FVC during initial evaluation. As the severity of the restriction increased, FEV1 /FVC increased, DLCO decreased but DLCO /VA remained normal.

{american2000idiopathic}

The typical findings of pulmonary function tests are consistent with restrictive impairment (reduced vital capacity [VC] and total lung capacity [TLC]) by body plethysmography \citep{ Wells1997Functional}. Unless a complicating airways disease occurs, isovolume flow rates are well maintained. The DLCO corrected for hemoglobin is reduced frequently and the decline in DLCO may precede abnormalities in lung volume. The maximal breathing capacity is usually normal. The resting arterial blood gases may be normal or reveal hypoxemia (secondary to ventilation and perfusion mismatch) and respiratory alkalosis, and these abnormalities may be elicited or accentuated by exercise.

**Ventilation-perfusion mismatching**

{crystal1976idiopathic}

Interestingly, 21% of our patients had decreased Pao 2 values when they rose from the supine to the upright position, in direct opposition to what occurs in normal individuals. In idiopathic pulmonary fibrosis, the reversal of position-dependent changes in Pao 2 is probably associated with alterations in pulmonary hemodynamics, causing greater ventilation-perfusion imbalance in the upright position \citep{mccarthy1973regional}.

It is generally thought that the hypoxemia of idiopathic pulmonary fibrosis is related to ventilation-perfusion mismatching, although limitation to oxygen diffusion may be present, especially during exercise \citep{wagner1976distribution}. As we will discuss later, much of the ventilation-perfusion mismatching may be related to abnormalities in ventilation. However, the latter is not due to abnormalities in the large airways because almost all patients with idiopathic pulmonary fibrosis have normal values for F E V 1%(Table 2) and airway resistance by body plethysmography \citep{bachofen1967lung}.

Even though the resting Pao2 can be normal in idiopathic pulmonary fibrosis, the resting alveolar-arterial oxygen gradient (D[A-a]o,) is almost invariably abnormal (97% of the patients). Even more sensitive physiologic monitors of idiopathic pulmonary fibrosis are the fall in Pao 2 and the widening of D(A-a)o 2 with exercise, findings that are universal in these patients (Figure 1, Top and Middle) \citep{ herbert1962pathophysiology, scadding1974diffuse, austrian1951clinical}.

Physiologic shunt at rest (as measured by 100% 02 ) can be significant in idiopathic pulmonary fibrosis but usually develops late in the course of the disease \citep{austrian1951clinical , finley1962cause}. Of our population, the four patients with the mildest disease had a physiologic shunt of less than 6%, whereas the four patients with the most advanced disease had a shunt of 15% to 30%. Thus, although physiologic shunt is generally not a significant cause of hypoxemia early in the disease, it becomes a major problem in the care of patients very late in their course, because even with very high inspired oxygen concentrations, they do not achieve adequate oxygenation.

As we discussed earlier, the major cause of hypoxemia in idiopathic pulmonary fibrosis has been attributed to ventilation-perfusion imbalance \citep{wagner1976distribution}. Because air flow mechanics (FEV-^, airway resistance by body plethysmography) are usually normal in these patients \citep{austrian1951clinical, finley1962cause, bachofen1967lung}, the abnormalities in distribution of ventilation have been ascribed to regional alterations in compliance \citep{ finley1962cause}.

These findings support the concept that a significant portion of hypoxemia in patients with idiopathic pulmonary fibrosis is due to ventilation-perfusion mismatching \citep{ finley1962cause, wagner1976distribution} and also confirm that the high dead space to tidal volume ratio found at rest in many of these patients \citep{ holland1960physiologic, herbert1962pathophysiology, fulmer1976diffuse} is well founded on anatomic grounds.

{strickland1993cause}

The cystic air spaces that are often seen on CT scans of patIents with idiopathic pulmonary fibrosis are unperfused (probably due to vascular obliteration) but are usually normally ventilated. This V/Q mismatch on scintigrams explains the large physiologic dead space seen at rest and on exercise and could suggest pulmonary embolism unless a CT scan is obtained. Conversely, the larger cystic spaces might be mistaken for emphysema unless V/Q scintigraphy is done.

In our study, we found that the zones of V/Q mismatch corresponded to the presence of cystic air spaces (honeycomb lung) seen on CT. In addition, many of the more elderly patients have smoked for many years and may have air-flow obstruction. In such cases, matched V/Q defects may be seen.

Thus, the V/Q scan can be used to distinguish between emphysema and idiopathic pulmonary fibrosis in the mixed case. In regions where emphysema predominates, the V/Q scan will tend to show a matched pattern with reduced ventilation (Figs. 1G and 1H) but in areas where fibrosis and cystic air spaces are dominant, a mismatched high-V/Q pattern will be seen. This may be a better discriminator than the CT findings alone.

**Ventilation**

{crystal1976idiopathic}

The equilibrium picture of 127 Xe distribution reflects the relative proportion of lung that is being ventilated. For example, little radioactivity would be detected over areas of pneumonia or noncommunicating bullae. Patients with idiopathic pulmonary fibrosis have patchy, nonsegmental areas of decreased ventilation, reflecting regions of airway obstruction or alveolar destruction.

{american2000idiopathic}

Patients with IPF increase their minute ventilation during exercise primarily by increasing their respiratory frequency. This method of increase differs from normal subjects in whom increased ventilation during mild exercise occurs by an increase in the VT rather than respiratory rate. Thus, patients with IPF have an elevated minute ventilation during exercise that is in part related to the increase in dead space (VD) ventilation. As well, the ratio of VD to VT is increased at rest and is maintained or decreases with exercise. On occasion, the VD to VT ratio may increase in interstitial lung disorders that have a prominent pulmonary vascular component, such as scleroderma. In patients with IPF, an increase in the VD/VT ratio should raise concern about pulmonary vascular disease, especially chronic pulmonary emboli, or associated emphysema.

**Perfusion**

{crystal1976idiopathic}

In addition, there is often a shift in perfusion to the upper lobes (reflecting pulmonary hypertension) so that areas of relatively low ventilation-perfusion ratios are seen in the upper zones.