Chapter 1

Background

In order to quantitatively explore the link between structure and lung function of patients with idiopathic pulmonary fibrosis (IPF), some background knowledge of the disease is ~~IPF are~~ required. ~~for us to have a better understanding of this disease, and thus helping with the parameterization of computational models of lung function more reliably in the next stage~~. This chapter provides an ~~summarises available information of IPF, which includes~~ introduction to ~~of~~ IPF, its epidemiology, etiology, pathogenesis, diagnosis, clinical courses, comorbidities, and physiological alterations.

1.1 Introduction to ~~of~~ idiopathic pulmonary fibrosis (IPF)

1.1.1 Definition

Idiopathic pulmonary fibrosis is a chronic, progressive, irreversible, and lethal lung disease of unknown cause. It usually manifests over several years during ~~in~~ which progressive ~~lung~~ scarring occurs in the supporting structural framework (interstitium) of the lungs tissue ((Meltzer and Noble, 2008; King Jr et al., 2011; Raghu et al., 2011)). This ~~The~~ fibrotic condition is generally thought to ~~generate~~ result from abnormal wound healing after repeated pulmonary tissue damage. Several causes of alveolar injury have been implicated in IPF ~~suggested~~, including cigarette smoke, enviromental exposure to toxins (e.g. asbestos, avian toxins), gastro-oesophageal reflux, viral infection, and internal mechanisms such as autoimmunity, genomic instability or telomerase length (Raghu et al., 2011; Ahluwalia et al., 2014).

In IPF patients' lungs, some healthy tissues are replaced by altered extracellular matrix and a destroyed alveolar architecture, which leads to decreased lung compliance, disrupted gas exchange, and ultimately respiratory failure and death (Richeldi et al., 2017). The fibrosing areas are generally observed ~~often thought~~ to begin at the basal and peripher~~ic~~al region ~~part~~ of the lungs, and then gradually progress to involve all lung tissues (Martinez et al., 2017). The prominent symptoms of IPF are exercise-induced breathlessness and chronic dry cough (Meltzer and Noble, 2008), which will eventually have a devastating effect on a patient's quality of life (QOL) (Kim et al., 2015). IPF usually affects middle-aged and elderly adults (median age at diagnosis 66 years, range 55-75 years). The disease ~~It~~ is ~~limited~~ isolated to the lungs, and is associated with the radiological and/or histological pattern of usual interstitial pneumonia (UIP) (King Jr et al., 2011; Raghu et al., 2011; Xaubet et al., 2017). A typical UIP pattern is usually characteristi~~c~~zed by honeycombing, traction bronchiectasis, and peripheral alveolar septal thickening (Martinez et al., 2017), which will be introduced briefly in Section 1.3.2.

check: is it peripheral or posterior?

1.1.2 Disease classification

IPF belongs to the family of interstitial lung disease (ILD) or, more accurately, the diffuse parenchymal lung diseases (DPLD). All the ILDs result in damage to the lung interstitium, with varying patterns of inflammation and fibrosis. Within the ~~this~~ broad category of ILDs, IPF belongs to a subgroup known as idiopathic interstitial pneumonia

(IIP) (Meltzer and Noble, 2008). By definition, the etiology of IIPs is unknown. The distinction between IPF and other kinds of IIP ~~disease~~ is particularly important ((Corte et al., 2015; Troy and Corte, 2012)), as the prognosis for other IIPs is generally much more favorable than that for IPF (Meltzer and Noble, 2008). Over the past decade, IIPs have been ~~are~~ classified into seven distinct disease s, differentiated by specific clinical features and pathological patterns, which includes: idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, cryptogenic organising pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia, and lymphocytic interstitial pneumonia ((Katzenstein and Myers, 1998; Troy and Corte, 2012)) (Figure 1.1).

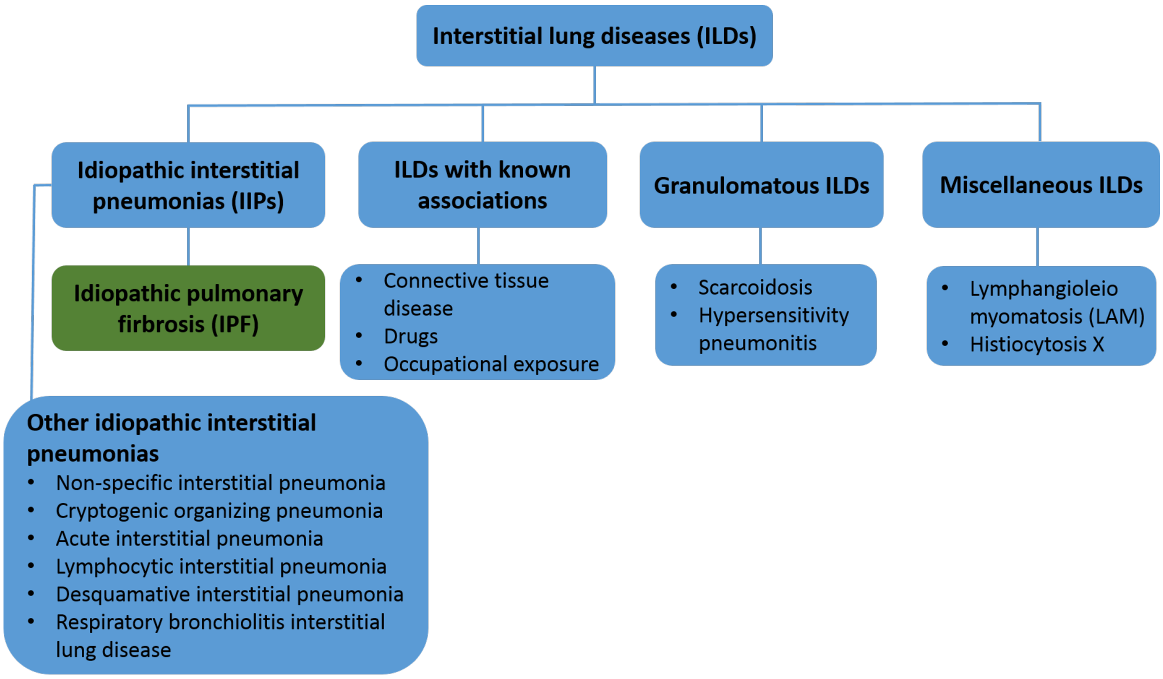


Figure 1.1: Classification of the interstitial lung disease S (Troy and Corte, 2012).

1.2 Epidemiology, etiology and pathogenesis

1.2.1 Epidemiology

Although IPF is considered a rare ~~to happen,~~ disease this disease is the most common form of IIPs (Travis et al., 2013). The incidence of IPF is similar to that of stomach, brain, and testicular cancers and has risen over time (Richeldi et al., 2017). A cohort study including patients diagnosed with ILDs at Aarhus University Hospital showed that IPF was the most common diagnosis (28%) followed by connective tissue disease-related ILD (14%), hypersensitivity pneumonitis (7%) and non-specific interstitial pneumonia (NSIP) (7%) (Hyldgaard et al., 2014). Although there is little data available to show a worldwide incidence, a recent study shows that in Europe and North America, the prevalence of IPF is estimated to range between 2.8 and 18 cases per 100,000 people per year, and this value might be lower in Asia and South America, where it is estimated to range from 0.5 to 4.2 cases per 100,000 individuals per year (Richeldi et al., 2017). IPF is more likely to affect men than women, and is rare in people younger than 50 years ~~(~~(Raghu et al., 2011, 2006)~~)~~. The incidence is estimated to be 13 cases/100,000 in women and 20 cases/1000,000 in men (Xaubet et al., 2017). In addition, the incidence of IPF increases with age (Meltzer and Noble, 2008). It has been reported that the incidence is becoming higher in recent years, probably because of ~~the~~ improved diagnostic methods and ~~the~~ increased life expectancy (Xaubet et al., 2017).

1.2.2 Etiology and pathogenesis

The term ”idiopathic” means there are no known causes for IPF, therefore the etiology of IPF is unknown (Meltzer and Noble, 2008; Xaubet et al., 2017). Historically, idiopathic pulmonary fibrosis was considered a chronic inflammatory disorder, which gradually progressed to established fibrosis (Richeldi et al., 2017). Now idiopathic pulmonary fibrosis is generally regarded as a consequence of multiple interacting factors, in which repetitive local micro-injuries to an ageing alveolar epithelium plays an important role. These micro-injuries initiate aberrant epithelial-fibroblast communication, the induction of matrix-producing myofibroblasts, and considerable extracellular matrix accumulation and remodelling of lung interstitium (Richeldi et al., 2017). Although the etiology of IPF is unknown, currently, environmental exposures and genetic factors have been supported as providing important inducement by some researchers (Taskar and Coultas, 2006; Meltzer and Noble, 2008; Xaubet et al., 2017; Richeldi et al., 2017). In addition, gastroesophageal reflux (GER), exposure to silica, brass, steel and wood dust, livestock and agriculture work, and the construction of wooden houses are also potential risk factors for the pathogenesis of IPF ((Taskar and Coultas, 2006; Xaubet et al., 2017))

Environmental exposures

The relationship between environmental exposures and IPF has been consistently demonstrated by case studies and some research~~es~~ in other pulmonary disease, such as asbestosis, in which environmental material is associated with pulmonary fibrosis (Meltzer and Noble, 2008). There are studies indicating that the pathogenesis and progression of IPF are influenced by particulate inhalation, which is ~~can be~~ supported by the ~~a~~ fact that the development of IPF consistently relates to cigarette smoking history in most patients ((Baumgartner et al., 1997; Richeldi et al., 2017)). Additionally, ~~Meanwhile,~~ some other environmental factors have also been mentioned in published papers, including metal and wood dusts, agriculture and farming, viruses, and stone and silica ((Raghu et al., 2011; Taskar and Coultas, 2006)).

Genetic factors

Increasing evidence indicates that genetic predisposition plays an essential part in the development of IPF (Xaubet et al., 2017; Richeldi et al., 2017). The correlation of ~~the~~ genetic factors and IPF is based on the existence of familial forms of the disease, and it ~~is~~ has been shown that around 2.2% to 3 % of IPF ~~patients~~ cases are familial (Xaubet et al., 2017). The most likely mode of genetic transmission of pulmonary fibrosis in familial cases is autosomal-dominant with variable penetrance (Steele et al., 2005; Allam and Limper, 2006; Lee et al., 2005; Musk et al., 1986). Rare genetic variants have been identified in ~~the~~ cases ~~which~~ where ILDs affect two or more members of the same biological family, including genes associated with alterations in host defence (MUC5B, ATP11A, TOLLIP), telomere maintenance (TERT, TERC, PARN, RTEL, OBFC1), surfactant dysfunction (SFTPC, SFTPA2) and epithelial barrier function (DSP, DPP9) (Alder et al., 2008; Raghu et al., 2011; Seibold et al., 2011; Xaubet et al., 2017). Among them, MUC5B, a promoter site of an airway mucin gene, is the most strongly associated with development of both familial and sporadic IPF (Richeldi et al. (2017)). MUC5B encodes a mucin-5B precursor protein that contributes to airway mucous production and might have an important role in lung host defense. ~~In the meantime, it should be noticed~~ It has also been noted.... that members of the same biological family may be affected by different types of ILDs, such as non-specific interstitial pneumonia and cryptogenic organizing pneumonia (Xaubet et al., 2017).

1.3 Diagnosis

The diagnosis of IPF often requires a multidisciplinary discussion, involving pulmonologists, chest radiologists, and chest pathologists experienced in the field of ILDs ~~to~~

~~make an accurate diagnosis of IPF~~ (Flaherty et al., 2004; King Jr et al., 2011; Raghu et al., 2011). This multidisciplinary approach has been accepted in consensus guidelines all over the world and has helped to standardize IPF diagnosis (Raghu et al., 2011; Richeldi et al., 2017). Usually, IPF is diagnosed by identification of a pattern of UIP on the basis of radiological or histological criteria in patients without evidence of an alternative cause. The biggest challenge of diagnosis to clinicians is how to exclude other idiopathic interstitial pneumonias, fibrotic nonspecific interstitial pneumonia, and interstitial lung disease associated with occupational or environmental exposure, connective tissue disease, and drugs (King Jr et al., 2011; Richeldi et al., 2017). This differential diagnosis is really important, since typical UIP is not exclusive to IPF, but may associate with some other conditions, such as chronic hypersensitivity pneumonitis and asbestosis. Many patients have a history of environmental exposures or medicine treatment which ~~need~~ clinicians need to take ~~the cause of disease~~ into consideration for diagnosis (Richeldi et al., 2017).

1.3.1 Clinical presentations

Patients with IPF usually suffer from unexplained progressive dyspnea on exertion and chronic dry cough, bibasilar inspiratory crackles, and finger clubbing. Bibasilar inspiratory crackles are heard on chest auscultation and ~~frequently~~ finger clubbing is found in about 30% of patients (Raghu et al., 2011; King Jr et al., 2011; Richeldi et al., 2017). Chest pain, fatigue, malaise, and weight loss are also typical symptoms for IPF patients (Douglas et al., 2000; King Jr et al., 2001). These clinical presentations might initially be attributed to aging or some comorbidities such as cardiovascular disease, or obesity. Therefore, in order to avoid diagnostic delays, it is necessary for primary care physicians to have ~~do~~ clinical suspicion of IPF. Some patients, usually accompanied by fever and influenza-like symptoms, may present with ~~an~~ acute respiratory exacerbations within a few days or weeks. In these cases, clinicians require careful diagnostic distinction from other forms of acute IIDs (Richeldi et al., 2017). Pulmonary function tests (PFTs) of IPF patients usually show~~s~~ a restricted pattern with low percent predicted ~~reduced~~ total lung capacity (TLC) and diffusion capacity for carbon monoxide (DLCO). But for some patients with early disease, PFT results might be normal or mildly abnormal ~~mild~~ (Douglas et al., 2000; Raghu et al., 2006).

1.3.2 Radiographic features

HRCT of the chest has become an essential tool for the diagnosis of IPF, which is usually associated with identification of a UIP pattern. The presence of UIP pattern on HRCT is characterised by appearance of honeycombing cysts, reticular opacities and ground-glass abnormalities (Figure 1.2) (King Jr et al., 2011; Raghu et al., 2011; Richeldi et al., 2017). Honeycombing is common, and essential for a definite diagnosis (Raghu et al., 2011). On HRCT, honeycombing is presented as clustered cystic airspaces with a typical diameter~~s~~ of 3-10mm but occasionally as large as 2.5cm, and in a predominantly subpleural and posterior basal distribution (Hansell et al., 2008; Richeldi et al., 2017). Reticular opacities are often associated with traction bronchiectasis (Nishimura et al., 1992; Johkoh et al., 1999). Groundglass is a common characteristic of UIP pattern, although it is sometimes less extensive than reticular. The distribution of abnormalities are often basal, peripheral and patchy (Raghu et al., 2011). If patients show micronodules, airtrapping, nonhoneycomb cysts, extensive ground glass opacities, consolidation, or a peribronchovascular-predominant distribution, alternative diagnosis should be taken into account (Hwang et al., 2009; Souza et al., 2006). If patients show reticular ab-

check: should it be "honeycomb" or "honeycombing"?

?
normalities located in subpleural and basal regions, but no honeycombing peformance, possible UIP patterns should be taken into consideration, then ~~the~~ a surgical lung biopsy is suggested to make a definite diagnosis (Raghu et al., 2011; Richeldi et al., 2017).

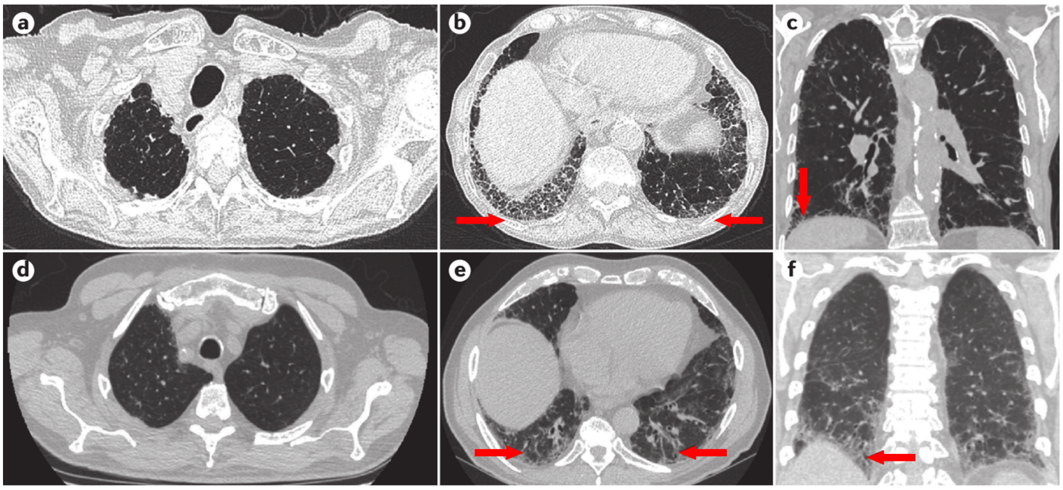


Figure 1.2: HRCT images of UIP pattern from two patients. The first is from a woman with progressive cough and dyspnoea, showing her upper (a), lower (b) lung zones and a ~~the~~ sagittal plane of the lungs (c). These images show lower lobe-predominant peripheral honeycomb change (b and c, arrows), which is typical of UIP pattern. This patient had no systemic disease or exposures that would exclude idiopathic disease, the diagnosis of IPF is certain. By contrast, the second is a woman with progressive breathlessness, could be diagnosed with possible IPF. T ~~t~~he upper (d), lower (e) lung zones and sagittal image of the lungs (f) demonstrate~~d~~ peripheral, basilar-predominant, reticular densities with traction bronchiectasis (e and f, arrows) consistent with fibrosis. Surgical lung biopsy is suggested. Reproduced from (Martinez et al., 2017))

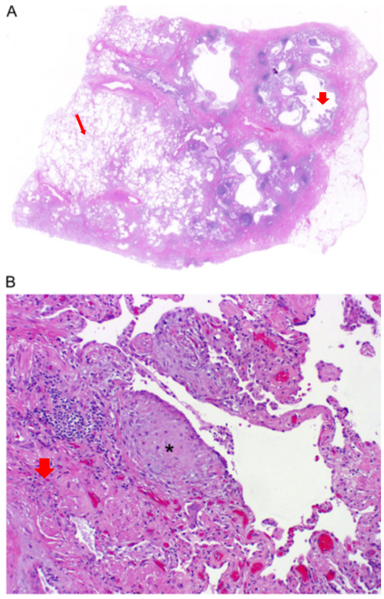
.

1.3.3 Histopathology

When HRCT features are not enough for a certain diagnosis of IPF, surgical lung biopsy is suggested (Richeldi et al., 2017). The main histopathologic hallmark ~~hall marks~~ of UIP pattern is characterized by a heterogeneous appearance, best seen at low magnification, in the areas of subpleural and paraseptal fibrosis with scarring and honeycomb (i.e., cystic

? doesn't quite make sense

fibrotic airspaces lined by bronchiolar epithelium and often filled by mucin and variable numbers of inflammatory cells), alternating with areas of less affected or normal parenchyma (Society et al., 2000; Travis et al., 2002) (Figure 1.3). Small areas of active fibrosis (fibroblast foci) are present in the background of collagen deposition, and they reflect the temporal heterogeneity of the process and indicate current ongoing disease (King Jr et al., 2011). Another feature of UIP pattern is that the inflammation is often absent or mild and consists of a patchy interstitial infiltrate of lymphocytes and plasma cells (Raghu et al., 2011; King Jr et al., 2011). Although surgical lung biopsy is essential for a correct diagnosis, careful consideration is required for every patient to estimate whether the risks of surgical lung biopsy outweigh the potential benefits of the histopathologic information. For older patients with comorbidities or clinically significant physiological impairment, it is suggested to avoid surgical lung biopsy (Richeldi et al., 2017).



arrows and asterisk too small !

Figure 1.3: Surgical lung biopsy specimens of UIP pattern. (A) Scanning power microscopy showing a patchy process with honeycomb spaces (thick arrow), some preserved lung tissue regions (thin arrow), and fibrosis extending into the lung from the subpleural regions. (B) Adjacent to the regions of more chronic fibrosis (arrow) is a fibroblast focus (asterisk), recognized by its convex shape and composition of edematous fibroblastic tissue, suggestive of recent lung injury. Reproduced from (Raghu et al., 2011))

.

1.3.4 Diagnos~~is~~tic criteria

The gold standard diagnos~~is~~tic criteria ~~of~~ for IPF ~~has~~ have been developed by the American Thoracic Society (ATS) and European Respiratory Society (ERS) in a statement of published guildlines ~~published~~ (Raghu et al., 2011):

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).

2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.

3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

Beyound that, minor criteria ~~has~~ have also been set for the daignosis of IPF in the absence of a surgical lung biopsy (Raghu et al., 2011):

1. Age $>$ 50 years.

2. Insidious onset of otherwise unexplained dyspnea on exertion.

3. Duration of illness being over 3 months.

4. Bibasilar inspiratory crackles (dry or ”Velcro” type).

Figure 1.4 shows the diagnostic workflow for adult patients with ILD and suspected IPF. If the high-quanlity HRCT evidence is sufficient enough for the recognition of histopathologic UIP pattern, surgical lung biopsy ~~will be~~ is not essential (Hunninghake et al., 2001; Raghu et al., 1999; Flaherty et al., 2003; Quadrelli et al., 2010). However, the multidisciplinary discussion among experienced clinical, radiologic and histopathologic experts is particularly important when the radiologic and histopathologic paterns are discordant (e.g., HRCT is inconsistent with UIP and histopathology is UIP) (Raghu et al., 2011). Radiologic or pathologic UIP pattern is not 100% specific to IPF (Lynch et al., 2006; Trahan et al., 2008; Silva et al., 2008a).

1.4 Clinical course~~s~~

Some studies indicate that IPF patients have median survival time between 2 and 3 years from the time of diagnosis (Bjoraker et al., 1998; Flaherty et al., 2002; Nicholson et al., 2000; Rudd et al., 2007; KING JR et al., 2001; King Jr et al., 2011). For most

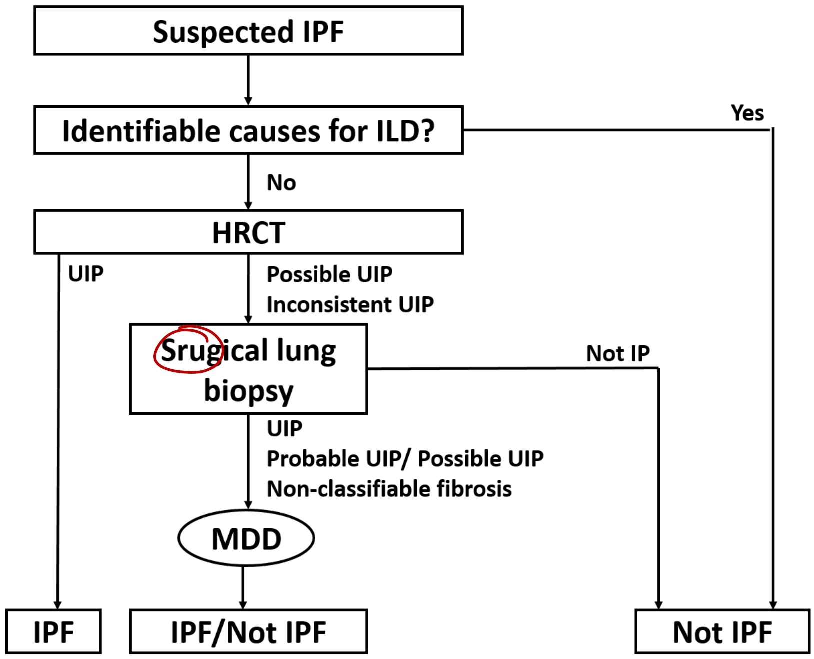


Figure 1.4: Diagnostic algorithm for IPF. Patients with suspected IPF (i.e., patients with unexplained dyspnea on exertion and/or cough with evidence of ILD)should be carefully evaluated for identifiable causes of ILD. In the absence of an identifiable cause for ILD, an HRCT demonstrating UIP pattern is diagnostic of IPF. In the absence of UIP pattern on HRCT, IPF can be diagnosed by the combination of specific HRCT and histopathological patterns. The accuracy of the diagnosis of IPF increases with multidisciplinary discussion (MDD) among ILD expert. (Reproduced from (Raghu et al., 2011))

IPF patients, the clinical course~~s~~ has ~~have~~ been described as a general decline in pulmonary function until eventual~~ly~~ death ~~die~~ from respiratory failure or complicating comorbidity (Carrington et al., 1978; Tukiainen et al., 1983; Gross and Hunninghake, 2001), however, the individual disease progression can be highly variable (Kim et al., 2006b; Meltzer and Noble, 2008). It appears that there are several possible clinical~~l~~ courses for patients with IPF (shown in Figure 1.5) (Raghu, 1987): slow and gradual progression over many years(the most common) (Ryu et al., 2014; Meltzer and Noble, 2008; Raghu et al., 2011); rapid and accelerated decline (Kim et al., 2006b; Selman et al., 2007); a~~A~~cute exacerbations king2011idiopathic,xaubet2017idiopathic. Currently, it is quite hard to predict the natural history of disease progression for a given patient at the time of the diagnosis (Raghu et al., 2011). Whether the different clinical courses are influenced by geographic, ethnic, cultural, racial, or other factors remains unknown. But some evidence has been suggested that worsening prognosis may be associated with older ~~aging~~ people (> 70 years old), smoking history, low body mass index (BMI), severe physiological impairment, large radiological extent of disease, and pulmonary hypertension (Ley et al., 2011). And other comorbidities such as emphysema and pulmonary hypertension may also have a impact on the disease course (Mejía et al., 2009; Wells et al., 2003; Lettieri et al., 2006).

1.4.1 Slow and rapid progressive course

Most IPF patients deteriorate relatively slowly, and their pulmonary function usually decreases gradually over ~~the~~ months to years after the first clinical symptoms (cough and progressive dyspnoea) (Ryu et al., 2014; Meltzer and Noble, 2008; Raghu et al., 2011). Patients usually experience reduction of lung volumes and hypoxemia at rest

~~and~~ that worsens with exercise. ~~It can be seen~~ This is accompanied by a decline of forced vital capacity (FVC) by a mean of 0.13L to 0.21L ~~each~~ per year (Ley et al., 2011). In contrast, a subgroup of patients with IPF, mainly male cigarette smokers, experience a rapid worsening of symptoms, and insufficiency of pulmonary function (Kim et al., 2006b; King Jr et al., 2011), known as accelerated IPF. The patients with rapid progression have reduced survival time relative to those with a slowly progressive clinical course.

1.4.2 Acute exacerbations of IPF

Acute exacerbation was first proposed by Japanese physicians to describe acute, unexpected worsening of respiratory functions and severe hypoxemia in patients with IPF, without a clear trigger (Kondoh et al., 1993; Gross, 1962). The rapid deterioration occurs in a small minority of patients with IPF (about 5-10%), with absence of infection, heart failure, pneumothorax, or pulmonary embolism (Azuma et al., 2005; King Jr et al., 2011; Raghu et al., 2011). The prognosis for patients with acute exacerbations is poor, and it may happen at any stage in the course of IPF (Kim et al., 2006a; Parambil et al., 2005; Sakamoto et al., 2009; Kondoh et al., 2010). Patients with this acute exacerbation usually experience poor respiratory decline, worsened cough, fever and increased sputum ... production (Ambrosini et al., 2003; Kim et al., 2006a). The mortality is over 60% (Wootton et al., 2011; Lettieri et al., 2006); ~~especially~~ for ~~the~~ cases requiring mechanical ventilation, the mortality is ~~even~~ close to 100% (King Jr et al., 2011; Xaubet et al., 2017).

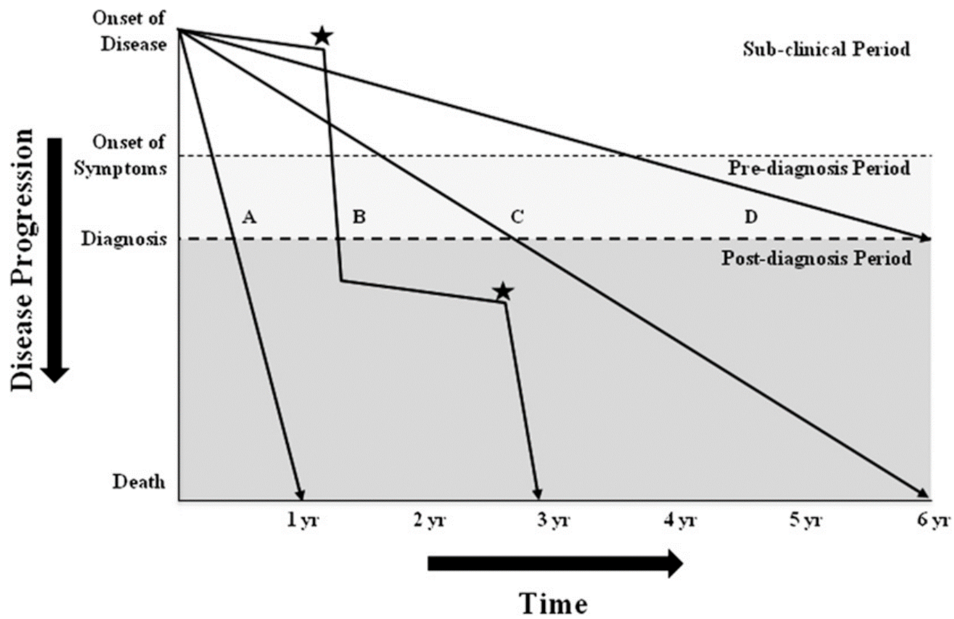


Figure 1.5: Schematic representation of potential clinical courses of IPF. A subclinical period of disease progression exists during which only radiographic evidence of disease may be noted. This is followed by a symptomatic phase comprising clinical stages (both pre-diagnosis and post-diagnosis). The rate of deterioration and progression to death may be fast (line A), mixed (line B), or slow (lines C and D), with phases of relative disease stability interspersed with acute decline (asterisks).(Reproduced from (Ley et al., 2011))

1.5 Complications and comorbidities

Complications and comorbidities can occur in patients with IPF that may influence the clinical course and prognosis (Xaubet et al., 2017; King and Nathan, 2017; Martinez et al., 2017). It is reported that only 12% of patients with IPF have no comorbid illness, 58% of patients ~~had~~ have comorbidities (Raghu et al., 2011; Kim et al., 2015) and 30% ~~had~~ have comorbid conditions (King Jr et al., 2011; Baddini-Martinez and Pereira, 2015; Esposito et al., 2015; Harari et al., 2016; Kreuter et al., 2016). ~~Combined pulmonary fibrosis and~~ Emphysema and pulmonary hypertension are both important comorbid conditions in IPF

what is the difference between 'comorbidities' and 'comorbid conditions'?

patients (Raghu et al., 2015; Martinez et al., 2017).

1.5.1 IPF and emphysema

Several research groups have described a syndrome in which IPF coexists with pulmonary emphysema ((Wells et al., 1997, 2003; Cottin et al., 2005; Meltzer and Noble, 2008)). In 2005, Cottin et al. (2005) ~~firstly~~ presented a ~~designed~~ syndrome named 'combined pulmonary fibrosis and emphysema' (CPFE). There is ~~It is noted with~~ evidence that both IPF and emphysema are associated with a significant smoking history, and CPFE is strongly associated with exercise hypoxemia, severe dyspnea on exertion, upper lobe emphysema and lower lobe fibrosis, unexpected subnormal lung volumes, and severe reduction of carbon monoxide transfer (Silva et al., 2008b; Mejía et al., 2009; Cottin et al., 2010; King Jr et al., 2011; Lin and Jiang, 2015). Currently, whether CPFE is a distinct clinical entity or not remains unknown, i.e. ~~and~~ whether this is just the presence of two different diseases running in parallel is unclear (King Jr et al., 2011; Lin and Jiang, 2015). Some researchers suggest that CPFE should be regarded as a distinct clinical entity ~~other than emphysema or IPF alone~~, since it has a characteristic pulmonary function feature and unique natural history that is different from pure emphysema or IPF alone (Cottin et al., 2005; Lin and Jiang, 2015; Xaubet et al., 2017). CPFE occurs more frequently ~~commonly~~ in males than in females and its prevalence is about 30% to 47% in patients with IPF (Xaubet et al., 2017). It is often associated with ~~observed~~ a significant drop of DLCO and severe hypoxemia ~~in CPFE patients~~ during exercise due to the additive effect of emphysema and fibrosis (Xaubet et al., 2017).

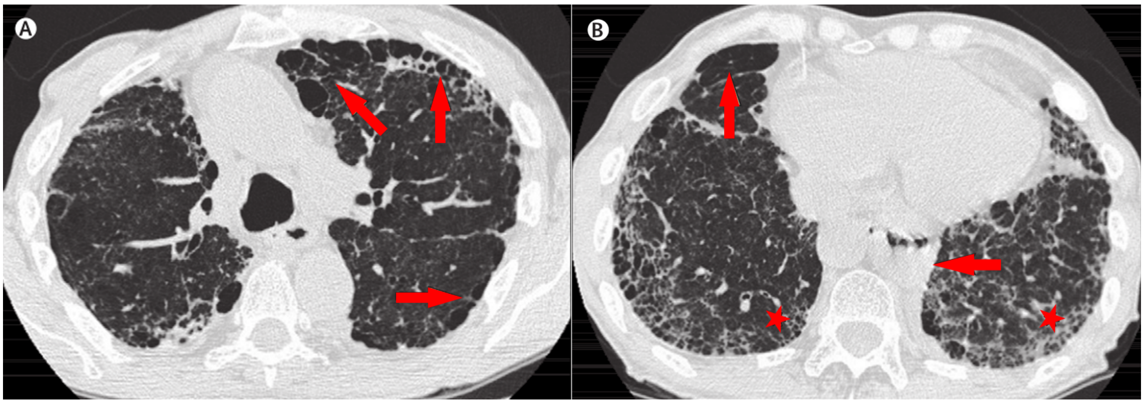


Figure 1.6: Combined pulmonary fibrosis and emphysema. High-resolution CT shows emphysematous lesions (arrows) in the upper lobes. (A) Emphysema (arrow) and usual interstitial pneumonia-like lesions (stars) in the lower lobes (B). A hiatal hernia is also present (arrowhead). (Reproduced from (King Jr et al., 2011))

I can't tell which one!

1.5.2 IPF and pulmonary hypertension

Pulmonary hypertension (PH) (defined as a mean pulmonary artery pressure of > 25 mm Hg at rest) is a ~~more~~ frequent form of comorbid condition in patients with IPF and is the main determinant of poor prognosis, which is worse than in IPF without emphysema (Raghu et al., 2011; Xaubet et al., 2017). It is estimated that the incidence of pulmonary hypertension is around 30% to 50% in IPF patients (King and Nathan, 2017). In general, pulmonary hypertension occurs due to several factors, ~~and~~ with chronic hypoxia-induced vasoconstriction and destruction of the pulmonary capillary bed induced by fibrosis ~~are~~ being the two main causes (Hayes Jr et al., 2016). The presence and development of pulmonary hypertension is associated with significant dyspnea, function al impairment (particularly in DLCO) and decreased exercise capacity, and may increase risk of mortality for patients with IPF (Mejía et al., 2009; Lettieri et al., 2006; Nadrous et al., 2005). Some studies show that combined pulmonary fibrosis and pulmonary hypertension has a significantly negative effect on the survival in patients with IPF, probably caused by the increased pulmonary vascular resistance (Raghu et al., 2011; King Jr et al., 2011). Currently, whether IPF with pulmonary hypertension represents a distinct clinical entity (IPFPH) is still unclear (Raghu et al., 2011).

1.6 Physiological alterations

The clinical presentation~~s~~ of IPF is often strongly related to multiple physiological alterations of the lung. These alterations have a complex and negative impact on all compartments of the respiratory system, from lung volume and compliance to gas exchange, from conducting airways to lung vasculature (Plantier et al., 2018). In general, patients with IPF usually have reduced lung volumes, reduced lung compliance, reduced diffusing capacity, increased forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC), and arterial hypoxemia that worsens with exercise (Crystal et al., 1976; Society et al., 2000; Cortes-Telles et al., 2014; Plantier et al., 2018). These multiple alterations in lung physiology are summarized in Table 1.1.

1.6.1 Alterations in the mechanical properties of the lung

Reduction in lung compliance

IPF disease often results in reduction in lung compliance (i.e. the lung tissue stiffens). ~~, which increases the stiffness of the lung in IPF patients~~. ~~It is supported by~~ Studies have shown that the reduced lung compliance is caused by reduction~~s~~ in the compliance of the lung extracellular matrix and by alterations in the pulmonary surfactant (Plantier et al., 2018). In patients with IPF, lung surfactant shows alterations in its lipid profile (Gunther et al., 1999; Schmidt et al., 2002), which leads to severely impaired surface activity (Gunther et al., 1999). In the

this is really important! It could explain the 'extra stiffness' that you see is required in the model. We must include this in your discussion/explanation.

Table 1.1: Alterations of lung function tests in idiopathic pulmonary fibrosis (IPF) (Reproduced from (Plantier et al., 2018))

	Mild IPF	**Moderate to severe IPF**
Static lung volumes		
- TLC	Normal	Decreased
- FRC	Normal	Decreased
Spirometry		
- FVC	Normal	Decreased
- FEV_1/FVC	Normal or increased	Normal or increased
Airways		
- Cough reflex	Increased	Increased
- Airway resistance	Decreased	Decreased
Blood gases at rest		
- P_aO_2	Normal	Decreased
- P_aCO_2	Normal	Decreased
Carbon monoxide transfer		
- DLCO	Decreased	Decreased
- V_A	May be normal	Decreased
- K_{CO}	May be normal	Decreased
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
Pulmonary haemodynamics at rest		
- PAP	May be increased	Frequently increased
- PCWP	Normal	May be 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; DLCO : 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; 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} : alveolararterial oxygen tension difference.

meantime, the reduction in lung compliance may happen from an early stage of IPF (Plantier et al., 2018). A study with 31 IPF patients from Zielonka et al. (2010) showed that the static lung compliance was ~~constantly~~ consistently and significantly reduced by 44 ± 6%. A similar result was found ~~in~~ by Orens et al.'s (1995)~~'s~~ group that all of the measured IPF patients had abnormal static lung compliance, which suggests that the measurement of lung compliance could help with the early diagnosis of IPF.

The alterations of lung compliance in IPF patients appears to be strongly correlated with the degree of lung fibrosis, as assessed by scoring of lung biopsies(Fulmer et al., 1979; Plantier et al., 2018). Nava and Rubini (1999) measured the dynamic lung compliance in seven patients with end-stage IPF, which showed that the reduction in lung compliance may be correlated with progress of disease. Currently, whether the reductions in lung compliance relate to clinical presentations (e.g. dyspnoea) remains unclear, but it is highly likely that the lung compliance has a strong relationship with the respiratory muscles and thus having ~~a~~ an impact on the work of breathing (Plantier et al., 2018). In addition, as the distribution of disease is heterogeneous in IPF lungs, the lung compliance is expected to be uneven among lung regions (Organ et al., 2015), but more evidence is still needed for a further discussion.

Reduction of lung volumes

The restriction of lung volumes (total lung capacity (TLC), functional residual capacity (FRC), forced vital capacity (FVC), and residual volume (RV)) is typical in patients with IPF, and often occurs at some time point in the clinical course of IPF (Society et al., 2000; Plantier et al., 2018). But sometimes the lung volumes may be normal ~~at~~ in the early stage of IPF, especially for patients with superimposed chronic obstructive pulmonary disease (Martinez and Flaherty, 2006). Cherniack et al. (1995) studied 96 patients with biopsy-confirmed IPF. The range of TLC was from 42% to 125% pred and the range of FVC was from 26% to 112% pred. It is shown by some researches that the reduction in lung volumes consistently relates to an increased risk of death (Martinez and Flaherty, 2006), but is weakly associated with dyspnoea or quality of life (Du Bois et al., 2011). However, whether the reduced lung volumes reflects the disease progression of IPF is still unknown (Plantier et al., 2018). Interestingly, it is found that patients with CPFE have higher RV and TLC compared to the patients with IPF alone (Mura et al., 2006), which may be caused by the effects of comorbid pulmonary eomphysema on lung compliance (Doherty et al., 1997).

Alterations in the conducting airways

Some evidence suggest that alterations also occur in conducting airways in patients with IPF, involving in airway epithelial cell proliferation (Vuorinen et al., 2008) and differentiation (Plantier et al., 2016), and increased numbers of bronchioles in the distal regions (Chilosi et al., 2002). Reduction in conducting airway resistance was found in IPF lungs, which may lead to an increased ratio of FEV1 to FVC (Pastre et al., 2015). In 2016, Plantier et al. (2016)'s group used volumetric capnography to measure the volume of conducting airways in patients with IPF, patients with other ILDs and healthy people. The results showed that conducting airway volume was significantly higher in IPF lungs in comparison with non-IPF ILD lungs and healthy lungs. However, this change in airway volume was not associated with the severity of alveolar lesions, dyspnea, cough or quality of life (Plantier et al., 2016). The increasement of airway volume in IPF may reflect dilation of airways consistent with the characteristic extent of bronchiectasis in this disease, and a commonly accepted view is that bronchiectasis in IPF may be caused by fibrotic retraction of peribronchiolar alveolar attachments and subsequent airway dilation (Sumikawa et al., 2008). However, a recent study found that bronchiectasis had a weak relationship with total fibrosis extent observed from CT imaging (Walsh et al., 2015), which means the development of conducting airways in IPF may be dissociated from alveolar fibrosis (Plantier et al., 2016). Patients with IPF usually have ~~a~~ more rapid breaths with the progression of disease (Kornbluth and Turino, 1980; Renzi et al., 1982), and have a relatively increased flow rate in the conducting airways due to the increased static elastic recoil (Society et al., 2000). Additionally, it is suggested that at least part of the ventilation abnormalities is associated with small airways disease with ~~showing~~ peribronchiolar fibrosis and inflammation, and 70% of the IPF patients have ~~occur~~ narrowed airways (Crystal et al., 1976).

Alterations in lung vasculature

Vascular lesions are observed in the pulmonary vasculature in patients with IPF, and often lead to disproportionate increases in the pulmonary vascular resistance (PVR) and pulmonary hypertension (PH) (Plantier et al., 2018). The tissues adjacent to the areas of fibrosis have been show~~ed~~n to have an increase in vessel profusion, whereas the fibrotic tissue itself demonstrates a reduced number of vessels (Cosgrove et al., 2004; Ebina et al., 2004). Jacob et al.'s (2016a)~~'s~~ group explored the relationship between pulmonary vessel volume (PVV) and interstitial lung disease (ILD) extent (includes ground glass, reticular and honeycomb patterns). It ~~is~~ was found that PVV had strong links with ILD extent ($R^2 = 0.73$, $P < 0.0001$) by using linear regression analysis. Furthermore, PVV was demonstrated to be an independent predictor of mortality and a stronger predictor of mortality than all the other traditional CT features and pulmonary functional variables (Jacob et al., 2016a). The ~~incresement~~ increase of PVV in more advanced fibrosis may be caused by the vascular capacitance of spared lung (the upper and middle lobes in patients with

IPF, a predominantly basal disease), and may also relate to the increased negative intrathoracic pressure which noncompliant fibrotic lungs need to generate during inspiration (Jacob et al., 2016b).

1.6.2 Alter~~r~~ations in pulmonary gas exchange

IPF is associated with multiple physiological changes in pulmonary gas exchange. The lesions of the alveolar-capillary membrane in IPF lungs will impair both the diffusion capacity and ventilation/perfusion (V/Q) relationship, increase dead space ventilation and alveolar-arterial oxygen tension difference ($P_{A-a}O_2$), and finally cause chronic arterial hypoxaemia (Crystal et al., 1976; Plantier et al., 2018; Society et al., 2000).

Reduced diffusing capacity of the lung

The diffusing capacity is reduced in almost all patients with IPF. However, in clinical examination, the diffusing capacity of oxygen is technically very difficult to measure. Therefore, the clinical test actually measures the diffusing capacity of carbon monoxide (DLCO) which provides a valid estimate of the general gas-exchanging function of the whole lungs (Plantier et al., 2018). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells, and is usually tested in a single breath where the partial pressure difference between inspired and expired carbon monoxide is recorded (Rosenberg, 1996; Plantier et al., 2018). The carbon monoxide transfer coefficient (KCO) is an index of the efficiency of alveolar transfer of carbon monoxide. It can be referred to as $DLCO/VA$, ~~and~~ where VA is the alveolar volume where gas exchange takes place (Graham et al., 2017).

It has been shown ~~is measured~~ that DLCO is reduced in 98% of IPF patients at the initial diagnosis, need to define

although 27% of them had normal TLC volumes and normal FVC ~~happened~~ in 56% of patients (Cortes-Telles et al., 2014). Interestingly, KCO is within the normal range in up to 30% of IPF patients (Wallaert et al., 2012), particularly in patients with moderately reduced DLCO (Pastre et al., 2015). But a normal KCO value in IPF patients does not mean that pulmonary gas exchange is normal (Plantier et al., 2018). It has been noted that both DLCO and KCO are significantly associated with the degree of IPF measured from CT scans (Wells et al., 1997), but DLCO correlates more strongly with exertional increases of $P_{A-a}O_2$ (Agusti et al., 1994) and highly relates to both dyspnoea (Swigris et al., 2012) and survival time (Hamada et al., 2007).

Dead space ventilation

Increased physiologic dead space ventilation (increased ratio of dead space volume to tidal volume (VD / VT)) is an important characteristic of fibrosis lungs and happens in most IPF patients both at rest and at exercise (Fulmer et al., 1976; Crystal et al., 1976; Agustí et al., 1991; Miki et al., 2009). The increased dead space is mainly caused by two physiologic features: the first is the increased anatomical dead space, which is a result ~~from~~ of the dilation of conducting airways in IPF as discussed in Section 1.6.1 (Plantier et al., 2016); the second is the regional V/Q mismatching (increased variation in regional V/Q ratio). In IPF lungs, the fibrotic (i.e. honeycomb or reticular) areas that are not perfused or poorly perfused but still receive normal ventilation will have an increased regional V/Q ratio (Strickland et al., 1993; Plantier et al., 2018). An early paper indicated that patients with IPF will often have a VD/VT ratio of greater than 0.4 ~~averagely~~ compared

With a you need to say the ratio for normal

~~to~~ normal person (Crystal et al., 1976). In normal individuals the efficiency of ventilation improves with exercise (that is the VD/VT falls) (Jones et al., 1966; Wasserman and Whipp, 1975), but in more than 90% of IPF patients VD/VT ratio stays constant or may increase (Crystal et al., 1976).

Ventilation-perfusion mismatching

It is generally thought that the hypoxemia of IPF ~~lung~~ is related to ~~ventilation-perfusion~~ V/Q mismatching (Wagner et al., 1976; Crystal et al., 1976; Society et al., 2000). The ~~ventilation-perfusion~~ V/Q mismatching may be associated with ~~the~~ abnormalities both in ventilation and perfusion (Crystal et al., 1976; Strickland et al., 1993). In Crystal et al.'s (1976)~~'s~~ study, ~~the~~ an equilibrium picture of 127 Xe distribution was used to reflect ventilated proportion of the lung, which showed that patients with IPF have patchy, nonsegmental areas of decreased ventilation where airway obstruction or alveolar destruction ~~happened~~ occurred. As for perfusion, a shift of perfusion was observed to the upper lobes (reflecting pulmonary hypertension) due to the basal distribution of fibrotic lesions, so that areas of relatively low ~~ventilation-perfusion~~ V/Q ratios mostly presented in the upper zones (Crystal et al., 1976). However, Strickland et al. (1993) indicated that the CT based cystic air spaces (i.e. honeycomb) were observed as poorly perfused (probably due to vascular obliteration) but were usually normally ventilated, which explains the increase in physiologic dead space seen at rest and with exercise. Thus, ~~it can be seen~~ a higher V/Q ratio can be seen in areas where fibrosis and cystic air spaces are dominant, which could be used to distinguish IPF from emphysema (Strickland et al., 1993). In addition, ~~the~~ an increased minute ventilation was found in most patients with IPF during exercise. ~~It~~ This is mainly due to the increased respiratory frequency, and in part relates to the increase in dead space ventilation as well (Society et al., 2000).

Arterial hypoxaemia

Alterations in the mechanical properties of the lungs, impairment of diffusion capacity and ventilation/perfusion mismatching will finally lead to early-onset exertional chronic arterial hypoxaemia and later-onset resting chronic arterial hypoxaemia in IPF (Hempleman and Hughes, 1991; Hughes et al., 1991; Plantier et al., 2018). Some studies support that the major cause of arterial hypoxaemia in a large proportion of IPF patients is not the diffusion barrier to oxygen or the anatomic shunts, as was originally suspected, but is due to ventilation-perfusion mismatching (Finley et al., 1962; Wagner et al., 1976; Society et al., 2000). The alveolar-arterial oxygen gradient ($P_{A-a}O_2$), which is calculated from arterial oxygen tension (P_aO_2) and arterial carbon dioxide tension (P_aCO_2) may increase, resulting from the reduced V/Q ratios, right-to-left shunting, or impairment of oxygen diffusion (Plantier et al., 2018). The increase in $P_{A-a}O_2$ is the main mechanism driving hypoxaemia in IPF (Agustí et al., 1991). In a study of 29 IPF patients, the measured average resting arterial PO2 ~~hypoxemia~~ was 69.3 mmHg, and four ~~of them~~ had normal resting P_aO_2. However, although the resting P_aO_2 can be normal in some IPF patients, the resting $P_{A-a}O_2$ is invariably abnormal in most patients (97%) (Crystal et al., 1976).

1.7 Summary

IPF is a devastating lung disease characterized by an irreversible decline of lung function, and its incidence ~~is~~ increas~~ing by~~es with years. The current efforts of ~~the~~ studies in IPF ~~are~~ mostly focus on the accurate identification and diagnosis of early IPF, underlying mechanisms of pathogenesis, and potential biomarkers that can indicate the patient-specific clinical course~~s~~. The presence of IPF is variable in most patients, but some common characteristics and progressions can be summarized, although this is challenging. The clinical and physiological features of IPF reviewed in this chapter provides background information for ~~our~~ further quantitative analysis (Chapter 4) and computational modeling (Chapter 5) of IPF.

List of References

Agustí, A. G., Roca, J., Gea, J., Wagner, P. D., Xaubet, A., and Rodriguez-Roisin, R. (1991). Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. American Review of Respiratory Disease, 143(2):219–225. [Cited on pages 25 and 27.]

Agusti, C., Xaubet, A., Agusti, A., Roca, J., Ramirez, J., and Rodriguez-Roisin, R. (1994). Clinical and functional assessment of patients with idiopathic pulmonary fibrosis: results of a 3 year follow-up. European Respiratory Journal, 7(4):643–650. [Cited on page 25.]

Ahluwalia, N., Shea, B. S., and Tager, A. M. (2014). New therapeutic targets in idiopathic pulmonary fibrosis. aiming to rein in runaway wound-healing responses. American journal of respiratory and critical care medicine, 190(8):867–878. [Cited on page 2.]

Alder, J. K., Chen, J. J.-L., Lancaster, L., Danoff, S., Su, S.-c., Cogan, J. D., Vulto, I., Xie, M., Qi, X., Tuder, R. M., et al. (2008). Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proceedings of the National Academy of Sciences, 105(35):13051–13056. [Cited on page 6.]

Allam, J. S. and Limper, A. H. (2006). Idiopathic pulmonary fibrosis: is it a familial disease? Current opinion in pulmonary medicine, 12(5):312–317. [Cited on page 6.]

Ambrosini, V., Cancellieri, A., Chilosi, M., Zompatori, M., Trisolini, R., Saragoni, L., and Poletti, V. (2003). Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. European Respiratory Journal, 22(5):821–826. [Cited on page 15.]

Azuma, A., Nukiwa, T., Tsuboi, E., Suga, M., Abe, S., Nakata, K., Taguchi, Y., Nagai, S., Itoh, H., Ohi, M., et al. (2005). Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 171(9):1040–1047. [Cited on page 15.]

Baddini-Martinez, J. and Pereira, C. A. (2015). How many patients with idiopathic pulmonary fibrosis are there in brazil? Jornal Brasileiro de Pneumologia, 41(6):560–561. [Cited on page 16.]

Baumgartner, K. B., Samet, J. M., Stidley, C. A., Colby, T. V., and Waldron, J. A. (1997). Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 155(1):242–248. [Cited on page 5.]

Bjoraker, J. A., Ryu, J. H., Edwin, M. K., Myers, J. L., Tazelaar, H. D., Schroeder, D. R., and Offord, K. P. (1998). Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 157(1):199–203. [Cited on page 12.]

Carrington, C. B., Gaensler, E. A., Coutu, R. E., FitzGerald, M. X., and Gupta, R. G. (1978). Natural history and treated course of usual and desquamative interstitial pneumonia. New England Journal of Medicine, 298(15):801–809. [Cited on page 14.]

Cherniack, R. M., Colby, T. V., Flint, A., Thurlbeck, W. M., Waldron Jr, J. A., Ackerson, L., Schwarz, M. I., and King Jr, T. E. (1995). Correlation of structure and function in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 151(4):1180–1188. [Cited on page 21.]

Chilosi, M., Poletti, V., Murer, B., Lestani, M., Cancellieri, A., Montagna, L., Piccoli, P., Cangi, G., Semenzato, G., and Doglioni, C. (2002). Abnormal re-epithelialization and lung remodeling in idiopathic pulmonary fibrosis: the role of δn-p63. Laboratory investigation, 82(10):1335. [Cited on page 22.]

Corte, T. J., Collard, H., and Wells, A. U. (2015). Idiopathic interstitial pneumonias in 2015: A new era. Respirology, 20(5):697–698. [Cited on page 3.]

Cortes-Telles, A., Forkert, L., ODonnell, D. E., and Morán-Mendoza, O. (2014). Idiopathic pulmonary fibrosis: New insights to functional characteristics at diagnosis. Canadian respiratory journal, 21(3):e55–e60. [Cited on pages 19 and 25.]

Cosgrove, G. P., Brown, K. K., Schiemann, W. P., Serls, A. E., Parr, J. E., Geraci, M. W., Schwarz, M. I., Cool, C. D., and Worthen, G. S. (2004). Pigment epithelium–derived factor in idiopathic pulmonary fibrosis: a role in aberrant angiogenesis. American journal of respiratory and critical care medicine, 170(3):242–251. [Cited on page 23.]

Cottin, V., Le Pavec, J., Prévot, G., Mal, H., Humbert, M., Simonneau, G., Cordier, J.-F., et al. (2010). Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. European Respiratory Journal, 35(1):105–111. [Cited on page 17.]

Cottin, V., Nunes, H., Brillet, P., Delaval, P., Devouassoux, G., Tillie-Leblond, I., Israel-Biet, D., Valeyre, D., Cordier, J., et al. (2005). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. European Respiratory Journal, 26(4):586–593. [Cited on page 17.]

Crystal, R. G., Fulmer, J. D., Roberts, W. C., Moss, M. L., Line, B. R., and Reynolds, H. Y. (1976). Idiopathic pulmonary fibrosis: clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. Annals of internal medicine, 85(6):769–788. [Cited on pages 19, 23, 24, 25, 26, and 27.]

Doherty, M., Pearson, M., O'grady, E., Pellegrini, V., and Calverley, P. (1997). Cryptogenic fibrosing alveolitis with preserved lung volumes. Thorax, 52(11):998–1002. [Cited on page 22.]

Douglas, W. W., Ryu, J. H., and Schroeder, D. R. (2000). Idiopathic pulmonary fibrosis: impact of oxygen and colchicine, prednisone, or no therapy on survival. American journal of respiratory and critical care medicine, 161(4):1172–1178. [Cited on pages 7 and 8.]

Du Bois, R. M., Weycker, D., Albera, C., Bradford, W. Z., Costabel, U., Kartashov, A., Lancaster, L., Noble, P. W., Raghu, G., Sahn, S. A., et al. (2011). Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 184(4):459–466. [Cited on page 22.]

Ebina, M., Shimizukawa, M., Shibata, N., Kimura, Y., Suzuki, T., Endo, M., Sasano, H., Kondo, T., and Nukiwa, T. (2004). Heterogeneous increase in cd34-positive alveolar capillaries in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 169(11):1203–1208. [Cited on page 23.]

Esposito, D. B., Lanes, S., Donneyong, M., Holick, C. N., Lasky, J. A., Lederer, D., Nathan, S. D., OQuinn, S., Parker, J., and Tran, T. N. (2015). Idiopathic pulmonary fibrosis in united states automated claims. incidence, prevalence, and algorithm validation. American journal of respiratory and critical care medicine, 192(10):1200–1207. [Cited on page 16.]

Finley, T., Swenson, E., and Comroe, J. (1962). The cause of arterial hypoxemia at rest in patients with alveolar-capillary block syndrome. The Journal of clinical investigation, 41(3):618–622. [Cited on page 27.]

Flaherty, K., Thwaite, E., Kazerooni, E., Gross, B., Toews, G., Colby, T. V., Travis, W., Mumford, J., Murray, S., Flint, A., et al. (2003). Radiological versus histological diagnosis in uip and nsip: survival implications. Thorax, 58(2):143–148. [Cited on page 12.]

Flaherty, K., Toews, G., Travis, W., Colby, T., Kazerooni, E., Gross, B., Jain, A., Strawderman, R., Paine, R., Flint, A., et al. (2002). Clinical significance of histological classification of idiopathic interstitial pneumonia. European Respiratory Journal, 19(2):275–283. [Cited on page 12.]

Flaherty, K. R., King Jr, T. E., Raghu, G., Lynch III, J. P., Colby, T. V., Travis, W. D., Gross, B. H., Kazerooni, E. A., Toews, G. B., Long, Q., et al. (2004). Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? American journal of respiratory and critical care medicine, 170(8):904–910. [Cited on page 7.]

Fulmer, J., Roberts, W., von Gal, E. R., and Crystal, R. (1979). Morphologic-physiologic correlates of the severity of fibrosis and degree of cellularity in idiopathic pulmonary fibrosis. The Journal of clinical investigation, 63(4):665–676. [Cited on page 21.]

Fulmer, J. D., Crystal, R. G., and Roberts, W. C. (1976). Diffuse fibrotic lung disease: a correlative study. Chest, 69(2):263–265. [Cited on page 25.]

Graham, B. L., Brusasco, V., Burgos, F., Cooper, B. G., Jensen, R., Kendrick, A., MacIntyre, N. R., Thompson, B. R., and Wanger, J. (2017). 2017 ers/ats standards for single-breath carbon monoxide uptake in the lung. European Respiratory Journal, 49(1):1600016. [Cited on page 24.]

Gross, P. (1962). The concept of the hamman-rich syndrome: a critique. American Review of Respiratory Disease, 85(6):828–832. [Cited on page 15.]

Gross, T. J. and Hunninghake, G. W. (2001). Idiopathic pulmonary fibrosis. New England Journal of Medicine, 345(7):517–525. [Cited on page 14.]

Gunther, A., Schmidt, R., Nix, F., Yabut-Perez, M., Guth, C., Rosseau, S., Siebert, C., Grimminger, F., Morr, H., Velcovsky, H., et al. (1999). Surfactant abnormalities in idiopathic pulmonary fibrosis, hypersensitivity pneumonitis and sarcoidosis. European Respiratory Journal, 14(3):565–573. [Cited on page 19.]

Hamada, K., Nagai, S., Tanaka, S., Handa, T., Shigematsu, M., Nagao, T., Mishima, M., Kitaichi, M., and Izumi, T. (2007). Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest, 131(3):650–656. [Cited on page 25.]

Hansell, D. M., Bankier, A. A., MacMahon, H., McLoud, T. C., Muller, N. L., and Remy, J. (2008). Fleischner society: glossary of terms for thoracic imaging. Radiology, 246(3):697–722. [Cited on page 8.]

Harari, S., Madotto, F., Caminati, A., Conti, S., and Cesana, G. (2016). Epidemiology of idiopathic pulmonary fibrosis in northern italy. PLoS One, 11(2):e0147072. [Cited on page 16.]

Hayes Jr, D., Black, S. M., Tobias, J. D., Kirkby, S., Mansour, H. M., and Whitson, B. A. (2016). Influence of pulmonary hypertension on patients with idiopathic pulmonary fibrosis awaiting lung transplantation. The Annals of thoracic surgery, 101(1):246–252. [Cited on page 18.]

Hempleman, S. C. and Hughes, J. (1991). Estimating exercise dlo2 and diffusion limitation in patients with interstitial fibrosis. Respiration physiology, 83(2):167–178. [Cited on page 27.]

Hughes, J., Lockwood, D., Jones, H., and Clark, R. (1991). Dlco/q and diffusion limitation at rest and on exercise in patients with interstitial fibrosis. Respiration physiology, 83(2):155–166. [Cited on page 27.]

Hunninghake, G. W., Zimmerman, M. B., Schwartz, D. A., KING JR, T. E., Lynch, J., Hegele, R., Waldron, J., Colby, T., Muller, N., Lynch, D., et al. (2001). Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 164(2):193–196. [Cited on page 12.]

Hwang, J.-H., Misumi, S., Sahin, H., Brown, K. K., Newell, J. D., and Lynch, D. A. (2009). Computed tomographic features of idiopathic fibrosing interstitial pneumonia: comparison with pulmonary fibrosis related to collagen vascular disease. Journal of computer assisted tomography, 33(3):410–415. [Cited on page 8.]

Hyldgaard, C., Hilberg, O., Muller, A., and Bendstrup, E. (2014). A cohort study of interstitial lung diseases in central denmark. Respiratory medicine, 108(5):793–799. [Cited on page 4.]

Jacob, J., Bartholmai, B. J., Rajagopalan, S., Brun, A. L., Egashira, R., Karwoski, R., Kokosi, M., Wells, A. U., and Hansell, D. M. (2016a). Evaluation of computer-based computer tomography stratification against outcome models in connective tissue disease-related interstitial lung disease: a patient outcome study. Bmc Medicine, 14(1):190. [Cited on page 23.]

Jacob, J., Bartholmai, B. J., Rajagopalan, S., Kokosi, M., Nair, A., Karwoski, R., Walsh, S. L., Wells, A. U., and Hansell, D. M. (2016b). Mortality prediction in ipf: evaluation of automated computer tomographic analysis with conventional severity measures. European Respiratory Journal, 49(1):ERJ–01011–2016. [Cited on page 24.]

Johkoh, T., Muller, N. L., Cartier, Y., Kavanagh, P. V., Hartman, T. E., Akira, M., Ichikado, K., Ando, M., and Nakamura, H. (1999). Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section ct in 129 patients. Radiology, 211(2):555–560. [Cited on page 8.]

Jones, N., McHardy, G., Naimark, A., and Campbell, E. (1966). Physiological dead space and alveolar-arterial gas pressure differences during exercise. Clinical science, 31(1):19–29. [Cited on page 25.]

Katzenstein, A.-L. A. and Myers, J. L. (1998). Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. American journal of respiratory and critical care medicine, 157(4):1301–1315. [Cited on page 3.]

Kim, D., Park, J., Park, B., Lee, J., Nicholson, A., and Colby, T. (2006a). Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. European Respiratory Journal, 27(1):143–150. [Cited on page 15.]

Kim, D. S., Collard, H. R., and King Jr, T. E. (2006b). Classification and natural history of the idiopathic interstitial pneumonias. Proceedings of the American Thoracic Society, 3(4):285–292. [Cited on pages 14 and 15.]

Kim, H. J., Perlman, D., and Tomic, R. (2015). Natural history of idiopathic pulmonary fibrosis. Respiratory medicine, 109(6):661–670. [Cited on pages 2 and 16.]

King, C. S. and Nathan, S. D. (2017). Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities. The Lancet Respiratory Medicine, 5(1):72–84. [Cited on pages 16 and 18.]

King Jr, T. E., Pardo, A., and Selman, M. (2011). Idiopathic pulmonary fibrosis. The Lancet, 378(9807):1949–1961. [Cited on pages 1, 2, 7, 8, 10, 12, 15, 16, 17, 18, and 19.]

KING JR, T. E., Schwarz, M. I., Brown, K., Tooze, J. A., Colby, T. V., WALDRON JR, J. A., Flint, A., Thurlbeck, W., and Cherniack, R. M. (2001). Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. American journal of respiratory and critical care medicine, 164(6):1025–1032. [Cited on page 12.]

King Jr, T. E., Tooze, J. A., Schwarz, M. I., BROWN, K. R., and CHERNIACK, R. M. (2001). Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. American journal of respiratory and critical care medicine, 164(7):1171–1181. [Cited on page 7.]

Kondoh, Y., Taniguchi, H., Kataoka, K., Keisuke, K., Suzuki, R., Ogura, T., Johkoh, T., Yokoi, T., Wells, A. U., and Kitaichi, M. (2010). Prognostic factors in rapidly progressive interstitial pneumonia. Respirology, 15(2):257–264. [Cited on page 15.]

Kondoh, Y., Taniguchi, H., Kawabata, Y., Yokoi, T., Suzuki, K., and Takagi, K. (1993). Acute exacerbation in idiopathic pulmonary fibrosis: analysis of clinical and pathologic findings in three cases. Chest, 103(6):1808–1812. [Cited on page 15.]

Kornbluth, R. and Turino, G. (1980). Respiratory control in diffuse interstitial lung disease and diseases of the pulmonary vasculature. Clinics in chest medicine, 1(1):91–102. [Cited on page 23.]

Kreuter, M., Ehlers-Tenenbaum, S., Palmowski, K., Bruhwyler, J., Oltmanns, U., Muley, T., Heussel, C. P., Warth, A., Kolb, M., and Herth, F. J. (2016). Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis. PLoS One, 11(3):e0151425. [Cited on page 16.]

Lee, H.-L., Ryu, J. H., Wittmer, M. H., Hartman, T. E., Lymp, J. F., Tazelaar, H. D., and Limper, A. H. (2005). Familial idiopathic pulmonary fibrosis: clinical features and outcome. Chest, 127(6):2034–2041. [Cited on page 6.]

Lettieri, C. J., Nathan, S. D., Barnett, S. D., Ahmad, S., and Shorr, A. F. (2006). Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest, 129(3):746–752. [Cited on pages 14, 15, and 18.]

Ley, B., Collard, H. R., and King Jr, T. E. (2011). Clinical course and prediction of survival in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 183(4):431–440. [Cited on pages 14, 15, and 16.]

Lin, H. and Jiang, S. (2015). Combined pulmonary fibrosis and emphysema (cpfe): an entity different from emphysema or pulmonary fibrosis alone. Journal of thoracic disease, 7(4):767. [Cited on page 17.]

Lynch, J. P., Saggar, R., Weigt, S. S., Zisman, D. A., and White, E. S. (2006). Usual interstitial pneumonia. In Seminars in respiratory and critical care medicine, volume 27, pages 634–651. Copyright© 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. [Cited on page 12.]

Martinez, F. J., Collard, H. R., Pardo, A., Raghu, G., Richeldi, L., Selman, M., Swigris, J. J., Taniguchi, H., and Wells, A. U. (2017). Idiopathic pulmonary fibrosis. Nature Reviews Disease Primers, 3:17074. [Cited on pages 2, 9, 16, and 17.]

Martinez, F. J. and Flaherty, K. (2006). Pulmonary function testing in idiopathic interstitial pneumonias. Proceedings of the American Thoracic Society, 3(4):315–321. [Cited on pages 21 and 22.]

Mejía, M., Carrillo, G., Rojas-Serrano, J., Estrada, A., Suárez, T., Alonso, D., Barrientos, E., Gaxiola, M., Navarro, C., and Selman, M. (2009). Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest, 136(1):10–15. [Cited on pages 14, 17, and 18.]

Meltzer, E. B. and Noble, P. W. (2008). Idiopathic pulmonary fibrosis. Orphanet journal of rare diseases, 3(1):8. [Cited on pages 1, 2, 3, 4, 5, 14, and 17.]

Miki, K., Maekura, R., Hiraga, T., Hashimoto, H., Kitada, S., Miki, M., Yoshimura, K., Tateishi, Y., Fushitani, K., and Motone, M. (2009). Acidosis and raised norepinephrine levels are associated with exercise dyspnoea in idiopathic pulmonary fibrosis. Respirology, 14(7):1020–1026. [Cited on page 25.]

Mura, M., Zompatori, M., Pacilli, A. M. G., Fasano, L., Schiavina, M., and Fabbri, M. (2006). The presence of emphysema further impairs physiologic function in patients with idiopathic pulmonary fibrosis. Respiratory care, 51(3):257–265. [Cited on page 22.]

Musk, A., Zilko, P., Manners, P., Kay, P., and Kamboh, M. (1986). Genetic studies in familial fibrosing alveolitis: possible linkage with immunoglobulin allotypes (gm). Chest, 89(2):206–210. [Cited on page 6.]

Nadrous, H. F., Pellikka, P. A., Krowka, M. J., Swanson, K. L., et al. (2005). The impact of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis. Chest, 128(6):616S. [Cited on page 18.]

Nava, S. and Rubini, F. (1999). Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. Thorax, 54(5):390–395. [Cited on page 21.]

Nicholson, A. G., Colby, T. V., Dubois, R. M., Hansell, D. M., and Wells, A. U. (2000). The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. American journal of respiratory and critical care medicine, 162(6):2213–2217. [Cited on page 12.]

Nishimura, K., Kitaichi, M., Izumi, T., Nagai, S., Kanaoka, M., and Itoh, H. (1992). Usual interstitial pneumonia: histologic correlation with high-resolution ct. Radiology, 182(2):337–342. [Cited on page 8.]

Orens, J. B., Kazerooni, E. A., Martinez, F. J., Curtis, J. L., Gross, B. H., Flint, A., and Lynch III, J. P. (1995). The sensitivity of high-resolution ct in detecting idiopathic pulmonary fibrosis proved by open lung biopsy: a prospective study. Chest, 108(1):109–115. [Cited on page 21.]

Organ, L., Bacci, B., Koumoundouros, E., Barcham, G., Milne, M., Kimpton, W., Samuel, C., and Snibson, K. (2015). Structural and functional correlations in a large animal model of bleomycin-induced pulmonary fibrosis. BMC pulmonary medicine, 15(1):81. [Cited on page 21.]

Parambil, J. G., Myers, J. L., and Ryu, J. H. (2005). Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. Chest, 128(5):3310–3315. [Cited on page 15.]

Pastre, J., Plantier, L., Planes, C., Borie, R., Nunes, H., Delclaux, C., and Israël-Biet, D. (2015). Different k co and va combinations exist for the same dl co value in patients with diffuse parenchymal lung diseases. BMC pulmonary medicine, 15(1):100. [Cited on pages 22 and 25.]

Plantier, L., Cazes, A., Dinh-Xuan, A.-T., Bancal, C., Marchand-Adam, S., and Crestani, B. (2018). Physiology of the lung in idiopathic pulmonary fibrosis. European Respiratory Review, 27(147):170062. [Cited on pages 19, 20, 21, 22, 23, 24, 25, and 27.]

Plantier, L., Debray, M.-P., Estellat, C., Flamant, M., Roy, C., Bancal, C., Borie, R., Israël-Biet, D., Mal, H., Crestani, B., et al. (2016). Increased volume of conducting airways in idiopathic pulmonary fibrosis is independent of disease severity: a volumetric capnography study. Journal of breath research, 10(1):016005. [Cited on pages 22, 23, and 25.]

Quadrelli, S., Molinari, L., Ciallella, L., Spina, J. C., Sobrino, E., and Chertcoff, J. (2010). Radiological versus histopathological diagnosis of usual interstitial pneumonia in the clinical practice: does it have any survival difference? Respiration, 79(1):32–37. [Cited on page 12.]

Raghu, G. (1987). Idiopathic pulmonary fibrosis: a rational clinical approach. Chest, 92(1):148–154. [Cited on page 14.]

Raghu, G., Amatto, V. C., Behr, J., and Stowasser, S. (2015). Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. European Respiratory Journal, 46(4):1113–1130. [Cited on page 17.]

Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., Colby, T. V., Cordier, J.-F., Flaherty, K. R., Lasky, J. A., et al. (2011). An official ats/ers/jrs/alat statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American journal of respiratory and critical care medicine, 183(6):788–824. [Cited on pages 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, and 19.]

Raghu, G., Mageto, Y. N., Lockhart, D., Schmidt, R. A., Wood, D. E., and Godwin, J. D. (1999). The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: a prospective study. Chest, 116(5):1168–1174. [Cited on page 12.]

Raghu, G., Weycker, D., Edelsberg, J., Bradford, W. Z., and Oster, G. (2006). Incidence and prevalence of idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 174(7):810–816. [Cited on pages 4 and 8.]

Renzi, G., Milic-Emili, J., and Grassino, A. (1982). The pattern of breathing in diffuse lung fibrosis. Bulletin europeen de physiopathologie respiratoire, 18(3):461–472. [Cited on page 23.]

Richeldi, L., Collard, H. R., and Jones, M. G. (2017). Idiopathic pulmonary fibrosis. The Lancet, 389(10082):1941–1952. [Cited on pages 2, 4, 5, 6, 7, 8, 9, and 10.]

Rosenberg, E. (1996). The 1995 update of recommendations for a standard technique for measuring the single-breath carbon monoxide diffusing capacity (transfer factor). American journal of respiratory and critical care medicine, 154(3):827–828. [Cited on page 24.]

Rudd, R. M., Prescott, R. J., Chalmers, J., and Johnston, I. D. (2007). British thoracic society study on cryptogenic fibrosing alveolitis: response to treatment and survival. Thorax, 62(1):62–66. [Cited on page 12.]

Ryu, J. H., Moua, T., Daniels, C. E., Hartman, T. E., Eunhee, S. Y., Utz, J. P., and Limper, A. H. (2014). Idiopathic pulmonary fibrosis: evolving concepts. In Mayo Clinic proceedings, volume 89, pages 1130–1142. Elsevier. [Cited on page 14.]

Sakamoto, K., Taniguchi, H., Kondoh, Y., Ono, K., Hasegawa, Y., and Kitaichi, M. (2009). Acute exacerbation of idiopathic pulmonary fibrosis as the initial presentation of the disease. European Respiratory Review, 18(112):129–132. [Cited on page 15.]

Schmidt, R., Meier, U., Markart, P., Grimminger, F., Velcovsky, H., Morr, H., Seeger, W., and Gunther, A. (2002). Altered fatty acid composition of lung surfactant phospholipids in interstitial lung disease. American Journal of Physiology-Lung Cellular and Molecular Physiology, 283(5):L1079–L1085. [Cited on page 19.]

Seibold, M. A., Wise, A. L., Speer, M. C., Steele, M. P., Brown, K. K., Loyd, J. E., Fingerlin, T. E., Zhang, W., Gudmundsson, G., Groshong, S. D., et al. (2011). A common muc5b promoter polymorphism and pulmonary fibrosis. New England Journal of Medicine, 364(16):1503–1512. [Cited on page 6.]

Selman, M., Carrillo, G., Estrada, A., Mejia, M., Becerril, C., Cisneros, J., Gaxiola, M., Pérez-Padilla, R., Navarro, C., Richards, T., et al. (2007). Accelerated variant of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. PloS one, 2(5):e482. [Cited on page 14.]

Silva, C. I. S., Muller, N. L., Lynch, D. A., Curran-Everett, D., Brown, K. K., Lee, K. S., Chung, M. P., and Churg, A. (2008a). Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section ct. Radiology, 246(1):288–297. [Cited on page 12.]

Silva, D. R., Gazzana, M. B., Barreto, S. S. M., and Knorst, M. M. (2008b). Idiopathic pulmonary fibrosis and emphysema in smokers. Jornal Brasileiro de Pneumologia, 34(10):779–786. [Cited on page 17.]

Society, A. T. et al. (2000). Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. Am J Respir Crit Care Med, 161:646–664. [Cited on pages 10, 19, 21, 23, 24, 26, and 27.]

Souza, C. A., Muller, N. L., Lee, K. S., Johkoh, T., Mitsuhiro, H., and Chong, S. (2006). Idiopathic interstitial pneumonias: prevalence of mediastinal lymph node enlargement in 206 patients. American Journal of Roentgenology, 186(4):995–999. [Cited on page 8.]

Steele, M. P., Speer, M. C., Loyd, J. E., Brown, K. K., Herron, A., Slifer, S. H., Burch, L. H., Wahidi, M. M., Phillips III, J. A., Sporn, T. A., et al. (2005). Clinical and pathologic features of familial interstitial pneumonia. American journal of respiratory and critical care medicine, 172(9):1146–1152. [Cited on page 6.]

Strickland, N., Hughes, J., Hart, D., Myers, M., and Lavender, J. (1993). Cause of regional ventilation-perfusion mismatching in patients with idiopathic pulmonary fibrosis: a combined ct and scintigraphic study. AJR. American journal of roentgenology, 161(4):719–725. [Cited on pages 25 and 26.]

Sumikawa, H., Johkoh, T., Colby, T. V., Ichikado, K., Suga, M., Taniguchi, H., Kondoh, Y., Ogura, T., Arakawa, H., Fujimoto, K., et al. (2008). Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. American journal of respiratory and critical care medicine, 177(4):433–439. [Cited on page 23.]

Swigris, J. J., Han, M., Vij, R., Noth, I., Eisenstein, E. L., Anstrom, K. J., Brown, K. K., and Fairclough, D. (2012). The ucsd shortness of breath questionnaire has longitudinal construct validity in idiopathic pulmonary fibrosis. Respiratory medicine, 106(10):1447–1455. [Cited on page 25.]

Taskar, V. S. and Coultas, D. B. (2006). Is idiopathic pulmonary fibrosis an environmental disease? Proceedings of the American Thoracic Society, 3(4):293–298. [Cited on page 5.]

Trahan, S., Hanak, V., Ryu, J. H., and Myers, J. L. (2008). Role of surgical lung biopsy in separating chronic hypersensitivity pneumonia from usual interstitial pneumonia/idiopathic pulmonary fibrosis*: Analysis of 31 biopsies from 15 patients. Chest, 134(1):126–132. [Cited on page 12.]

Travis, W. D., Costabel, U., Hansell, D. M., King Jr, T. E., Lynch, D. A., Nicholson, A. G., Ryerson, C. J., Ryu, J. H., Selman, M., Wells, A. U., et al. (2013). An official american thoracic society/european respiratory society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. American journal of respiratory and critical care medicine, 188(6):733–748. [Cited on page 4.]

Travis, W. D., King, T. E., Bateman, E. D., Lynch, D. A., Capron, F., Center, D., Colby, T. V., Cordier, J. F., DuBois, R. M., Galvin, J., et al. (2002). American thoracic society/european respiratory society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. American journal of respiratory and critical care medicine, 165(2):277–304. [Cited on page 10.]

Troy, L. and Corte, T. J. (2012). Management of the idiopathic interstitial pneumonias. Australian Prescriber, 35(6):202–6. [Cited on page 3.]

Tukiainen, P., Taskinen, E., Holsti, P., Korhola, O., and Valle, M. (1983). Prognosis of cryptogenic fibrosing alveolitis. Thorax, 38(5):349–355. [Cited on page 14.]

Vuorinen, K., Ohlmeier, S., Leppäranta, O., Salmenkivi, K., Myllärniemi, M., and Kinnula, V. L. (2008). Peroxiredoxin ii expression and its association with oxidative stress and cell proliferation in human idiopathic pulmonary fibrosis. Journal of Histochemistry & Cytochemistry, 56(10):951–959. [Cited on page 22.]

Wagner, P., Dantzker, D., Dueck, R., De Polo, J., Wasserman, K., and West, J. (1976). Distribution of ventilation-perfusion ratios in patients with interstitial lung disease. Chest, 69(2):256–257. [Cited on pages 26 and 27.]

Wallaert, B., Wemeau-Stervinou, L., Salleron, J., Tillie-Leblond, I., and Perez, T. (2012). Do we need exercise tests to detect gas exchange impairment in fibrotic idiopathic interstitial pneumonias? Pulmonary medicine, 2012. [Cited on page 25.]

Walsh, S. L., Wells, A. U., Sverzellati, N., Devaraj, A., von der Thüsen, J., Yousem, S. A., Colby, T. V., Nicholson, A. G., and Hansell, D. M. (2015). Relationship between fibroblastic foci profusion and high resolution ct morphology in fibrotic lung disease. BMC medicine, 13(1):241. [Cited on page 23.]

Wasserman, K. and Whipp, B. J. (1975). Exercise physiology in health and disease. American Review of Respiratory Disease, 112(2):219–249. [Cited on page 25.]

Wells, A. U., Desai, S. R., Rubens, M. B., Goh, N. S., Cramer, D., Nicholson, A. G., Colby, T. V., Du Bois, R. M., and Hansell, D. M. (2003). Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. American journal of respiratory and critical care medicine, 167(7):962–969. [Cited on pages 14 and 17.]

Wells, A. U., King, A. D., Rubens, M. B., Cramer, D., Du Bois, R., and Hansell, D. M. (1997). Lone cryptogenic fibrosing alveolitis: a functional-morphologic correlation based on extent of disease on thin-section computed tomography. American journal of respiratory and critical care medicine, 155(4):1367–1375. [Cited on pages 17 and 25.]

Wootton, S. C., Kim, D. S., Kondoh, Y., Chen, E., Lee, J. S., Song, J. W., Huh, J. W., Taniguchi, H., Chiu, C., Boushey, H., et al. (2011). Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 183(12):1698–1702. [Cited on page 15.]

Xaubet, A., Ancochea, J., and Molina-Molina, M. (2017). Idiopathic pulmonary fibrosis. Medicina Clínica (English Edition), 148(4):170–175. [Cited on pages 2, 4, 5, 6, 15, 16, 17, and 18.]

Zielonka, T., Demkow, U., Radzikowska, E., Bialas, B., Filewska, M., Zycinska, K., Obrowski, M., Kowalski, J., Wardyn, K., and Skopinska-Rozewska, E. (2010). Angiogenic activity of sera from interstitial lung disease patients in relation to pulmonary function. European journal of medical research, 15(2):229. [Cited on page 21.]