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# MECHANICAL PROPERTIES AND ELASTIC BEHAVIOUR OF THE FIBROTIC LUNG WITH USUAL INTERSTITIAL PNEUMONIA PATTERN UNDER MECHANICAL VENTILATION: DEVELOPMENT AND CLINICAL SIGNIFICANCE OF THE "SQUISHY BALL" LUNG THEORY

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## Abstract

Patients with acute exacerbation (AE) of interstitial lung disease (ILD) and usual interstitial pneumonia (UIP) pattern may experience severe acute hypoxic respiratory failure, even requiring ventilatory assistance. Patho-physiologically, AE-ILD resembles an acute respiratory distress syndrome (ARDS), since it mainly consists of diffuse alveolar damage (DAD) superimposed on a background of fibrosing ILD. While protective ventilatory strategies have contributed to significant improvements in ARDS mortality mitigating the risk of ventilator induced lung injury, specific evidence concerning lung mechanics and optimal ventilatory setting (either invasive or non-invasive) during AE-ILD are lacking. Given that pulmonary fibrosis may be the trajectory towards which a wide variety of clinical conditions (e.g. ARDS) are directed, understanding the peculiar physiological changes occurring in the fibrotic lung while subjected to ventilatory support, could help critical care physicians to tailor respiratory assistance and optimize ventilatory strategies. Thus, the purpose of this 3-years research project was to explore the mechanical properties and elastic behavior of the fibrotic lung with UIP pattern under invasive and non-invasive respiratory assistance for AE of disease.

The research question has been firstly addressed through a critical review of available literature on mechanical ventilation (MV) and ILD as compared to ARDS. Then a theoretical hypothesis –the "squishy ball" lung theory– of a mechanical model able to explain the elastic response of the fibrotic lung when subjected to ventilatory support was formulated and detailed, and the potential biological consequences on mechano-transduction were illustrated. The mechanical principles underlying the model were further investigated by means of two clinical studies hold at the Respiratory Intensive Care Unit of the University Hospital of Modena between 2016 and 2021.

First and as introduction, we have explored and discussed similarities and differences between AE of idiopathic pulmonary fibrosis (IPF) and ARDS and we have analysed the available evidence on physiopathology, mechanical ventilation settings and other treatments available for AE-IPF.

In the second chapter, we have reviewed the effects of MV in AE-ILD to increase the knowledge on the characteristics of fibrotic lung during artificial ventilation and we have introduced and detailed the concept of "squishy ball lung" to illustrate the mechanical behavior of the fibrotic lung with UIP pattern when subjected to positive end-expiratory pressure (PEEP).

In the third chapter, we have analyzed available evidence on the relationship between mechanical forces acting on the lung and biological responses in pulmonary fibrosis, with a focus on the

progression of damage in the fibrotic lung during spontaneous breathing and assisted ventilatory support.

In the fourth chapter, we have quantified the inspiratory effort as assessed by esophageal manometry and the respiratory mechanics of 10 consecutive AE-IPF patients before and after a 2-hour non-invasive ventilation (NIV) trial and compared it with a historic matched cohort of ARDS patients. We have showed that patients with AE-IPF displayed a high inspiratory effort, whose intensity was reduced by NIV application without any significant improvement in respiratory mechanics, at difference with ARDS patients.

In the fifth chapter, we have explored the mechanical behavior of the fibrotic lung with UIP pattern while on AE, once subjected to MV and PEEP titration based on end-expiratory transpulmonary pressure ($P_{LEEX}$) and we have compared the mechanical response of AE-ILD-UIP lungs with that of pulmonary ARDS during MV. We have showed that positive value of $P_{LEEX}$ may be achieved in the lung of patients with AE-ILD-UIP when PEEP is increased, despite a significant worsening in lung mechanics.

Overall, with this project we have reviewed clinical data regarding the interaction between mechanical forces and the lung of patients with a UIP pattern. Starting from this evidence, we have elaborated an original theoretical model that might explain the mechanical behavior of the fibrotic lung when subjected to MV and its implication on clinical outcomes and unfavorable mechanotransduction towards fibrosis progression. Finally, we have given clinical evidence to confirm the “squishy ball” lung model in patients with lung fibrosis and UIP pattern experiencing AE of disease that require non-invasive and invasive ventilatory assistance.

**List of abbreviations**

AE, acute exacerbation; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; ARDS, acute respiratory distress syndrome; DAD, diffuse alveolar damage; MV, mechanical ventilation; IPF, idiopathic pulmonary fibrosis; PEEP, positive end-expiratory pressure; NIV, non-invasive ventilation; $P_{LEEX}$, end-expiratory transpulmonary pressure.

## Sinossi

I pazienti con riacutizzazione di interstiziopatia polmonare (AE-ILD) e pattern di polmonite interstiziale specifica (UIP) possono sviluppare una grave insufficienza respiratoria ipossiemica che richiede assistenza ventilatoria. Da un punto di vista fisiopatologico, le AE-ILD possono essere paragonate alla sindrome da distress respiratorio acuto (ARDS), in quanto si osserva la sovrapposizione di un danno alveolare diffuso (DAD) su un substrato di ILD fibrosante. Se le strategie di ventilazione protettiva hanno ridotto il rischio di danno indotto da ventilazione e la mortalità dei pazienti con ARDS, mancano evidenze specifiche sulla meccanica polmonare e sulle strategie ventilatorie durante le AE-ILD. Considerando che la fibrosi polmonare può essere la traiettoria verso cui evolvono diverse condizioni cliniche (ad esempio l'ARDS), la comprensione dei cambiamenti fisiologici che intervengono nel polmone fibrotico sottoposto a supporto ventilatorio, potrebbe aiutare gli intensivisti a sviluppare strategie ventilatorie adeguate per questa tipologia di pazienti. In questo scenario, l'obiettivo del presente progetto di ricerca è stato quello di esplorare le proprietà meccaniche e il comportamento elastico del polmone interessato da fibrosi a pattern UIP sottoposto ad assistenza respiratoria invasiva e non invasiva per riacutizzazione di malattia. Abbiamo quindi condotto una revisione critica della letteratura sulla ventilazione meccanica e le ILD. Sulla base di queste evidenze, è stata formulata un'ipotesi teorica –polmone "squishy ball"– per spiegare, attraverso l'elaborazione di un modello meccanico, la risposta elastica del polmone fibrotico in corso di supporto ventilatorio e le possibili conseguenze in termini di meccano-trasduzione sulla progressione della patologia fibrosante. I principi meccanici che sottendono il modello sono stati poi indagati in due studi clinici condotti presso l'Unità di Terapia Intensiva Respiratoria dell'Azienda Ospedaliero Universitaria Policlinico di Modena fra il 2016 e il 2021.

Nel primo capitolo abbiamo discusso analogie e differenze fra riacutizzazione di fibrosi polmonare idiopatica (IPF) e ARDS, analizzando le evidenze disponibili sulla fisiopatologia e sulle impostazioni della ventilazione meccanica (MV) nelle AE-IPF.

Nel secondo capitolo, abbiamo revisionato gli effetti della MV nelle AE-ILD e abbiamo introdotto e dettagliato il concetto del polmone "squishy-ball" per illustrare il comportamento meccanico del polmone fibrotico a pattern UIP quando sottoposto a pressione positiva tele-espiratoria (PEEP).

Nel terzo capitolo, abbiamo analizzato i dati disponibili sulla relazione fra le forze meccaniche agenti sul polmone e la risposta biologica del polmone fibrotico, focalizzandoci sulla progressione del danno durante il respiro spontaneo assistito e non assistito.

Nel quarto capitolo, abbiamo quantificato lo sforzo inspiratorio e la meccanica respiratoria (misurati mediante manometria esofagea) di 10 pazienti con AE-IPF prima e dopo un trial di 2 ore di ventilazione non-invasiva (NIV) confrontandoli con una coorte appaiata di pazienti ARDS e dimostrando come i pazienti con AE-IPF presentino un elevato sforzo respiratorio, la cui intensità è, a differenza dei pazienti ARDS, ridotta dall'applicazione della NIV senza miglioramento dei parametri di meccanica.

Nel quinto capitolo, abbiamo esplorato il comportamento meccanico del polmone con pattern UIP sottoposto a titolazione della PEEP sulla base della pressione transpolmonare di fine espirio ($P_{LEEX}$), confrontando la risposta meccanica dei pazienti con AE-ILD-UIP con i pazienti ARDS. Abbiamo dimostrato che nei pazienti con AE-ILD-UIP è possibile ottenere valori positivi di $P_{LEEX}$ incrementando i valori di PEEP, a prezzo di un significativo peggioramento della meccanica polmonare.

In conclusione, con questa ricerca abbiamo revisionato le evidenze riguardanti l'interazione fra stress meccanico e polmone fibrotico a pattern UIP per poi elaborare un modello teorico originale che spieghi il comportamento meccanico del polmone fibrotico sottoposto a ventilazione e le sue implicazioni sugli outcome clinici e sulla progressione della fibrosi. Abbiamo infine fornito evidenza clinica per confermare il modello del polmone "squishy ball" nei pazienti con fibrosi polmonare a pattern UIP che richiedono assistenza ventilatoria invasiva e non-invasiva.

**Lista delle abbreviazioni**

AE-ILD, riacutizzazione di interstiziopatia polmonare; UIP, polmonite interstiziale specifica; ARDS, sindrome da distress respiratorio acuto; DAD, danno alveolare diffuso; IPF, fibrosi polmonare idiopatica; MV, ventilazione meccanica; PEEP, pressione positiva tele-espiratoria; NIV, ventilazione non-invasiva; $P_{LEEX}$, pressione transpolmonare di fine espirio.

## General introduction

### *Acute exacerbation of idiopathic pulmonary fibrosis in critical care setting – lesson learned from acute respiratory distress syndrome*

**Abstract**

Idiopathic pulmonary fibrosis (IPF) is a devastating fibrotic lung disease characterized by progressive loss of lung function and poor prognosis. The onset of an acute deterioration of respiratory function, so called acute exacerbation of IPF (AE-IPF), may lead to severe hypoxemia requiring respiratory support up to mechanical ventilation in intensive care unit. AE-IPF shares several pathophysiological features with the acute respiratory distress syndrome (ARDS), a very severe respiratory condition commonly treated in this setting. During AE-IPF a diffuse alveolar damage and massive loss of aeration occur, similarly to what is observed in patients with severe ARDS. At difference with ARDS, no studies have concluded yet on the optimal ventilatory strategy and intensive care management in AE-IPF developing severe hypoxemic respiratory failure. Despite the lack of specific evidence, a protective ventilation with low tidal volume and low driving pressure is likely to be recommended. Moreover, high level of positive end-expiratory pressure has still to be elucidated in these patients, as well as the precise role of other types of respiratory assistance (i.e. extracorporeal membrane oxygenation or prone positioning). The use of systemic drugs (such as steroids or immunosuppressive agents) in AE-IPF is associated with weak evidence and potential increased risk of serious adverse reactions (e.g. infections). In conclusion, although there is a rationale to translate to AE-IPF at least part of the lessons learned from ARDS, specific studies investigating the peculiar mechanical features of the fibrotic lung while on respiratory assistance are extremely needed.

**Definition of acute exacerbation of idiopathic pulmonary fibrosis**

Idiopathic pulmonary fibrosis (IPF) is a chronic disease of unknown etiology, characterized by the deterioration of the structure of lung parenchyma, resulting in a progressive decline of respiratory function and early mortality (1). The presence of a radiological pathological pattern of usual interstitial pneumonia (UIP) is mandatory criterion, although not sufficient, for diagnosis of IPF. The median survival of the disease is approximately 3 years from diagnosis, and respiratory failure is the leading cause of death (2). Although two new antifibrotic drugs (pirfenidone and nintedanib) have shown efficacy in several clinical trials in slowing the decline of lung function, there is still no evidence of improved overall survival (3-5). In selected patients, the only long-term therapeutic option is lung transplantation (LTx), which offers a significant benefit in survival, though lower than for other indications for LTx (6).

In the course of the disease, patients suffering from IPF may develop acute deterioration of respiratory function, referred to as 'acute exacerbation of IPF' (AE-IPF), which can lead to a clinical presentation characterized by acute respiratory failure, sharing common features with the acute respiratory distress syndrome (ARDS). The diagnostic criteria for AE-IPF are the following: 1) previous diagnosis of IPF; 2) unexplained respiratory deterioration within the previous 30 days; 3) exclusion of other causes of respiratory failure, e.g. lung infection, heart failure or thromboembolism (7).

Recently, the diagnostic criteria for AE-IPF have been modified and now include the new onset of radiological evidence of diffuse alveolar opacities (8). This new definition identifies patients with severe impairment of respiratory function and radiological findings of diffuse alveolar damage, which cannot be explained by different causes, and has a wide overlap with the definition of ARDS in the context of IPF (see **Table 1**). Of notice, patients with ARDS have a limited number of conditions preceding the clinical manifestation that are known to be associated with the development of the syndrome, while AE-IPF patients typically have no such risk factors (9).

**Table 1.**

| AE-IPF | ARDS |
|---|---|
| **Revised definition**<br>An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality | **Berlin Definition**<br>A type of acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (i.e. edema, inflammation, hyaline membrane, or hemorrhage) |
| **Diagnostic criteria**<br>- Previous or concurrent diagnosis of IPF | **Definition criteria**<br>- Onset of lung injury within 1 week of a known clinical insult or new or worsening respiratory symptoms. |
| - Acute worsening or development of dyspnea typically < 1 month duration | - Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules |
| - Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern<br>- Deterioration not fully explained by cardiac failure or fluid overload | - Respiratory failure not fully explained by cardiac failure or fluid overload |

**Table 1.** Differences and similarities between the diagnostic criteria of AE-IPF and ARDS.

*AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; ARDS, acute respiratory distress syndrome*

Patients with AE-IPF frequently receive mechanical ventilation in the intensive care setting, but few studies report the in-hospital mortality rates in this specific population (10). Moreover, while several studies have proved that protective mechanical ventilation with low tidal volume is essential to improve the survival of patients with ARDS, in AE-IPF the least harmful mechanical ventilation strategy has not been fully identified and no clear recommendations are available.

**ARDS and AE-IPF: common features and differences**

*Diffuse alveolar damage*

The typical pathological feature of AE-IPF is the presence of diffuse alveolar damage (DAD) superimposed to the UIP pattern (11). DAD is also considered the histologic hallmark of ARDS, although this feature can only be found at the biopsy in about half of cases, and it is associated with higher mortality than in ARDS without DAD (12). The term 'diffuse alveolar damage' was initially proposed by Katzenstein to describe a non-specific acute reaction of the lung to several different pathogenic *noxae*, including sepsis, pneumonia, and exposure to high concentration oxygen (13).

Large retrospective studies show that among patients who met the criteria set by the Berlin definition of ARDS, only 45% had a *post-mortem* histology characterized by DAD. Moreover, at the histologic examination, the incidence of DAD increased with the severity classes of the Berlin definition of ARDS (14). The histological patterns of DAD in ARDS change over time. An exudative phase develops during the first week from onset, which is predominantly characterized by endothelial and alveolar epithelial injury with cellular exudate and hyaline membrane deposition. In patients with a disease lasting longer than 3 weeks, proliferative proliferation of alveolar cell type 2 and fibroblasts is the most relevant finding, with fibrotic deposition observed in 2/3 of cases (15). Studies on histological evolution over time of DAD in AE-IPF are not yet available, however it is very likely, due to the common pathophysiological background, that alveolar damage in survivors may lead to a proliferative phase and lung fibrosis.

A retrospective analysis performed on patients with ARDS who underwent open lung biopsy, showed a significant increase in hospital mortality in those patients with histological diagnosis of DAD as compared with non-DAD (71.9% vs 45.5%) (16). Despite several evidence showing that mortality of ARDS with DAD is very high, prognosis is still better than that of AE-IPF patients treated with invasive mechanical ventilation, which approaches 95% according to a study in 2008 (17). Several factors could play a role in this extremely elevated mortality: 1) the greater susceptibility of the lung with DAD on pre-existing UIP to develop ventilator-induced lung injury (VILI); 2) the impaired ability to repair the acute alveolar damage in the lung with IPF; 3) the age of patients that might be higher in patients with IPF compared to ARDS.

Some evidence shows that clinical features and prognosis of AE-IPF according to the mentioned definition are very similar to the exacerbation of IPF with known cause such as pneumonia or aspiration (18). Since exacerbation in both idiopathic and non-idiopathic disease results in the

development of DAD superimposed to a UIP pattern, a revision of the definition of IPF exacerbation was proposed, focusing on the pathobiology of AE-IPF. According to this proposal, AE-IPF has been defined as the occurrence of clinical and radiological acute lung injury with DAD regardless of the trigger condition (19). As such, prognosis of patients with lung disease of a different nature is not related to the triggering cause, but it is rather due to the development of DAD itself. In fact, in retrospective studies investigating the clinical features and the outcome of patients with lung biopsies confirming DAD, the overall mortality was not influenced by the different trigger factors, except for AE-IPF in which the risk of death was nearly double (20).

*Lung inflammation*

During an exacerbation of IPF, the percentage of neutrophils in the bronchoalveolar lavage (BAL) fluid is significantly increased compared with the baseline chronic condition, while lymphocytes and macrophages are reduced, and eosinophils remain stable (21). This cell pattern is very similar to that found in patients with ARDS, which suggests a common inflammatory pathway. In AE-IPF, the upregulation of M1 macrophage activation chemokines such as IL-8 and CXCL1, results in neutrophils chemo-attraction. Interestingly, in animal models, the increased expression of CXC chemokines and their interaction with the CXCR2 receptor is involved in the lung sequestration of neutrophils following the mechanical stress due to ventilation, thus suggesting a role in the development of VILI (22). On the other hand, some studies indicate a relationship between IL-8 overexpression in BAL and the development of ARDS in patients at risk (23). Acute hypoxia could act as a pro-inflammatory stimulus leading to the rapid increase of intrapulmonary IL-8, released by alveolar macrophages with attraction of neutrophils and subsequent alveolar and endothelial injury (24). Different studies have also analyzed BAL fluid to evaluate the expression of other cytokines such as IL-1β, with a pro-inflammatory role in ARDS but not in AE-IPF, and TNF-alpha, which is not expressed in both diseases (25,26).

The alternative M2 macrophage activation pathway, was also observed in AE-IPF, playing a determinant role in damage healing (21, 27). Indeed, a direct link between injury to type II alveolar epithelial cells and the accumulation of interstitial collagen by M2 pathway activation was reported (28), that could stimulate repair by fibroblasts proliferation and epithelial-mesenchymal transition. This repair process, however, appears to fail in AE-IPF resulting in a persistent M2 pathway activation resulting in irreversible lung fibrosis (29).

Overall, both ARDS and AE-IPF show an overexpression of pro-inflammatory cytokines produced by alveolar macrophages with chemotaxis of neutrophils. However, an overexpression of anti-inflammatory M2 cytokines with pro-fibrotic role is simultaneously present in AE-IPF. Furthermore, recent studies on the lung of IPF patients who underwent transplantation, showed that inflammatory infiltration and DAD are present not only during AE but also in stable IPF with an accelerated functional decline, suggesting a role for inflammation in the disease progression (30). **Figure 1** illustrates the interaction between these inflammatory pathways in AE-IPF.

**Figure 1.**

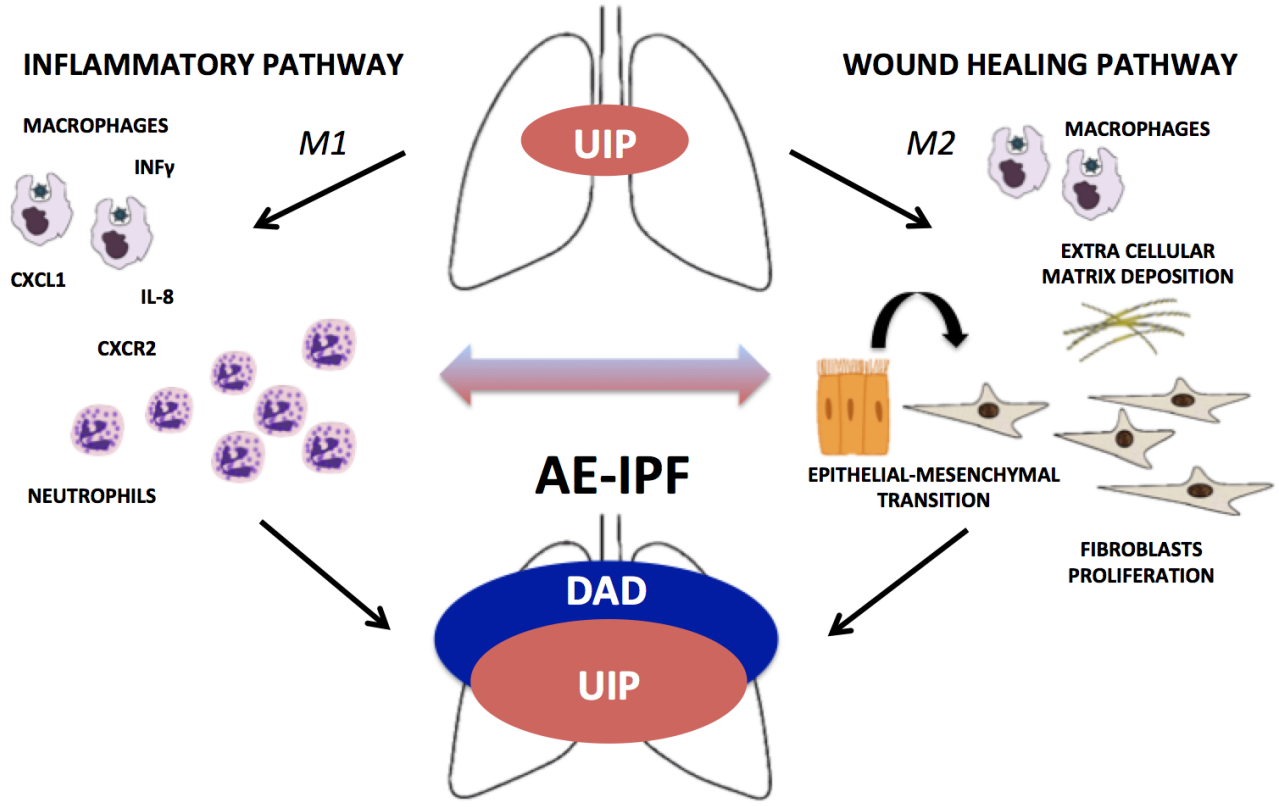


**Figure 1.** During AE-IPF, lung inflammation is driven by up regulation of macrophage activation pathways. The M1 pathway is classically activated by Th1 cytokines (IFN-γ) and lead to an increased IL-8 and CXCL1 expression and neutrophils recruitment though CXCR2 receptor. The M2 pathway is activated by type II alveolar epithelial cells injury and might perpetuate lung fibrosis boosting collagen deposition, fibroblasts proliferation and epithelial-mesenchymal transition.

*UIP, usual interstitial pneumonia; DAD, diffuse alveolar damage; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; IFN-γ, interferon-γ; IL-8 interleukin-8; CXCL1, chemokine (C-X-C motif) ligand 1; CXCR2, CXC chemokine receptor 2*

**Respiratory mechanics and ventilator-induced lung injury**

In patients with ARDS, many studies have documented changes in lung mechanics and the role of mechanical ventilation on the development of VILI and the consequent increased risk of death (31). Much less is known concerning the impact of VILI on mortality in AE-IPF patients, but several common pathophysiological features shared by the two conditions provide a rationale for translating, at least in part, lessons derived from ARDS patient ventilatory management to AE-IPF. Moreover, there is rising interest towards the fact that VILI can occur also in patients without ARDS, (32) possibly even in those with healthy lungs, providing a stringent rationale for developing lung-protective strategies for all indications of mechanical ventilation, from the operating room to any critically ill patient.

Over the past 20 years, following the awareness that VILI can significantly contribute to the high mortality rates observed in ARDS, the objective of mechanical ventilation in ARDS has changed: from improving gas exchange to protecting lung from the mechanical damage deriving from mechanical ventilation (33,34). The physical forces responsible for the development of VILI are unphysiological stress (distension of force per unit area) and the strain (deformation) applied to the lung tissue (35). In pathophysiological terms, the effects of mechanical ventilation on the lungs have been classically classified in two distinct factors: the stress, defined as the transpulmonary pressure reached at end inspiration, and the strain, namely the ratio of tidal volume to the end-expiratory lung volume ($V_T$/EELV) (36). Nonetheless, defining a threshold of safety for stress and strain remains a challenge (37). The transpulmonary pressure is the difference between airway and pleural pressure ($P_{pl}$) and can be estimated assuming that the $P_{pl}$ is acceptably approximated by the esophageal pressure ($P_{es}$) (38). Transpulmonary pressure measurement could add information in AE-IPF patients that, in addition to the expected increase in lung elastance, also have increased chest wall stiffness, as is the case of morbidly obese patients. Since stress and strain are not routinely measured, the plateau pressure and the tidal volume (Vt) are considered, even imprecise, surrogates of stress and strain respectively, so that their levels are referred in the clinical practice when setting the ventilator in patients with ARDS. Currently it is recommended to maintain an airway plateau pressure below 30 cmH2O and set a Vt less than 6 ml/kg of ideal weight (33). Notwithstanding, we must consider that, despite the plateau pressure and the Vt are easily recordable parameters during mechanical ventilation, these are inadequate to truly represent the stress and the strain applied to the lung (37).

Recently, there has been increasing interest towards the variation of airway pressure achieved during tidal breath: the airway driving pressure (ΔP). ΔP equals plateau pressure minus positive end-expiratory pressure. ΔP can be considered the 'dynamic stress' and represents the ratio between $V_T$ and the compliance of the respiratory system. It is reasonable to assume that compliance and EELV, being both associated with the severity of lung injury, are tightly correlated: under this assumption, ΔP would also reflect $V_T$/EELV, *i.e.* strain. Thus, the driving pressure of the respiratory system or the lung (from transpulmonary) represents an easy method at the bedside during controlled mechanical ventilation to monitor the injuriousness of ventilation.

The transpulmonary pressure ($\Delta P_L$) and the absolute level of transpulmonary pressure at end-inspiration depend by the ratio between the lung elastance ($E_L$) and the total elastance of the respiratory system ($E_{TOT}$=$E_L$ + chest wall elastance [$E_{CW}$]) according to the formula (54):

$$P_L = P_{aw} * E_L/E_{TOT}$$

This ratio is normally 0.5 at functional residual capacity. In patients with ARDS, acute lung injury is known to cause a significant increase in total elastance secondary to the increase in lung elastance, but possibly also due to an alteration of the $E_{cw}$ (39). The $E_L/E_{TOT}$ ratio, may vary substantially and ranges from 0.2 to 0.8 (40). This means that patients with the same plateau pressure can have harmful or safe transpulmonary pressures (41). Another aspect that must be considered in ARDS is that the inhomogeneity of the lung might act regionally as a stress raiser, increasing the pressure applied in patent respiratory units surrounded by non-aerated units (42).

In the last two years, the concepts of mechanical energy (43) and power (44) have been introduced to describe VILI in terms of energy transfer from the ventilator to the respiratory system. These concepts are new and require extensive validation but have the advantage of trying to combine the different aspects of VILI in a single parameter.

These features specifically refer to ARDS, and much less is known in AE-IPF. In a single study evaluating the respiratory mechanics of mechanically ventilated end/stage IPF patients (45), a marked increase in the elastance of the respiratory system (51 $cmH_2O/L$) was reported, mainly due to an abnormal lung (46 $cmH_2O/L$) but normal (5 $cmH_2O/L$) chest wall elastance: under these conditions, the $E_L/E_{TOT}$ is around 0.9. In this case, the application of a plateau pressure of 30 $cmH_2O$ and a PEEP of 4 $cmH_2O$, which are elevated pressures often seen in AE-IPF patients, causes a ΔP of 30-4 = 26 $cmH_2O$, while an absolute end-inspiratory transpulmonary pressure of 30x0.9 = 27 $cmH_2O$.

Both these values are above acceptable levels. If feasible in terms of gas exchange, a reduction of plateau pressure and driving pressure would be warranted. Furthermore, alveolar collapse and consolidation, that are responsible for permanent derecruitment, are present in IPF and do not improve with the application of positive pressure to the airways. Collapse induration is characterized by septal wall thickening and alveolar epithelial hyperplasia with formed entrances to the alveoli overgrown by enlarged alveolar epithelial type II cells (46). It is easy to understand that the application of high PEEP to these lungs cannot result in recruitment of hypo-ventilated areas but can instead facilitate overinflation in the spared areas of the lung, with further deterioration of the mechanical properties of the lung. In line with this concept, one study showed that high PEEP level in patients with interstitial lung disease undergoing mechanical ventilation is independently associated with increased mortality (47). Therefore, despite some similarities with ARDS, AE-IPF is characterized by some unique pathophysiological properties, namely the constant presence of collapse induration areas, the extremely elevated lung elastance and inhomogeneity that might make it more susceptible to VILI. **Figure 2** summarizes the mechanisms that lead to VILI in AE-IPF.

**Figure 2.**

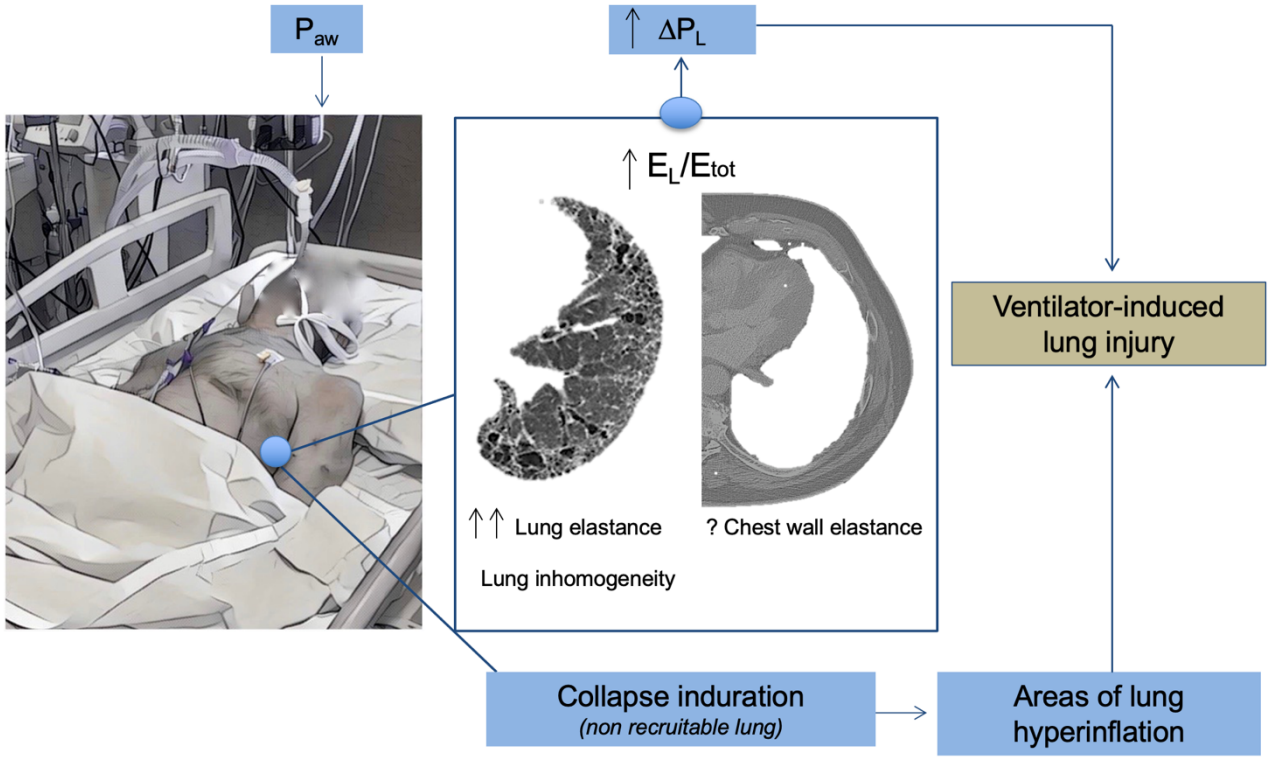


**Figure 2.** Mechanisms of ventilation induced lung injury in patients with AE-IPF.

*$E_L$, lung elastance; $E_{tot}$ total elastance; $P_{aw}$ airways pressure; $\Delta P_L$ driving transpulmonary pressure*

**Respiratory assistance**

Few studies have evaluated the outcome of patients with AE-IPF receiving mechanical ventilation in the ICU, in addition they all share several important limitations: 1) single-centered and retrospective analysis; 2) very limited number of included patients; 3) mode of ventilation and respiratory mechanics poorly or not reported; 4) heterogeneous use of drugs (see **Table 2**) (11,45,47-61). Notwithstanding, the results are consistent in stating that invasive mechanical ventilation cannot significantly modify the prognosis of these patients, being the overall mortality rate up to 90% (17). Thus, based on the little evidence available, the 2011 American Thoracic Society guidelines recommended the use of mechanical ventilation only in few selected patients with AE-IPF (1). However, the abovementioned studies were performed before the extensive use of protective mechanical ventilation, therefore a part of the observed mortality could have been partly due to VILI.

A recent multicenter retrospective cohort study in the United States, documented an overall mortality rate of 51% in a large group of mechanically ventilated AE-IPF patients (10), which is higher than that reported in severe ARDS (about 40%) (62), but less than described previously. One could speculate that the pathophysiological advances leading to a better management and outcome of patients with ARDS may have also positively modified the outcomes following mechanical ventilation in AE-IPF.

However, inconsistency of data and lack of extensive evidence suggest considering ICU admission and invasive ventilation only in selected cases of AE-IPF, also based on the following aspects: 1) time from diagnosis (the average survival is 3 years); 2) patient's age and comorbidities; 3) chances for a transplantation, considering respiratory assistance as a bridge.

Since the best mechanical ventilation strategy to adopt in AE-IPF has not yet been determined by specific studies, every recommendation is necessarily speculative rather than evidence-based. Several options are available: controlled ventilation, invasive or non-invasive assisted ventilation and extracorporeal membrane oxygenation (ECMO).

**Table 2.**

| Study | Time frame | N | MV | AE-IPF | NIV | Ventilator setting | ICU mortality | Hospital mortality |
|---|---|---|---|---|---|---|---|---|
| Molina-Molina et al. (48) | 1986-2002 | 14 | 14 | NR | NR | NR | NR | 85% (11/13) |
| Nava and Rubini (45) | 1998 | 7 | 7 | NR | 0 | Vt 8.3 ml/kg | 86% (6/7) | NR |
| Stern et al. (49) | 1991-1999 | 23 | 23 | 16 | NR | Vt 8-13 ml/kg | 96% (22/23) | 96% (22/23) |
| Blivet et al. (50) | 1989-1998 | 15 | 15 | 6 | 5 | NR | 73% (11/15) | 87% (13/15) |
| Saydain et al. (51) | 1995-2000 | 38 | 19 | 15 | 7 | NR | 68% (13/19) | 61% (23/38) |
| Fumeaux et al. (52) | 1996-2001 | 14* | 14 | NR | 11 | Vt 7-9 ml/kg | 100% (14/14) | 100% (14/14) |
| Al-Hameed and Sharma (53) | 1998-2000 | 25 | 25 | 25 | 3 | PEEP 7 $cmH_2O$ | 84% (21/25) | 96% (24/25) |
| Kim et al. (11) | 1990-2003 | 10 | 9 | 9 | NR | NR | 78% (7/9) | 78% (7/9) |
| Pitsiou et al. (54) | 2001-2005 | 12 | 12 | NR | NR | NR | 100 (12/12) | 100% (12/12) |
| Rangappa and Moran (55) | 1996-2006 | 24 | 19 | 8 | NR | NR | 67% (16/24) | 92% (22/24) |
| Fernandez-Pèrez et al. (47) | 2002-2006 | 30 | 30 | NR | NR | Vt 7-8 ml/kg | NR | 60% (18/30) |
| Mollica et al. (56) | 2000-2007 | 34 | 34 | 22 | 19 | Vt 7.5 ml/kg or PS/PEEP 18/7 $cmH_2O$ | 100% MV, 73% NIV | 85% (29/34) |
| Yokoama et al. (57) | 1998-2004 | 11 | 11 | 11 | 11 | CPAP 10 $cmH_2O$, PS/PEEP 5/10 $cmH_2O$ | NR | 56% (6/11) (3 months) |
| Gungor et al. (58) | 2000-2007 | 96 | 96 | NR | 28 | Vt 6-8ml/kg, PEEP 5-7 $cmH_2O$ | 64% (61/96) | NR |
| Vianello et al. (59) | 2005-2013 | 18 | 18 | 6 | 18 | PEEP 5-8 $cmH_2O$ | 56% (10/18) | NR |
| Gaudry et al. (60) | 2002-2009 | 22 | 22 | NR | 0 | Vt 5.9 ml/kg, PEEP 7.1 $cmH_2O$ | 67% (17/22) | NR |
| Aliberti et al. (61) | 2004-2009 | 60 | 60 | 24 | 60 | CPAP 8 $cmH_2O$, PS/PEEP 5/15 | NR | 35% (21/60) |
| **Total** | | 453 | 428 | 142 | 162 | | | |

*3 non IPF

**Table 2.** Studies investigating the use of mechanical ventilation in patients experiencing AE-IPF and major outcomes.

*AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; ICU, intensive care unit; Vt, tidal volume; NR, not reported; CPAP, continuous positive airway pressure, PS, pressure support; PEEP, positive end expiratory pressure; NIV, non-invasive mechanical ventilation; MV, mechanical ventilation*

*Controlled ventilation modes*

Pressure- or volume-controlled ventilation is the mostly applied mode of invasive respiratory support for AE-IPF. As learned from ARDS, even in AE-IPF, given the fragility of the lung and the risk of VILI, the main objective of ventilation should be lung-protection, namely avoiding VILI while ensuring an acceptable, but not necessarily optimal, gas exchange. As reported in the literature, it is reasonable to use a tidal volume even lower than 6 mL/kg of ideal body weight, eventually to obtain a plateau pressure lower than 30 $cmH_20$, as in patients with high amount of non-aerated tissue lower thresholds, e.g. 27 $cmH_20$ should be targeted (63). Moreover, these patients, due to an increased physiologic dead space, require higher respiratory rate and minute ventilation, often requiring permissive hypercapnia. Despite the lack of studies about the usage of neuromuscular blockade in IPF patients, we could hypothesize that a complete muscle paralysis at the early onset of severe AE-IPF could help reduce the lung stress and strain, avoiding patient-ventilator asynchrony and the deleterious interaction of spontaneous and mechanical breath (64). Positive end-expiratory pressure (PEEP) should be set at low-moderate levels (e.g. 4-6 $cmH_20$), taking into account the intrinsic low recruitability potential, with high risk of hyperinflation. An 'open lung approach' with recruitment maneuvers, recently questioned also for early ARDS (65) have no physiological rationale in AE-IPF and should therefore be avoided. Patients with ARDS of late onset (>1 week) are typically not good recruiters; therefore, they have mechanical properties similar to patients with AE-IPF. The poor benefit of high end-expiratory pressure in patients with interstitial lung disease was documented in a cohort of patients, where high PEEP was independently associated with mortality (47).

Even the use of a $V_T$ lower than 6 mL/kg to reduce strain, has the disadvantage of relating $V_T$ to the size of a healthy lung, while in ARDS and AE-IPF the proportion of lung receiving tidal ventilation is markedly reduced. The compliance of the respiratory system (CRS) can estimate the amount of functional size of the lung in severe injury with DAD, as in the case of ARDS.

Driving pressure (ΔP) (difference between end-inspiratory and total end-expiratory airway pressure) could be considered useful for the clinical assessment of cyclic lung strain (66). ΔP is a parameter inversely proportional to the compliance of the respiratory system ($\Delta P = V_T/CRS$) and it has the advantage of normalizing VT to the functional size of the lung, i.e. is related to strain. Amato and coworkers, analyzing data from nine randomized trials compared different mechanical ventilation strategies from nine randomized trials in ARDS; they have shown that ΔP is the ventilatory variable more strongly associated with survival, probably because it may help in identifying patients at risk

for developing VILI. In particular, a ΔP higher than 14 $cmH_20$ is associated with an increased risk of death, and the beneficial effect on survival of protective ventilation was present only in case of a concomitant reduction in ΔP (67). Also, the incidence of postoperative pulmonary complications in patients without previous lung injury ventilated during general anesthesia for surgery is associated with higher ΔP, suggesting its relevance in all mechanically ventilated patients. (68) Although no data are currently available on ΔP in AE-IPF, the measurement of this parameter might be important to monitor the dynamic stretch and possibly to adjust ventilation settings.

In patients with AE-IPF with high plateau pressure, the measurement of $P_{es}$ as a surrogate of pleural pressure, may allow to identify more precisely the lung stress and the risk of damage from ventilation by calculating the transpulmonary pressure. Although currently inspiratory transpulmonary pressure safety limits are not totally clear in humans, experimental models suggest setting the protective mechanical ventilation to a "probably safe" $P_L$ (36), namely below 20 $cmH_2O$ in homogeneous lungs, or below 12 cmH2O in inhomogeneous lungs such as in AE-IPF (38).

*Prone position*

Prone position (PP) was used since the 70's as a rescue therapy for severe hypoxemia in patients with ARDS (69). The improvement of oxygenation with PP takes place regardless of the cause of ARDS, and it is most evident during the exudative early phase of the disease (70). Recently, the PROSEVA study demonstrated a significant survival advantage with early PP (within 72 hours) applied for an average of 17 hours per day in moderate-to-severe ARDS ($PaO_2$ / $FiO_2$ <150 mmHg) (71). The reasons of this favorable outcome are due to the complex physiological changes that occur during PP: 1) reduction of the compression of the lungs by the heart when prone (decompression of the left lower lobe and a portion of the right lower lobe), 2) improvement of ventilation in dorsal-caudal areas, due to favorable diaphragm displacement, 3) more homogeneous regional distribution of transpulmonary pressure and stress-strain ratios, 4) delay in the onset of VILI and reduction in its severity, 5) overall improvement in ventilation/perfusion matching and oxygenation, 6) easier lung recruitment with lowering of the opening pressure threshold of the collapsed airway (69).

Only one study has evaluated the effect of PP on gas exchange in pulmonary fibrosis and has analyzed the effect of PP compared with hydrostatic pulmonary edema and ARDS. In patients with fibrosis, changing position from supine to prone did not improve oxygenation, while there was an increase of the plateau pressure and a reduction in Crs (72). The benefit of pronation was limited only to the diseases characterized by significant pulmonary edema without fibrosis. Therefore,

changing from supine to prone position in AE-IPF is not recommended. Notwithstanding it is important to clarify that in acute setting, as AE-IPF can be difficult to distinguish from ARDS in patients without a previously established IPF diagnosis, the use of prone position could be justified when differential diagnosis remains uncertain, considering its beneficial effects in ARDS population.

*Invasive and non-invasive assisted ventilation modes*

Increasing evidence suggests that spontaneous assisted breathing can have beneficial effects on shunt reduction and improvement in oxygenation, maintaining diaphragmatic tone and increase in dependent lung ventilation, but only when the respiratory failure is not severe (73-74). Nonetheless, experimental data suggest that spontaneous breathing activity can improve lung function and decrease inflammation in moderately injured lungs (75).

During assisted spontaneous breathing, inspiratory muscle activity leads to negativity of the pleural pressure, and thoracic structures are subject to negative forces. Patients with AE-IPF have a significant hyperactivation of the respiratory drive with a pleural swing that can even reach -30 to -40 $cmH_2O$. This means that, during assisted ventilation, there is a major contribution to the total transpulmonary pressure due to the pressure, also when airway pressure is apparently low. Even in similar flow and volume conditions, the transpulmonary pressure swing in controlled ventilation or assisted spontaneous breathing do not differ; spontaneous breathing can be more injurious when patients present a high respiratory drive (76). The reason for this effect on pulmonary stress depends on several factors.

First, airway pressure can fall under end-expiratory pressure during spontaneous breathing, when performing vigorous inspiratory efforts (77). In this case, pulmonary vessels are subject to negative pressure, with increased transmural vascular pressure, risk of alveolar edema, and progression to VILI. Second, the change in transpulmonary pressure during the respiratory effort occurs inhomogeneously, resulting in a heterogeneous lung expansion without a gain in $V_T$ (78), also due to *pendelluft* phenomenon (79). *Pendelluft* is the fast exchange of gas volume that occurs during strong effort between different regions of the lung before starting $V_T$, with deflation of non-dependent regions and gas swing towards the dependent regions, which leads to increase in local stretch. The regional inflation-deflation pattern is considered one of the causes of lung injury. Third, the patient-ventilator asynchrony may increase the risk of lung injury (78). These potential deleterious effects caused by assisted spontaneous breathing may be counteracted by the early use

of neuromuscular blocking agents in severe ARDS ($PaO_2/FIO_2$ < 120 mmHg), then resulting in significant benefit of survival (13.8%) (80).

Patients with AE-IPF in assisted spontaneous breathing have a high respiratory drive and increased minute ventilation and may be at risk of self-inflicted lung injury (SILI) secondary to an excessive activation of respiratory muscles. The monitoring of respiratory drive with occlusion pressure ($P_{01}$), $P_{es}$ and $V_T$, could be therefore helpful in identifying patients with a deleterious breathing pattern, and in evaluating its modification after the application of pressure support (76). It should also be kept in mind that respiratory drive is not only affected by the level of pressure support, but also by the degree of sedation: sedatives could be considered a part of a protective ventilation strategy in patients with an increased respiratory drive. **Figure 3** shows two patients with AE-IPF subject to the same pressure support ventilation, but with different activation of the respiratory drive, as seen from $P_{es}$ swing, and different pulmonary stress.

Non-invasive ventilation (NIV) is a method of spontaneous breathing support not requiring, endotracheal intubation, thus potentially reducing the risk of ventilator associated pneumonia (VAP). Retrospective studies that have analyzed the effectiveness of NIV in AE-IPF showed a mortality rate ranging from 45 to 75%. These studies are retrospective and quite heterogeneous; thus, it is difficult to recognize a unique NIV timing strategy. Generally, the decision to start NIV was based on the presence of moderate to severe dyspnea, respiratory rate higher than 30 breaths/min, signs of increased work of breathing or $PaO_2/FIO_2$ ratio below 250 mmHg. In most of these studies, NIV was initially delivered continuously in the first 24 to 48 hours, then interrupted for progressively longer intervals, compatibly with clinical conditions and gas exchange. In all studies, mortality was related to respiratory failure (57-59). More recently, an observational study on a large cohort of patients with AE-IPF who underwent mechanical ventilation showed lower mortality rate (30.9%) when NIV was applied as compared to conventional mechanical ventilation (51.6%) (10). At least theoretically, the survival advantage could be due to the early application of NIV on patients with less severe general conditions, and the capacity of preventing VAP. Furthermore, patients who have a high activation of the respiratory drive despite NIV, and who are subject to excessive work of breathing should be carefully monitored being at risk of rapid deterioration and NIV failure.

Recently, high flow rates of oxygen gas delivered through nasal cannulae (HNFO) have proved efficacy in the management of non-hypercapnic acute hypoxemic respiratory failure (81). To date no randomized clinical trials (RCTs) are available on the effects of HFNO in patients experiencing AE-IPF. Notwithstanding, a case series by Horio and co-workers have showed that, when used in IPF

patients during acute exacerbation, HFNO is well tolerated and associated with increased ventilation efficiency, decreased respiratory rate and reduced work of breathing (82). The use of HFNO should be carefully investigated in this specific subset of hypoxic patients with particular reference to potential role of a long-term exposure to high concentrations of oxygen in enhancing fibrotic damages in the lungs. Multicenter RCTs are needed to compare safety and efficacy between HFNO and NIV or mechanical ventilation in patients with AE-IPF.

**Extracorporeal membrane oxygenation**

Extracorporeal life support is a salvage strategy increasingly applied in ARDS with severe hypoxemia. Veno-venous extracorporeal membrane oxygenation (ECMO) is able to provide adequate gas exchange allowing "lung rest" from mechanical ventilation and can potentially reduce the injurious effects of positive pressure ventilation (83). The best strategy to ventilate patients receiving ECMO is still debated, however also in this setting higher driving pressure was associated with increased in-hospital mortality (84).

Since some studies show that mechanically ventilated pre-transplant patients have a significantly higher post-transplant mortality than non-ventilated patients, treatment with ECMO should be provided as early as possible (85). Indeed, more recently ECMO was used in awake non-intubated patients to preserve the tone of respiratory muscles, as well as to achieve early mobilization and to facilitate post-transplant weaning (86). One study evaluated patients with mixed diseases bridged to transplant with ECMO as an alternative to invasive mechanical ventilation, showing improved six-month survival with ECMO than with mechanical ventilation (62% versus 35%). In this analysis, that evaluated 14 studies of patients undergoing ECMO before transplant, IPF population ranged from 27% to 62%. The mortality rate of patients on ECMO before lung transplant was reported in ten studies ranging between 17% and 50%; diagnosis of pulmonary fibrosis was not associated with increased mortality (87). In selected cases of AE-IPF, ECMO might be thus proposed as bridge to lung transplantation. Indeed, maintaining spontaneous breathing without any support or with NIV during ECMO could be a promising strategy in these patients. However, reduced availability and high costs limit its use in this disease.

**Other treatments**

*Pharmacological treatments*

At present, no randomized controlled trials on drug treatments in AE-IPF are available, therefore recommendations of international consensus are based on weak evidence. ATS/ERS/JRS/ALAT guidelines recommend treatment with corticosteroids, although dose, route of administration and duration of treatment are not specified (1). Seeing again ARDS as a model, we can consider perpetuated DAD as a dysregulated systemic and pulmonary inflammation. As shown by some studies, ARDS patients with persistent elevation of inflammatory cytokines in blood and bronchoalveolar lavage present a worse prognosis (88). Glucocorticoids (GC), through their interaction with the glucocorticoid receptor (GR), can block nuclear translocation of NF-kB, the main pathway of inflammatory cytokines synthesis. Using an ex vivo model of systemic inflammation, Meduri and collaborators have shown that the ability of GC-GRα to downregulate NF-kB activation is critical for the resolution of systemic and pulmonary inflammation in ARDS (89). Despite this scientific rationale, the use of steroids in ARDS is not routinely recommended, as clinical trials have not been able to demonstrate a clear benefit in survival, despite improvements in both oxygenation and lung mechanics (90-91). Studies on the correlation between systemic inflammation and prognosis in AE-IPF are lacking. Indeed, one study in AE-IPF showed that ST2 serum levels (a protein expressed in T-helper type 2 cells and induced by pro-inflammatory stimuli) were significantly higher than those in stable IPF or in healthy controls, suggesting that severe systemic inflammation is a feature of the exacerbation phase of the disease (92). Therefore, anti-inflammatory drugs like steroids could, at least theoretically, play a role in AE-IPF. Notwithstanding, retrospective analyses of patients with AE-IPF treated with only steroids as immunosuppressive therapy did not show any reduction in overall mortality: in these studies, in-hospital mortality was 55% in 65 patients treated with methylprednisolone pulse ≥500 mg/day or prednisolone in high (≥0.5 mg/kg) or low doses (≤0.5 mg/kg) and 3-month mortality was 82% in 11 patients that received methylprednisolone 1 g/day for 3 days (93). French guidelines also support the use of intravenous cyclophosphamide, in addition to steroids (94). A retrospective study analyzed 10 patients with AE-IPF treated with the combination of high dose methylprednisolone (1000 mg) on days 1-3 followed by cyclophosphamide infusion (500 mg) on day 4, increasing by 200 mg every 2 weeks up to 1,500 mg, showing 50% survival rate at 3 months. Despite authors here concluded to suggest a possible benefit resulting from such combination therapy, other small retrospective studies did not show any improvement in outcomes

(95,96). Finally, many other cytotoxic agents (e.g. azathioprine, cyclosporine A, tacrolimus) have been the subject of small retrospective reports, but at present there is no sound evidence to suggest their use (95). **Table 3** summarizes the drugs currently researched in AE-IPF, but extreme caution is warranted due to the limited quality of evidence available.

*Polymyxin-B direct hemoperfusion*

Polymyxin-B (PMX-B) is a polypeptide antibiotic with bactericidal activity towards Gram negative bacteria that binds circulating endotoxins (97). In patients with severe sepsis, septic shock or refractory shock, the use of PMX-B hemoperfusion cartridge has proven high efficacy in reducing the level of circulating endotoxin (98). Other studies have demonstrated how direct hemoperfusion with PMX-B immobilized fiber column (PMX-DHP) can remove blood cytokines and activated neutrophils, thus reducing the endothelial damage caused by reactive oxygen species (ROS) (99). Despite all this experimental evidence, the impact on mortality in specific populations, such as septic shock, is much more debated (100). Furthermore, the use of PMX-B DHP has been studied in patients with ARDS developing DAD – similarly to what happens in AE-IPF, where DAD overlaps with the typical UIP pattern – showing a significant improvement in blood oxygenation (101). In patients with AE-IPF, the use of PMX-B DHP was first investigated by Japanese authors with an open-label pilot study, followed by two case reports that assessed the safety of the procedure (102). A retrospective review on 19 patients with AE-IPF treated with PMX-B DHP showed a median survival of 22 days from diagnosis, and survival rates of 47%, 32% and 26% at 1, 2 and 3 months respectively. Interestingly, authors observed that survivors presented increased values of serum interleukin-7 (IL-7), an inhibitor of Transforming Growth Factor-β (TGF-β) production, identifying in the mitigation of pro-fibrotic signaling pathways a potential mechanism of action of PMX-B DHP in patients with AE-IPF (103). A retrospective analysis on 160 patients with interstitial pneumonia of different etiology, including 73 with IPF, showed significant improvement in the $PaO_2/FIO_2$ ratio (from 173.9 ± 105.4 to 195.2 ± 106.8 mmHg, p = 0.003) following PMX-B DHP blood perfusion in patients with AE-IPF. Oishi et al. have hypothesized that the therapeutic effect of PMX-B DHP might be due to the absorption of pro-inflammatory, pro-fibrotic and pro-angiogenic cytokines; in particular, the removal of VEGF may contribute to improvement in oxygenation by reducing pulmonary vascular permeability (104). A recent retrospective study by Enomoto et al. compared the survival rates of 31 patients with AE-IPF, 14 of which treated with PMX-DHP. Other than showing improvement in P/F ratio, they described a 1-year survival rate significantly higher in patients receiving PMX-DHP B

compared with those under supportive care plus steroids alone (48.2% % vs 5.9, respectively). Moreover, the study demonstrated that the efficacy of PMX-B DHP was higher in patients with more severe underlying disease being 57.1% the survival rate in patients with GAP index score 2 or 3 as compared with 0% in similar patients of the control group. They concluded that PMX-DHP is an independent predictor of a better prognosis in patients with AE-IPF (65% of risk reduction) (105).

*Lung transplantation*

Pulmonary transplantation is often able to increase life expectancy, and in end-stage IPF it is the only therapeutic option. In patients under 65 years of age, pulmonary transplantation should be considered early in the course of the disease, especially when a functional respiratory worsening is documented despite ongoing treatments (pirfenidone, nintedanib). The International Society for Heart and Lung Transplantation indicates the following parameters for a prompt evaluation for transplant list registration: 1) accelerated functional respiratory decline (loss of forced vital capacity $\geq$ 10% and carbon dioxide lung diffusion $\geq$ 15% at 6 months), 2) CT scan with honeycombing changes (fibrosis score >2), 3) pulmonary hypertension, 4) significant desaturation during 6-min walk test (oxygen saturation decrease below 88%), 5) alveolar diffusion test less than 39% (106). In pre-transplant evaluation, a genetic analysis can be helpful in identifying the subset of patients with telomerase mutation that often have extra-thoracic diseases such as bone marrow failure. In fact, in case of a documented telomer defect, postoperative management is more difficult, with frequent haematological complications and sometimes dialysis is needed for acute tubular injury (107). Studies on the outcome of patients undergoing pulmonary transplantation show a 5-year survival of about 50% in IPF (108). Patients with AE-IPF already included in a lung transplantation list should be admitted to intensive care and transferred as soon as possible to the ECMO reference center. Some countries have developed a procedure for the inclusion of critical patients in an emergency list for transplantation. In these participating countries, the procedure is reserved to young patients (under 50 years of age) who are admitted to Intensive Care Unit due to a rapid deterioration of their respiratory disease, requiring invasive ventilation or ECMO assistance. Studies analyzing the effectiveness of urgent pulmonary transplantation showed an acceptable but greater mortality compared to elective surgery, with a 1 and 3-years survival rate of 67% and 59% respectively (109). Furthermore, a high SAPS score (>24), the need for ECMO assistance, and an elevation of procalcitonin levels, were associated with a poor outcome (110).

**End of life and palliative care**

IPF is a disease with a prognosis comparable to many malignant disorders. About 80% of patients suffering from this disease die in the hospital for progressive respiratory failure, and some of these patients are admitted to Intensive Care Unit. Patients who died in the ICU often did not receive enough information about end-of-life or palliative care as an alternative treatment option before admission. Life prolonging treatments are commonly used during the last weeks of life, regardless of hospital setting and disease stage (111). End-of-life decisions and do not resuscitate orders are made in less than 50% of the cases and late in the patient's life. Patients with AE-IPF are often subjected to futile treatments. Access to intensive care should be restricted to patients who can benefit from it. Young age, registration on transplantation list, eligibility features for urgent transplant, no significant comorbidity, recent IPF diagnosis, are characteristics that make the patient suitable for intensive care treatment. Most patients do not present with these features and palliative treatments should be started early. Studies on IPF populations showed that systemic morphine can be used to control dyspnea without side effects such as respiratory depression (112). Benzodiazepines have unclear efficacy for the relief of breathlessness in people with advanced lung disease and should be considered as a second line treatment (113). In patients without cognitive impairment, depressive symptoms in the last weeks of life are common and have a great impact on the quality of life, therefore antidepressant therapy should be offered (114). For intensive care clinicians, the decision to suspend treatments such as invasive mechanical ventilation is often very difficult, but we must always keep in mind that the modern life support technique has created an intermediate time between life and death, where an organic life continues often in conflict with the patient capacity of suffering. In this context, the end-of-life decision may sometimes be the most valuable treatment.

**Conclusions**

AE-IPF shares similar pathophysiological features with ARDS, and while the optimal ventilation strategy in these patients has not been defined, the extreme fragility of fibrotic lungs suggests adopting protective ventilation strategies. NIV should be considered as an early measure, while monitoring the level of respiratory drive activation. ECMO has a role as a bridge to lung transplantation and should be started early. Drug therapies currently used in AE-IPF (corticosteroids, immunosuppressive agents) provided no clear evidence on their ability to change prognosis.
Notwithstanding these uncertainties, the most recent studies show better survival in patients with AE-IPF. The reason for this finding is not clear yet, however it might be due to a more protective ventilatory management. Due to the lack of specific studies in the field, it seems that applying the lesson learned so far from ARDS to AE-IPF would be the best option to optimally manage such a severe and critical clinical condition affecting the lungs.

**List of abbreviations**

IPF, idiopathic pulmonary fibrosis; AE-IPF, acute exacerbation of IPF; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MV, mechanical ventilation; NIV, non-invasive mechanical ventilation; CPAP, continuous positive airway pressure; HFNO, high flow nasal oxygen; PS, pressure support; PEEP, positive end expiratory pressure; DAD, diffuse alveolar damage; VILI, ventilator-induced lung injury; $P_L$, transpulmonary pressure; Vt, tidal volume; $E_L$, lung elastance of lung; $E_{tot}$, total elastance; $E_{cw}$, chest wall elastance; $P_{pl}$, pleural pressure; $P_{aw}$ airways pressure; FRC, functional residual capacity; CRS, compliance of respiratory system; ΔP, driving pressure; $P_{es}$, esophageal pressure; $\Delta P_L$, transpulmonary driving pressure; SILI, self-inflicted lung injury; VAP, ventilator associated pneumonia; ECMO, extracorporeal membrane oxygenation; PMX-B, polymyxin-B; PMX-DHP, polymyxin-B fiber column; GC , glucocorticoid; GR, glucocorticoid receptor; NR, not reported; PP, prone position; LTx, lung transplantation

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## Chapter 1

# *Ventilatory support and mechanical properties of the fibrotic lung acting as a "squishy ball"*

*Marchioni A, Tonelli R, Rossi G, Spagnolo P, Luppi F, Cerri S, Cocconcelli E, Pellegrino MR, Fantini R, Tabbì L, Castaniere I, Ball L, Malbrain MLNG, Pelosi P, Clini E. Ventilatory support and mechanical properties of the fibrotic lung acting as a "squishy ball". Ann Intensive Care. 2020 Feb 4;10(1):13. doi: 10.1186/s13613-020-0632-6. PMID: 32020548; PMCID: PMC7000609.*

**Abstract**

Protective ventilation is the cornerstone of treatment of patients with the acute respiratory distress syndrome (ARDS); however, no studies have yet established the best ventilatory strategy to adopt when patients with acute exacerbation of interstitial lung disease (AE-ILD) are admitted to the intensive care unit. Due to the severe impairment of the respiratory mechanics, the fibrotic lung is at high risk of developing ventilator-induced lung injury, regardless of the lung fibrosis etiology. The purpose of this review is to analyze the effects of mechanical ventilation in AE-ILD and to increase the knowledge on the characteristics of fibrotic lung during artificial ventilation, introducing the concept of "squishy ball lung". The role of positive end-expiratory pressure is discussed, proposing a "lung resting strategy" as opposed to the "open lung approach". The review also discusses the practical management of AE-ILD patients discussing illustrative clinical cases.

## Introduction

Interstitial lung diseases (ILD) represent a group of heterogeneous clinical conditions of both idiopathic and secondary nature, characterized by the coexistence of various degrees of inflammation and lung fibrosis (1,2). Many patients with ILD can develop an acute exacerbation in the course of the disease (AE-ILD), and often require ICU hospitalization and mechanical ventilation (MV). Idiopathic pulmonary fibrosis (IPF) is the most common and severe form of idiopathic ILD, often worsened by acute exacerbation episodes (AE-IPF). During these dramatic events, the typical usual interstitial pneumonia pattern (UIP) – the radiologic and histologic hallmark of IPF– is overlapped with diffuse alveolar damage (DAD), sharing similarities with the acute respiratory distress syndrome (ARDS)(3). Little is known about the outcome of latter patients receiving MV, and the influence of the extent of lung fibrosis component on ventilator management (4).

The purposes of this viewpoint paper are: 1) to describe the mechanical characteristics of the fibrotic lung during MV, introducing the concept of *"squishy ball lung"* and 2) to discuss the impact of MV in ICU patients with acute exacerbations of ILD

## Specific pathophysiology

Independent of the underlying condition, the fibrotic lung has particular structural, biochemical and anatomical alterations resulting in profound changes in the mechanics of breathing.

### *The extracellular matrix in the fibrotic lung*

The extracellular matrix (ECM) consists of a complex network of protein structures (collagen, fibronectin, elastin, glycoproteins and proteoglycans), which play a crucial role in determining the mechanical stability and elastic recoil of the lung. The ECM is a dynamic structure, constantly remodeled by enzymatic processes. In the fibrotic lung, there is a dysregulation of this remodeling process, with imbalance between protein secretion and degradation, with an increase in the deposition of collagen, elastin, proteoglycans and fibronectin (5). Considering that the main stress-bearing constituents of lung tissue are collagen and elastin fibers, their quantitative and architectural modification can influence the elastic recoil of the lung. Elastin and collagen differ significantly in their mechanical properties. In fact, elastin is responsible for elasticity, especially at

low stress levels, and can be stretched by more than 250% of its original length before breaking, while collagen is more rigid and significantly less stretchable being extendable only by 1-2% compared to the initial length (6). Collagen fibers, which in the resting position are folded, are stretched only at high pulmonary volumes, close to the total lung capacity, and act as a blocking system determining the limitation of distention of the lung, and the origin of the curvilinear stress-strain relationship (7,8) (**Figure 1**). Therefore, elastin fibers are the main determinants of the maximum pulmonary volume that can be reached during inflation, beyond which there is a risk of barotrauma and volutrauma due to the breakdown of collagen fibers. This concept can be applied not only to the entire lung, but also to the different lung regions that have their maximum total regional capacity (7). This is particularly relevant in the fibrotic lung, where the composition of the ECM has a high regional heterogeneity. In IPF, collagen fibers accumulate around myofibroblasts in fibroblastic foci, stiffening the corresponding regions (9).

**Figure 1**

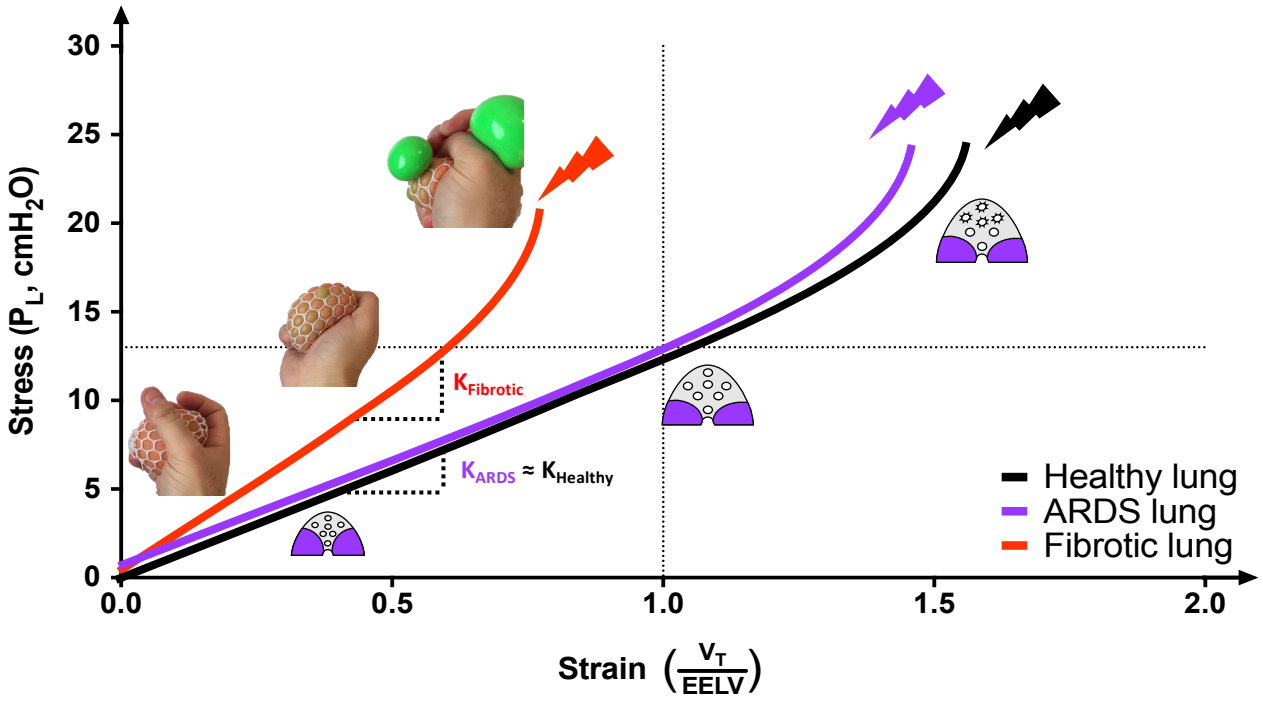


**Figure 1.** Relationship between stress and strain in healthy, ARDS and fibrotic lungs. The specific elastance (K) is the slope of the curve in its linear portion. Although ARDS lungs are characterized by low compliance, its elastic properties follow those of healthy lungs provided that the deformation induced by tidal ventilation is normalized to the end-expiratory lung volume. In ARDS, the "baby lung" (gray area) inflates until a certain

level where hyperinflation occurs and the linearity of the stress-strain relation is lost, approaching the breakdown limit of the extracellular matrix constituents (lightning). In fibrotic lungs, the specific elastance is higher thus the stress-strain curve is steeper. During inflation, the healthy regions protrude through the fibrotic walls, as illustrated by the hand progressively squeezing the "squishy ball". Compared to ARDS, the breakdown is reached at lower stress and lower strain.

*ARDS: acute respiratory distress syndrome; Vt tidal volume; EELV end-expiratory lung volume; $P_L$ transpulmonary pressure.*

*Histopathological characteristics of the fibrotic lung*

Several histopathological patterns can characterize the lung during AE-ILD; among these, the most severe and common manifestation is the coexistence of DAD overlapped to a UIP pattern. The histopathological hallmarks of the UIP pattern are spatial heterogeneity, temporal heterogeneity with fibroblastic foci and micro honeycombing. Spatial heterogeneity is defined as the presence of areas of normal tissue interposed to areas with fibrotic alterations. Temporal heterogeneity is the concomitant presence of areas with only slight modifications of the ECM structure and proliferative fibroblast and myofibroblasts aggregates, adjacent to areas of intense fibrosis composed of dense acellular collagen, indicating different coexisting stages of the disease. Honeycomb lesions are areas consisting of dilated air spaces with anelastic walls of epithelium-coated fibrous tissue(10). Given these premises, it is clear how the mechanical properties of the fibrotic lung must reflect this histological heterogeneity.

*Mechanical properties of the fibrotic lung*

The lung is commonly modeled as an elastic body characterized by minor distortions during inflation. In the non-fibrotic lung, the properties of the parenchyma can be described using two independent elastic modules, which are a function of the transpulmonary pressure ($P_L$). The bulk modulus describes the lung behavior during uniform expansion, while the shear modulus (G) describe the non-uniform distortion behavior (11). The shear modulus modifies approximately linearly as a function of transpulmonary pressure according to the following equation:

$$G = \alpha \cdot P_L \quad (1)$$

where represents the constant of proportionality that is variable according to mammal species.

The relationship between stress and strain is determined by the relationship:

$$Stress = Y \cdot Strain \quad (2)$$

Where the proportionality constant Y is the Young's modulus. Stress is the equal and opposite force that develops in an elastic material when an external force is applied, namely the transpulmonary pressure ($P_L$), while strain is the resulting deformation compared from the resting position, thus the ratio of the tidal volume ($V_T$) to the end-expiratory (resting) lung volume (EELV). Equation 2 can thus be rewritten as follows:

$$P_L = K \cdot \frac{V_t}{EELV} \quad (3)$$

where K corresponds to the specific elastance (**Figure 1**), a coefficient describing the elastic properties of the lung whose value in healthy humans is around 13.5 $cmH_2O$ (12). It can be interpreted as the $P_L$ resulting in lung volume doubling compared to the EELV. When the $P_L$ results in a lung volume above the total lung capacity, stretching of the collagen fibers occurs, causing VILI. Therefore, stress and strain are major determinants of VILI, respectively involved in barotrauma and volutrauma.

This simple model is not applicable in presence of severe distortion of the pulmonary parenchyma, where $P_L$ is no longer a function of linear elasticity modules, such as occurs in the fibrotic lung where anatomical inhomogeneities result in an anisotropic behavior: the application of $P_L$ in a lung with a patchwork of mechanical-elastic properties has unpredictable consequences on the stress-strain coupling of the various areas of the lung, with high parenchymal distortion during insufflation and consequent increased risk of VILI. In fibrotic lungs, the high retraction forces due to the exaggerated parenchymal rigidity might translate into reduced overall strain. Nevertheless, given the parenchymal heterogeneity, the lung zones without fibrosis might be subjected to intense deformation. In fact, in presence of relevant inhomogeneities the macroscopic lung mechanics parameters do not necessarily reflect what happens at the micro-scale, where inhomogeneities act as local stress raisers and increase the local $P_L$(13).

*The squishy ball lung theory*

In fibrotic lungs, the effect of positive end expiratory pressure (PEEP) can determine the protrusion of the most distensible lung areas through dense anelastic fibrotic tissue circles, causing increased rigidity and facilitating tissue breakdown. The effect that is determined in some areas of the lung is similar to that shown in stress balls called 'squishy balls' (**Figures 1** and **2**). When the squishy ball is compressed, the increase of the pressure inside the object causes throttling of the elastic part of the body through the inelastic net that wraps the ball. The result is the formation of vesicles that protrude outside the net mesh, until reaching the elastic limit. The "squishy ball effect" in some

areas of the lung may be the cause of mechanical disadvantages achieved using high airway and $P_L$ in the lungs with fibrosis and could confirm the role of static strain in generating VILI. Moreover, when the most recruitable areas are subject to high $P_L$, the subsequent over inflation is exacerbated by the mechanical geometry of the fibrotic lung as the anelastic areas act as stress raisers.

**Figure 2**

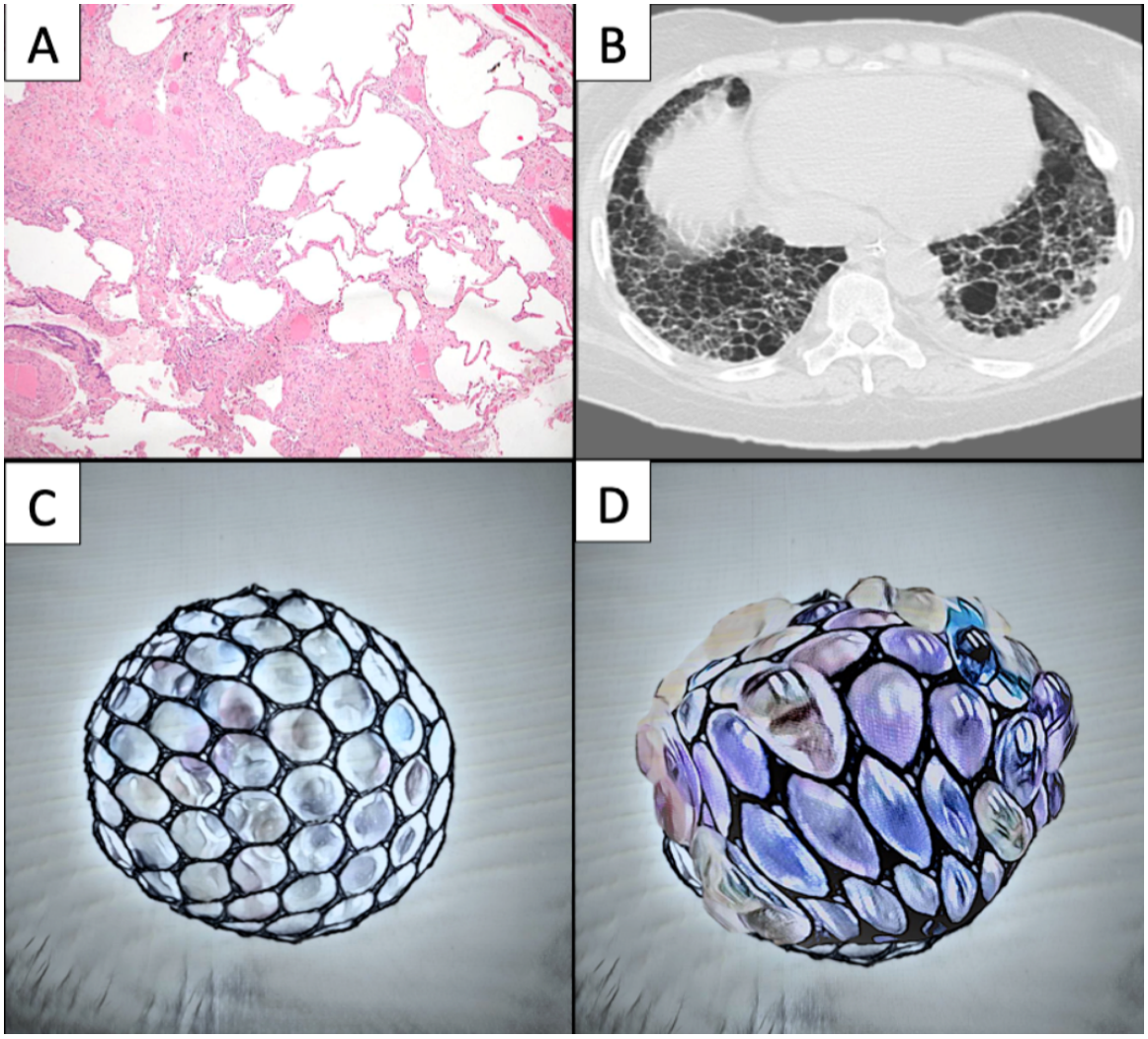


**Figure 2.** A) Histological evidence of spatial heterogeneity with relatively spared alveolar spaces surrounded by patchy areas of fibrosis with multiple fibroblastic foci in a patient with IPF. B) CT appearance of UIP pattern in a patient with IPF. C) Graphical appearance of a "squishy ball" depicting the elastic features of fibrotic lung in resting position. D) Squishy ball subjected to the application of an internal pressure: the increase of the pressure inside the object causes throttling of the elastic part of the body through the inelastic net that wraps the ball determining a mechanical disadvantage during the expansion.

*CT, computed tomography; UIP, usual interstitial pneumonia; IPF, idiopathic pulmonary fibrosis*

**Clinical implications**

The mentioned pathophysiological and histological characteristics of AE-ILD have implications for the application of MV, titration of PEEP and respiratory monitoring.

*Mechanical ventilation and clinical outcome in patients with AE-ILD*

Low tidal volume protective MV is widely recognized as the cornerstone in the treatment of ARDS patients, while in patients with AE-ILD admitted to the ICU, studies have not established yet the best ventilatory strategy. As illustrated above, patients receiving MV for AE-IPF have severe alterations in respiratory mechanics with an increase in the elastance of the respiratory system, mainly due to an abnormal lung elastance while chest wall elastance may be normal (**Table 1**) (14). Based on the concepts derived from physiologic studies, experts recommend keeping the static $P_L$ at end-inspiration below 15-20 $cmH_2O$ in homogeneous and below 10-12 $cmH_2O$ in inhomogeneous lung parenchyma, such as in ARDS.

While several studies show that in IPF patients the need for MV is associated with high mortality, little is known about the prognostic impact of MV in ILD other than IPF (15,16). In a recent cohort study in patients with ILD of different etiology hospitalized for acute respiratory failure, survival at 60 months was comparable in IPF and non-IPF patients and ICU admission and the use of MV were the only independent predictors of in-hospital death (17). Nonetheless, when patients with AE-ILD of different etiology receive MV, the presence of pulmonary hypertension and the evidence of diffuse fibrosis on CT scan are associated with worse prognosis, while the radiologic extension of lung fibrosis is directly correlated with worse respiratory mechanics and increased mortality (18) .

Interestingly, in a case series of mechanically ventilated patients with interstitial pneumonia with autoimmune features, mortality was lower compared to patients with ARDS of known cause (19). These data may sound surprising but can be linked to the peculiar radiological patterns reported in the series as none of the patients presented a UIP pattern on CT scan, while signs of inflammatory alveolar disease and ground-glass opacities were predominant. These observations suggest that the prognosis of patient with ILD in MV is related to the extension of the lung fibrosis and the presence a UIP pattern on CT scan rather than to the ILD etiology.

*Effects of PEEP in AE-ILD*

In ARDS, lung protection is provided using low tidal volumes, low plateau transpulmonary and driving pressures, but also a PEEP level sufficient to maintain oxygenation while preventing the opening-closing of alveolar units causing shear stress throughout the respiratory cycle (20). Clinical trials in ARDS investigated the effect of an *open lung* strategy, namely involving the use of PEEP levels higher than those strictly required to maintain acceptable oxygenation (21), often in conjunction with recruitment maneuvers to maximize lung aeration (22). Such studies have not been able to show clear advantages in terms of outcome compared to ventilation with lower PEEP levels. Furthermore, an aggressive recruitment strategy used in one study resulted even in increased mortality (23). Some authors started to suggest that lung pressures, including PEEP, should be minimized to reduce VILI in patients with injured and non-injured lungs (24–26); these concepts seem to be promising also for fibrotic lungs where susceptibility to VILI is particularly high.

Interestingly, in the patients with fibrotic lung and superimposed DAD, retrospective data showed an association between higher PEEP levels and mortality (16). Compared to ARDS, physiology of MV in IPF patients is much less known (3), and it is unclear whether opening and closing of alveolar units during tidal breathing occurs, as what exactly the role of PEEP is on alveolar recruitment.

Monitoring $P_L$ through esophageal pressure assessment (27) has been proposed to identify patients with regional alveolar collapse at the end of expiration, suggested by a negative end-expiratory $P_L$. Physiologic studies confirmed that $P_L$ estimated by esophageal manometry reflects the regional $P_L$ of dependent lung areas where atelectasis predominate (28,29). Titrating PEEP to target a positive $P_L$ at end-expiration maximizes lung recruitment and improves respiratory mechanics and oxygenation in ARDS(30), but did not improve survival in ARDS when compared to empirical high PEEP (31). This particular technique is one of the methods proposed to achieve an “open lung approach”. However, despite decades of intense clinical research in ARDS, ventilatory strategies aimed at achieving an *‘open lung’* (open the lung and keep it open) with the use of PEEP failed to translate these findings in the clinical setting (32), and some author suggested the ‘lung rest’ (close the lung and keep it resting) strategy (24). Despite the lack of physiological data in AE-ILD patients, it might be assumed that expiratory derecruitment occurs in parenchymal areas spared from fibrosis with preserved elasticity. Despite a possible role of incremental PEEP in the recruitment of these areas, the reported association between higher PEEP levels and mortality in AE-ILD (16), indicates a critical role of static strain in determining VILI in patients with fibrotic lungs, and might suggest that limiting airway pressures, including PEEP, could be preferable.

**Practical management tips**

This paragraph illustrates practical aspects of the clinical management of patients with AE-ILD.

*Clinical pathway of patients with AE-ILD*

Overall, AE-ILD has a poor prognosis and the choice to initiate MV or to admit the patient to the ICU can be challenging, particularly in patients with IPF (3). In several clinical settings, ICU physicians tend to be reluctant to admit IPF patients if they are not already listed for transplant, considering invasive ventilation as a *bridge-to-transplant* therapy (16). Nevertheless, evidence shows that also patients with ILD other than IPF may present with acute exacerbation during the natural course of the disease (33) requiring ICU admission and MV (15)(34). Autopsy studies show that the majority of patients who died from AE-ILD other than IPF often present with a DAD superimposed on a UIP pattern at the histologic examination, resembling what usually is found on biopsies of patients that died from AE-IPF (34,35). The presence of a UIP pattern on histology is strictly correlated with peculiar features on CT scan, namely radiological UIP pattern (33). Therefore, intensivists should be able to promptly recognize the UIP pattern at the CT scan, as it is the main determinant of the *squishy-ball* behavior of the fibrotic lung subject to MV.

*How to identify the AE-ILD radiological pattern*

The correct identification of UIP pattern at the CT scan can be useful in the clinical evaluation of patients with AE-ILD whose lung mechanical substrate is more prone to the development of VILI once subjected to MV with worst clinical outcomes. The ultimate guidelines on diagnosis of IPF defined the typical radiographic features of UIP pattern on CT. The radiologic hallmark of UIP is the presence of honeycombing, multiple layers of sub-pleural clustered cystic airspaces with thick, well-defined walls and typically consistent diameter (3–10 mm, but occasionally larger). A fine reticular pattern containing traction bronchiectasis ranging from subtle irregularity of the bronchial/bronchiolar wall to marked airway distortion and varicosity is another key feature of UIP pattern. The typical distribution of these abnormalities follows a cranio-caudal gradient with sub-pleural predominance(36). Ground-glass opacifications as defined by hazy increased opacity of lung airspaces with substantial preservation of the bronchial and vascular margins on CT, represent the usual radiological appearance of inflammatory alveolar abnormalities, including DAD (37) but may be also present in patients with ILD (38). When ground-glass opacifications result superimposed on

a fine reticular pattern surrounded by traction bronchiectasis they should be referred to alveolar fibrosis and might identify a subgroup of patients at extremely high risk of VILI(39-40). In summary, in the context of ILD of different etiology, the presence of a UIP pattern identify a mechanical substrate more prone to VILI as a consequence of the *"squishy ball"* behavior. In this setting a lung resting approach might be preferable to prevent possible damages. In AE-ILD patients with ground glass abnormalities in the absence of significant UIP pattern, mechanical behavior of the lung might be similar to ARDS.

*How to set mechanical ventilation*

There is lack of specific evidence concerning MV settings in AE-ILD. Some of the recommendations can be derived from the evidence concerning ARDS, but several other aspects need to be elucidated in further research(3). Advanced respiratory monitoring, including esophageal pressure where available, is important to identify those patients more prone to VILI(41).

Concerning tidal volume, we recommend targeting 6 ml/kg of predicted body weight, as established in ARDS(42). In case of high driving and/or plateau pressures a further reduction could be considered(43), however this strategy in AE-ILD can lead to unacceptable hypercapnia. The respiratory rate should be set to avoid respiratory acidosis, tolerating hypercapnia if the arterial pH remains above 7.25. Attention should be paid to the presence of intrinsic PEEP, namely a careful inspection of the flow-time curve should be performed to ensure that the expiratory flow reaches zero at end-expiration.

The use of high PEEP levels does not seem appropriate, due to the peculiar characteristics of the fibrotic lung. We advocate the adoption of a *"lung resting strategy"*, tolerating moderate atelectasis titrating PEEP to the minimal values necessary to achieve minimal oxygenation, i.e. an arterial partial pressure of oxygen above 50-60 mmHg or a $SpO_2$ above 88-90%. In patients in which a DAD or ground glass opacities at the CT predominate over the UIP pattern, higher PEEP levels might be considered, similarly to ARDS.

**Illustrative cases**

We assessed retrospectively clinical data of three patients with AE-ILD of different etiology admitted to the Respiratory Intensive Care Unit of the University Hospital of Modena, Italy from January 2016

to January 2018 to receive invasive controlled MV: one had IPF and two had chronic hypersensitivity pneumonitis (CHP). All patients presented a UIP pattern with superimposed ground-glass opacities on the CT scan (**Figure 3A).** Patients were non-obese males (body mass index, mean ± standard deviation of 22.8 ± 2.3 kg/$m^2$), aged 62.6 ± 9.1 (age at diagnosis 60 ± 8.5 years). All patients underwent transpulmonary pressure monitoring with esophageal manometry (**Figure 3B**).

**Table 1.**

| **Measurement** | **Patient 1 (CHP)** | | **Patient 2 (IPF)** | | **Patient 3 (CHP)** | |
|---|---|---|---|---|---|---|
| **PEEP setting technique** | Lower | Titrated | Lower | Titrated | Lower | Titrated |
| **Set PEEP ($cmH_2O$)** | 4 | 12 | 4 | 12 | 4 | 12 |
| **Driving pressure ($cmH_2O$)** | 17.0 | 18.0 | 14.5 | 18.0 | 12.0 | 16.0 |
| **Transpulmonary pressure ($cmH_2O$)** | | | | | | |
| End-inspiratory | 14.0 | 16.7 | 9.9 | 16.0 | 10.0 | 13.9 |
| End-expiratory | -2.2 | 0.2 | -4.0 | 0.3 | -1.0 | 1.6 |
| Driving pressure | 16.2 | 16.5 | 14.0 | 16.3 | 11.0 | 12.3 |
| **Elastance ($cmH_2O$/L)** | | | | | | |
| Respiratory system | 44.6 | 51.6 | 34 | 47 | 40 | 43 |
| Pulmonary | 42.5 | 47.0 | 33.0 | 45.0 | 35.0 | 37.9 |
| Chest wall | 2.1 | 4.6 | 1.0 | 2.0 | 5.0 | 5.8 |
| **Blood arterial $PaO_2/FiO_2$** | 92 | 78 | 113 | 110 | 85 | 79 |

**Table 1.** Lung mechanical properties of three patients experiencing acute exacerbation of interstitial lung disease. Patient 1 and 3 presented CHP while patient 2 presented IPF. The negative end-expiratory transpulmonary pressure values achieved at 4 $cmH_2O$ PEEP suggest that low levels of PEEP do not prevent tidal alveolar de-recruitment. Nevertheless, higher levels of PEEP determined mild to critical increase in lung elastance and non-clinically relevant worsening of gas exchange.

*CHP, chronic hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; PEEP, positive end expiratory pressure*

**Table 1** shows respiratory mechanics and gas exchange parameters of these patients, when PEEP was set according to a "lung resting strategy" (low level of PEEP 4 $cmH_2O$) and after PEEP titration on an "open lung approach" aiming at achieving positive end-expiratory transpulmonary pressure values. In all patients, with low levels of PEEP aimed at achieving minimal acceptable oxygenation, end-expiratory $P_L$ was negative. This suggests that even in the fibrotic lung with diffuse alveolar damage tidal de-recruitment of the dependent zones during the expiration might occur. Nevertheless, in these patients a PEEP titration strategy to maintain a positive end-expiratory $P_L$ resulted in a significant mechanical disadvantage. In these patients, higher PEEP levels lead to an increase in the driving pressure, lung elastance and end-inspiration $P_L$ values. This suggest that PEEP is able to counteract alveolar recruitment-derecruitment, but at the price of a remarkable lung parenchymal stress. The mechanical disadvantages determined by high PEEP, suggests that in the fibrotic lung with diffuse alveolar damage, the static strain might play a relevant role.

**Figure 3**

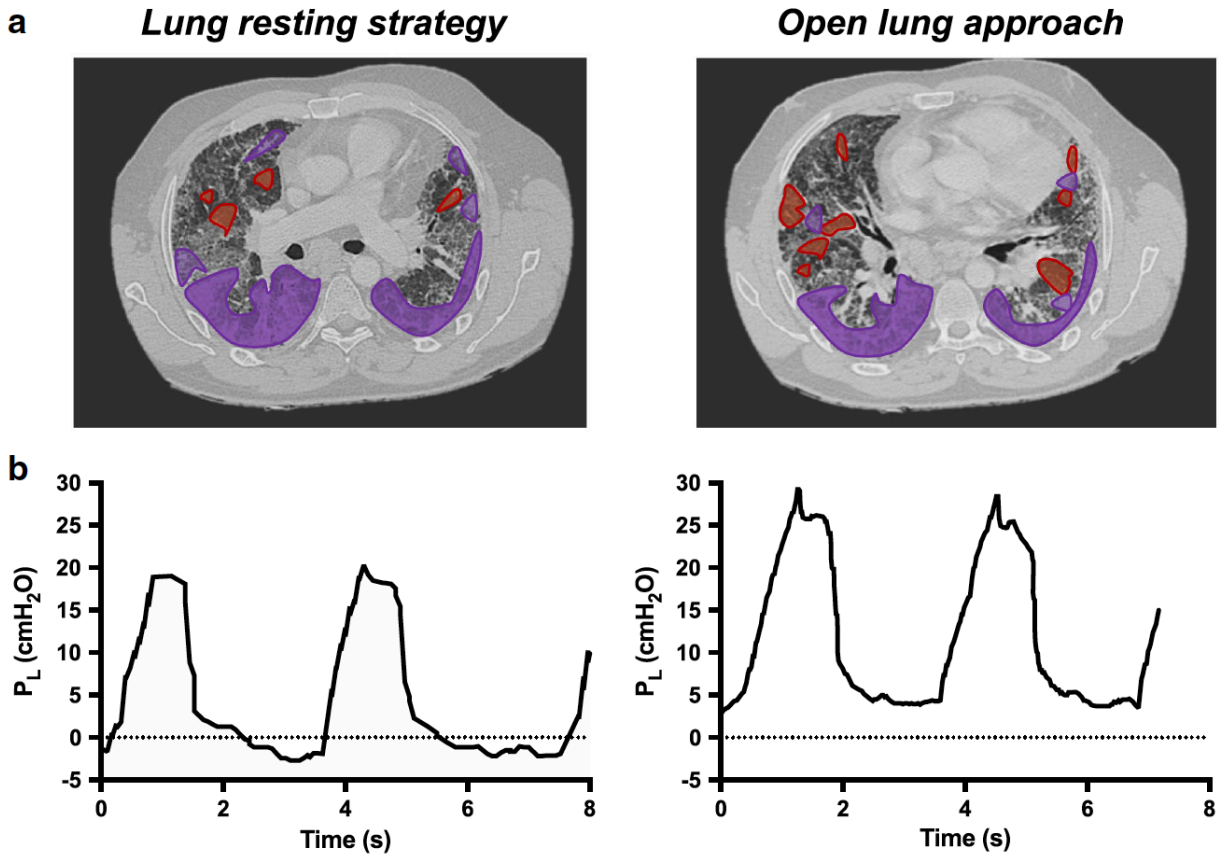

**Figure 3.** CT scan images and transpulmonary pressure monitoring of a representative patient with UIP pattern and superimposed ground-glass during an AE-ILD, with PEEP set according to a "lung resting strategy" (left, PEEP 4 cmH2O) or with an "open lung approach" titrated to achieve positive end expiratory transpulmonary pressure (right, PEEP 12 $cmH_2O$). End-inspiratory transpulmonary pressure values significantly rise when higher values of PEEP are applied. Purple areas represent lung collapse, opacities and fibrous regions. Red circles highlight areas of over-inflation.
*CT, computed tomography; $P_L$, transpulmonary pressure; AE-ILD, acute exacerbation of interstitial lung disease; PEEP, positive end-expiratory pressure*

## Conclusions

The management of the patient with lung fibrosis in the ICU is a challenge for the intensivist. The lack of studies defining the mechanical ventilation strategy, and the different underlying etiologies, make it difficult to decide which patient can benefit from ICU admission and MV. The few data that are available show that the prognosis of patients with non-IPF pulmonary fibrosis subjected to MV is dependent on the degree of extensive fibrosis present on CT scan, rather than the underlying etiology. The architecture of the fibrotic lung makes it particularly fragile when subjected to high PEEP. The presence of conserved lung areas, next to areas of dense anelastic fibrosis, does not prevent the phenomenon of alveolar recruitment-derecruitment during tidal volume. The use of high PEEP to keep alveolar units opened during expiration exposes the lung at risk of injury by forming "squishy ball" lung areas that aggravate the end-inspiratory transpulmonary pressure effects. Pending further studies to define the optimal strategy to ventilate these lungs, we herein suggest using a "lung resting strategy", as opposed to "open lung" in patients affected by pulmonary fibrosis and UIP pattern under MV, regardless of the underlying etiology.

**List of abbreviations**

AE, acute exacerbation; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung diseases; UIP, usual interstitial pneumonia; DAD, diffuse alveolar damage; $P_L$, transpulmonary pressure; EELV, end-expiratory lung volume; ICU, intensive care unit; PEEP, positive end expiratory pressure; MV, mechanical ventilation; Vt, tidal volume; ARDS, acute respiratory distress syndrome; VILI, ventilator-induced lung injury; ARF, acute respiratory failure; CHP; chronic hypersensitivity pneumonitis; CT, computed tomography; ECM, extracellular matrix

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## Chapter 2

## *Pulmonary stretch and lung mechanotransduction: implications for progression in the fibrotic lung*

*Marchioni A, Tonelli R, Cerri S, Castaniere I, Andrisani D, Gozzi F, Bruzzi G, Manicardi L, Moretti A, Demurtas J, Baroncini S, Andreani A, Cappiello GF, Busani S, Fantini R, Tabbì L, Samarelli AV, Clini E. Pulmonary Stretch and Lung Mechanotransduction: Implications for Progression in the Fibrotic Lung. Int J Mol Sci. 2021 Jun 16;22(12):6443. doi: 10.3390/ijms22126443. PMID: 34208586; PMCID: PMC8234308.*

**Abstract**

Lung fibrosis results from the synergic interplay between regenerative deficits of the alveolar epithelium and dysregulated mechanisms of repair in response to alveolar and vascular damage, followed by progressive fibroblast and myofibroblast proliferation and excessive deposition of extracellular matrix. The increased parenchymal stiffness of fibrotic lungs significantly affects respiratory mechanics, making the lung more fragile and prone to non-physiological stress during spontaneous breathing and mechanical ventilation. Given their parenchymal inhomogeneity, fibrotic lungs may display an anisotropic response to mechanical stresses with different regional deformations (micro-strain). This behavior is not described by the standard stress-strain curve but follows the mechano-elastic models of "squishy balls", where the elastic limit can be reached due to the excessive deformation of parenchymal areas with normal elasticity, surrounded by inelastic fibrous tissue or collapsed induration areas, which tend to protrude outside the fibrous ring. Increasing evidence has shown that non-physiological mechanical forces applied to fibrotic lungs with associated abnormal mechanotransduction could favor the progression of pulmonary fibrosis. With this review we aim at summarizing the state of the art on the relation between mechanical forces acting on the lung and biological response in pulmonary fibrosis, with a focus on the progression of damage in the fibrotic lung during spontaneous breathing and assisted ventilatory support.

## Introduction

Mechanical homeostasis is defined as the capacity to generate and maintain a tissue mechanical environment to support organs' physiological functions. This complex and dynamic process is the base of the relationship between structure and function, and is regulated at a subcellular level by actin cytoskeleton's tension and integrin-mediated focal adhesion, directly interacting with external biophysical stimuli to trigger downstream cellular signals (1). Physical forces (e.g. stress and strain) act on this biological system, affecting cell's behavior and function, finally resulting in tissue remodeling through cellular mechanotransduction, both during organ development and tissue damage (2,3). The lung is an organ exposed to continuous mechanical stimuli during the respiratory cyclic stretch. The extracellular matrix (ECM) provides resident cells with a scaffold, acting as a mechanical support for the respiratory function; the ECM also plays a major role in transmitting external physical forces to cells. The influence by the lung's mechanical load on the interaction between cells and the ECM contributes to a healthy mechanical tissue homeostasis (4). However, the biological response to mechanotransduction could also affect the regenerative potential of the lung following an external insult, resulting in a pathological process (5). As the lung is exposed to non-physiological stretch, especially when tissue injuries disrupt the mechanical homeostasis underlying normal tissue architecture and function, aberrant mechanisms of repair might be triggered. Pulmonary fibrosis can be considered as the final consequence of failure to restore physiological mechanical homeostasis caused by an abnormal tissue repair process driven by alveolar epithelium and leading to progressive fibroblast and myofibroblast proliferation and excessive deposition of ECM. Furthermore, increasing evidence has shown that non-physiological mechanical load applied onto the lung and dysregulated mechanotransduction could both play an essential role in progression of lung fibrosis (6). Idiopathic pulmonary fibrosis (IPF) is a chronic disease of unknown origin, characterized by progressive loss in lung function, culminating in respiratory failure and death (7,8). In IPF, increased ECM stiffness and progressive scarring of lung tissue significantly change respiratory mechanics, making the lung more fragile and exposed to non-physiological stress during spontaneous breathing and mechanical ventilation, promoting lung damage and dysregulation of mechanotransduction and tissue repair (9). The purpose of this review is to summarize the state of the art on the relation between mechanical forces acting on the lung and biological response in pulmonary fibrosis, with a focus on the progression of damage in the fibrotic lung during spontaneous breathing and assisted ventilatory support.

**Matrix abnormalities and mechanical behavior in pulmonary fibrosis**

Lung ECM is organized into two basic compartments: basement membranes, which are thin sheets of glycoproteins covering the basal side of epithelia and endothelia, and interstitial matrices, which form a loose and fibril-like meshwork that interconnects structural cell types within tissues and provides mechanical stability and elastic recoil of the lung (10). Biomechanical features of the lung are the result of ECM composition, and depend on a complex network of fibrous proteins, glycoproteins, proteoglycans and associated modifying molecules (e.g. metalloproteases, matricellular proteins) that represent the non-cellular portion of lung structure, also called "*matrisome*" (11). *Matrisome,* the overarching architecture of the lung, mainly consist of fibrillar collagens (types I, II,III,V and XI) and elastic fibers, which exhibit different mechanical properties and represent the main stress-bearing constituents of lung tissue. Indeed, fibrillar proteins such as collagens are characterized by great tensile strength but low elasticity, while elastic fibers, mainly composed of elastin, show high elasticity and low tensile strength. Therefore, the quantitative and architectural changes of these components can influence the elastic return of the lung and the non-linear stress/strain characteristics during breath. In particular, collagen fibers, which are folded in the resting position, are stretched only at high pulmonary volumes close to total lung capacity, and act as a blocking system determining both a limitation in lung distention and the origin of the curvilinear stress-strain behavior, whereas elastin molecules account for the lung elastic recoil (12). The ECM in fibrotic lungs shows different mechanical properties and biochemical composition to healthy lungs. Excessive deposition of fibrillar collagen, predominantly around myofibroblasts, is the key feature of architectural derangement in IPF, and results in stiffness of the area within fibroblastic foci (13). Some studies have described a significant change in collagen composition in IPF, with an increase in the amount of type I and type V collagen, and a decrease in the amount of type III collagens (14). However, an increase in the expression of proteoglycans such as versican and decorin, and glycoproteins such as fibronectin, have also been reported in experimental models of lung fibrosis (15). Furthermore, studies on animal models of bleomycin pulmonary fibrosis and on IPF lungs have also shown an increasing expression of elastin in the fibrotic area, suggesting a process of "fibroelastosis" rather than an exclusive process of fibrosis, in acute and chronic idiopathic interstitial pneumonia (16,17) . Recent evidence suggests that ECM composition not only defines the tissue architecture of the lung, but it is also important in promoting fibrotic changes and disease progression in fibrotic lung. Elastin and glycoprotein such as fibronectin are both essential

in driving cells towards profibrotic phenotype with the induction of myofibroblast differentiation through β1 pathway amplification (18). Some experimental evidence shows that when fibroblasts are cultured on stiffer IPF matrix, they develop an activated myofibroblast phenotype with typical features reported in IPF disease (19) . However, in IPF lungs, fibrosis areas and stiffer matrix distribution are uneven, with histological and radiological appearance which has been named as usual interstitial pneumonia (UIP). The key of UIP pattern is the distribution of fibrosis that mainly involves the lower lobes with subpleural accentuation. In these regions, areas of airspace enlargement and fibrotic retraction, namely honeycombing, are a marker of advanced stage of the disease. Moreover, the microscopical appearance is characterized by spatial and temporal heterogeneity, the latter resulting in a patchy fibrotic reaction with prevalent involvement of the peripheral area of the secondary pulmonary lobule, while the central portion is often spared (20). Studies that analyzed IPF lung with electron microscopy have shown loss of type 1 alveolar epithelium, denudation of alveolar basal lamina, and subsequent incorporation of denuded basal lamina into the interstitial alveolar septum. This process has been named "collapse induration" and is associated with permanent obliteration of alveolar unit and impaired lung mechanics. Based on these assumptions, the fibrotic lung is characterized by a highly inhomogeneous mechanical microenvironment, where lung areas with preserved elasticity are contiguous to areas of rigid lung resulting in a peculiar mechanical behavior during inflation, especially in terms of stress/strain relationship.

**Stress and strain behavior of the normal and pathologic lung**

Stress is defined as the magnitude and direction of forces acting on a body, while strain is the magnitude and direction of the consequent deformations (21). Elastic (Young's) modulus is a measure of the ability of a material to change in length when stretched or compressed and it is defined as stress/strain relationship. Biological networks show highly nonlinear stress-strain behavior and are characterized by tissues that stiffens up when exposed to increasing deformation. High values of Young's elastic modulus ($E_Y$) lead to lower values of extensibility and of elongation-at-break ($\lambda_{max}$). The relationship between stress ($\sigma$), deformation ratio ($\lambda$, defined as the ratio of the sample's instantaneous size to its initial size) and $E_Y$ is described as a constitutive equation for all equilibrium network deformations, and has been validated for a broad range of complex networks:

$$A.\ \ \sigma true(\lambda) = \frac{Ey}{9}(\lambda^2 - \lambda^{-1})\left[1 + 2\left(1 - \frac{\beta(\lambda^2 + 2\lambda^{-1})}{3}\right)^{-2}\right]$$

in which $\beta$ is the strand-extension ratio (22). Tissue and organs possess different $E_Y$ elastic moduli depending on ECM composition, fat content, cell types and degree of mineralization, and range from extremely low value (blood plasma, about 50 Pa) to very high value in stiff tissues (bone, about 100.000kPa) (11). Different biomechanical models consider the lung as a homogeneous elastic continuum undergoing only small distortions from a state of uniform inflation, whose behavior can be described with different elastic moduli: $E_Y$, describing tensile elasticity, bulk modulus (K), describing a uniform inflation, and shear modulus ($\mu$), describing an isovolumetric deformation. Normal human lung parenchyma has a mean $E_Y$ of 1.96 kPa, but this value depends on the assessed lung region (23).

Fibrotic lung diseases are characterized by increased lung stiffness and show significantly higher $E_Y$ compared to the healthy lung. In measurements performed in IPF lungs, lung elastic modulus displayed a bimodal distribution of stiffness with an $E_Y$ average of 16.55 kPa, but with a wide variability. The different zonal elasticity in the IPF lung is related to the spatial and temporal heterogeneity of the areas of fibrosis that are located close to areas of spared lung. This elastic patchwork has profound implications on the stress-strain curve and on the consequences of the mechanical load exerted on the lung scaffold, both in spontaneous breathing and during mechanical ventilation.

In engineering terms, the behavior of a solid body under the action of a physical force can be described using a *stress-strain* curve of the material (**Figure 1**). A *stress-strain* curve consists of an initial part in which the relationship between the two elements is linear (elastic area), represented by the *constitutive equation of an elastic solid (Hooke's Law):*

$$B.\ \ \sigma = E_Y \, x \, Strain$$

The elastic limit on a *stress-strain* curve is the point in which the behavior of the material switches from elastic to plastic (**Figure 1**). When the elastic limit is exceeded, the plastic strain cannot recover when the load is removed and will remain as permanent set.

**Figure 1**

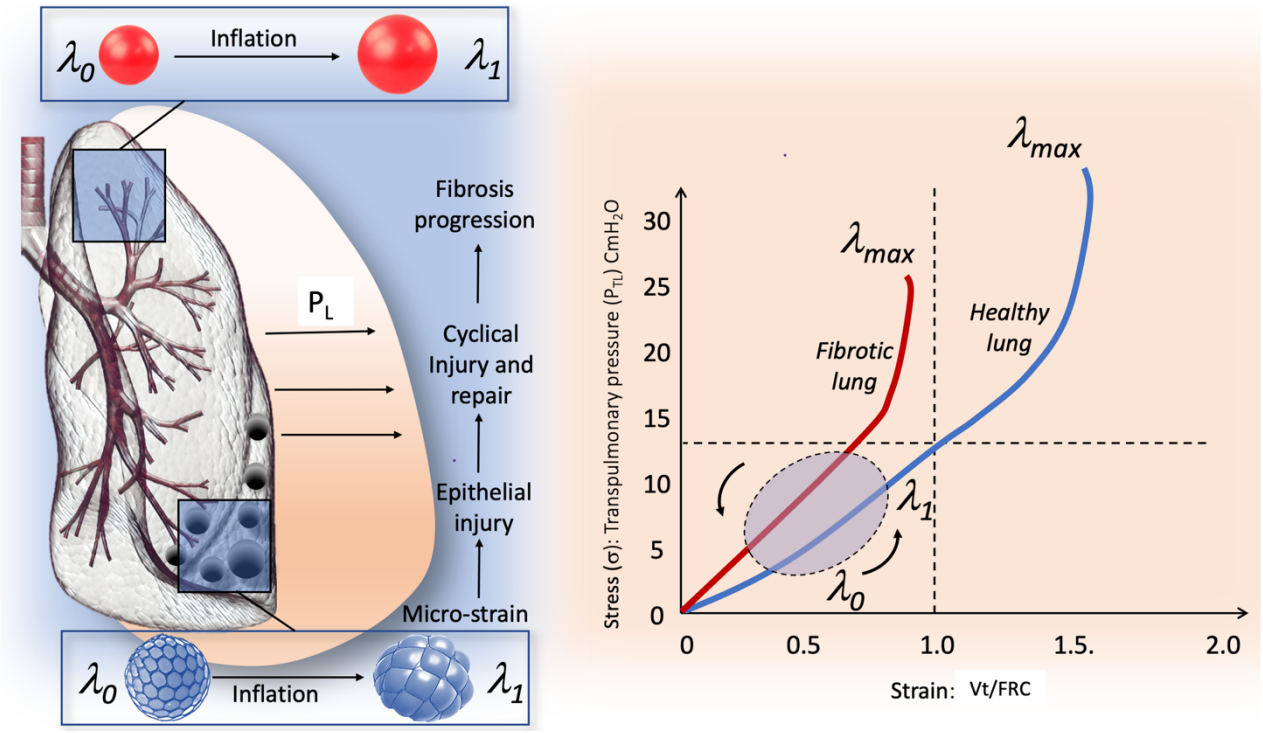


**Figure 1.** Relationship between micro-strain and global stress-strain curve in human lung. *The right part* of the figure illustrates the stress-strain curve in the healthy lung (blue line) and in the fibrotic lung (red line). In the fibrotic lung the stress-strain is steeper compared to healthy lung, due to the higher specific elastance (the slope of the curve in its linear portion), therefore the transition from elastic to plastic behavior is achieved for lower stress-strain values. *The left part* of the figure illustrates the behaviors of IPF lung during inflation, from λ0, which correspond to the elastic equilibrium of respiratory system (i.e. functional residual capacity) to λ1, which correspond to the end of tidal volume. The fibrotic lung is made up of a patchwork of areas of different elasticity predominantly in the basal and subpleural zone, in which, areas of dense fibrosis and areas of spared lung tissue are contiguous. During inflation, areas of the lung with normal elasticity surrounded by inelastic tissue, protrude outside the lung surface exhibiting squishy ball-like behavior, thus in these areas the global lung strain does not represent the micro-strain. The traction exerted by the non-physiological cyclic micro-strain could result in epithelial injury and finally in fibrosis progression.
*$P_L$, transpulmonary pressure; Vt, tidal volume; FRC, functional residual capacity*

Studies in animal models show that the respiratory system presents a viscoelastic body behavior that fulfills the constitutive equation of a solid (Hooke's law)(24).
In physiological terms, the equation *"B"* can be written as follows:

$$C. \quad P_L = E_{Y\,x}\,\frac{Vt}{FRC}$$

in which $P_L$ is transpulmonary pressure (or retraction pressure of the lung), that is defined by the difference between alveolar pressure ($P_{alv}$) and pleural pressure ($P_{pl}$). $P_L$ is the force that causes lung inflation, and that can be referred to as the stress applied to the lung. Vt refers to tidal volume (volume of air moved during each ventilation cycle), and FRC is functional residual capacity (that corresponds to the volume of air at the end of expiration). Therefore, the relationship between these two parameters (Vt/FRC) represents the pulmonary deformation during the respiratory cycle and can be defined as the lung strain. $E_Y$, in terms of respiratory physiology, coincides with *specific elastance* of the lung, which corresponds to the value of $P_L$, needed to double the volume of FRC. The value of specific elastance in a healthy human lung is 13.5 $cmH_2O$, and it doesn't seem to change with age (25-28) . In animal models of mechanical ventilation, the linear relationship between stress and strain is preserved for a strain value less than 1 (elastic area), while for strain values between 1.5 and 2 the relationship loses its linearity until the elastic limit is reached and lung injury begins to occur (24). Furthermore, in mechanically ventilated patients with ARDS, increased strain is associated with alveolar proinflammatory response that could be explained by different mechanisms, among which a mechanotransduction process activated beyond a certain threshold of lung deformation may have a major role (29-34).

**The micro-strain concept in the fibrotic lung**

In the fibrotic lung, the *specific elastance* of the lung is higher than normal, and the stress/strain curve reaches the elastic limit at lower stress and strain values than in healthy lung (**Figure 1**). Moreover, the large regional distortion during inflation to which the lung is subjected can allow the dysregulation of mechanotransduction and the occurrence of microdamage of the epithelial and pulmonary scaffold even at low levels of global strain. Part of this phenomenon can be explained by the regional differences between the isotropic expansion of the lung (healthy lung) and the anisotropic behavior (fibrotic lung) during inflation, introducing the concept of micro-strain. For isotropic homogeneous materials, like healthy lung, uniform expansion could simply be described by K, while non-uniform distortion could be described by $\mu$ both related to $E_Y$ and Poisson's ratio (v) through the following equation:

D. $K = \frac{\mathrm{Ey}}{3(1-2\mathrm{V})} \qquad \mu = \frac{\mathrm{Ey}}{2(1+\nu)}$

In this situation, the lung parenchyma is usually modelled by elastic moduli that are solely functions of the transpulmonary pressure. Indeed, the experimental measurement is approximately dependent upon $P_{L:}$

E. $\mu = \alpha \mathrm{PL}$

where $\alpha$ is the constant of proportionality.

Based on these laws, the healthy lung that is exposed to physiological inflation is on the elastic part of the stress-strain curve, where the linear relationship makes the load to which the lung is exposed predictable, and the physical forces are distributed homogeneously in the different lung regions (28). In pulmonary fibrosis, the parenchyma becomes physically inhomogeneous, and its properties become globally anisotropic. If during lung inflation deformations are large, the linear theory becomes invalid, and the elastic moduli cannot be regarded as constant for a given $P_L$. The distortion of the parenchyma causes a re-orientation and an associated change in strain of the load bearing components; as a result, moduli are functions not only of $P_L$ but also of the type and magnitude of the distortion (29). In particular, during an inspiratory effort, the IPF lung may exhibit anisotropic behavior with different regional deformations not described by the standard stress-strain curve. Especially in the interface regions between fibrotic and spared lung areas, the elastic limit can be reached due to the excessive deformation of parenchymal areas with normal elasticity, surrounded by inelastic fibrous tissue or collapsed induration areas, which tend to protrude outside the fibrous ring, with consequent lung damage. The effect observed in some lung areas is similar to that shown in stress balls called “squishy balls” and can be amplified by mechanical ventilation (**Figure 1**) (30). Therefore, in the fibrotic lung, macro-strain is not descriptive of regional micro-strain, even when the analysis of the global stress/strain curve of the whole lung appears to be in the elastic area (**Figure 1**). Micro-strain could act, during lung inflation, as a mechanical stimulus on the ECM, which in turn is transmitted to alveolar cells, by activating mechanotransduction. Furthermore, in highly inhomogeneous fibrotic lungs, this mechanical phenomenon may promote cyclic tractional epithelial injury in adjacent lung tissue during spontaneous breathing with persistent damage and

repair that finally results in fibrosis progression. Although no data are available to describe the extent of lung strain needed to cause pulmonary fibrosis, Albert RK et al suggested that the relationship between strain and fibrosis could be represented as follows:

$$\text{pulmonary fibrosis} \approx \text{strain} \times f \times t$$

where strain is represented by the deformation above the threshold that initiates mechanotransduction, while f and t represent the frequency and duration, respectively, over which strain is applied (31). Moreover, the honeycomb appearance in end-stage disease could be explained by a persistent "traction-like phenomenon" causing micro-strain to occur around the area of dense fibrosis or "collapse induration". Indeed, the mainly basal distribution of honeycombing observed in pulmonary fibrosis could also be the result of the increased $P_L$ swings that occur in this region during ventilation, that promote recurrent tractional injury (32–34). The micro-strain concept and the regional "squishy ball" phenomenon can also explain mechanical ventilation damage that may occur during protective mechanical ventilation. **Figure 1** describes the relationship between global stress/strain curve and regional micro-strain in fibrotic lung.

**The mechanotransduction process: biological response to stretch and progression in the fibrotic lung**

Cells respond to mechanical forces in their environment through cell division, differentiation, and migration, as well as promoting morphogenesis and tissue repair. During the respiratory cycle, stress and strain act on the ECM; from the ECM these physical signals are then transferred to the cells, promoting specific biological functions of alveolar cells in healthy subjects. It is widely believed that stretch of alveolar type II cells, occurring during breathing, is one of the main triggers for surfactant release (35). The most relevant mediators involved in transducing signals from the biomechanical environment to intracellular pathways include integrins, growth factor receptors, G-protein-coupled receptors, mechanoresponsive ion channels (e.g., $Ca^{2+}$), and cytoskeletal strain responses (36). Integrins are part of a large family of heterodimeric transmembrane receptor proteins. They consist of two domains: a cytoplasmic domain, linked to the actin cytoskeleton, and an extracellular domain, that recognizes specific polypeptide sequences in the ECM molecules. The transduction of

mechanical forces is modulated through mechanosensitive focal adhesion proteins, a complex macromolecular structure consisting of scaffolding, docking, and intracellular signaling proteins that collectively serve as interface between integrins and actin cytoskeleton (37). Integrin receptors, once activated, can modulate the recruitment of focal adhesion proteins, promote actin polymerization, enhance adhesion stability and contractility, as well as activate mechanosensitive genes. Focal adhesion kinase (FAK) is one of the first molecules recruited in intracellular mechanotransduction; autophosphorylation of FAK leads to its activation and a series of downstream signals within the cytoplasm. Other cytoplasmatic proteins take part in the integrin adhesion process by linking the cytoskeleton to the ECM. Talin is a 270 kDa protein consisting of three components: a N-terminal globular head that interacts with the cytoplasmatic domain of □-integrin, a rod domain containing several binding sites for vinculin, and a C-terminal helical domain. Vinculin is a multidomain cytoplasmatic protein able to interact with other adhesion complex proteins, and it acts as the main partner of talin in the mechano-sensing process. Cooperating with talin, vinculin links integrin to actin cytoskeleton. In the absence of mechanical strain, the talin rod remains fully structured and no vinculin binding sites are exposed. On the other hand, once a force is applied, the amount of vinculin sites available for binding depends on the magnitude of the physical force itself. The talin-vinculin mechanosensitive cooperation is considered essential to stabilize the talin-F-actin interaction and to transmit the magnitude of the signal down intracellular pathways (38). Although the molecular process by which mechanical signals are conveyed from the periphery to the cell nucleus has not been fully understood, some studies suggest that the nucleus has a mechanosensitive apparatus of its own, and that the cytoskeleton can transmit forces across the nuclear envelope altering the nuclear environment and promoting genes transcription (39). Nuclear envelope spectrin-repeat proteins (nesprin) are a super family of proteins, located into the nuclear envelope, that establish nuclear-cytoskeleton connections. Nesprin contains an evolutionary conserved c-terminal Klarsicht ANC-1 and Syne Homology (KASH) transmembrane domain; it binds to the C-terminal domain of the trimeric SUN protein that interacts with the nuclear lamina. Nuclear lamina structures provide the internal surface of the nuclear envelope with a scaffold and link the cytoskeleton to the nucleoskeleton through SUN-KASH bridges, and the lamina protein emerin. (40,41).

In conditions of excessive lung stretch, animal models have shown different signaling pathways involved in the induction of pulmonary fibrosis through mechanical transduction, including: Rho/ROCK, MRTF-A and YAP/TAZ signaling pathways (6). Rho GTPases (Rac, Rho and CDC42) are

signaling G proteins, distributed across the lower surface of the cell, that regulate cytoskeletal dynamics by controlling actin polymerization and myosin II-mediated contraction. One of the main biological action of Rho is achieved by its effector Rho-associated protein kinase (ROCK, presenting in two isoforms ROCK1 and ROCK2). Rho/ROCK regulation of actin cytoskeletal dynamics acts as a trigger of the activity and the nuclear localization of myocardin-related transcription factor (MRTF) and the Hippo pathway effector YES-associated protein (YAP) and its paralog transcriptional coactivator with PDZ-binding motif (TAZ) (42,43).

Some studies suggest that Rho/ROCK activity plays a crucial role in the development and progression of pulmonary fibrosis. Observations from experimental mice models of lung fibrosis and from human subjects with IPF suggest that the activation of the Rho/ROCK pathway sustains progressive fibrotic disorders (44). The blockade of the Rho/ROCK pathway prevents lung fibroblast differentiation into myofibroblasts and inhibits the development of pulmonary fibrosis secondary to lung injury *in vivo*. Furthermore, in animal models, ROCK1- and ROCK2-haploinsufficient mice exhibited protection from bleomycin-induced pulmonary fibrosis (44–47). Rho-mediated actin polymerization results in MRTF-A (also known as MKL-1) nuclear translocation, activation of $\alpha$-smooth muscle actin ($\alpha$-SMA) gene expression and type I collagen synthesis (48). In particular, in the nuclear environment, MRTF interacts with the Serum Response Factor (SRF) resulting in enhanced transcription via conserved CArG box DNA element of type I collagen $\alpha$2 chain (COL1A2) gene promoter. SRF/MRTF signaling is considered as having a central role in the differentiation of fibroblasts into myofibroblasts phenotype. Both molecular and mechanical factors associated with fibrosis, including TGF-$\beta$1 and exposure to stiff substrates, have been found to promote MRTF-A nuclear translocation in fibroblasts. Furthermore, the blockade of the nuclear action of SRF/MRTF attenuates myofibroblast's differentiation and enhances myofibroblast's susceptibility to apoptosis *in vitro* (49). Rho/ROCK activity is also required for YAP/TAZ nuclear translocation to allow its different biological functions such as modulation of genes transcription. YAP/TAZ are central transcriptional coactivators, interacting with DNA-binding transcription factors to regulate targeted gene expression; being coactivators, they are in fact unable to directly bind to DNA (50) . In mammalians, TEAD family transcription factors (TEAD 1-4) are the main partners of YAP in driving gene transcription, while the role of other transcriptional factors, including Smad, RUNX1/2, p63/p73, and ErbB4, is less clear (51). Recently, some studies have shown that mechanical signals arising from cells microenvironment control both localization and activity of YAP/TAZ. High mechanical stress induced by cell spreading or by culture on a hard surface promotes TAZ/YAP

nuclear accumulation and mechano-activation (52). Specifically, TAZ/YAP nuclear accumulation is controlled by cell shape, by rigidity and topology of the ECM, and by shear stress. YAP and TAZ are usually located in the cell cytoplasm of cells that receive low levels of mechanical signaling (cells attached to a soft ECM); conversely, they are accumulated in the nucleus of cells exposed to high mechanical stress or experiencing deformation and cytoskeletal tension. YAP/TAZ exerts its profibrotic effect through interaction with nuclear transcriptional factors, and activation of different ECM genes including plasminogen activator inhibitor-1 (PAI-1), connective tissue growth factor (CTGF), and COL1A1 and COL1A2. Some studies have demonstrated the presence of nuclear YAP accumulation and YAP targeted gene expression in lung fibroblasts grown on stiff matrices and in IPF epithelial cells, suggesting the ability of YAP/TAZ activation to drive profibrotic response in the lung (53,54) . Furthermore, nuclear exclusion and subsequent suppression of YAP/TAZ gene transcription could inhibit the profibrotic activity induced by TGF-β1 in fibroblasts *in vitro* (55,56). **Figure 2** summarizes the mechanotransduction pathways involved in the progression and development of lung fibrosis currently identified in animal models.

**Figure 2**

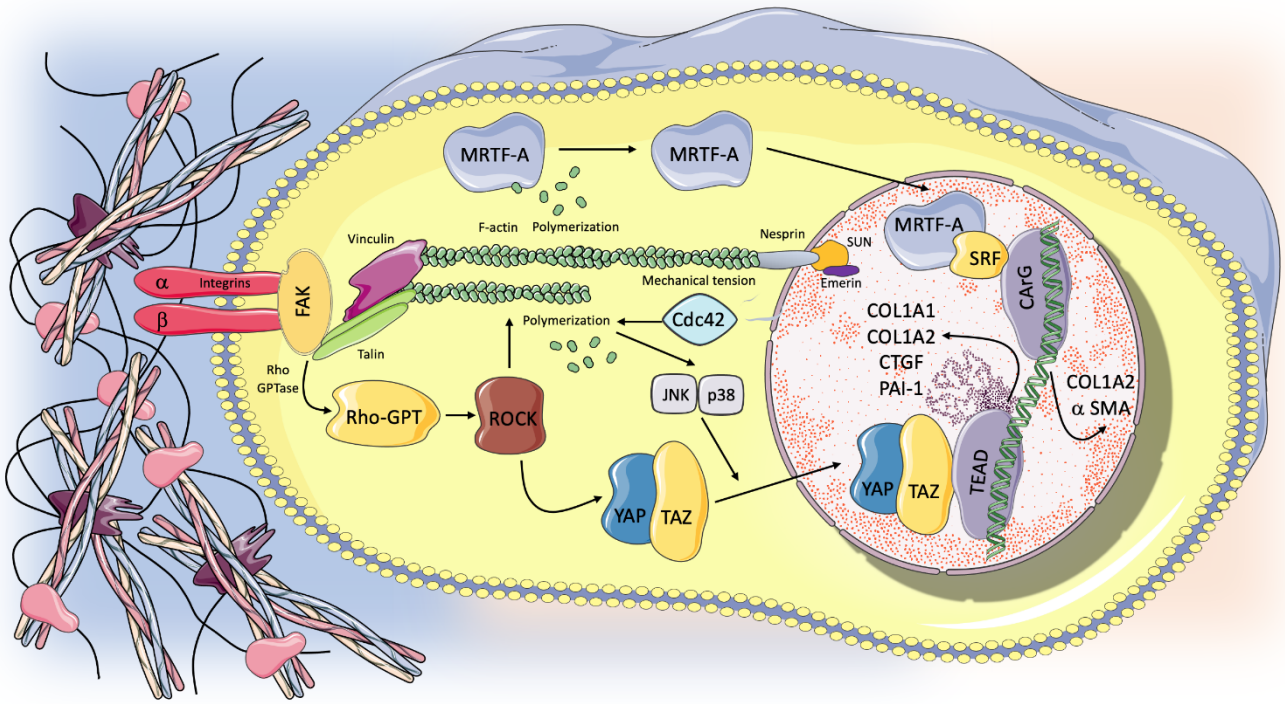


**Figure 2.** Mechanotransduction and intracellular pathways potentially involved in pulmonary fibrosis progression. Unphysiological mechanical stimuli act on ECM which in turn transmitted the physical force to

integrins at the cells surface. Integrin clustering, through mechanosensitive focal adhesion proteins (i.e. FAK, talin, vinculin), promotes actin polymerization and cytoskeletal remodeling that can transmit forces across the nuclear envelop through specialized proteins (nesprin, SUN, emerin), potentially influencing gene transcription. Furthermore, different intracellular pathways implicated in the induction of pulmonary fibrosis could be activated via mechanotransduction process. Rho through its effectors ROCK acts as a trigger for activity and nuclear localization of MRTF and YAP-TAZ, which in turn activated the transcriptions of profibrotic genes (COL1A1, COL1A2, CTGF, PAI-1, $\alpha$–SMA). Cdc-42, a GTPase protein which is part of the Rho family, is involved in alveolar regeneration after increased of mechanical tension in response to lung injury via JNK/p38 activation and nuclear YAP expression in AT2 cells. Therefore, loss of Cdc-42 function could result in a dysfunction in alveolar renewal after lung damage. For further details see the text.

*ECM, extracellular matrix; FAK, focal adhesion kinase; SUN, Sad1, UNC84; MRTF, myocardin-related transcription factor; YAP, yes-associated protein; TAZ, transcriptional co-activator; COL1A1, collagen type I alpha 1; COL1A2, collagen type I alpha 2; CTGF, connective tissue growth factor; PAI-1 plasminogen activator inhibitor-1; $\alpha$-SMA, alpha smooth muscle actin; Cdc-42, cell division control protein 42 homolog; GTP, guanosine 5'-triphosphate; AT2, alveolar type 2*

**Role of alveolar type 2 cells in the progression of lung fibrosis**

Alveolar type II (AT2) cells are considered as the main cell type for the synthesis and secretion of lung surfactant. Pulmonary surfactant appears to play a key role in the evolution of acute respiratory disease towards fibrosis. Abnormalities in the synthesis and function of surfactant, especially of its structural proteins, SP-A and SP-D, both acquired and inherited, are associated with a higher prevalence of development of pulmonary fibrosis compared to healthy volunteers without protein alterations (57,58) . Additionally, several studies also described the association between genetic polymorphisms for surfactant proteins and ARDS (59). A rare mutation of the gene encoding SP-A2, is associated with development of familial idiopathic pulmonary fibrosis (60). Furthermore, several gram-negative infections seem to alter the endogenous surfactant by inhibiting the biosynthesis of phospholipids and / or its biophysical function with the secretion of elastase which favoring the path towards fibrosis (61,62).

Focusing on the role of AT2 apart from their contribution in the genesis of surfactant, it has recently been shown that AT2 cells also function as alveolar stem cells in the lungs, being able to self-renew and differentiate into alveolar type I (AT1) cells, which are the main epithelial component of the

alveolar-capillary barrier in gas exchange. Hence their key role in regeneration and repair after lung injury (63). Recent evidence suggests that AT2 cells depletion and/or dysfunction could play a relevant role in the pathogenesis and progression of lung fibrosis (64) . Multiple elements, including genetic, environmental stress and age-related factors, could contribute to AT2 cells dysfunction and loss of their homeostatic role in IPF. A prevailing concept is that AT2 cells depletion due to repeated micro-injury in the alveolar epithelium could constitute an early event in IPF pathogenesis. Furthermore, AT2 apoptosis correlates with severe or prolonged endoplasmic reticulum (ER) stress, which is in turn associated with development of fibrotic disorders in multiple organs (65). Susceptibility to ER stress is also associated with different factors, such as smoking and aging, which are linked with IPF development (65–67). However, in addition to the depletion of epithelial cells, in pulmonary fibrosis AT2 cell dysfunction could alter their ability to repair alveolar tissue after chronic micro-injury, resulting in a modification of mechanical homeostasis. Indeed, some observations have shown that in fibroblastic foci AT2 cells have an impaired renewal capacity and could promote fibrogenesis with profibrotic factors production (68,69). Recent studies show that in AT2 cells YAP is a key mediator in regulating mechanical tension-induced alveolar regeneration in response to lung injury through the activation of Cdc42/F-actin/MAPK/YAP signaling cascade (70). Cell division control protein 42 homolog, also known as Cdc42, is a small GTPase protein which is part of the Rho family, and whose function is involved in control c-Jun N-terminal kinases (JNK)-p38 kinases activation and phosphatidylinositol 4,5-bisphosphate (PIP2)-induced actin assembly (71). Cdc42 pathway is also involved in premature epithelial cellular senescence, a cellular process linked to IPF (72) .

Pneumonectomy is one of the main models employed to study mechanical forces driving alveolar regeneration. Indeed, loss of alveoli after PNX causes significantly increased mechanical tension on the remaining alveolar epithelium, while an efficient alveolar regeneration response is able to reduce the intensity of the mechanical tension to which the alveoli are exposed. It has been shown that Cdc42-controlled actin remodeling is required for JNK and p38 activation and nuclear YAP expression in AT2 cells during PNX-induced alveolar regeneration (70). Moreover, a recent study has shown that AT2 cells that lack Cdc42 function are not able to differentiate into AT1 cells in PNX-treated or aged mice, and are therefore unable to regenerate new alveoli after lung injury, resulting in increased mechanical tension on the alveolar epithelium (73). Furthermore, in Cdc42-null mice, loss of Cdc42 functions in AT2 cells leads to progressive lung fibrosis in post-PNX lungs, with a pattern similar to IPF (from the periphery to the center of the lung). Fibrotic development was

reduced in CdC42-null mice when mechanical tension was released. It is known that the application of mechanical stretch on AT2 cells is able to activate the TGF-β1 pathway, which induces disturbance of the homeostatic microenvironment leading to an aberrant wound healing promoting the fibrotic process. In an *ex vivo* model, mechanical tissue stretch induces the activation of TGF-β1 signals through Rho/ROCK and αv integrins interactions (74). Wu et al suggested that an increased mechanical tension, caused by defective AT2 cells alveolar renewal capacity, associated with tissue stretch occurring during spontaneous breathing could cause an aberrant TGF-β1 signaling loop activation resulting in fibrosis progression (73). Mechanical stress is heterogeneously distributed during lung inflation with the posterior bases of the lower lobes being the sites where the magnitude of transpulmonary swing is more evident. With this assumption the progression of lung fibrosis could start in these regions, progressively extending in a caudal-cranial mode along the axis of distribution of mechanical forces. We can speculate that in the lung with IPF, the micro-strain due to the regional squishy ball behavior can behave as a catalyst of the profibrotic mechanotransduction pathways in a spatial manner, facilitating the progression of fibrosis from the periphery of the lung towards the center. Furthermore, this coupling of pulmonary stretch and profibrotic pathways can be partly promoted by the altered mechanical homeostasis due to the dysfunction of AT2 cells that are unable to renew damaged alveolar tissue.

**Conclusions**

Mechanical stresses might be involved in triggering and promoting dysregulation of the key molecular pathways governing lung tissue repair, thus leading to fibrotic changes. In this complex scenario, the presence of established fibrosis may enhance the impact of lung stretch during both spontaneous breathing and mechanical ventilation. Several factors may influence the relationship between alveolar architecture and the response to the physical stimuli applied to the lung. Structural changes occurring in respiratory system with advancing age, such as the decrease of lung elasticity and the stiffness of the chest wall, may predispose the ageing lung to harmful responses once subjected to stress. In this line, cellular senescence leads to replicative arrest, apoptosis resistance, and the acquisition of a senescence-associated secretory phenotype, that involves the release of several inflammatory, growth-regulating and tissue-remodeling factors and could thus contribute to pro-fibrotic responses (75). Furthermore, several form of acute lung injury (namely

ARDS) can amplify the mechanical stresses to which the lung is subjected. In particular, parenchymal inhomogeneity can act as stress raiser at the interface of regions characterized by different tissue elasticity, thus enhancing lung damage and abnormal repair response. The activation of the aforementioned pathways of mechanotransduction could be implied in the onset and progression of lung fibrosis related to acute lung injury.

Interstitial lung diseases (not limited to IPF) showing UIP pattern are subjected to acute exacerbations with dramatic gas exchange impairment requiring ventilatory assistance (76). Once mechanical ventilation is needed a protective strategy is advisable in order to reduce lung stretch and consequently avoid fibrotic lung damage progression via mechanotransduction (9). Differently from the recommended ventilatory management of ARDS patients, an open lung approach with high level of PEEP to prevent atelectotrauma should be rather avoided. Indeed, it is even arguable that elevated PEEP values are able to contrast the alveolar recruitment-derecruitment phenomenon, this happening at the cost of a remarkable lung parenchymal stress. Although data regarding the mechanical behavior of fibrotic lungs exposed to $P_L$-titrated PEEP are lacking, a preliminary report on five patients with AE-ILD undergoing MV showed a remarkable (or significant, to avoid repetitions) mechanical disadvantage (30). These physiological changes may be explained by the mechano-elastic model of the lung acting as a “squishy-ball”, in which the lung is represented by a patchwork of extremely different elasticities arranged contiguously. Further research in this field is required to clarify the complex interaction between mechanical stressors and lung response in patients with fibrotic lung disease and UIP pattern.

**List of abbreviations**

ECM, extracellular matrix; FAK, focal adhesion kinase; SUN, Sad1, UNC84; MRTF, myocardin-related transcription factor; YAP, yes-associated protein; TAZ, transcriptional co-activator; COL1A1, collagen type I alpha 1; COL1A2, collagen type I alpha 2; CTGF, connective tissue growth factor; PAI-1 plasminogen activator inhibitor-1; $\alpha$–SMA, alpha smooth muscle actin; Cdc-42, cell division control protein 42 homolog; GTP, guanosine 5'-triphosphate; AT2, alveolar type 2; SP, surfactant protein; $P_L$, transpulmonary pressure; Vt, tidal volume; FRC, functional residual capacity; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia; KASH, Klarsicht ANC-1 and syne homology transmembrane; ROCK, rho-associated protein kinase; PDZ, post synaptic density protein; MKL-1, /megakaryoblastic leukemia 1; SRF, serum response factor; TGF-$\beta$1, transforming growth factor $\beta$1; DNA, deoxyribonucleic acid; TEAD, TEA domain transcription factor; ErbB4, erb-b2 receptor tyrosine kinase 4; ER, endoplasmic reticulum; PIP2, phosphatidylinositol 4,5-bisphosphate; PEEP, positive end-expiratory pressure; MV, mechanical ventilation; AE-ILD, acute exacerbation of interstitial lung disease; ARDS, acute respiratory distress syndrome

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## Chapter 3

### *Inspiratory effort and respiratory mechanics in patients with acute exacerbation of idiopathic pulmonary fibrosis: a preliminary matched control study*

*Tonelli R, Castaniere I, Cortegiani A, Tabbì L, Fantini R, Andrisani D, Gozzi F, Moretti A, Bruzzi G, Manicardi L, Cerbone C, Nani C, Biagioni E, Cerri S, Samarelli V, Busani S, Girardis M, Marchioni A, Clini E. Inspiratory Effort and Respiratory Mechanics in Patients with Acute Exacerbation of Idiopathic Pulmonary fibrosis: A Preliminary Matched Control Study. Pulmonology. 2022 Sep 27:S2531-0437(22)00204-5. doi: 10.1016/j.pulmoe.2022.08.004. Epub ahead of print. PMID: 36180352.*

**Abstract**

**Background**

Patients with acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) may experience severe acute respiratory failure, even requiring ventilatory assistance. Physiological data on lung mechanics during these events are lacking.

**Methods**

Patients with AE-IPF admitted to Respiratory Intensive Care Unit to receive non-invasive ventilation (NIV) were retrospectively analyzed. Esophageal pressure swing ($\Delta P_{es}$) and respiratory mechanics before and after 2 hours of NIV were collected as primary outcome. The correlation between positive end-expiratory pressure (PEEP) levels and changes ~~of~~ in dynamic compliance ($dynC_{RS}$) and $PaO_2/FiO_2$ ratio was assessed. Further, an exploratory comparison with a historical cohort of ARDS patients matched 1:1 by age, sequential organ failure assessment score, body mass index and $PaO_2/FiO_2$ level was performed.

**Results**

At baseline, AE-IPF patients presented a high respiratory drive activation with ΔPes = 27 (21–34) cmH2O, respiratory rate (RR) = 34 (30–39) bpm and minute ventilation (VE) = 21 (20–26) L/min. Two hours after NIV application, ΔPes, RR and VE values showed a significant reduction (16 (14–24)

cmH2O, p<0.0001, 27 (25–30) bpm, p=0.001, and 18 (17–20) L/min, p=0.003, respectively) while no significant change was found in dynamic transpulmonary pressure, expiratory tidal volume (Vte), dynCRS and dynamic mechanical power. PEEP levels negatively correlated with $PaO_2/FiO_2$ ratio and $dynC_{RS}$ (r=–0.67, p=0.03 and r=–0.27, p=0.4, respectively). When compared to AE-IPF, ARDS patients presented lower baseline $\Delta P_{es}$, RR, VE and dynamic mechanical power. Differently from AE-IPF, in ARDS both Vte and $dynC_{RS}$ increased significantly following NIV (p=0.01 and p=0.004 respectively) with PEEP levels directly associated with $PaO_2/FiO_2$ ratio and $dynC_{RS}$ (r=0.24, p=0.5 and r=0.65, p=0.04, respectively).

**Conclusions**

In this study, patients with AE-IPF showed a high inspiratory effort, whose intensity was reduced by NIV application without a significant improvement in respiratory mechanics. In an exploratory analysis, AE-IPF patients showed a different mechanical behavior under spontaneous unassisted and assisted breathing compared with ARDS patients of similar severity.

**Introduction**

Idiopathic pulmonary fibrosis (IPF) is a life-threatening lung disease characterized by progressive deterioration of lung function and a median survival time of 3-5 years from diagnosis (1). Acute exacerbation of IPF (AE-IPF) leads to an acute deterioration of respiratory function, and severe hypoxemia, further worsening the prognosis. (2). During these events, the typical usual interstitial pneumonia pattern (UIP) – the radiological and histological hallmark of IPF– overlaps with diffuse alveolar damage (DAD), sharing similarities with ~~the~~ acute respiratory distress syndrome (ARDS) and often requiring respiratory support (3). Several studies show that the need for mechanical ventilation (MV) is associated with high mortality (4,5) in IPF patients. This is probably related to the pathophysiological properties of UIP-like fibrotic lung (i.e. collapsed induration) areas, elevated lung elastance, high inhomogeneity) that makes it more susceptible to ventilatory-induced lung injury (VILI) (3,6).

Based on a large number of clinical observations available in literature, and on some physiopathological speculations (3,7), we have theorized an elastic model with the aim to explain the mechanical behavior of the fibrotic lung when subjected to positive end-expiratory pressure (PEEP) during invasive MV, namely the "squishy-ball" theory. According to this hypothesis, the application of PEEP on a UIP-like lung pattern can determine the protrusion of the more distensible areas through a dense anelastic fibrotic tissue circle. This causes an increased rigidity~~,~~ and worse compliance, thus easing tissue breakdown. Despite lack of extensive evidence, we ~~have~~ suggested to consider MV only in selected cases of AE-IPF (3). In this scenario, non-invasive mechanical ventilation (NIV) may therefore represent an alternative option to assist these patients, although no specific recommendations have been made so far (3,8,9). In ARDS, the efficacy of NIV in reducing the patient's inspiratory effort early after its application has been related to a favorable clinical outcome (10). Indeed, the mitigation of the respiratory drive might result in a lower risk of self-inflicted lung injury (SILI) during spontaneous breathing. Indeed, SILI is very likely to worsen outcomes in patients undergoing acute respiratory failure (ARF) (11).

To our knowledge there are still no available data on inspiratory effort and lung mechanics in patients with AE-IPF either during unassisted or assisted spontaneous breathing. The aims of this study were to explore inspiratory effort and respiratory mechanics, at baseline and 2 hours after NIV in AE-IPF patients and to compare the data with ARDS patients matched for clinical severity.

## Materials and methods

*Study setting and design*

This retrospective single center cohort study was carried out at the Respiratory Intensive Care Unit (RICU) of the University Hospitals of Modena (Italy) and conducted in accordance with the pre-existing Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 348/18). Informed consent to participate in the study and to allow their clinical data to be analyzed and published were obtained from participants, as appropriate. For study purposes we further conducted a retrospective sub-analysis of data prospectively collected within a pre-registered clinical trial ClinicalTrial.gov (NCT03826797) and in accordance with the pre-existing Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 266/16).

*Study population*

Patients with IPF developing an AE and consecutively admitted to the Respiratory Intensive Care Unit and to the Intensive Care Unit of the University Hospital of Modena over the period August 1$^{st}$, 2016 to January 1$^{th}$, 2022 were retrospectively considered eligible for enrollment.

Inclusion criteria were as follows: age >18 years; previously established diagnosis of IPF with a UIP pattern on a high resolution computed tomography (HRCT) scan; acute exacerbation of IPF as defined by an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality on chest HRCT scan and presence of ARF with $PaO_2/FiO_2$ ratio <300 mmHg (12); having received a NIV trial while on RICU stay; inspiratory effort assessment and monitoring through esophageal manometry. Patients were excluded if they presented any of the followings: acute cardiogenic pulmonary edema, concomitant hypercapnic respiratory failure ($PaCO_2$ >45 mmHg) of any etiology, neuromuscular disease or chest wall deformities, home long-term oxygen therapy, lacking core data (i.e. clinical characteristics at baseline and physiological measurement) at medical record analysis. AE-IPF population was then matched 1:1 by age, $PaO_2/FiO_2$ ratio, body mass index (BMI), sequential organ failure assessment (SOFA) score, to a group of patients with ARDS under spontaneous breathing extracted from our dataset and treated between 2016 and 2022. All patients underwent a common and standardized intervention (including esophageal pressure monitoring) and data were collected using a standard collection protocol. The values of $PaO_2/FiO_2$ ratio used for matching these groups were those measured immediately before starting NIV.

*General measurements*

Medical reports, electronical charts and available clinical and physiological datasets were investigated to collect data on demographics, clinical characteristics, arterial blood gases, $PaO_2/FiO_2$ ratio, respiratory rate (RR), blood lactate level, clinical severity (as assessed by the SOFA score on RICU admission), esophageal manometry and respiratory mechanics before and after NIV trial.

*Physiological measurements*

**Figure 1**

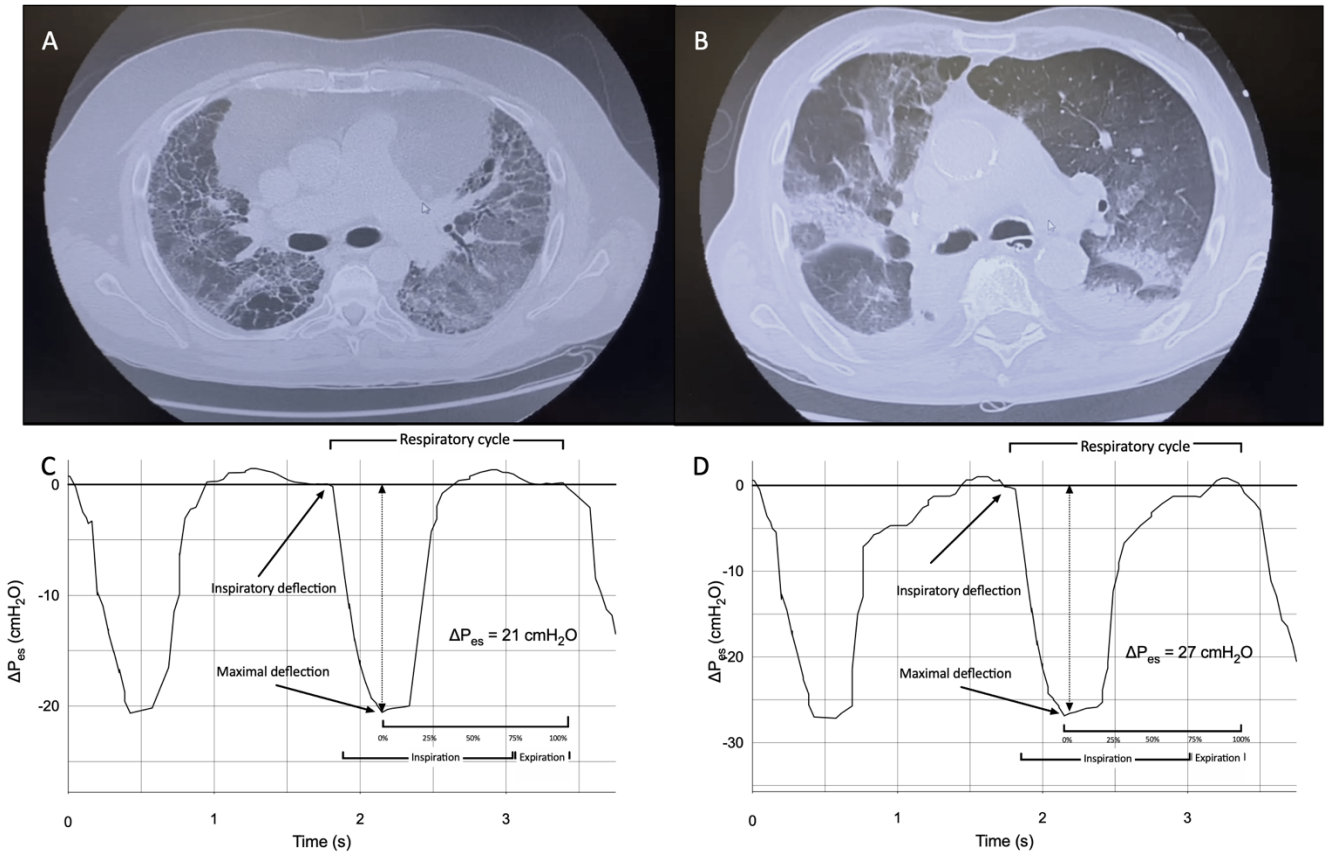



**Figure 1.** Panel A. CT scan images of a patient with AE-IPF showing UIP pattern with superimposed ground-glass. Panel B. CT scan images of a patient with ARDS showing diffuse ground glass opacities and consolidations. Panel C. Graphical representation $P_{es}$ swings waveform during AE-IPF. Panel D. Graphical representation $P_{es}$ swings waveform during ARDS. The beginning of the inspiratory phase was identified at the time of $P_{es}$ initial decay, while the end of inspiration was considered at the point of $P_{es}$ that elapsed 25% of time from its maximum deflection to return to baseline.

*CT, computed tomography; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome; $P_{es}$, esophageal pressure*

According to our local protocol, esophageal manometry was performed with a multifunctional nasogastric tube with a pressure transducer (NutriVent$^{TM}$, SIDAM, Mirandola, Italy) connected to a dedicated monitoring system (OptiVent$^{TM}$, SIDAM, Mirandola, Italy) recording swings in esophageal ($P_{es}$) and dynamic transpulmonary ($P_L$) pressures. The NutriVent$^{TM}$ was placed before starting NIV as previously reported (10) and according to (or following the) the recommended calibration protocol (13,14). To avoid using absolute values for $P_{es}$ and $P_L$, we always referred to $\Delta P_{es}$ and $\Delta P_L$ from the end-expiratory level, respectively, calculated as recommended (15). For all the measurements, the beginning of the inspiratory phase was identified at the instant of $P_{es}$ initial decay while the end of inspiration was the value of $P_{es}$ where 25% of the time had elapsed from maximum deflection to baseline (**Figure 1**). The respiratory flow was measured through an external heated pneumotachograph (Fleisch No.2, Lausanne, Switzerland) inserted between the patient's oronasal facemask (Bluestar$^{TM}$, KOO Medical Equipment, Shanghai, PRC) and a connector with a side port for measurements. Expiratory tidal volume (Vte) was obtained by numerical integration of the flow signal; Vte was then adjusted to the predicted body weight (PBW) to derive Vte/kg of PBW. Minute ventilation (VE) was calculated as the product of Vte and RR. Vte/$\Delta P_L$ was measured as a surrogate for respiratory system compliance and named "dynamic compliance" ($dynC_{RS}$). Air Leaks from the oronasal facemask were computed using dedicated ventilator-integrated software (GE Healthcare Engstrom Carestation$^{TM}$, GE Healthcare, Finland) based on the equation: leaks (L/min) = (inspiratory Vt – expiratory Vt) x RR. A surrogate of mechanical power (i.e. "dynamic mechanical power") was then calculated as 0.098 * RR * Vte * ($\Delta P_L$ + Positive end-expiratory pressure (PEEP)) (15). In every patient of both groups, measurements were recorded under standardized conditions over five consecutive minutes of unassisted spontaneous breathing, and repeated 2-hours after the initiation of NIV. Data were numerically stored and downloaded from a USB stick at each time point.

*NIV trial*

According to our local protocol, patients' treatment was escalated to a trial of NIV if deemed indicated by the attending clinician, blinded to the study purposes and physiological measurements. The criteria to upgrade to NIV included $PaO_2/FiO_2$ ratio below 100 mmHg and/or RR > 30 bpm and/or persistence of respiratory distress and dyspnea despite HFNC set at 60 L/min. NIV was started and set by a skilled respiratory physician. Patients were connected to a conventional circuit via an appropriately sized oronasal facemask equipped with a dedicated output for probes (Bluestar$^{TM}$, KOO Medical Equipment, Shanghai, PRC) to a high-performance ventilator (GE Healthcare Engstrom

Carestation™, GE Healthcare, Finland) set in pressure support mode. A heat and moisture exchanger (HME) (Hygrobac, DAR, Mirandola, Italy) was inserted into the ventilator circuit's Y-piece. The delivered $FiO_2$ was adjusted to target a $SpO_2$ of 88–94%. None of the patients received any kind of sedation under NIV treatment. PEEP was initially set at 6 $cmH_2O$ and subsequently fine-tuned to target a peripheral oxygen saturation ($SpO_2$) >92% with a delivered inspiratory fraction of oxygen ($FiO_2$) less than 0.7. Pressure support (PS) was increased from 10 $cmH_2O$, according to tidal volume (Vte/kg of body weight predicted-PBW), to target a Vte/kg <9.5 mL/kg of PBW (16) and a RR <30 breaths/min. The inspiratory trigger and respiratory cycling were set at 3 L/min and at 25% of the inspiratory peak flow, respectively. An oronasal fitted mask was tightened to target a leak flow lower than 20 L/min. According to our local protocol, after 2 hours of NIV patients were re-assessed on a clinical and physiological basis.

*Analysis plan*

The primary aim of the study was to explore inspiratory effort and respiratory mechanics, at baseline and 2-h following NIV application, in patients with AE-IPF. Data were displayed as median and IQR (interquartile range) for continuous variables and numbers and percentages for dichotomous variables. The paired Student's *t*-test assessed the difference between variables before and after NIV application, when distributed normally; otherwise, the Wilcoxon test was used. The relationship between PEEP and relative change in $dynC_{RS}$ and $PaO_2/FiO_2$ ratio 2 hours after starting NIV was tested with the Pearson correlation coefficient and assessed through linear regression. As an exploratory analysis, we compared the mechanical variables of AE-IPF patients with an ARDS population extracted from our dataset and including patients~~,~~ studied by our group between 2016 and 2022. The ARDS comparison cohort was built using a one-to-one propensity score matching procedure with the nearest-neighbor method without replacement. The logit of the score was taken with a caliper of 0.2 in order to maximize the number of patients without comprising the match. Comparison between continuous variables was performed with Student's *t*-test distributed normally; otherwise, the Wilcoxon test was used. Dichotomous variables were compared using the $\chi^2$ test or Fisher's exact test, where appropriate. ANOVA and Kruskal-Wallis were used to test an interaction for whether the change in physiological variables 2 hours after NIV were different between groups. Statistics was performed using SPSS version 25.0 with PSMATCHING3 R Extension command (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, Ca, USA) unless otherwise indicated.

## Results

*Clinical features of study population*

**Figure 2**

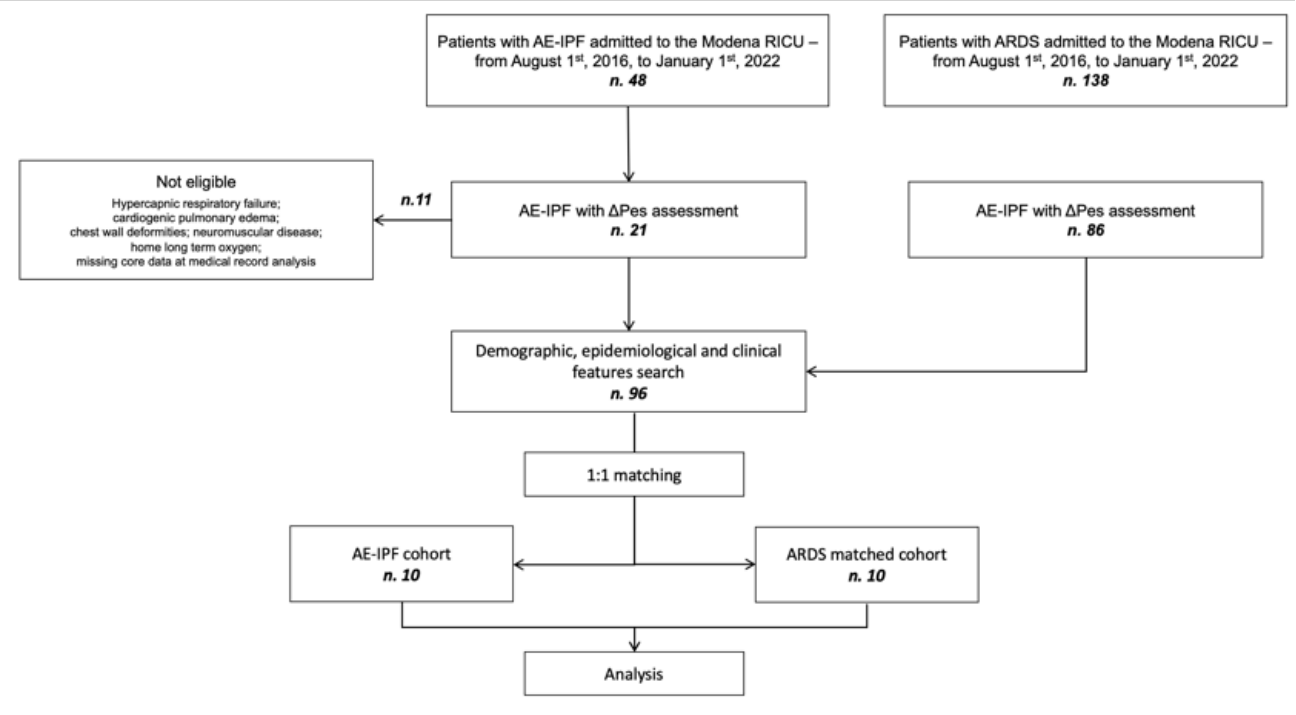



**Figure 2.** Study algorithm.

*AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; ARDS, acute respiratory distress syndrome; RICU, respiratory intensive care unit, $\Delta P_{es}$, esophageal pressure swing*

The flowchart of this study is shown in **Figure 2**. Over the study period a total of 48 patients with AE-IPF were eligible for enrollment. Of these, 10 patients were analyzed. All of them were diagnosed with IPF based on the presence of a definite UIP pattern on HRCT scan. Patients were prevalently male (7/10) with a median age of 75 years (65–78) (**Table 1**). The median value of clinical severity scores was 2 (2 – 2), 12.5 (9.8 – 21) and 30.5 (29 – 37.5) for SOFA, APACHE II and SAPS II scores respectively. The median time interval between IPF diagnosis and AE-IPF onset was 25 (15–33) months, while time lapse from hospital admission to NIV upgrade while in AE was 12 (7.5–27) hours. All patients died as inpatients.

**Table 1.**

| Parameter | AE-IPF | ARDS | p value |
|---|---|---|---|
| **Number of patients** | 10 | 10 | |
| **Age, years** | 75 (65 – 78) | 75 (65 – 78) | 0.9 |
| **Male, n** | 7 (70) | 7 (70) | 0.9 |
| **BMI, kg/m$^2$** | 23 (21 – 25) | 23 (21 – 25) | 0.9 |
| **Charlson index, score** | 3 (3 – 5) | 4 (3 – 5) | 0.9 |
| **Kelly scale, score** | 1 (1-1) | 1 (1-1) | 0.9 |
| **SOFA, score** | 2 (2 – 2) | 2 (2 – 2.5) | 0.9 |
| **APACHE, score** | 12.5 (9.8 – 21) | 11 (10 – 21) | 0.9 |
| **SAPS II, score** | 30.5 (29 – 37.5) | 33 (32 – 38) | 0.8 |
| **HACOR, score** | 7 (6 – 8) | 5.5 (5 – 6) | 0.01 |
| **†$PaO_2/FiO_2$, mmHg** | 108 (80 – 126) | 105 (83 – 125) | 0.9 |
| **†pH, value** | 7.49 (7.47 – 7.52) | 7.48 (7.44 – 7.5) | 0.9 |
| **†$PaCO_2$, mmHg** | 31 (28 – 32) | 33 (29 – 34) | 0.3 |
| **Blood lactate, mmol/L** | 1.2 (1 – 1.9) | 1 (0.9 – 1.2) | 0.1 |
| **Serum creatinine, mg/dL** | 0.9 (0.7 – 1.4) | 0.7 (0.6 – 1.4) | 0.9 |
| ***PEEP, cm$H_2O$** | 6 (5.5 – 6.5) | 7 (6 – 8) | 0.1 |
| ***PSV, cm$H_2O$** | 12 (10 – 12) | 12 (10 – 12.5) | 0.7 |

**Table 1.** General and clinical characteristics in the study groups on admission. Data are presented as number (n) and percentage for dichotomous values or median and interquartile ranges (IQR) for continuous values.
*AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; ARDS, acute respiratory distress syndrome; BMI, body mass index; HACOR, heart rate, acidosis, consciousness, oxygenation, respiratory rate; SOFA, subsequent organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; SAPS II, simplified acute physiology score II; PEEP, positive end-expiratory pressure; PSV pressure support*
** PEEP and PSV values reported were those measured during the first 2 hours of NIV.*
*† The values of $PaO_2/FiO_2$ ratio used for matching these groups as well as pH and $PCO_2$ values were those measured during high-flow nasal oxygen immediately before starting NIV.*

*Respiratory mechanics during AE-IPF*

Respiratory mechanics of IPF before and after 2 hours of NIV are showed in **Table 2**.

**Table 2.**

| Parameter | Before NIV | After 2 hours NIV | p-value |
|---|---|---|---|
| **RR, bpm** | 34 (30 – 39) | 27 (25 – 30) | 0.001 |
| **$\Delta P_{es}$, $cmH_2O$** | 27 (21 – 34) | 16 (14 – 24) | <0.0001 |
| **$\Delta P_L$, $cmH_2O$** | 27 (21 – 34) | 27 (25 – 36) | 0.2 |
| **VE, L/min** | 21 (20 – 26) | 18 (17 – 20) | 0.003 |
| **Vte, mL/kg of PBW** | 9.1 (8.7 – 10.1) | 9.3 (8.7 – 9.9) | 0.2 |
| **$DynC_{RS}$, $mL/cmH_2O$** | 28 (19 – 31) | 26 (18 – 28) | 0.1 |
| **Dynamic mechanical power*, J/min** | 71 (49 – 94) | 60 (51 – 74) | 0.1 |

**Table 2**. Physiological variables of the AE-IPF population at baseline and 2 hours apart of NIV. Data are presented as median value and interquartile range.

*$\Delta P_{es}$, esophageal pressure swing; $\Delta P_L$, dynamic transpulmonary pressure; RR, respiratory rate; VE, minute ventilation; Vte, expiratory tidal volume; $DynC_{RS}$ = dynamic respiratory system compliance; NIV, non-invasive mechanical ventilation*

**Dynamic mechanical power = 0,098 * ($\Delta P_L$ + PEEP) * Vte * RR*

During unassisted breathing, IPF patients displayed a median value of $\Delta P_{es}$ ($\Delta P_L$) of 27 (21 – 34) $cmH_2O$ and a RR of 34 bpm. $DynC_{rs}$ was 28 $mL/cmH_2O$ while dynamic mechanical power was 71 J/min. After 2 hours of NIV, $\Delta P_{es}$ was significantly reduced (16 (14 – 24) $cmH_2O$, p<0.0001). Similarly, NIV application lowered both RR and VE (27 (25 – 30), p 0.001 bpm and 18 (17 – 20) L/min, p.003, respectively) while $\Delta P_L$, Vte, $dynC_{RS}$ and dynamic mechanical power did not change significantly.

In AE-IPF patients, after two-hours of NIV, PEEP levels were significantly inversely correlated with $PaO_2/FiO_2$ ratio (r=–0.67, p=0.03, **Figure 3, panel A**). Similarly, an inverse correlation between PEEP levels and $dynC_{RS}$ variation was observed (r=-0.27, p=0.4, **Figure 3, panel B**), although statistical significance was not reached.

**Figure 3**

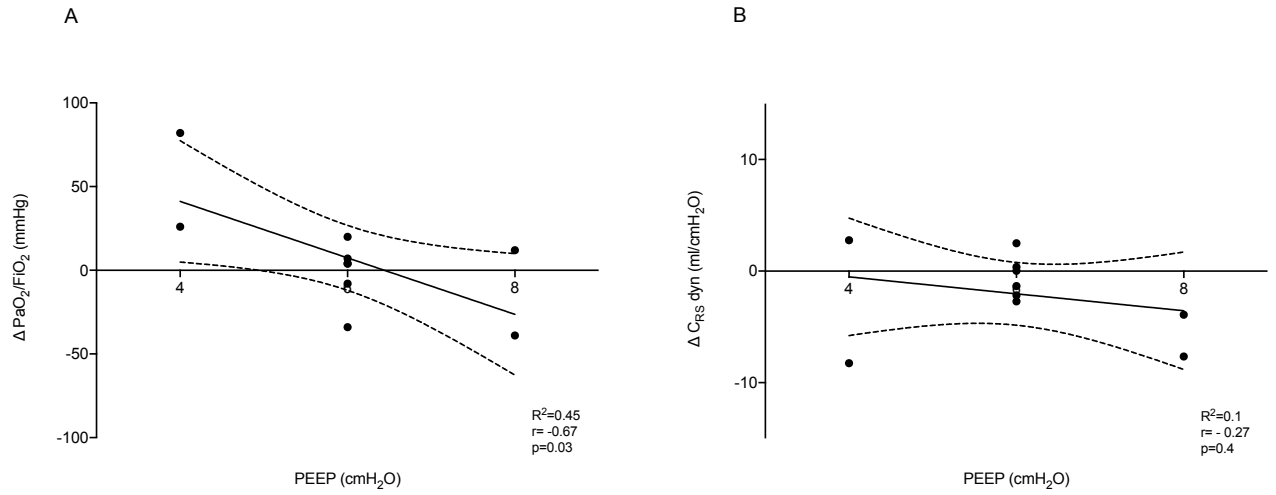



**Figure 3.** Correlation between PEEP values and change in both $PaO_2/FiO_2$ and $dynC_{RS}$ ratio in AE-IPF (panel A and B, respectively). PEEP levels were inversely correlated with both $PaO_2/FiO_2$ ratio (r=–0.67, p=0.03) and $dynC_{RS}$ (r=–0.27, p=0.4) in AE-IPF, although statistical significance was not achieved for the latter.
*AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; $dynC_{RS}$, dynamic respiratory system compliance; PEEP, positive end-expiratory pressure*

*AE-IPF as compared with ARDS*

AE-IPF and matched ARDS group were similar for clinical severity scores at inclusion and no differences were found between pressure values set during the NIV trial (**Table 1**). All ARDS patients had pulmonary ARDS occurring from lung infection (4 viral, 4 bacterial and 2 pneumocystosis).
Before starting NIV, ARDS patients showed a lower $\Delta P_{es}$ as compared to matched AE-IPF patients (24 (22 – 28) $cmH_2O$, p=0.004). Similarly, ARDS group showed a lower baseline RR (27 (26 – 30) bpm, p=0.0004), VE (18 (17 – 21) L/min, p=0.04) and dynamic mechanical power (48 (52 – 62) J/min, p=0.01). Conversely, ARDS patients showed comparable values of baseline Vte (9.9 (9.6 – 11) mL/kg of PBW, p=0.1) and baseline $dynC_{RS}$ (28 (25 – 33) mL/$cmH_2O$, p=0.3). Compared to AE-IPF, patients with ARDS still presented a lower median value of RR, $\Delta P_{es}$, $\Delta P_L$, and dynamic mechanical power 2-hours after the initiation of NIV (21 (18 – 22) bpm, p<0.0001, 9 (8 – 13) $cmH_2O$, p=0.001, 21.5 (19.5 – 25) $cmH_2O$, p=0.003, 44 (40 – 68) J/min, p=0.01). At that time point both Vte and $dynC_{RS}$ were significantly higher in ARDS as compared to AE-IPF (11.6 [11 –14.2] $cmH_2O$, p=0.001 and 41 [35 –46] mL/$cmH_2O$, p=0.001 respectively). Two-hours after starting NIV and differently from AE-IPF, ARDS patients showed a direct correlation between PEEP and $dynC_{RS}$ (r=0.65, p=0.04, **Figure 4, panel A**), while no direct association was found with $PaO_2/FiO_2$ ratio (r=0.24, p=0.5, **Figure 4, panel B**).

**Figure 4**

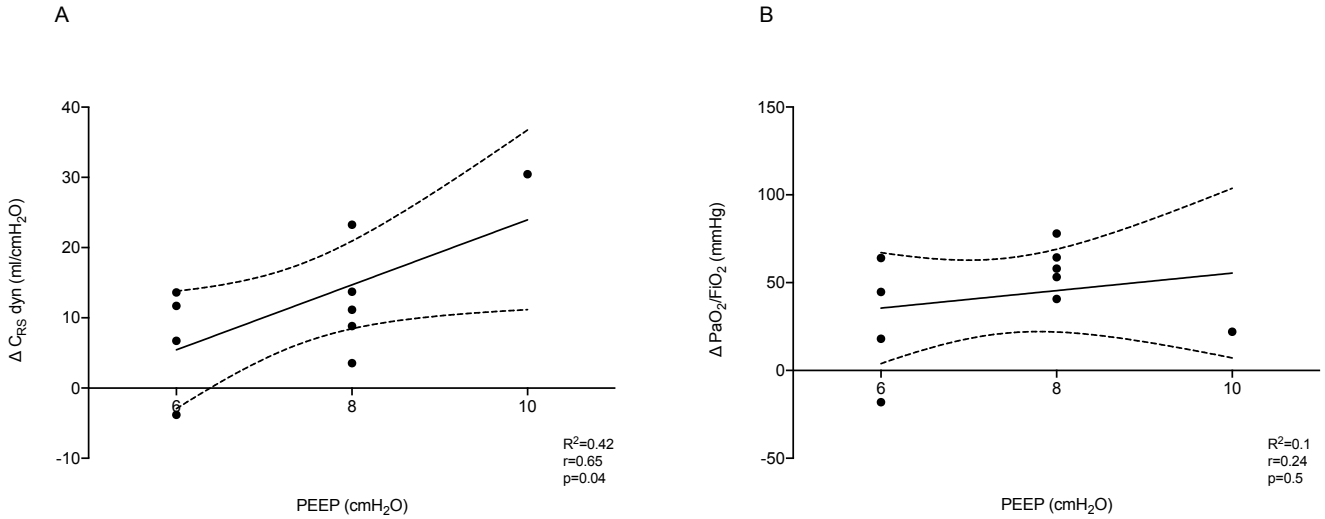
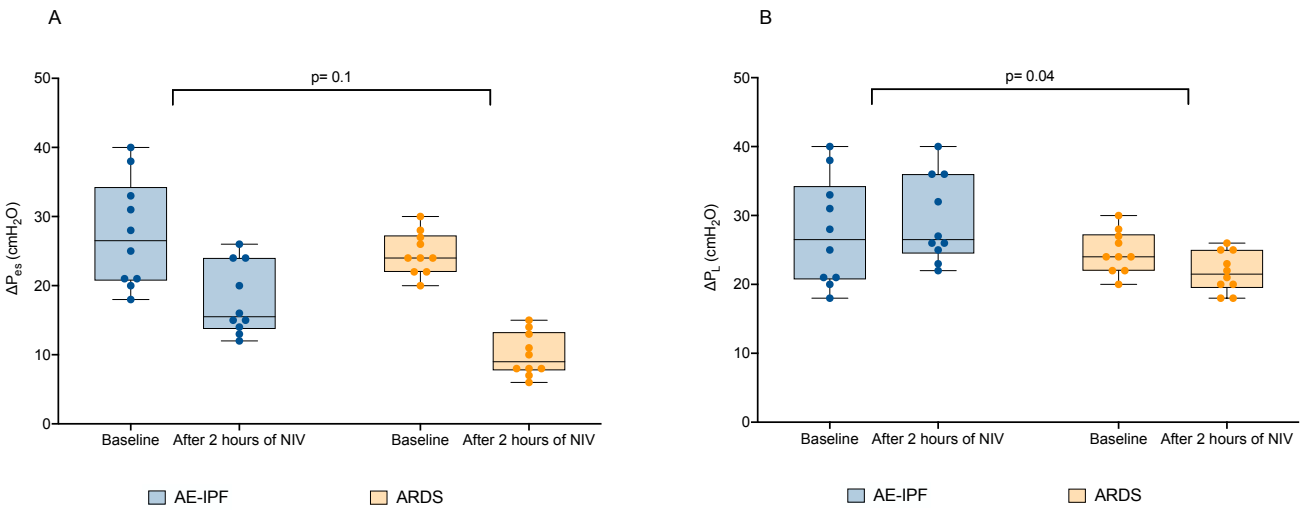


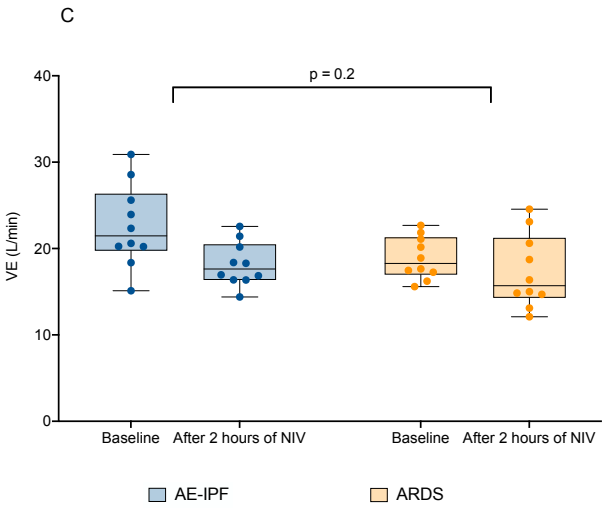

**Figure 4.** Correlation between PEEP values and change in both $dynC_{RS}$ and $PaO_2/FiO_2$ ratio in ARDS (panel A and B, respectively). PEEP levels were directly correlated with both $PaO_2/FiO_2$ ratio (r=0.24, p=0.5) and $dynC_{RS}$ (r=0.65, p=0.04), although statistical significance was found only for this latter.

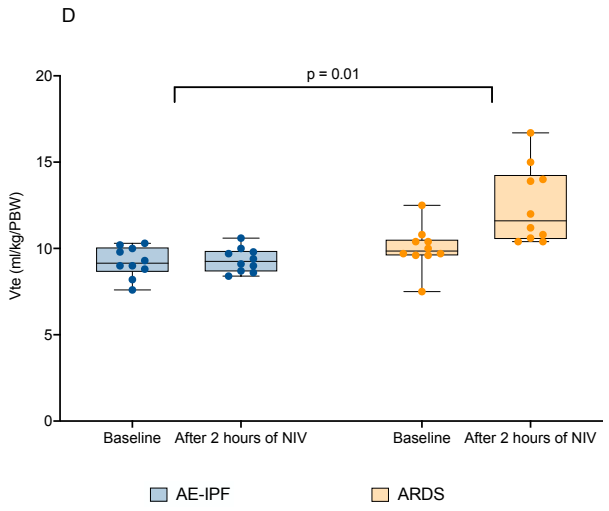
*ARDS, acute respiratory distress syndrome; $dynC_{RS}$ = dynamic respiratory system compliance; PEEP, positive end-expiratory pressure*

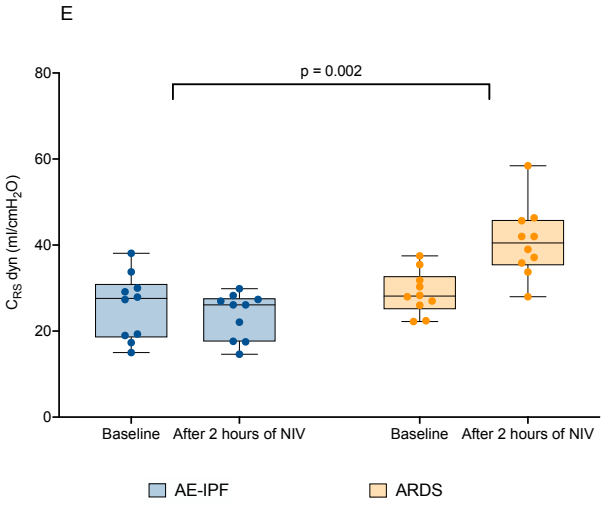
When testing whether there was a difference between groups concerning the change in physiological variables 2-hour after NIV, $\Delta P_L$ displayed an opposite response to NIV, being increased in AE-IPF and reduced in ARDS (p=0.04, **Figure 5, panel B**). Vte, and $dynC_{RS}$ increased following NIV application in the ARDS cohort as compared to AE-IPF, (p=0.01 and p=0.002 respectively, **Figure 5 panel D and E**), whereas no significant change in $\Delta P_{es}$, VE and dynamic mechanical power was found (**Figure 5, panel A, C, and F**).


A
p= 0.1
$\Delta P_{es}$ ($cmH_2O$)
50
40
30
20
10
0
Baseline
After 2 hours of NIV
Baseline
After 2 hours of NIV
AE-IPF
ARDS


B
p= 0.04
$\Delta P_L$ ($cmH_2O$)
50
40
30
20
10
0
Baseline
After 2 hours of NIV
Baseline
After 2 hours of NIV
AE-IPF
ARDS


C
p = 0.2
VE (L/min)
40
30
20
10
0
Baseline
After 2 hours of NIV
Baseline
After 2 hours of NIV
AE-IPF
ARDS


D
p = 0.01
Vte (ml/kg/PBW)
20
15
10
5
0
Baseline
After 2 hours of NIV
Baseline
After 2 hours of NIV
AE-IPF
ARDS


E
p = 0.002
$C_{RS}$ dyn (ml/$cmH_2O$)
80
60
40
20
0
Baseline
After 2 hours of NIV
Baseline
After 2 hours of NIV
AE-IPF
ARDS

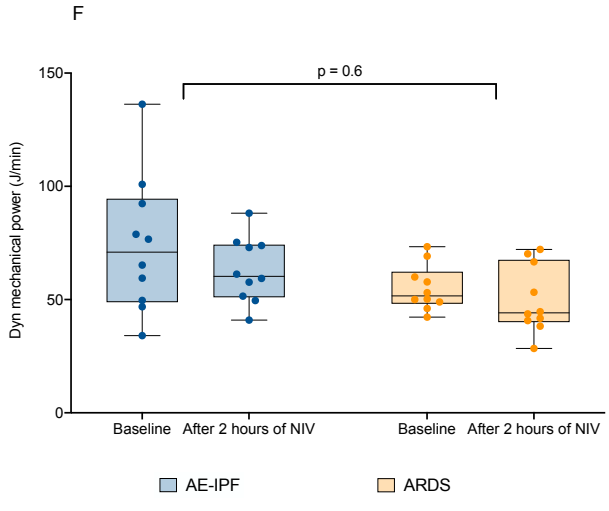

F
p = 0.6
Dyn mechanical power (J/min)
150
100
50
0
Baseline
After 2 hours of NIV
Baseline
After 2 hours of NIV
AE-IPF
ARDS

**Figure 5.** Measured individual values of $\Delta P_{es}$, $\Delta P_L$, VE, Vte, $dynC_{RS}$ and dynamic mechanical power in the matched study groups both at baseline and 2-hour after initiating NIV. When testing as an interaction for whether the change in physiological variables 2 hours after starting NIV was different between AE-IPF and ARDS, statistical difference was found for $\Delta P_L$ (panel B, p=0.04), Vte (panel D, p=0.01) and $dynC_{RS}$ (panel E, p=0.002).

*AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; ARDS, acute respiratory distress syndrome; $\Delta P_{es}$, esophageal pressure swing; $\Delta P_L$, dynamic transpulmonary pressure; VE, minute ventilation; $dynC_{RS}$ = dynamic respiratory system compliance; Vte, expiratory tidal volume; NIV, non-invasive mechanical ventilation*

**Discussion**

To our knowledge this is the first study that quantifies the inspiratory effort and explores the respiratory mechanics in patients with AE-IPF under spontaneous unassisted and noninvasive assisted breathing. Overall, when compared to ARDS, patients with AE-IPF: 1) report a peculiar increase in inspiratory effort which reflects a high activation of the respiratory drive during unassisted breathing; 2) reduce effort and respiratory frequency but not transpulmonary pressure under short-term NIV without any improvement in dynamic compliance; 3) show a detrimental effect of increased values of external PEEP to $PaO_2/FiO_2$ ratio and $dynC_{RS}$. All these issues deserve discussion.

First, keeping spontaneous breathing preserved may have several potential benefits in patients with ARF including the avoidance of sedation and/or use of myorelaxants, the prevention of muscle mass loss, the spare of diaphragmic function, and the risk reduction for delirium onset. This seems even more important in AE-IPF for whom the upgrade to invasive MV is often burdened by a high risk of VILI with unfavorable outcomes (4,5,17). However, a growing body of evidence has strengthened the hypothesis that the presence of intense respiratory effort during ARF plays a critical role in promoting SILI (10,18-20) and unfavorable ventilatory outcomes (10). In patients with IPF, specifically, the excessive inspiratory effort may be even more detrimental as fibrotic lungs are a patchwork of different tissue elasticities (7). Thus, during spontaneous breathing, pleural pressure swing distribution is even more inhomogeneous and lung tissue deformation occurs unevenly, being some lung areas subjected to harmful level of stress/strain (21). In our cohort, the baseline value of inspiratory effort of AE-IPF was 27 $cmH_2O$, as quantified by the esophageal manometry; the inspiratory effort was even higher than that reported in matched patients with ARDS. Similarly, baseline RR resulted more elevated in AE-IPF than in ARDS. Although it is difficult to give reason for the difference observed in the activation of respiratory drive, we can speculate that $dynC_{RS}$ may not be fully representative of the regional lung stretch, being the fibrotic lung subjected to anisotropic behavior during inflation (7). In line with this, we could hypothesize that the physical stimuli derived from micro-strain could act as a mechanical input in the hyperactivation of respiratory drive of AE-IPF patients (22). Furthermore, given that the baseline $dynC_{RS}$ was similar between groups, one could speculate that factors other than gas exchange impairment might have boosted the respiratory drive of IPF patients, namely lung inflammation (23).

Secondly as expected, and similarly to ARDS patients, NIV was effective in reducing both inspiratory effort and RR in AE-IPF. However, the change in respiratory mechanics was different between the two types of patients. Indeed, $dynC_{RS}$ displayed a significant improvement following NIV in ARDS but not in AE-IPF. Moreover, the values of dynamic transpulmonary pressure resulted persistently high in AE-IPF patients 2 hours following NIV application, thus suggesting a less favorable interaction with the ventilatory assistance.

Third, values of external PEEP applied by NIV were inversely correlated with $PaO_2/FiO_2$ ratio and $dynC_{RS}$ at 2-hours in AE-IPF, at difference with ARDS patients. These data suggest that the response to PEEP might reflect a different lung recruitability in AE-IPF and ARDS. Nevertheless, it was shown that a negative end-expiratory transpulmonary pressure can be reverted by incrementing PEEP values during controlled MV (7). These findings may suggest that fibrotic lungs also exhibit end-expiratory de-recruitment in the dependent lung zones during an acute exacerbation. However, PEEP titration to a positive end expiratory transpulmonary pressure seemed to worsen all the static respiratory measurements (namely driving pressure, lung compliance, end-inspiratory transpulmonary pressure). We do believe that the PEEP-induced mechanical derangement in the fibrotic lung may be explained by the "squishy ball effect": high PEEP set to keep alveolar units open during expiration hyper-inflates recruitable lung areas through the anelastic surrounding zones, thus enhancing the end-inspiratory transpulmonary pressure effect, and exposing the lung at risk of substantial injury. The dynamic mechanical response exhibited by our patients mirrors the one reported in intubated and mechanically ventilated ones, thus suggesting that the UIP-like fibrotic lung displays a "squishy ball" behavior even with PEEP applied during spontaneous breathing. In this scenario, and given the detrimental effect of PEEP on the hyper-inflation of the recruitable lung zones, a mild sedation intended to lower the RR might be suggested to lower the RR and thus allowing for prolonged expiratory time.

*Strengths and limitations*

The major strength of the study is the detailed and comprehensive measurement of respiratory effort and mechanics in a cohort of AE-IPF using a standard relatively invasive procedure (esophageal manometry). To our knowledge, these are the first data collected in this regard. Further, the standardized protocol for physiological variables collection applied at our center allows consistent measurements during esophageal manometry. Finally, the presence of a UIP pattern in all patients strengthens the homogeneity of mechanical data.

Our study also has several limits. First, the retrospective design and the reduced sample do only provide a preliminary pathophysiological insight in this condition. However, given that IPF is a rare condition, and that esophageal manometry can be extremely difficult to manage during an acute exacerbation of the disease, we are confident that these data might contribute to a better understanding of the mechanical behavior of fibrotic lung in spontaneous breathing. Second, the lack of a qualitative analysis of radiological images (namely the proportion of hyper-inflated lung tissue (24,25)) during exacerbations may weaken the interpretation of results. Third, a further comparison of AE-IPF patients under HFNC might have contributed to better specify the potential detrimental effect of NIV on the respiratory mechanics in these patients. Fourth, although the cohorts were matched according to clinical, mechanical and oxygenation criteria, the small sample size of the ARDS cohort may not reflect the heterogenous features of this population. Indeed, a more homogenous ARDS population could have improved the quality of the matching. Finally, given the retrospective nature of the study, NIV settings were decided by the attending physician, neither we did assess any specific local nor systemic biomarkers of inflammation (i.e. cytokines) that might have contributed to understand the role of disease severity on the respiratory drive.

**Conclusions**

In this physiologic, preliminary retrospective study, spontaneously breathing patients with IPF showed an elevated inspiratory effort while on acute exacerbation of the disease. The application of NIV with an external PEEP was effective in reducing their respiratory drive but at the cost of deteriorating mechanics. Additional prospective studies with a larger sample size are required to further define the local mechanical consequences and ~~even~~ the local or systemic biological features in patients with fibrotic lungs during assisted and non-assisted spontaneous breathing. More research is also needed to focus on the different mechanical behavior of AE-IPF compared with ARDS of similar severity.

**List of abbreviations**

IPF, idiopathic pulmonary fibrosis; AE-IPF, acute exacerbation of IPF; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; bpm, breaths per minute; MV, mechanical ventilation; ETI, endotracheal intubation; NIV, non-invasive mechanical ventilation; PEEP, positive end-expiratory pressure; PBW, predicted body weight; PSV, pressure support; SILI, self-inflicted lung injury; HACOR, heart rate, acidosis, consciousness, oxygenation, respiratory rate; SOFA, subsequent organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; SAPS II, simplified acute physiology score; RICU, Respiratory Intensive Care Unit; $\Delta P_{es}$, esophageal pressure swing; $\Delta P_L$, dynamic transpulmonary pressure; RR, respiratory rate; VE, minute ventilation; VILI, ventilator-induced lung injury; Vte, expiratory tidal volume; $Vte/\Delta P_L$, expiratory tidal volume/transpulmonary pressure ratio; $C_{RS}$ respiratory system compliance; $DynC_{RS}$ = dynamic respiratory system compliance; IQR, interquartile range.

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## Chapter 4

## *Respiratory mechanics in patients with lung fibrosis and usual interstitial pneumonia pattern: a preliminary matched control study*


**Abstract**

**Background**

Patients with acute exacerbation of interstitial lung disease (AE-ILD) and usual interstitial pneumonia (UIP) pattern may experience severe acute respiratory failure, even requiring ventilatory assistance. Physiological data on lung mechanics during these events are lacking.

**Methods**

Patients with AE-ILD and UIP pattern (AE-ILD-UIP) admitted to Respiratory and general Intensive Care Unit to receive invasive mechanical ventilation (MV) were retrospectively analyzed. Respiratory mechanics within 24 hours from MV start and at different PEEP levels (i.e. zero end-expiratory pressure [ZEEP], 4-8 $cmH_2O$ [LOW PEEP] and PEEP titrated according to end-expiratory transpulmonary pressure [TITRATED PEEP] were collected. An exploratory comparison with a historical independent cohort of acute respiratory distress syndrome (ARDS) patients matched 1:1 by acute physiology and chronic health evaluation, body mass index and $PaO_2/FiO_2$ level was performed.

**Results**

At ZEEP, AE-ILD-UIP patients presented elevated lung elastance ($E_L$) (44.4 [39.7 – 50.7]) $cmH_2O/L$) and end-inspiratory transpulmonary pressure ($P_{LEI}$) (16.7 [14.8 – 19]) $cmH_2O$. During the LOW PEEP phase, end-expiratory transpulmonary pressure ($P_{LEEX}$) was still below 0 (-2.6) $cmH_2O$. During the TITRATED PEEP phase $P_{LEEX}$ reached positive values in all patients (0.8 [0.3 – 1.5] $cmH_2O$) while as compared to both ZEEP and LOW PEEP phases, $E_L$ significantly worsened ($p=0.04$ and $p<0.0001$, respectively) and $P_{LEI}$ markedly increased ($p=0.003$ and $p=0.0004$, respectively). Both driving pressure ($\Delta P_{aw}$) and transpulmonary driving pressure ($\Delta P_L$) resulted significantly higher as compared to LOW PEEP phase ($p=0.01$ and $p=0.003$, respectively). When compared to AE-ILD-UIP, ARDS patients presented lower baseline $E_L$, $P_{LEI}$ and $\Delta P_L$ at each level of PEEP. Differently from ARDS, in AE-ILD-UIP $E_L$ worsened for incremental PEEP values while $P_{LEI}$ experienced a steeper increase.

**Conclusions**

In this study, the lung of patients with AE-ILD-UIP resulted recruitable when PEEP was increased, despite a significant worsening in lung mechanics. AE-ILD-UIP patients showed a different mechanical behavior during MV and in response to PEEP compared with ARDS patients of similar severity.

**Introduction**

Interstitial lung diseases (ILDs) represent an umbrella term that includes heterogeneous clinical conditions characterized by the different mixture of inflammation and fibrosis within the lungs (1,2). Some patients suffering from ILD experience acute exacerbations (AE-ILD) in the course of the disease, a condition defined as acute respiratory deterioration (worsening or development of dyspnea) associated with new bilateral ground-glass opacites and/or consolidations at high resolution computed tomography (CT) scan (3). Patho-physiologically, AE-ILD resembles an acute respiratory distress syndrome (ARDS), since it mainly consists of diffuse alveolar damage (DAD) superimposed on a background of fibrosing ILD with the development of acute respiratory failure that usually requires respiratory support (4). However, morbidity and mortality associated with AE-ILD undergoing mechanical ventilation (MV) is very high as compared to ARDS, and retrospective studies suggest that the in-hospital mortality rate of patients with AE-ILD underwent to MV can exceed 80% (5-7). This scenario is even more critical when the fibrotic changes take shape of the usual interstitial pneumonia pattern (UIP) characterized by a patchy lung involvement with spared parenchymal areas surrounded by dense anelastic tissue, interstitial thickening, cystic abnormalities and traction bronchiectasis (8).

While protective MV strategies have contributed to significant improvements in ARDS mortality mitigating the risk of ventilator induced lung injury (VILI), specific evidence concerning MV setting in AE-ILD are lacking. PEEP titration guided by esophageal pressure ($P_{es}$) was proposed to reduce atelectrauma combined with protective lung ventilation strategy ($V_T$ typically 4-6 mL/Kg based on predicted body weight [PBW], plateau pressure ($P_{plat}$) kept below 30 cm $H_2O$) in patients suffering from ARDS (9). Despite there is no agreement to determine the ideal PEEP, and mortality benefit of this strategy remains doubtful, maintaining some amount of PEEP is considered essential in ARDS management (10-13). Esophageal manometry to guide PEEP titration, through transpulmonary pressure ($P_L$) estimation, assumes that negative end-expiratory $P_L$ ($P_{LEEX}$) values predispose to small airways closure during tidal ventilation, resulting in high local shear forces that enhance lung damage (11).

Fibrotic changes of lung parenchyma, due to excessive extracellular matrix (ECM) deposition within the lung, is a key feature of different ILD, but can also be reported as a sequela to persistent lung damage after ARDS or viral infections such as Middle East Respiratory Syndrome (MERS), influenza virus (H1N1 and H5N1) and severe acute respiratory syndrome (SARS-CoV, and SARS-CoV-2) (14). Some retrospective data suggests that the peculiar mechanical changes associated with fibrotic lung

and superimposed DAD make lung tissue more susceptible to physical stress and static strain during MV, raising the risk of VILI (8). Given that pulmonary fibrosis may be the trajectory towards which a wide variety of clinical conditions (e.g. ARDS) are directed, understanding the peculiar physiological changes occurring in the fibrotic lung while on MV, could help critical care physicians to tailor MV to avoid excessive stress-strain on lung parenchyma. Previous physiological observations compared fibrotic lung behavior to that shown in stress ball called “squishy ball”, suggesting the key role of static strain in generating VILI (15). The purpose of this study was to explore the mechanical behavior of the fibrotic lung with UIP pattern while on AE, once subjected to MV and PEEP titration based on $P_{LEEX}$. Further, we aimed at comparing the mechanical response of AE-ILD-UIP lungs with that of pulmonary ARDS during MV.

## Materials and methods

*Study setting and design*

This was a retrospective analysis of prospectively collected data. The study was carried out at the Respiratory Intensive Care Unit (RICU) and the Intensive Care Unit (ICU) of the University Hospital of Modena (Italy) and conducted in accordance with the Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 327/2022). The study has been registered on ClinicalTrial.gov (ID NCT05098717). Informed consent to participate in the study and to allow their clinical data to be analyzed and published were obtained from participants, as appropriate.

*Study population*

Patients with ILD and UIP pattern developing AHRF due to acute exacerbation of disease and consecutively admitted to the RICU and to the ICU of the University Hospital of Modena over the period August 1$^{st}$, 2016 to July 1$^{th}$, 2022 were considered eligible for enrollment.

Inclusion criteria were as follows: age >18 years; previously established diagnosis of ILD with a UIP pattern on a high-resolution computed tomography (HRCT) scan; onset of esophageal manometry; ETI and onset of MV in volume-controlled mode with PEEP titration according to $P_{Leex}$.

Patients were excluded if they presented any of the followings: chronic obstructive pulmonary disease of any etiology; neuromuscular disease; chest wall deformities; missing core data (i.e. data on respiratory mechanics) at medical record analysis.

AE-ILD-UIP population was then matched 1:1 by body mass index (BMI), $PaO_2/FIO_2$ and acute physiology and chronic health evaluation (APACHE) II score, to a group of patients with pulmonary ARDS with esophageal manometry and under MV with PEEP titrated according to $P_{LEEX}$ extracted from our dataset and treated between 2016 and 2022. All patients underwent a common and standardized intervention (including respiratory mechanics assessment), and data were collected using a standard collection protocol. The values of APACHE II and $PaO_2/FIO_2$ used for matching these groups were those measured at the time of RICU or ICU admission.

*Data collection*

Medical reports, electronical charts and available clinical and physiological datasets were investigated to collect data on demographics, clinical characteristics, arterial blood gases, $PaO_2/FiO_2$

ratio, clinical severity (as assessed by the APACHE II score on RICU and ICU admission), respiratory mechanics during MV.

***Respiratory mechanics assessment***

According to our local protocol, sedation was achieved with a midazolam-propofol-remifentanil infusion to obtain a bispectral index between 40 and 60. Patients received cisatracurium to obtain myorelaxation. All subjects were placed in a 30° head up position.

In all patients, a multifunctional nasogastric tube equipped with an esophageal balloon was placed (NutriVent$^{TM}$, nasogastric polyfunctional catheter; SIDAM, Mirandola, Italy), which was subsequently connected to a pressure transducer (OptiVent$^{TM}$ monitor; SIDAM, Mirandola, Italy) to allow the assessment of $P_{es}$ and the measurement of respiratory mechanics. The correct position of the esophageal catheter was confirmed by an end-expiratory occlusion test and with thoracic radiography (16). On admission, patients were ventilated with a Vt of 6 ml/kg of predicted body weight (PBW). The PBW of male patients was calculated as 50+0.91×(centimeters of height–152.4) and that of female patients as 45.5+0.91×(centimeters of height−152.4) (17). PEEP was initially set between 5–8 $cmH_2O$.

According to our local protocol, respiratory mechanics were further assessed in supine position within 24 hours from admission in three consecutive phases at different pressure levels.

a) In the first phase (ZEEP phase), measurements of static respiratory mechanics were performed a zero end-expiratory pressure (ZEEP phase).
b) In the second phase (LOW PEEP phase), static respiratory mechanics were assessed with PEEP set between 4 and 8 $cmH_2O$.
c) In the third phase (PEEP TITRATED phase), PEEP was titrated in order to achieve a $P_{Leex}$ of 0 to 10 $cmH_2O$ (18).

At each phase, PEEP level was maintained for 30 min before recording all respiratory parameters and blood withdrawal for blood gas analysis. Respiratory mechanics were performed using the end-inspiratory occlusion technique during constant flow inflation and the end-expiratory occlusion method (19).

***Computation of respiratory mechanics***

All measurements of static respiratory mechanics were performed after 30 minutes of constant flow MV. The value of pressure was obtained during baseline ventilation with an airway occlusion at the

end of expiration pressing the end-expiratory hold, until reaching a plateau pressure, and successively performing a similar procedure with an end-inspiratory occlusion. During the procedure, occlusions that did not produce a clean plateau were discarded (i.e., measures in which the airway pressure is not flat and has oscillations greater than 2-3 $cmH_2O$).
Static respiratory mechanics variables were computed as follows:

a) End-inspiratory transpulmonary pressure = End-inspiratory plateau pressure – End-inspiratory esophageal pressure

   $P_{LEI} = P_{plat} - P_{esEI}$

b) End-expiratory transpulmonary pressure = Total end-expiratory airway pressure – End-expiratory esophageal pressure

   $P_{LEEx} = PEEP_{tot} - P_{esEEx}$

c) Driving pressure = End-inspiratory plateau pressure – total end-expiratory airway pressure

   $\Delta P_{aw} = P_{plat} – PEEP_{tot}$

d) Tidal variation in esophageal pressure = End-inspiratory esophageal pressure – end-expiratory esophageal pressure

   $\Delta P_{es} = P_{esEI} – P_{esEEx}$

e) Transpulmonary driving pressure = Airway driving pressure – tidal variation in esophageal pressure

   $\Delta P_L = \Delta P_{aw} – \Delta P_{es}$

f) Respiratory system elastance = Airway driving pressure/tidal volume

   $E_{tot} = \Delta P_{aw}/Vt$

g) Chest wall elastance = Tidal variation in esophageal pressure/tidal volume

   $E_{cw} = \Delta P_{es}/Vt$

h) Lung elastance = Transpulmonary driving pressure/tidal volume

$E_L = \Delta P_L / Vt$

***Analysis plan***

The primary aim of the study was to explore the respiratory mechanics under MV at different PEEP levels in patients with AE-ILD-UIP. Data were displayed as median and IQR (interquartile range) for continuous variables and numbers and percentages for dichotomous variables. The paired Student's *t*-test assessed the difference between variables at different levels of PEEP, when distributed normally; otherwise, the Wilcoxon test was used. ANOVA and Kruskal-Wallis were used to test an interaction for whether the change in respiratory mechanics and physiological variables according to PEEP levels were different between groups.

As an exploratory analysis, we compared the mechanical variables of AE-IPF patients with an ARDS population extracted from our dataset and including patients~~,~~ studied by our group between 2016 and 2022. The ARDS comparison cohort was built using a one-to-one propensity score matching procedure with the nearest-neighbor method without replacement. The logit of the score was taken with a caliper of 0.2 in order to maximize the number of patients without comprising the match. Comparison between continuous variables was performed with Student's *t*-test distributed normally; otherwise, the Wilcoxon test was used. Dichotomous variables were compared using the $\chi^2$ test or Fisher's exact test, where appropriate. Statistics was performed using SPSS version 25.0 with PSMATCHING3 R Extension command (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, Ca, USA) unless otherwise indicated.

## Results

*Clinical features of study population*

**Figure 1**

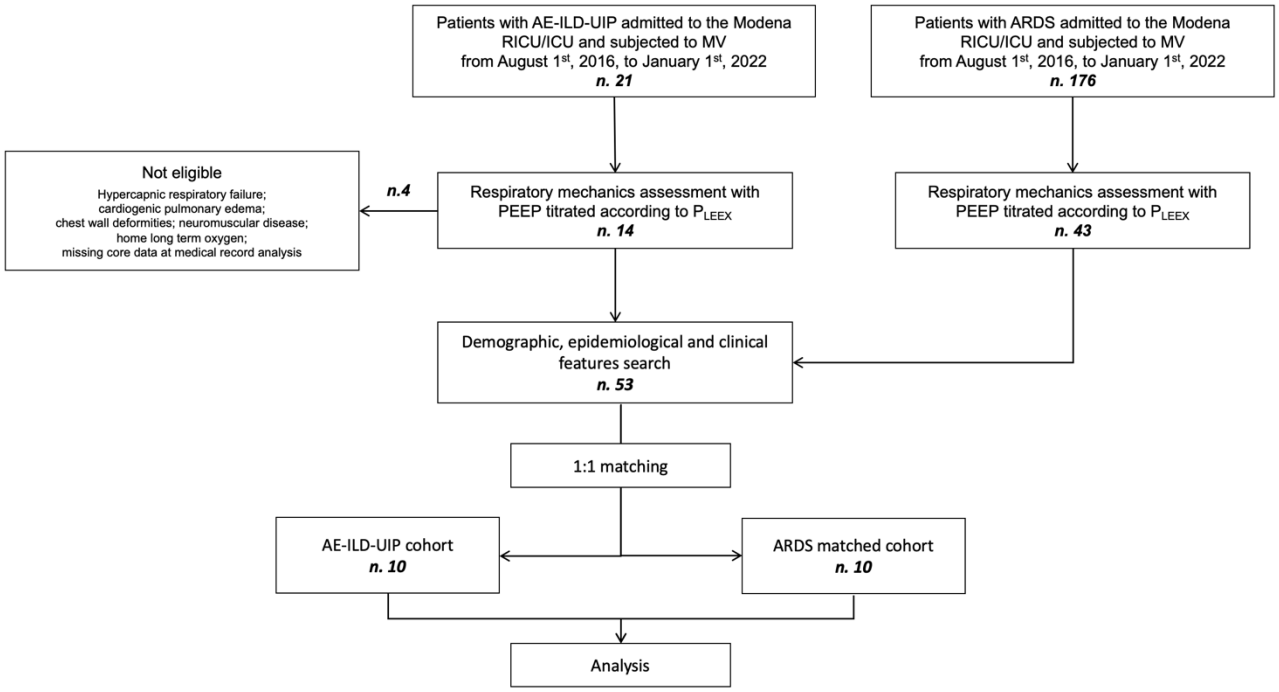


**Figure 1.** Study algorithm.

*AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome; RICU, Respiratory Intensive Care Unit; ICU, Intensive Care Unit; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; $P_{LEEX}$, transpulmonary end-expiratory pressure*

The flowchart of this study is shown in **Figure 1**. Over the study period a total of 21 patients with AE-ILD-UIP resulted eligible for enrollment. Of these, 10 patients were analyzed according to inclusion criteria. All of them were diagnosed with the presence of a definite UIP pattern on HRCT scan. Patients were prevalently male (n=8) with a median age of 67 years (63–69) (**Table 1**). Most of them (n=5) had idiopathic pulmonary fibrosis (IPF). Among the others, 2 were diagnosed with rheumatoid arthritis associated ILD, 2 had chronic hypersensitivity pneumonitis and one presented an undetermined ILD. All patients died as inpatients while on MV.

**Table 1**

| Parameter | All (n=20) | AE-ILD-UIP (n=10) | ARDS (n=10) | p value |
|---|---|---|---|---|
| **Age, years** | 68 (63.5 – 71.8) | 66.5 (63 – 68.9) | 69.5 (65 – 74) | 0.6 |
| **Male, n** | 15 (75) | 8 (80) | 7 (70) | 0.9 |
| **BMI, kg/m$^2$** | 22.8 (21.3 – 24.2) | 23.7 (21.7 – 25) | 22.3 (20.8 – 23.4) | 0.7 |
| **Charlson index, score** | 3 (3 – 5) | 3 (3 – 5) | 4 (3 – 5) | 0.9 |
| **APACHE, score** | 13.5 (12.8 – 15) | 13.5 (12.3 – 14) | 13.5 (13 – 15) | 0.7 |
| **SAPS II, score** | 31.5 (27 – 36) | 31.5 (27 – 34.5) | 32 (27 – 37.5) | 0.5 |
| **†$PaO_2/FiO_2$, mmHg** | 96.5 (88.8 – 125.8) | 95.5 (90.5 – 122.5) | 98.5 (88.3 – 126) | 0.9 |
| **RICU/ICU death, n** | 14 (70) | 10 (100) | 4 (40) | 0.02 |

**Table 1.** General and clinical characteristics in the study groups on admission. Data are presented as number (n) and percentage for dichotomous values or median and IQR for continuous values.

† The values of APACHE score and $PaO_2/FiO_2$ ratio used for matching these groups were those measured at the time of RICU or ICU admission

*AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS II; Simplified Acute Physiology Score; RICU, respiratory intensive care unit; ICU, intensive care unit; IQR, interquartile range*

*Respiratory mechanics of AE-ILD-UIP*

Respiratory mechanics of AE-ILD-UIP at different PEEP levels are showed in **Table 2** while **Figures 2** and **3** illustrate changes according to incremental PEEP values.

At ZEEP, the median $E_L$ resulted 44.4 $cmH_2O/L$, $\Delta P_L$ was 21.1 $cmH_2O$, $P_{LEEX}$ was -4.3 $cmH_2O$ while $P_{LEI}$ was 16.7 [14.8 – 19]) $cmH_2O$. During the LOW PEEP phase (median PEEP value = 4 [4 – 4] $cmH_2O$), $P_{LEEX}$ remained below 0 (-2.6 [-4.3 – -1.2]) $cmH_2O$, median $E_L$ was still above 40 $cmH_2O/L$ and $P_{LEI}$ was 15.3 $cmH_2O$ while $\Delta P_L$ significantly decreased from baseline (from 21.1 $cmH_2O$ to 18.4 $cmH_2O$, p=0.02, **Figure 3, panel G**). During the TITRATED PEEP phase (median PEEP value = 12 [10 – 14] $cmH_2O$), $P_{LEEX}$ reached positive values for all patients (0.8 [0.3 – 1.5]) while $E_L$ significantly worsened as compared to both ZEEP and LOW PEEP phases (p=0.04 and p<0.0001, respectively, **Figure 2, panel A**). Similarly, $P_{LEI}$ markedly increased as compared to both ZEEP and LOW PEEP phases (p=0.003 and

p=0.0004, respectively, **Figure 3, panel A**). Both $\Delta P_{aw}$ and $\Delta P_L$ resulted significantly higher as compared to LOW PEEP phase (p=0.01 and p=0.003, respectively, **Figure 3 panel E and G**)

**Table 2**

| Variable | AE-ILD-UIP | ARDS | p-value |
|---|---|---|---|
| ***ZEEP phase*** | | | |
| $E_L$, $cmH_2O/L$ | 44.4 (39.7 – 50.7) | 17.9 (9.9 – 23.3) | <0.0001 |
| $E_{cw}$, $cmH_2O/L$ | 3.2 (2.5 – 5.7) | 5.4 (4 – 7.4) | 0.12 |
| $E_{tot}$, $cmH_2O/L$ | 49 (43.9 – 54.7) | 22 (16.8 – 28) | <0.0001 |
| $P_{LEI}$, $cmH_2O$ | 16.7 (14.8 – 19) | 4.4 (2.9 – 6.3) | <0.0001 |
| $P_{LEEX}$, $cmH_2O$ | -4.3 (-7.6 – -2.3) | -4.1 (-7.6 – -2.9) | 0.66 |
| $\Delta P_{aw}$, $cmH_2O$ | 16.8 (13.8 – 19.3) | 14.4 (11.5 – 21.2) | 0.56 |
| $\Delta P_L$, $cmH_2O$ | 21.1 (17.8 – 23.6) | 9.3 (7 – 11.5) | <0.0001 |
| ***LOW PEEP phase*** | | | |
| $E_L$, $cmH_2O/L$ | 43.3 (36.8 – 53) | 14.6 (12.2 – 19.1) | <0.0001 |
| $E_{cw}$, $cmH_2O/L$ | 3.4 (2.3 – 5.6) | 5.7 (4.3 – 8.3) | 0.09 |
| $E_{tot}$, $cmH_2O/L$ | 48.5 (40 – 56.8) | 22.1 (19.1 – 25.2) | <0.0001 |
| $P_{LEI}$, $cmH_2O$ | 15.3 (11.3 – 18.7) | 10.5 (5 – 14) | 0.01 |
| $P_{LEEX}$, $cmH_2O$ | -2.6 (-4.3 – -1.2) | -2.5 (-4.6 – -0.5) | 0.75 |
| $\Delta P_{aw}$, $cmH_2O$ | 16.8 (14.3 – 18.6) | 15.1 (11.9 – 21.4) | 0.9 |
| $\Delta P_L$, $cmH_2O$ | 18.4 (15.6 – 21.8) | 12.3 (8.5 – 16.6) | 0.02 |
| PEEP, $cmH_2O$ | 4 (4 – 4) | 4 (4 – 5) | 0.2 |
| ***TITRATED PEEP phase*** | | | |
| $E_L$, $cmH_2O/L$ | 48.8 (59 – 42.8) | 15.2 (12.4 – 19.7) | <0.0001 |
| $E_{cw}$, $cmH_2O/L$ | 3.7 (3.2 – 5.9) | 5.7 (4.7 – 7.2) | 0.1 |
| $E_{tot}$, $cmH_2O/L$ | 55.3 (45.9 – 62.5) | 20.6 (19 – 24.5) | <0.0001 |
| $P_{LEI}$, $cmH_2O$ | 23.3 (21.3 – 26.7) | 16.9 (13.5 – 19.2) | 0.001 |
| $P_{LEEX}$, $cmH_2O$ | 0.8 (0.3 – 1.5) | 2.4 (0.6 – 4.9) | 0.04 |
| $\Delta P_{aw}$, $cmH_2O$ | 19.1 (16.1 – 21.6) | 15.3 (9.4 – 17) | 0.01 |
| $\Delta P_L$, $cmH_2O$ | 22.6 (20.8 – 25.8) | 13.9 (6.6 – 16.5) | 0.0001 |
| PEEP, $cmH_2O$ | 12 (10 – 14) | 14 (12 – 17.5) | 0.03 |

**Table 2.** Respiratory mechanics of the AE-ILD-UIP and the ARDS population at different PEEP levels. Data are presented as median value and IQR.

*AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome; IQR, interquartile range;* $\Delta P_L$, transpulmonary driving pressure; $P_{LEI}$, end-inspiratory transpulmonary pressure; $P_{LEEX}$, end-expiratory transpulmonary pressure; $P_{aw}$, driving pressure; $E_{tot}$, respiratory system elastance; $E_{cw}$, chest wall elastance; $E_L$, lung elastance; *PEEP, positive end-expiratory pressure*

**Figure 2**

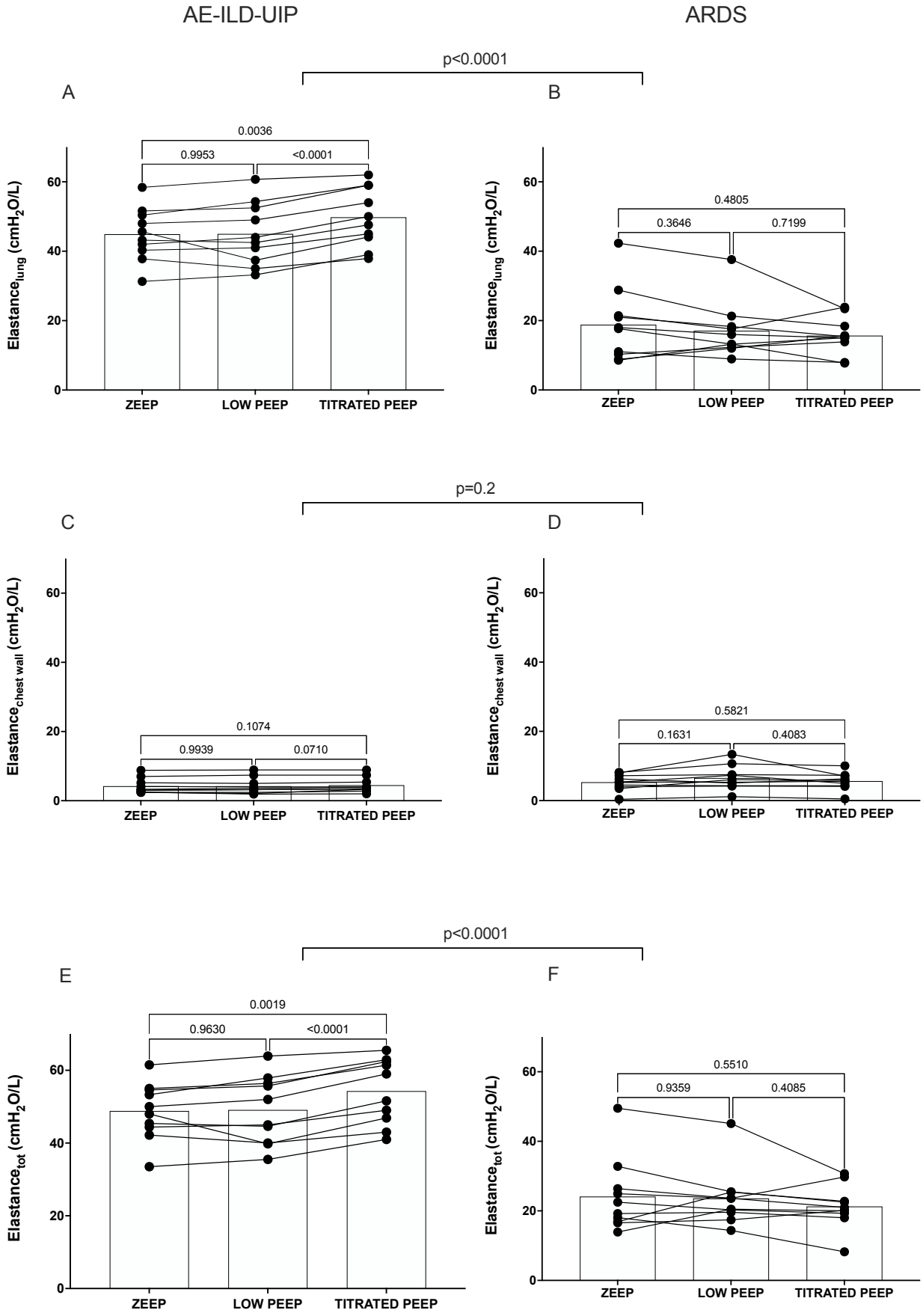
AE-ILD-UIP
ARDS
p<0.0001
A
B
0.0036
0.9953
<0.0001
0.4805
0.3646
0.7199
Elastance$_{lung}$ (cmH$_2$O/L)
ZEEP
LOW PEEP
TITRATED PEEP
p=0.2
C
D
0.1074
0.9939
0.0710
0.5821
0.1631
0.4083
Elastance$_{chest\ wall}$ (cmH$_2$O/L)
p<0.0001
E
F
0.0019
0.9630
<0.0001
0.5510
0.9359
0.4085
Elastance$_{tot}$ (cmH$_2$O/L)

**Figure 2.** Measured individual values of $E_L$, $E_{tot}$ and $E_{cw}$ in the matched study groups at ZEEP, LOW PEEP and TITRATED PEEP phase. When testing as an interaction for whether the change in physiological variables at different PEEP levels was different between AE-ILD-UIP and ARDS, statistical difference was found for $E_L$ (**panel A and B**, p<0.0001) and $E_{tot}$ (**panel E and F**, <0.0001)

*$E_L$, lung elastance; $E_{tot}$, respiratory system elastance; $E_{cw}$, chest wall elastance; ZEEP, zero positive end-expiratory pressure; PEEP, positive end-expiratory pressure; AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome*

<u>*AE-ILD-UIP as compared with ARDS*</u>

AE-ILD-UIP and matched ARDS groups were similar for clinical severity scores (APACHE and SAPS II, **Table 1**) at inclusion. Further, no group differences were found between pressure values set during the LOW PEEP phase (**Table 2**), while PEEP values needed to achieve positive $P_{LEEX}$ resulted higher in the ARDS group. All ARDS patients presented a pulmonary ARDS occurring from lung infection (6 viral, 1 bacterial and 3 pneumocystosis).

At ZEEP phase, ARDS patients showed a lower $E_L$ as compared to matched AE-ILD-UIP patients (17.9 [9.9 – 23.3] $cmH_2O/L$, p=<.0001, **Table 2**). Similarly, ARDS group showed a lower baseline $P_{LEI}$ (4.4 [2.9 – 6.3] $cmH_2O$, p<0.0001) and $\Delta P_L$ (9.3 [7 – 11.5] $cmH_2O$, p<0.0001) (see **Table 2**). Conversely, ARDS patients showed comparable values of baseline $\Delta P_{aw}$ (14.4 [11.5 – 21.2], p=0.6) and $P_{LEEX}$ (-4.1 [-7.6 – -2.9], p=0.7) (see **Table 2**).

During the LOW PEEP and the TITRATED PEEP phases, ARDS patients still showed better $E_L$ (14.6 $cmH_2O/L$, p<0.0001 and 15.2 $cmH_2O/L$, p<0.0001 respectively) and lower $P_{LEI}$ (10.5 $cmH_2O$, p<0.0001 and 16.9 $cmH_2O$, p=0.001 respectively) and $\Delta P_L$ (12.3 $cmH_2O$, p=0.02 and 13.9 $cmH_2O$, p=0.0001 respectively) as compared to AE-ILD-UIP (**see Table 2**).

When testing whether there was a difference between groups concerning the change in physiological variables according to PEEP levels, $E_L$ displayed a different response to PEEP, being worsened in AE-ILD-UIP and unchanged in ARDS (p<0.0001, **Figure 2, panel A and B**). Similarly the two groups resulted different regarding the $P_{LEI}$ changes at PEEP variation (p<0.0001, **Figure 3, panel A and B**). Of note, no significant difference between groups was found in the response of $P_{LEEX}$ to incremental PEEP (**Figure 3, panel C and D**).

**Figure 3**

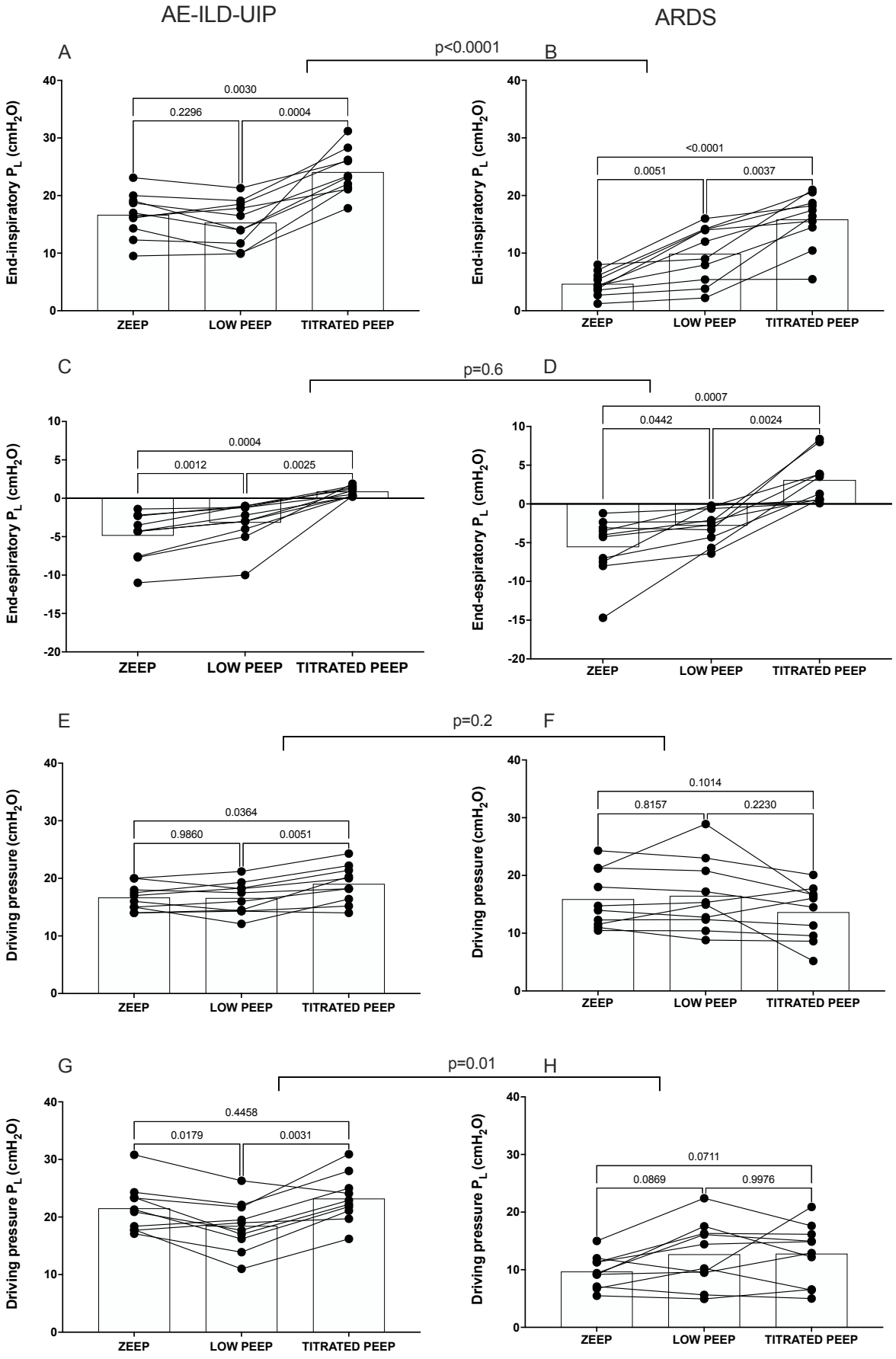
AE-ILD-UIP
ARDS
A
B
p<0.0001
0.0030
0.2296
0.0004
<0.0001
0.0051
0.0037
End-inspiratory $P_L$ ($cmH_2O$)
ZEEP
LOW PEEP
TITRATED PEEP
C
D
p=0.6
0.0004
0.0012
0.0025
0.0007
0.0442
0.0024
End-espiratory $P_L$ ($cmH_2O$)
E
F
p=0.2
0.0364
0.9860
0.0051
0.1014
0.8157
0.2230
Driving pressure ($cmH_2O$)
G
H
p=0.01
0.4458
0.0179
0.0031
0.0711
0.0869
0.9976
Driving pressure $P_L$ ($cmH_2O$)

**Figure 3.** Measured individual values of $P_{LEI}$, $P_{LEEX}$, $P_{aw}$, and $\Delta P_L$ in the matched study groups at ZEEP, LOW PEEP and TITRATED PEEP phase. When testing as an interaction for whether the change in physiological variables at incremental PEEP value was different between AE-ILD-UIP and ARDS, statistical difference was found for $P_{LEI}$ (**panel A and B**, p<0.0001) and $\Delta P_L$ (**panel G and H**, p=0.01) while no difference were reported for $P_{LEEX}$ (**panel C and D**, p=0.6) and $P_{aw}$ (**panel E and F**, p=0.2).

*$P_{LEI}$, end-inspiratory transpulmonary pressure; $P_{LEEX}$, end-expiratory transpulmonary pressure; $P_{aw}$, driving pressure; $\Delta P_L$, transpulmonary driving pressure; ZEEP, zero positive end-expiratory pressure; PEEP, positive end-expiratory pressure; AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome*

**Discussion**

In this matched cohort study we showed that: 1) mechanically ventilated AE-ILD-UIP patients at ZEEP showed both elevated $E_L$ and $P_{LEI}$ and negative values of $P_{LEEX}$; 2) although $P_{es}$ guided PEEP strategy allowed positive values of $P_{LEEX}$, a significant mechanical disadvantage was reported; 3) when compared to AE-ILD-UIP, ARDS patients presented lower baseline $E_L$, $P_{LEI}$ and $\Delta P_L$ at each PEEP level; 4) differently from ARDS, in AE-ILD-UIP, $E_L$ worsened for incremental PEEP values while $P_{LEI}$ experienced a greater increase. To our knowledge this is the first study on the mechanical behavior of the lung with UIP pattern when subjected to MV and $P_{LEEX}$ guided PEEP titration. Nava et al. solely assessed the respiratory mechanics during MV in seven patients affected by end stage IPF (20). The authors reported abnormal value of static lung elastance (46.1 $cmH_2O/L$) at ZEEP, similar to what found in our heterogenous population of patients with AE-ILD-UIP. However, all patients were studied at ZEEP and no assessment of changes in respiratory mechanics at different PEEP levels was performed. While appropriate PEEP titration within the protective ventilation approach is one of the key strategies proposed for the management of patients with acute lung injury under MV, the knowledge of the response of the fibrotic lung to incremental PEEP seems critical to prevent further lung damage. (21,22). In patients suffering from ARDS, $P_{es}$ guided PEEP titration may prevent repetitive opening and closing of recruitable alveolar units, thus improving the lung mechanical properties (23). Notwithstanding, in the EPVent-2 trial, $P_{es}$-guided PEEP to maintain $P_{LEEX}$ between 0 to 6 $cmH_2O$, compared with empirical high PEEP-$FiO_2$, resulted in no significant difference in a composite outcome that incorporated death and days free from MV in patients with moderate to severe ARDS (12). However, esophageal manometry as a surrogate of pleural pressure, remains a valid method for the assessment of the mechanical behavior of the lung during MV allowing to distinguish lung from chest wall mechanics; further, when used to titrate PEEP, it usually results in an improvement in oxygenation and lung compliance in moderate to severe ARDS (13). However, the beneficial effect of PEEP application on atelectrauma has to deal with the lung injury caused by overdistension of the lung areas spared from alveolar damage (24). Thus, the complex relationship between alveolar recruitment/alveolar overdistension after PEEP application, is affected by the heterogeneous mechanical features of injured lungs. Indeed, there is considerable variation in the amount of recruitable lung tissue in patients with ARDS, which results in a variable response to incremental PEEP (25). In this unpredictable scenario, a certain amount of PEEP is recommended in all patients with ARDS, while high PEEP may be applied in moderate-severe ARDS where the benefit

provided by recruitment may exceed the risk of clinically meaningful injury from overdistension. Patients suffering from AE-ILD-UIP exhibit a clinical syndrome comparable to ARDS, however fibrotic lungs affected by diffuse alveolar damage showed greater elastic complexity than lungs with ARDS, thus mechanical changes due to PEEP application could predispose the lung to excessive local overdistension (26). The histopathologic UIP pattern is characterized by a patchy pattern of interstitial fibrosis with sharp demarcations between areas of normal and abnormal lung, and by a temporal heterogeneity among the damaged areas, as shown by the mixture of old and new fibrosis randomly identified in biopsy specimens. Therefore, fibrotic lung should be considered as an elastic patchy framework which, once subjected to mechanical stimuli as in the course of MV, responds with a complex anisotropic behavior.

The first mechanical feature highlighted by our study is that as in ARDS, lungs with AE-ILD-UIP showed negative values of $P_{LEEX.}$ This physiological behavior suggest that also fibrotic lung affected by DAD is subject to cyclic closure and reopening of small airways during MV, at least in some parts of the lungs. Furthermore, $P_{es}$ guided PEEP titration may prevent end-expiratory alveolar collapse. However, unlike ARDS, $P_{es}$ guided PEEP titration results in a significant mechanical disadvantage, as demonstrated by the worsening of $E_L$ and $P_{LEI}$. Thus, our study suggests that in patients suffering from AE-ILD-UIP the complex relationship between alveolar recruitment/alveolar overdistension after PEEP application, may results in a lung injury from overdistension, which invalidates the potential lung-protective benefit from PEEP. A second physiological feature shown by our study concerns the $P_{LEI}$ behavior during the progressive increase of PEEP. In ARDS group, $P_{LEI}$ showed a progressive increase from ZEEP to a PEEP guided by $P_{es}$ without significant modification of elastance. This behavior could be justified by the low amount of recruitable lung in the ARDS population included in our study. However, $P_{LEI}$ behavior in AE-ILD-UIP patients, clearly shows the different nature of the respiratory mechanics of the fibrotic lung compared to the ARDS patients. Indeed, the shift from low PEEP to $P_{es}$ guided PEEP titration resulted in a $P_{LEI}$ steep increase in all AE-ILD-UIP patients.

The mechanical behavior described in our study seems to reflect what was already hypothesized by our group on the basis of the anatomical features and of the initial physiological measurements performed in patients affected by AE-ILD-UIP: i.e. part of the fibrotic lung behaves mechanically like a *squishy ball*. (26). When the pressure applied inside the lung (i.e. PEEP applied) determines the tension of the parts of healthy lung surrounded by inelastic fibrotic tissue, the $P_{LEI}$ rises steeply to injurious values and the elastance of the lung worsens. At ZEEP, in patients affected by AE-ILD-UIP,

the amount of lung characterized by normal elasticity could be subject to expiratory derecruitment, while the part of the lung consisting of inelastic fibrotic tissue does not.

Our results could have implications for the clinical management of patients with AE-ILD-UIP under MV. First, we have confirmed the mechanical disadvantage associated with high PEEP levels as already indicated by retrospective observations in patients with ILD under MV (27,28). Second, our data may suggest that, in this subset of patients, a lung resting strategy may be preferable as compared to an open lung approach to prevent lung injury (26). Finally, these physiological assumptions should be kept in mind when evolutive fibro-proliferative abnormalities occur following severe ARDS.

Our study presents several limitations: first, the limited sample and the retrospective design do only provide a preliminary pathophysiological insight in this condition. Second, the lack of a qualitative and quantitative analysis of radiological images (namely the proportion of hyper-inflated lung tissue (29) during PEEP titration may weaken the interpretation of results. Third, the lack of volume assessment (namely end-expiratory lung volume) does not allow the comparison of strain between the two groups. Fourth, although the cohorts were matched according to clinical criteria, the small sample size of the ARDS group may not reflect the heterogenous features of this condition.

**Conclusions**

In this physiologic, preliminary retrospective study, although $P_{es}$ guided PEEP strategy allowed positive values of $P_{LEEX}$, a significant mechanical disadvantage was reported. AE-ILD-UIP patients showed a different mechanical behavior during MV and in response to PEEP when compared with ARDS patients of similar severity. Further prospective studies with larger sample size are needed to clarify the local mechanical consequences in patients with fibrotic lungs during controlled MV and to confirm the different mechanical behavior compared with ARDS of similar severity.

**List of abbreviations**

ILD, interstitial lung disease; AE-ILD, acute exacerbation of ILD; UIP, usual interstitial pneumonia; ARDS, acute respiratory distress syndrome; AHRF, acute hypoxic respiratory failure; bpm, breaths per minute; MV, invasive mechanical ventilation; ETI, endotracheal intubation; NIV, non-invasive mechanical ventilation; PEEP, positive end-expiratory pressure; PBW, predicted body weight; PSV, pressure support; APACHE II, acute physiology and chronic health evaluation II; SAPS II, Simplified Acute Physiology Score; IPF, idiopathic pulmonary fibrosis; RICU, respiratory intensive care unit; ICU, intensive care unit; $P_{es}$, esophageal pressure; $P_{esEI}$, end-inspiratory esophageal pressure; $P_{esEEX}$, end-expiratory esophageal pressure; $P_L$, transpulmonary pressure; $\Delta P_L$, transpulmonary driving pressure; $P_{LEI}$, end-inspiratory transpulmonary pressure; $P_{LEEX}$, end-expiratory transpulmonary pressure; $P_{plat}$, end-inspiratory plateau pressure; $\Delta P_{aw}$, driving pressure; $E_{tot}$, respiratory system elastance; $E_{cw}$, chest wall elastance; $E_L$, lung elastance; Vt, tidal volume; IQR, interquartile range.

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## General discussion

### *Evolving the concept of fibrotic lung deformation from "macro strain" to "micro strain"*

This research project has been focusing on the mechanical properties of the fibrotic lung while on mechanical ventilation (MV) with the aim to 1) provide insights on the key mechanisms of lung stress and stretch and its biological consequences; 2) elaborate a theoretical model able to explain the elastic behavior displayed by the lung with usual interstitial pneumonia (UIP) pattern while on MV; 3) challenge the assumptions of the model through clinical observations on patients with interstitial lung diseases (ILD) and UIP pattern undergoing non-invasive and invasive ventilatory support.

The pathological structural features of the fibrotic lung with UIP pattern result in mechanical changes that potentially make lung tissue more susceptible to physical stresses when controlled, assisted, and non-assisted breathing is required (1). This unphysiological interaction may be described by the mechano-elastic model of the lung acting as a "squishy-ball", in which the pulmonary parenchyma is represented by a patchwork of different elasticities arranged contiguously. Parenchymal inhomogeneity can act as a stress raiser at the interface of regions characterized by different elastic recoil, thus enhancing lung damage and abnormal repair response. Indeed pre-clinical studies have suggested that the result of these cyclic unphysiological mechanical stimuli on lung parenchyma can lead to 1) the amplifications of inflammation and alveolar rupture 2) a dysregulated cellular repair process and 3) progressive fibrotic damage (2). Progressive fibrosis is a self-sustaining phenomenon in several ILD and seems strongly linked with respiratory deterioration, morbidity, and mortality. In this line, the abnormal interaction between physical forces and fibrotic lung parenchyma could be enhanced by MV, thus raising the risk of a late onset ventilator-induced lung injury (VILI) that translates in fibrosis progression (2).

#### Computing a macro stress-strain curve for fibrotic UIP lung

Stress and strain are mathematically linked by a proportionality constant corresponding to the Young's modulus, that describes the elastic properties of a material undergoing tension or

compression in one direction. Higher Young's modulus corresponds to greater stiffness. In pulmonary physiology Young's modulus is called *specific lung elastance,* which describes the intrinsic elastic properties of the lung parenchyma open to gases. Studies focused on early ARDS patients showed that ARDS-lungs exhibit a specific lung elastance similar to healthy lungs, suggesting that the elastic properties of the aerated lung regions are not affected by diffuse alveolar damage (3). Starting from these assumptions, we conducted a post-hoc sensitivity analysis on data collected within the study illustrated in Chapter 4. We selected those patients from the AE-ILD-UIP and the ARDS cohort who underwent lung volume assessment (namely functional residual capacity [FRC] and end expiratory lung volume [EELV]) at each PEEP levels (for more details see Chapter 4, *Materials and methods* section). The EELV measurement was based on the nitrogen washout/washin technique through dedicated software (FRC Inview, GE Healthcare, IL, USA). Global lung strain was defined as $\Delta V/FRC$ where $\Delta V$ was computed as follows: EELV – FRC + Vt (4). Given the normal distribution of data, the paired Student's t-test was used to assess the difference between variables measured at different PEEP levels; ANOVA was used to test as an interaction for whether the change in lung stress according to PEEP levels was different between groups. Significance was set for p value < 0.05. The average value of lung strain at each PEEP level for the two cohorts of patients is shown in **Figure 1**.

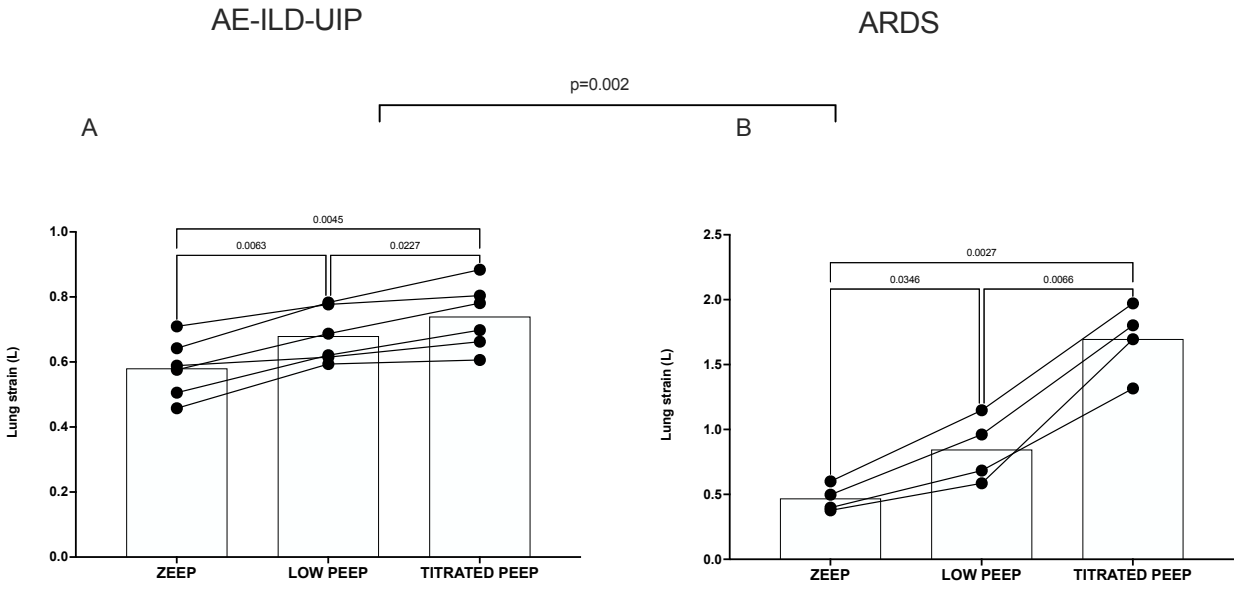


**Figure 1.** Measured individual values of lung stress in the matched study groups at ZEEP, LOW PEEP and TITRATED PEEP phase. When testing as an interaction for whether the change in lung stress at incremental PEEP value was different between AE-ILD-UIP (panel A) and ARDS (panel B), statistical significance was found (p=0.002).

*ZEEP, zero positive end-expiratory pressure; PEEP, positive end-expiratory pressure; AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome*

AE-ILD-UIP patients showed a limited trend towards global deformation for incremental PEEP levels as compared to ARDS for which higher value of strain were achieved. This is not surprising considering the architectural components of the fibrotic lung with UIP pattern. The main determinant of the elastic recoil of the lung are collagen and elastin fibers. The extracellular matrix (ECM) of fibrotic lungs is characterized by excessive deposition of fibrillar collagen, predominantly around myofibroblasts, that act as a blocking system and limit parenchymal distension.

In the post-hoc sensitivity analysis, lung stress was defined as end-inspiratory transpulmonary pressure ($P_{LEI}$). The stress-strain relation was further obtained by plotting the stress versus strain of digitized data. We further used a polynomial regression model to find out the best-fit curve. **Figure 2** illustrates the global stress-strain curve for AE-ILD-UIP and ARDS patients.

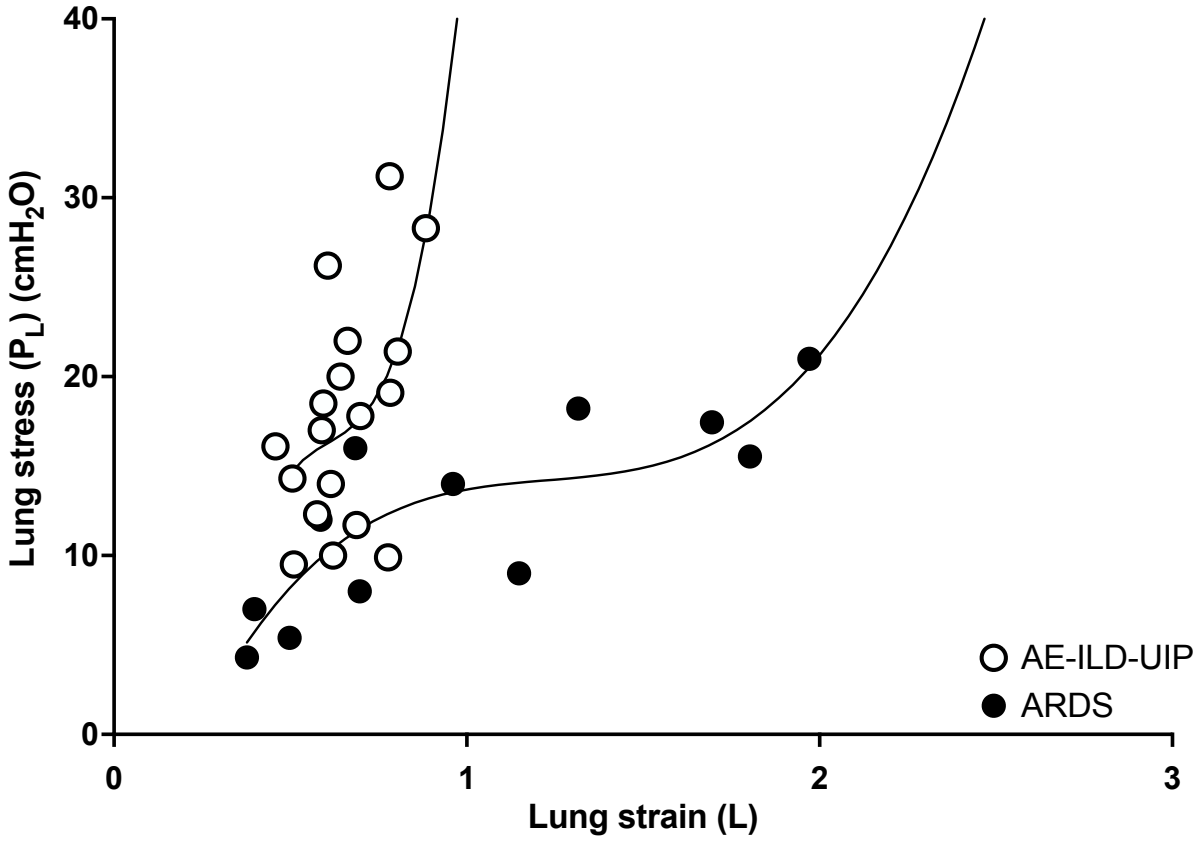


**Figure 2.** Stress-strain curve for AE-ILD-UIP (empty white dots) and ARDS patients (black dots). The polynomial regression analysis was performed starting with a first-order polynomial and then proceeded,

one order at a time, to a third-order polynomial (5). The goal of polynomial regression is to determine values for the parameters (A, B, C, and D) of the polynomial Y=A+Bx+Cx2+Dx3 that make the curve best fit the data points. The average deviation of the curve from the points is the square root of SS/df, where df indicates degrees of freedom (6). The transition point is given by the following formula: stress=−b2/3b3. This formula results from the second derivative of the third-order polynomial, which is f”(x)=6b3x+2b2. The point that zeroes the f”(x) represents the pressure (stress) at which the lung line of deformation diverges due to changes in lung elastic behavior. The polynomial equations computed for AE-ILD-UIP and ARDS are as follows:

AE-ILD-UIP, y = 16.88 + 14.05x + 57.3x2 + 403.3x3, R2 = 0.28

ARDS, y = 13.73 + 3.38x – 8.13x2 + 12.49x3, R2 = 0.72

*AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome*

The relationship between stress and strain in ARDS patients shows that the lung inflates until a certain level where the linearity of the stress-strain relation is lost, presumably approaching the breakdown limit of the extracellular matrix constituents. In fibrotic lungs, the specific elastance is much higher, the stress-strain curve is steeper (following an asymptotic trend), and the pressure breakdown is reached at lower strain value. To our knowledge this is the first report of clinical data on the *specific elastance* of patients with fibrotic lung disease and UIP pattern.

**The micro-strain concept in the fibrotic lung: unsafe protective ventilation and dangerous spontaneous breathing**

Healthy lung deformation usually follows an isotropic elastic modulus that is solely function of the stress applied upon homogeneous parenchymal surface. The fibrotic lung with UIP pattern shows a critically higher *specific elastance* with a stress/strain curve that reaches the elastic breakdown at lower strain values than ARDS (**Figure 2**). However, in fibrotic diseases with UIP pattern, the parenchyma results from an inhomogeneous patchwork of elasticities, and its properties become markedly anisotropic. Thus, the classical global stress/strain curve seems not able to give full representation of the elastic distortion to which the fibrotic lung is subjected. Indeed, the parenchymal deformation causes a cyclic re-distribution of the pressures generated at tissue

interfaces with associated change in stretch of the load bearing components; as a result, the elastic moduli that controls lung deformation while on MV are functions not only of lung stress but also of the type and extension of the distortion. Therefore, in the fibrotic lung, macro-strain is not descriptive of regional micro-strain, whose behavior is instead described by the regional "squishy ball" phenomenon. These speculations can give reason of the unfavorable clinical outcomes related to ventilatory damage observed even if protective MV is applied to fibrotic lung. Indeed, the concept of micro-strain does not allow to manage the ventilatory assistance of fibrotic lungs trusting the classical correspondence between the stress-strain curve and the ventilatory parameters recommended to protect the lung (i.e. tidal volume [Vt] < 6 ml/kg, plateau pressure < 25 $cmH_2O$, driving pressure < 15 $cmH_2O$). Therefore, mechanical ventilation might promote fibrosis progression even when the principles of protective mechanical ventilation strategy are rigorously followed. In this scenario, the "micro-strain" damage should be considered also during non-assisted spontaneous breathing. Indeed, the forces acting on the lung while the patient is breathing spontaneously may result in local deformations even without ventilatory assistance, thus favoring a feed-forward loop of parenchymal damage. In this line, elevated inspiratory effort resulting in high $P_L$ swings (i.e. during physical exercise) should be avoided as potentially harmful, particularly in those patients with advanced UIP pattern. Therefore, personalized strategies of clinical management (i.e. tailored pulmonary rehabilitation program, ultra-protective ventilatory strategies) for patients with fibrotic lung disease and UIP pattern should be encouraged, considering the mechanical properties of the lung exposed to physical stretch. Further research in this field is welcomed to understand the complex interplay between mechanical stressors and lung deformation in patients with fibrotic changes of the lung.

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**List of abbreviations**

MV, mechanical ventilation; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; ARDS, acute respiratory distress syndrome; AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; PEEP, positive end-expiratory pressure; ZEEP, zero positive end-expiratory pressure; $P_L$, transpulmonary pressure; $P_{LEI}$, end-inspiratory transpulmonary pressure; Vt, tidal volume; ECM, extracellular matrix; FRC, functional residual capacity; EELV, end expiratory lung volume