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Quantitative CT-analysis of over aerated lung tissue and correlation with fibrosis extent in patients with idiopathic pulmonary fibrosis

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Abstract

Introduction The usual interstitial pneumonia (UIP) pattern, hallmark of idiopathic pulmonary fibrosis (IPF), may induce harmful local overdistension during mechanical ventilation given the juxtaposition of different tissue elasticities. Mechanotransduction, linking mechanical stress and strain to molecular pro-fibrotic pathways, likely contributes to fibrosis progression. Understanding the mechanical forces and aeration patterns in the lungs of IPF patients is crucial for unraveling potential mechanisms of disease progression. Quantitative lung computed tomography (CT) can accurately assess the air content of lung regions, thus informing on zonal distension. This study aims to investigate radiological evidence of lung over aeration in spontaneously breathing UIP patients compared to healthy controls during maximal inspiration.

Methods Patients with IPF diagnosis referred to the Center for Rare Lung Diseases of the University Hospital of Modena (Italy) in the period 2020–2023 who underwent High Resolution Computed Tomography (HRCT) scans at residual volume (RV) and total lung capacity (TLC) using standardized protocols were retrospectively considered eligible. Patients with no signs of lung disease at HRCT performed with the same image acquisition protocol nor at pulmonary function test (PFTs) served as controls. Lung segmentation and quantitative analysis were performed using 3D Slicer software. Lung volumes were measured, and specific density thresholds defined over aerated and fibrotic regions. Comparison between over aerated lung at RV and TLC in the two groups and according to lung lobes was sought. Further, the correlation between aerated lung and the extent of fibrosis was assessed and compared at RV and TLC.

Results IPF patients (N = 20) exhibited higher over aerated lung proportions than controls (N = 15) both at RV and TLC (4.5% vs. 0.7%, $p < 0.0001$ and 13.8% vs. 7%, $p < 0.0001$ respectively). Over aeration increased significantly from RV to TLC in both groups, with no intergroup difference ($p = 0.67$). Sensitivity analysis revealed significant variations in over aerated lung areas among lobes when passing from RV to TLC with no difference within lobes ($p = 0.28$).

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Correlation between over aeration and fibrosis extent was moderate at RV ($r = 0.62$, $p < 0.0001$) and weak at TLC ($r = 0.27$, $p = 0.01$), being the two significantly different at interpolation analysis ($p < 0.0001$).

Conclusions This study provides the first evidence of radiological signs of lung over aeration in patients with UIP-pattern patients when passing from RV to TLC. These findings offer new insights into the complex interplay between mechanical forces, lung structure, and fibrosis and warrant larger and longitudinal investigations.

Keywords Interstitial lung disease, Pulmonary fibrosis, Usual interstitial pneumonia, Lung hyperinflation, Total lung capacity, Residual volume, Mechanotransduction

Background

Idiopathic Pulmonary Fibrosis (IPF) is a chronic and progressive interstitial lung disease (ILD) characterized by progressive parenchymal scarring, resulting in impaired pulmonary function and respiratory failure [1]. To date, the exact cause of IPF remains elusive, and existing therapies can only mitigate the decline in lung function [2, 3]. The anatomo-pathological hallmark of IPF is the usual interstitial pneumonia (UIP) pattern of fibrosis that consists of patchy lung involvement, with normal parenchymal areas surrounded by dense anelastic tissue, interstitial thickening, cystic abnormalities, and traction bronchiectasis [4]. The geometrical heterogeneity of alveolar distortion elicits on the lung an uneven distribution of mechanical forces, which are conveyed on the more distensible areas [5]. The mechanical disadvantage of the fibrotic lung is evident during mechanical ventilation (MV), wherein the trans-pulmonary pressure levels reached at the end of inspiration are harmful even when minimal strains is elicited [6]. Thus, ventilator-induced lung injury may be the fundamental physiological mechanism underlying the high mortality found in IPF patients requiring MV [7]. Based on our previous studies, we hypothesize that during maximal lung inflation, either generated mechanically or by spontaneous breathing, lung airspaces with higher compliance may undergo harmful overdistension resulting in dangerous stretching forces [8, 9]. This elastic response to regional stresses mirrors that of stress balls called "squishy-balls" and may constitute the mechanical substrate through which the lung undergoes further damage [10]. Given that the progression of fibrosis follows a mechanical gradient, extending from regions at higher stress (periphery, bases) to those at lower stress [11, 12], a contribution of mechanical stimuli in promoting fibrosis may be hypothesized also during spontaneous breathing. Mechanotransduction refers to the biological phenomenon wherein mechanical stress applied to biological tissue is translated to molecular pathways that elicit adaptive responses. This complex phenomenon has been closely linked to fibrosis and is believed to play a critical role in lung scarring [13].

Thus, it is assumed that abnormal mechanical forces occurring within the patchy fibrosis of the UIP pattern may result in areas of hyperinflation even during spontaneous breathing; moreover, this uneven stretching of the lung parenchyma might in turn activate abnormal mechanotransduction, thus promoting the progression of fibrosis [14].

Quantitative lung computed tomography (CT) analysis has acquired an increasingly relevant role in the clinical evaluation and management of different lung diseases [15]. In patients with interstitial lung diseases, threshold-based computational techniques allow the precise measurement of lung volumes and contribute to the accurate assessment of overdistension [16, 17].

The aim of the present study is therefore to investigate by means of a quantitative CT analysis whether the lungs of spontaneously breathing patients with a UIP pattern exhibit radiological evidence of lung over aeration when subjected to mechanical stress through volitional maximal inspiration, i.e. passing from residual volume to total lung capacity, as compared to healthy controls.

Methods

Study setting and design

This was a retrospective analysis of prospectively collected data. The study was carried out at Center for Rare Lung Diseases, Respiratory Disease Unit, of the University Hospital of Modena (Italy) and conducted in accordance with the Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 326/2022). 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

Consecutive patients referred to the Center for Rare Lung Diseases of the University Hospital of Modena between August 1st, 2020 and May 1th, 2023 were considered eligible for enrollment.

Inclusion criteria were age > 18 years and a high-resolution CT (HRCT) scan with protocolized images acquisition at TLC and RV (see below). Patients with diagnosis of combined pulmonary fibrosis and

emphysema (CPFE), or missing core data at record analysis (namely pulmonary function tests [PFTs] performed within 6 months from radiological examination, were excluded.

Individuals referred to the Respiratory Disease Unit who underwent HRCT under standardized condition (i.e. acquisition of images at TLC and RV, see below) for different clinical purpose served as controls patients. To be enrolled, they had to have no lung abnormalities on HRCT and normal PFTs both performed no more than 6 months apart. All HRCT were reviewed for inclusion by a radiologist experienced in interstitial lung disease.

Image acquisition

Chest CT scans were performed by a 64-slice CT (G.E. VCT Lightspeed, GE Healthcare, United States) and according to a standardized local protocol for the acquisition of images at TLC and RV; scans were performed during a single full inspiratory breath-hold, at TLC, and after a forced breath-hold expiration, at RV, while in supine position. The scans' technical parameters were standard as reported in [15]. The images in DICOM (Digital Imaging and COmmunications in Medicine) extension files were transferred to the Picture Archiving and Communication System (PACS) of our institution. Then they were collected and stored on a dedicated workstation. The hardware used was a MacBook Pro (Retina) (processor: Intel Core i5 dual-core (2.9 GHz), RAM: 8 GB 1867 MHz DDR3, graphic card: Intel Iris Graphics 6100 1536 MB).

Automatic lung segmentation

Once DICOM images had been acquired, the segmentation of the lung parenchyma was performed through a software-based evaluation on a dedicated workstation using the open-source 3D Slicer software (version 4.10.2, https://www.slicer.org) [18], by means of the software extension called "Chest Imaging Platform" and the tools called "Lung CT Segmenter". Further, the "Lung CT analyzer" and "Segment Editor" extensions were used to perform a quantitative image analysis to assess the over aerated areas and the extent of fibrosis as previously reported [15] (eFigure 1, Supplementary materials). Specific density thresholds expressed in Hounsfield unit (HU) were set according to available literature [16, 19]. Specifically, the HU values relating to the well-aerated lung parenchyma were defined within a threshold between − 950 and − 701 HU while the threshold between − 700 and − 250 HU was considered to identify the interstitial lung involvement [17, 20] (eFigure 2, Supplementary materials).

Data collection

Medical reports, electronical charts and available clinical and physiological datasets were investigated to collect data on demographics, clinical characteristics and PFTs.

Analysis plan

The primary endpoint of the study was the proportion of over aerated lung tissue at HRCT at different lung volumes (from RV to TLC) in IPF patients and healthy controls. Data were displayed as median and interquartile range (IQR) for continuous variables and numbers and percentages for dichotomous variables. The paired Student's *t*-test was used to assess the different proportion of over aerated lung tissue between RV and TLC. The unpaired Student's *t*-test was instead used to assess the difference in lung aeration categories between patients and controls; otherwise, the Wilcoxon test was used. ANOVA was used to test as an interaction for whether the change in over aerated lung tissue from RV to TLC levels was different between groups.

Furthermore, we compared the proportion of over aerated lung tissue between RV and TLC according to the lung lobes. The paired Student's *t*-test was used to this purposes and Kruskal–Wallis was used to test as an interaction for whether the change in over aerated lung tissue from RV to TLC levels was different according to different lobes.

Finally, as a sensitivity analysis, we evaluated the correlation between the proportion of over aerated lung tissue at different volumes and the extent of lung fibrosis as assessed by automatic quantitative CT analysis. Correlation was sought using Pearson's R or Spearman correlation coefficient as appropriate. The relationship between over aerated lung tissue and the extent of lung fibrosis at RV and TLC was sought and graphed by means of a second order polynomial (quadratic) interpolation curve. Further, curve comparison at RV and TLC was performed with nonlinear regression analysis, fitting the data from each curve to the model and then comparing the coefficients of the quadratic equations between the two curves.

Statistical analysis was performed using GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, Ca, USA) unless otherwise indicated.

Results

Study population

The flowchart of the study is shown in Fig. 1. Over the study period, 24 patients with IPF were deemed eligible for enrollment. All of them were diagnosed with the presence of a definite UIP pattern on HRCT scan within multidisciplinary discussion according to ATS/

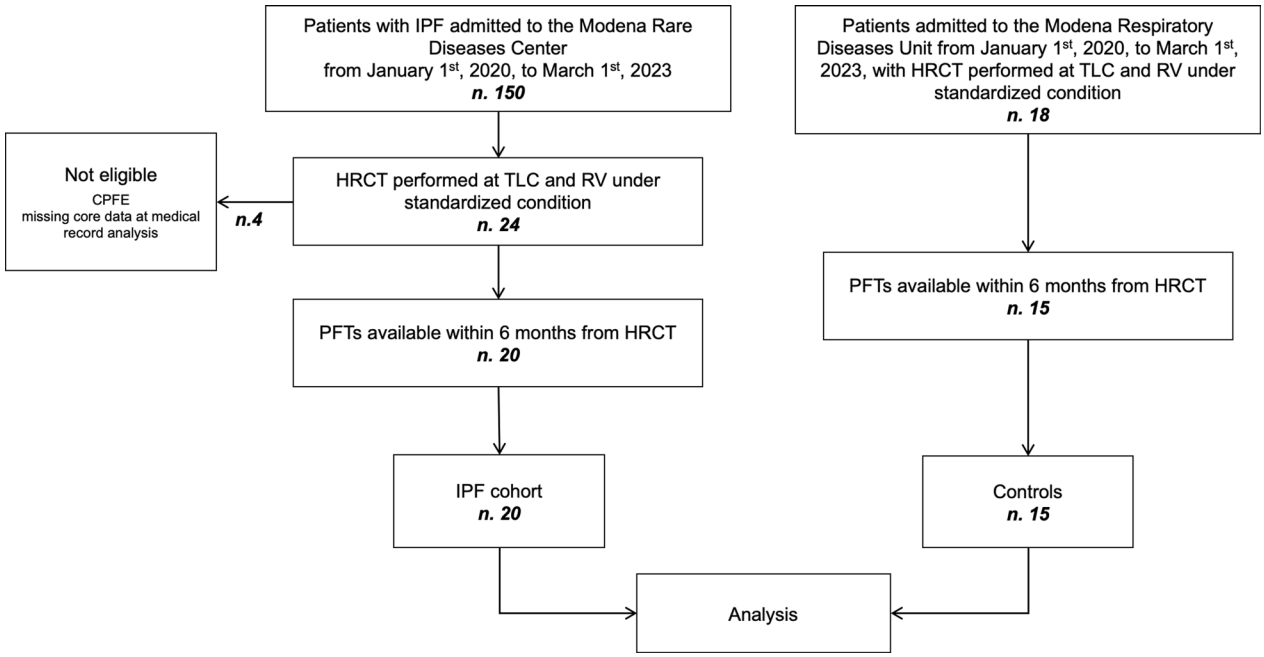

Fig. 1 Study algorithm. *IPF* idiopathic pulmonary fibrosis; *CPFE* combined pulmonary fibrosis and emphysema; *HRCT* high resolution computed tomography; *TLC* total lung capacity; *RV*, residual volume; *PFT* pulmonary function test

ERS/JRS/ALAT Guidelines [21, 22]. Four patients were then excluded due to incomplete data on PFTs. Thus, 20 patients and 15 controls were analyzed according to the inclusion criteria (Table 1).

Patients (median age 78 years) were mainly male (65%) and former smokers (75%) as displayed in Table 1. PFTs showed a restrictive pattern and significantly reduced lung gas transfer (see in Table 1). Controls were younger than patient (median age 68 years) and comparable to controls for smoking habit (73% former smokers) but showing PFTs within normal ranges. Eleven out of 15 controls (73%) were referred to the Respiratory Disease Unit to perform standardized HRCT for persistent cough with negative chest X-ray, while 4 underwent HRCT in the suspicion of excessive dynamic airway collapse.

Quantitative analysis of over aerated lung

The proportion of over aerated lung at RV and TLC for patients and controls is showed in Fig. 2. Both groups showed a significant increase in over aerated lung areas from RV to TLC ($p < 0.0001$ and $p < 0.0001$, respectively) which was similar ($p = 0.67$). However, the proportion of over aerated lung was higher in IPF compared to controls both at RV (4.5% VS 0.7%, $p < 0.0001$) and TLC (13.8% VS 7%, $p < 0.0001$) as shown in Table 2. Significant group differences were also found for non-aerated, poorly aerated, and well aerated lung tissue both at RV and TLC (Table 2).

Table 1 Demographic and clinical characteristics of the study groups at inclusion

Variable	IPF (n = 20)	Controls (n = 15)	p value
Demographics			
Age, years (IQR)	78 (73–83)	68 (58–72)	< 0.0001
Male, n (%)	13 (65)	7 (47)	0.3
BMI, kg/m^2 (IQR)	26.4 (25.3–27.6)	26.2 (24–28.9)	0.6
Smoking habit			
Never, n (%)	5 (25)	8 (53)	0.3
Former, n (%)	15 (75)	7 (47)	0.3
Active, n (%)	0 (0)	0 (0)	0.9
Pulmonary function test			
TLC, %pred (IQR)	71.5 (67–74)	95 (88–103)	< 0.0001
TLC, L (IQR)	4.2 (3.6–4.6)	6.4 (5.3–6.8)	< 0.0001
RV, %pred (IQR)	67.5 (65–70.8)	99 (93–117)	< 0.0001
RV, L (IQR)	1 (0.9–1.1)	1.5 (1.4–1.8)	< 0.0001
FVC, %pred (IQR)	65.6 (61.5–74.2)	99 (84–108)	< 0.0001
FVC, L (IQR)	3.3 (3–3.7)	5 (4.2–5.4)	< 0.0001
FEV1, %pred (IQR)	74 (63.5–81)	99 (83–110)	< 0.0001
FEV1, L (IQR)	3.1 (2.4–3.6)	4.2 (3.4–5.5)	< 0.0001
FEV1/FVC, % (IQR)	78.3 (75.8–83.6)	82.6 (78.9–85.4)	< 0.0001
DLCO, %predicted (IQR)	50 (38.3–58.8)	88 (78–91)	< 0.0001

Data are presented as number (n) and percentage for dichotomous values or median and interquartile ranges (IQR) for continuous values

IPF idiopathic pulmonary fibrosis; *BMI* body mass index; *CT* computed tomography; *TLC* total lung capacity; *RV* residual volume; *FVC* forced vital capacity; *FEV1* forced expiratory volume in 1 s; *DLCO* lung diffusion test for carbon dioxide; *IQR* interquartile range

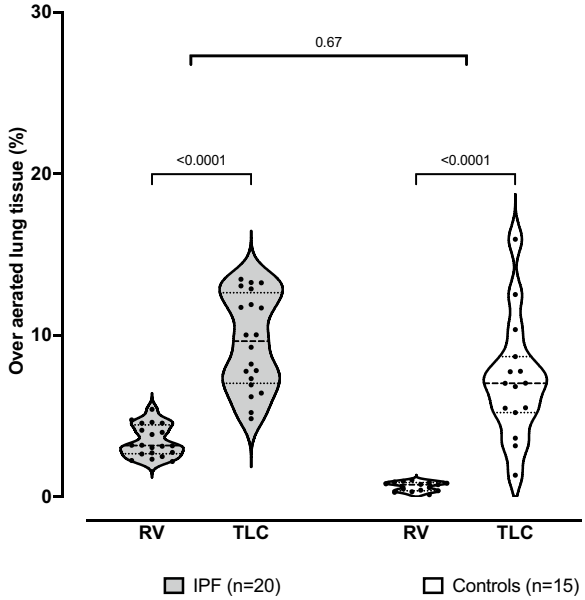

Fig. 2 Measured individual values of over aerated lung tissue in the study groups at RV and TLC. Both IPF and controls showed a significant increase in the proportion of over aerated lung tissue from RV to TLC ($p < 0.0001$ and $p < 0.0001$ respectively). When testing as an interaction for whether the change in the proportion of over aerated lung areas at different lung volume was different between IPF and controls, statistical difference was not found ($p = 0.67$). *IPF* idiopathic pulmonary fibrosis; *TLC* total lung capacity; *RV* residual volume

Table 2 Quantitative lung HRCT analysis at different lung volumes for IPF patients as compared to controls

Variable	IPF (n = 20)	Controls (n = 15)	p value
Quantitative HRCT lung analysis_RV			
Non-aerated lung, % (IQR)	2.2 (1.9–2.5)	1.2 (0.9–1.7)	< 0.0001
Poorly aerated lung, % (IQR)	20.8 (16.9–27.2)	13.5 (11.9–16.3)	< 0.0001
Well-aerated lung, % (IQR)	72 (64.1–76.8)	85.2 (81.9–88)	< 0.0001
Over aerated lung, % (IQR)	4.5 (3.8–6.5)	0.7 (0.4–0.9)	< 0.0001
Quantitative HRCT lung analysis_TLC			
Non-aerated lung, % (IQR)	1.3 (0.9–1.3)	0.5 (0.3–0.6)	< 0.0001
Poorly aerated lung, % (IQR)	8.9 (7.8–14.4)	2.1 (1.8–3.2)	< 0.0001
Well-aerated lung, % (IQR)	72 (67.6–80.4)	91.3 (88.4–94)	< 0.0001
Over aerated lung, % (IQR)	13.8 (10–18.2)	7 (5.2–8.7)	< 0.0001

Data are presented as median and interquartile ranges (IQR)

HRCT high resolution computed tomography; *TLC* total lung capacity; *RV* residual volume; *IQR* interquartile range

Sensitivity analyses

The change in over aerated lung from RV to TLC for different lung lobes is displayed in Fig. 3. The change in the proportion of over aerated lung areas from RV to TLC was significant for each lung lobe. However, this variation was not different within the lobes (Kruskal–Wallis test, $p = 0.28$).

Figure 4 shows the plot between the individual values of over aerated lung and parenchymal fibrosis extent at RV (panel A) and TLC (panel B), and for each different lobe. The correlation between the proportion of over aerated lung parenchyma and fibrosis extent was found to be moderate at RV ($r = 0.62$ 95%CI[0.48–0.73], $p < 0.0001$) and weak at TLC ($r = 0.27$ 95%CI[0.07–0.43], $p = 0.01$). Interpolation analysis showed that the relationship between over aerated lung and fibrosis extent was described by the equation $y = -0.006x^2 + 0.37x + 1.08$ at RV and by the equation $y = -0.027x^2 + 1.11x + 0.92$ at TLC. The two curves thus resulting were significantly different at the non-linear regression analysis ($p < 0.0001$).

Discussion

This study reports a significant proportion of over aerated lung as assessed by quantitative CT analysis in spontaneously breathing IPF patients when passing from RV to TLC. Further, a significant relationship between over aeration and the extent of lung fibrosis was reported, independent on the different lung lobes.

Radiological description of IPF lung at different volumes

To the best of our knowledge, this study presents the first evidence showing that patients with UIP pattern exhibit radiological signs of lung over aeration during the breathing transition from RV to TLC, similarly to what observed in healthy controls. Furthermore, the proportion of parenchyma experiencing over aeration within a maximal spontaneous inspiration is greater in patients with UIP pattern as compared to that observed in individuals with normal lung function. Moreover, in IPF, a proportion of lung parenchyma shows over aeration even during deflation, when RV level is reached.

For the first time, we here describe the dynamic behavior of the lung with UIP pattern, as based on the static morphometry, thus redefining the concept that describes pulmonary fibrosis as a disease only characterized by restriction of lung volumes with a homogeneous hypoaeration during lung inflation. Lung fibrosis causes a progressive reduction in lung volumes as a whole, as described by standard functional tests. However, the heterogeneity of the UIP pattern can generate a peculiar mechanical response and air distribution when subjected to deformation, such as during inflation. Indeed, The UIP

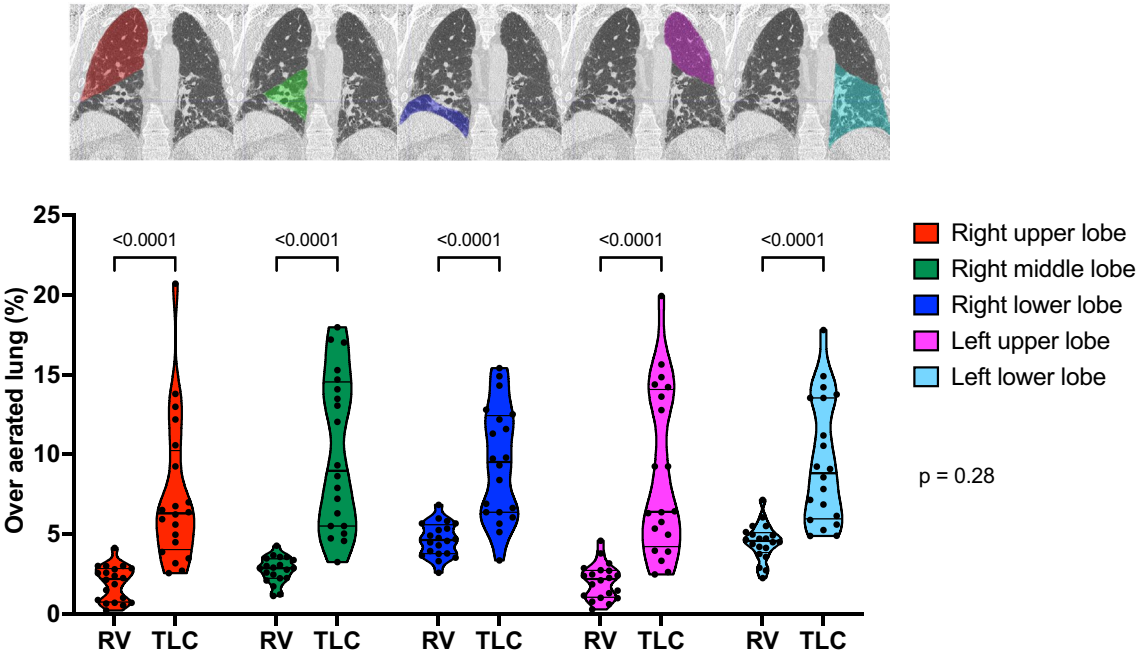

Fig. 3 Measured individual values of over aerated lung tissue at RV and TLC according to lung lobes in IPF patients. The change in the proportion of over aerated lung areas resulted significant for each lung lobe and was not influenced by lung topography as assessed by ANOVA (p = 0.28). *IPF* idiopathic pulmonary fibrosis; *TLC* total lung capacity; *RV* residual volume

lung architecture, consists of a patchwork of tissues with varying elasticities. When pressure is applied, it results distributed unevenly: the rigid areas resist deformation, while the more elastic regions bear the mechanical stress [23]. We firstly hypothesized this phenomenon in IPF patients undergoing MV. In this setting, the external application of positive end-expiratory pressure can cause the more flexible lung areas to protrude through the surrounding stiff fibrotic tissue, leading to increased rigidity and potential tissue breakdown [10]. This effect resembles that of "squishy balls" and may explain some mechanical disadvantages during ventilation. In the present study, we showed that the UIP pattern can facilitate a zonal increase in air content that can no longer be described by a standard functional evaluation (i.e. spirometry). This observation of zonal over-aeration in lung parenchyma on CT scans supports our "squishy ball" hypothesis, and extends this concept to IPF patients even when breathing spontaneously.

Relationship between fibrosis and over aeration and clinical implications

The concept of "zonal over-aeration" in the fibrotic lung should not be misleading. Indeed, it should not be confused with the phenomenon of lung hyperinflation which is typical of other diseases such as chronic obstructive pulmonary disease (COPD). The "*squishy ball*" theory has clearly different physiological and biological implications. Pulmonary hyperinflation is usually defined as an abnormal increase of the gas volume in the lungs at the end of tidal expiration (i.e. functional residual capacity) in patients suffering from COPD [24]. In this case, both reduction of the lung elastic recoil pressure and the increase of the airway resistance lead to increased time for lung emptying. The physiological consequence of this so called dynamic hyperinflation is the progressive air trap in the lung under specific conditions such as exercise or disease exacerbation, which leads in turn to exertional dyspnea and may have deleterious effects on diaphragm and cardiovascular functions [25].

Despite some physiological studies have shown an increase of airflow resistance in the small airways also of patients with ILD, the development of dynamic hyperinflation does not occur [26]. In addition, a recent study by Chuang did not report any exercise-induced dynamic hyperinflation in ILD patients during physical exercise [1].

Although it seems reasonable to understand that the physiological consequences of the zonal parenchyma over aeration of the fibrotic lung are less likely to increase symptoms per se in patients with ILD and at difference with COPD [27], the biological consequences could be different. Indeed, the protrusion of lung areas with spared elasticity (i.e. the areas of parenchyma with over aeration

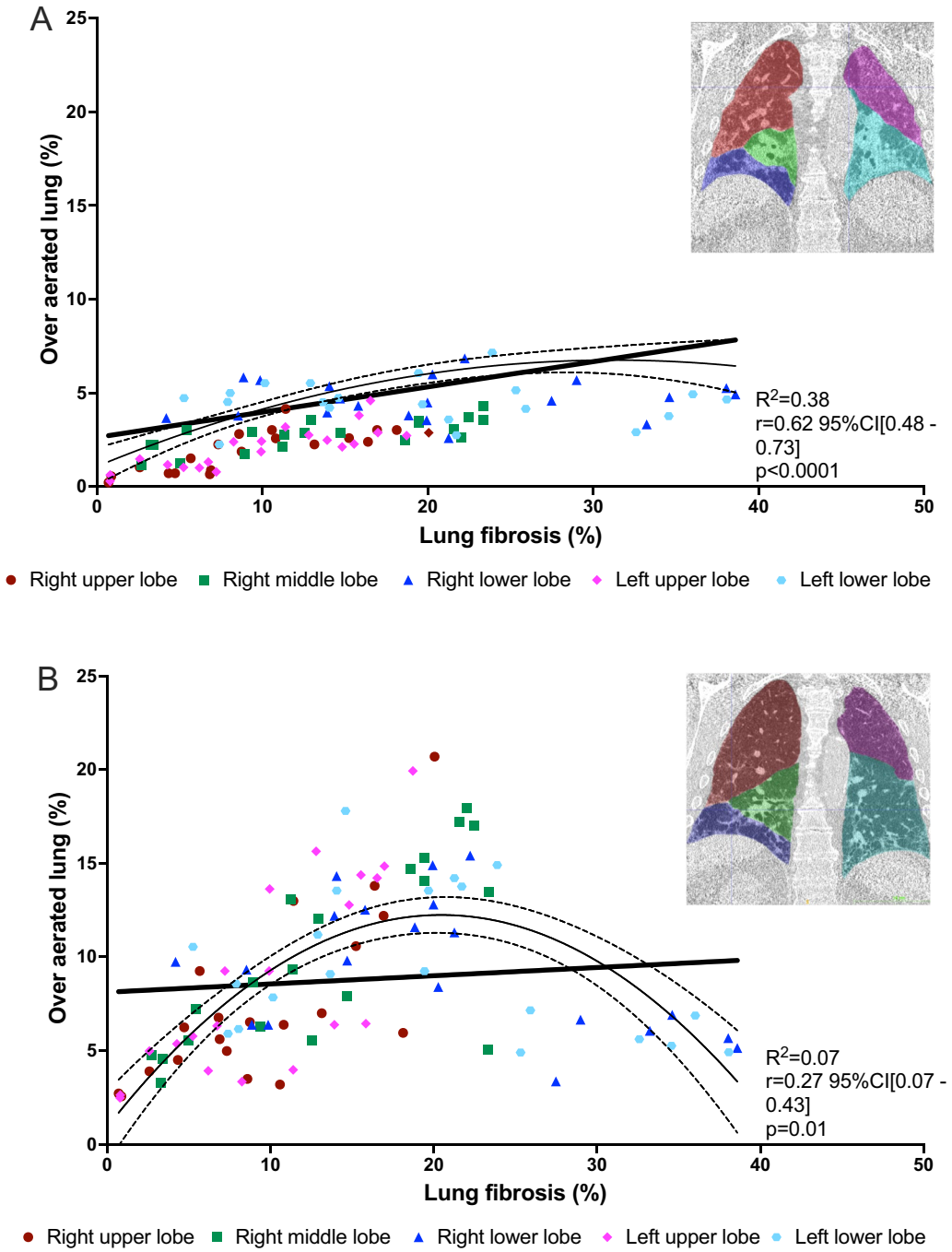

Fig. 4 Individual value of over aerated lung and fibrosis extent at RV (panel **A**) and TLC (panel **B**), according to lung lobes as showed by different symbols in IPF patients. Interpolation curves were sought and compared showing a statistical difference between the fitting results ($p < 0.0001$). The relationship between hyperinflated lung and fibrosis extent at RV is described by the equation $y = -0.006x^2 + 0.37x + 1.08$. The relationship between hyperinflated lung and fibrosis extent at TLC is described by the equation $y = -0.027x^2 + 1.11x + 0.92$. *IPF* idiopathic pulmonary fibrosis; *TLC* total lung capacity; *RV* residual volume

as described in our study) could occur within the context of dense inelastic fibrotic tissue; hence, the onset of non-physiological stretches may activate intracellular mechanotransduction pathways, thus favoring the progression of local fibrosis [13]. It Is now well known that cells receive mechanical cues via mechanosensitive proteins at the cell membrane-cytoskeletal cortex interface, and un-physiological mechanical stimuli, through the activation

of intracellular pathways, may transiently or persistently alter cellular programs that drive injury, repair, and fibrosis responses [3, 14].

The clinical observation that pulmonary fibrosis progresses along a mechanical stress gradient, supports the hypothesis that the elastic and mechanical behavior of the "*squishy ball*" model could be one of the key mechanisms of the abnormal activation of the mechanotransduction pathways, suggesting a link between non-physiological stretch and progression/extension of lung fibrosis. Particularly, we hypothesize that if the fibrotic UIP-lung reaches a certain extent of fibrosis it may undergo potentially hazardous deformations when subjected to significant volume changes (i.e. from RV to TLC). Such deformations could further activate unfavorable mechanotransduction pathways [14].

Therefore, this behavior might constitute a form of lung injury induced by the unfair interplay among areas of the lung having different elasticities, which we can so label as "*stiff tissue induced lung injury*".

Finally, present data have also shown that in patients with UIP lung, there exists a portion of over aeration even at RV. We speculate that this finding might be related to the impact of fibrosis on terminal airways, thus promoting tele-expiratory collapse and air trapping when lung volume reaches its minimum during expiration. ILD patients can show either a preserved or elevated RV/TLC ratio, given the premature closure of small airways and gas trapping [28].

Strengths and limitations

This study employs quantitative lung CT analysis to assess the abnormal proportion of over-aerated lung tissue during the spontaneous breathing transition from RV to TLC. The presence of over aeration even at RV suggests potential air trapping and tele-expiratory collapse in the fibrotic lung with UIP pattern, and challenges the traditional view of a uniform hypo-aeration during lung inflation in IPF. Moreover, the study's speculation on a possible "*stiff tissue-induced lung injury*" underscores the critical relevance of mechanical factors in the clinical progression of the disease.

Nevertheless, present investigation is burdened by several limitations. First, the single-center retrospective design and the limited sample may introduce bias and limit the ability to establish causation. The lack of a dynamic quantitative CT evaluation during spontaneous breathing further represents a major flaw.

Future prospective studies with larger and more diverse cohorts could validate and extend the current findings. Longitudinal assessments of change of lung mechanics in patients with IPF may provide insights into the evolution of zonal over-aeration in the lungs and, as such, its relationship to the progression of fibrosis.

Conclusions

As a proof-of-concept, this study provides valuable insights into the dynamic behavior of lungs during spontaneous breathing in patients with IPF. In the light of the proposed "*squishy ball*" theory and the mechanotransduction hypothesis, we have added a novel dimension to the understanding of IPF pathogenesis, emphasizing the potential role of mechanical forces in the disease progression. If confirmed, these findings may have implications for the development of targeted treatments aimed at mitigating the impact of non-physiological stretch on the fibrotic lung tissue.

Abbreviations

ILD	Interstitial lung disease
UIP	Usual interstitial pneumonia
IPF	Idiopathic pulmonary fibrosis
HRCT	High resolution computed tomography
PFT	Pulmonary function test
TLC	Total lung capacity
RV	Residual volume
IQR	Interquartile range
CPFE	Combined pulmonary fibrosis and emphysema
MV	Mechanical ventilation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-024-02970-4.

Additional file 1.

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Author contributions

RT designed the study, enrolled the patients, analyzed the data, and wrote the paper. MRS critically reviewed the design of the study, analyzed the data and wrote the paper. RT and MRS should be considered as first authors. IC, GDC, DA, FG and GB collected data the data and produces figures. SC, AVS, GR made substantial contributions to the literature review, data collection, and paper writing. PS, LB, RR, FP AND LDLB critically analyzed data, wrote, reviewed and edited the manuscript. EC and AM designed the study, wrote, reviewed, and edited the manuscript and share senior authorship. All authors have read and approved the final version of the manuscript.

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None.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval
The study was conducted in accordance with the study protocol, the Declaration of Helsinki, and applicable regulatory requirement. The Ethics Committee "Area Vasta Emilia Nord" approved the protocol (registered protocol number 326/2022).

Consent for publication
Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Competing interests
Authors have no competing interests with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript.

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