Comparison of pulmonary and small airway function between idiopathic inflammatory myopathies patients with and without interstitial lung disease

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Abstract

Objective

To evaluate pulmonary and small airway function in patients with idiopathic inflammatory myopathies (IIM) and make comparisons between patients with and without interstitial lung disease (ILD).

Methods

Newly diagnosed IIM patients with and without ILD determined by high resolution computed tomography were included in the study. Pulmonary and small airway function was assessed by spirometry, diffusing capacity for carbon monoxide (DLCO), body plethysmography, single and multiple breath nitrogen washout, impulse oscillometry and measurement of respiratory resistance by the interrupter technique (R_{int}) using the Q-box system. We used discrepancies between lung volumes measured by multiple breath nitrogen washout and body plethysmography to evaluate for small airway dysfunction.

Results

Study cohort comprised of 26 IIM patients, 13 with and 13 without ILD. IIM-ILD patients presented more frequently with dyspnoea, fever, arthralgias and positive anti-synthetase antibodies, compared to IIM patients without ILD. Classic spirometric parameters and most lung physiology parameters assessing small airway function did not differ between the two groups. Predicted total lung capacity and residual volume (TLC_{N2WO}, RV_{N2WO}) measured by multiple breath nitrogen washout and the TLC_{N2WO}/TLC_{pleth} ratio were significantly lower in IIM-ILD patients compared to those without ILD (mean: 111.1% vs. 153.4%, p=0.034, median: 171% vs. 210%, p=0.039 and median: 1.28 vs. 1.45, p=0.039, respectively). R_{int} tended to be higher among IIM-ILD patients (mean:100.5% vs. 76.6%, p=0.053).

Conclusion

Discrepancies between lung volumes measured by multiple breath nitrogen washout and body plethysmography in IIM-ILD patients indicate an early small airways dysfunction in these patients.

Key words

dermatomyositis, polymyositis, interstitial lung disease, small airways

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Introduction

Dermatomyositis (DM) and polymyositis (PM), typically classified into idiopathic inflammatory myopathies (IIM), are systemic autoimmune diseases, affecting mainly skeletal muscles with progressive symmetric proximal muscle weakness, but may also involve other organs, including skin, joints, gastrointestinal tract, heart and lungs. Pulmonary manifestations include interstitial lung disease (ILD) of various forms, respiratory muscle weakness and associated complications such as infections, aspiration pneumonia, drug induced pneumonitis and malignancy (1). ILD is a common extra-muscular manifestation of IIM, with a prevalence ranging from 17 to 36% (2, 3). Pulmonary involvement contributes substantially to the morbidity and mortality of patients and frequently determines the final clinical outcome of IIM (2).

Pulmonary function testing (PFTs) could be clinically very useful in the detection and monitoring of lung involvement in IIM since it is performed non-invasively and is not associated with any radiation exposure. ILD causes a restrictive pattern with reduced forced vital capacity (FVC), vital capacity (VC) and total lung capacity (TLC). It is also associated with impaired gas transfer and diffusing capacity for carbon monoxide (DLCO), which usually decreases before FVC or TLC (2, 4). So far, small airway function has not been studied among IIM patients and especially among those with ILD. It is noteworthy that non autoimmune ILD forms *per se* have been linked to small airway disease as part of the ILD pathogenesis, due to expansion of the inflammatory response into the small airways compartment (5-7), while relevant symptoms seem to be relieved after bronchodilators in these patients (8). There are several available PFTs, evaluating small airways, including indices measured during classic spirometry, single breath nitrogen washout test, impulse oscillometry and measurement of respiratory resistance by the interrupter technique. Forced expiratory flow after an expiration of 25% to 75% of FVC (FEF_{25-75}) in spirometry and respiratory resistance measured by the interrupter technique (R_{int}) are some of the parameters related to small airway function (9, 10). Impulse oscillometry parameters, including the difference between resistance at 6Hz and at 20Hz (R6-R20), reactance at 6 Hz (X6) and resonance frequency (Fres) are also associated with small airway function (11).

Despite the existence of many indices of small airway function, none has been established as the gold standard and investigators try to assess which combination of biomarkers, physiological tests, and imaging markers best measure the presence and extent of small airway dysfunction (SAD) in patients with specific diseases (such as the ATLANTIS study for asthma) (12). Furthermore, body plethysmography is the gold standard for measuring lung volumes, whereas multiple breath nitrogen washout seems impaired, considering that it "underestimates" lung volumes in patients with small airway obstruction due to gas trapping (13, 14). Thus, discrepancies between lung volumes measured by those two techniques might be an indication of early SAD.

The objectives of this single-centre prospective study are to assess pulmonary and small airway function in IIM patients and make comparisons between patients with and without ILD. We hypothesised that SAD would be present in IIM patients, especially with ILD derangements. Clinical, laboratory, immunological and imaging features are also described.

Methods

Patients' cohort

In this single-centre, prospective study, naïve IIM patients with either DM or PM who were diagnosed and followed up in the outpatient rheumatology clinic of the Department of Pathophysiology, between June and December 2021 were included. All IIM patients fulfilled the 2016 EULAR/ACR classification criteria (15). During recruitment of patients, we excluded those with concomitant or other causes of small airway diseases based on history, medications and health records, including but not limited to asthma, chronic obstructive pulmonary disease, bronchiectasis and treatment with medica-

tions affecting small airways (*e.g.*, beta blockers). Patients were evaluated for clinical symptoms and signs associated with IIM, including those related to muscle, articular, skin and lung involvement. Arthralgias were defined as joint pain reported by patients for at least 30 minutes daily and for 3 consecutive months accompanied by morning stiffness. Arthritis was defined as the presence of synovitis documented by the attending physician. Respiratory failure was defined as arterial oxygen tension (PaO2) lower than 60mmHg in breathing air (21% oxygen) or/and arterial carbon dioxide tension (PaCO2) greater than 50mmHg. Active smokers were defined as patients who were smoking at the time of inclusion in the study or had quit smoking less than a year. Former smokers were defined as patients who had ever smoked and had quit smoking more than a year before inclusion (16).

All IIM patients underwent high resolution computed tomography (HRCT) of the lungs as baseline standard of care at the time of diagnosis. HRCT scans were evaluated by a special radiologist blindly, for the presence of ILD and the imaging pattern, such as nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) and organizing pneumonia (OP), according to Fleischner Society definitions (17, 18). Clinical, laboratory and immunologic data were collected from all IIM recruited patients at the time of diagnosis.

Immunological work-up included indirect immunofluorescence for antinuclear antibodies (ANA) on commercially available Hep-2 cells and ethanol-fixed neutrophils using the NOVA Lite HEp-2 ANA kit (Inova Diagnostics Inc, San Diego, CA, USA), according to manufacturer's instructions, and immunoblotting for extractable nuclear antigen antibodies (ENA), including anti-Ro, anti-La, anti-U1 ribonucleoprotein (anti-U1RNP) and anti-Sm antibodies, using the Euroline Anti-ENA ProfilePlus1 (IgG) kit (Euroimmun, Lübeck, Germany). Myositis specific and myositis associated autoantibodies (MSAs, MAAs) were evaluated by line immunoblot assay (EUROLINE: Autoimmune Inflammatory Myopathies 16 Ag, EUROIMMUN, Lübeck, Germany). This assay detects the presence of the MSAs: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-Mi-2 alpha, anti-Mi-2 beta, anti-MDA5, anti-SAE1, anti-NXP2, anti-SRP anti-TIF1γ, as well as the MAAs: anti-Ro-52, anti-PM-Scl75, anti-PM-Scl100 and anti-Ku.

The study has been approved by the ethics committee of the School of Medicine, National and Kapodistrian University of Athens (ethics approval number: 461/23.03.2022). All patients were explicitly informed about the nature of the study and the investigations performed and they gave written consent for their participation and use of the study data for research purposes.

Assessment of pulmonary and small airway function

Standard spirometry was performed using the Q-Box (Cosmed Micro Quark, Italy). FVC, forced expiratory volume in 1 second (FEV_1), FEV_1/FVC, FEF_{25-75} were measured. Age, gender, height and weight were recorded and predicted values of respiratory parameters were calculated automatically, by comparing each respiratory parameter of patients to an average for a person of the same gender, height and age. DLCO was measured with the single breath holding technique using CH4 and CO as tracer gases. Corrections were made for the arterial haemoglobin concentration. The measurement of static lung volumes [total lung capacity (TLC), residual volume (RV)] and airway resistance and conductance (Raw, Gaw) were performed through body plethysmography technique.

Static lung volumes were also measured by the multiple breath nitrogen washout technique. Maximal inspiratory and expiratory pressures (MIP, MEP) were measured with a standard flanged mouthpiece connected to the Q-Box, with computation of the average pressure sustained over one second. Predicted values were those of the European Respiratory Society (19-21), except for MIP and MEP in which case predicted values were of Evans *et al.* (22).

Respiratory resistance was measured by the interrupter technique (R_{int}) and as predicted values those of asthma UK were used (10).The respiratory resistance, reactance and resonance frequency were measured using impulse oscillometry (IOS) equipment (MS-IOS Jaeger) according to ERS protocols (23). IOS was performed before spirometry because forced expiration might change airway tone and predicted values of the European Respiratory Society were employed (24). A more detailed description of the contemporary pulmonary function tests and the relevant techniques is provided in the supplementary material.

Statistical analysis

Statistical analysis for categorical data was performed by Fisher exact test when cell counts <5 patients or χ^2 square test with Yates correction accordingly and numerical data with Man-Whitney test or t test after applying the Shapiro-Wilk normality test. Correlations between the extent of ILD and conventional or contemporary parameters of pulmonary function or between pulmonary function parameters were explored by either point biserial or Pearson coefficient. Statistical analysis was performed in Python 3.6 and GraphPad 7.0a.

Results

Clinical features of IIM patients with and without ILD

The study cohort comprised of 26 naïve IIM patients, 13 with and 13 without ILD (IIM-ILD and IIM-non-ILD respectively). Nine patients had classical DM (4 patients with and 9 without ILD), 9 patients had antisynthetase syndrome with concomitant ILD and 4 patients had frank PM without ILD. The majority of patients were women (77%) and the mean ± SD age was 58.9±13.1 years. 27% of patients were active smokers who had smoked for a mean ± SD of 9.0±6.7 pack-years and 27% were former smokers who had smoked for a mean±SD of 11.1±9.7 pack-years. Gender, age, smoking history and total pack-years did not differ significantly between the two groups of patients (IIM-ILD patients *vs.* IIM

Table I. Clinical and immunological characteristics of IIM patients with and without ILD.

	IIM-ILD patients (n=13)	IIM patients without ILD (n=13)	*p*-value
Female gender*	11 (85)	9 (69)	0.65
Age**	59.9±8.2	57.9±16.1	0.71
Positive smoking history*#	5 (38)	9 (69)	0.29
Active smokers*	2 (15)	5 (38)	0.38
Total pack-years for smokers*#	9.8 ± 9.1	10.2 ± 8.0	0.93
Fever*	8 (62)	1 (8)	**0.011**
Fatigue/malaise*	4 (31)	2 (15)	0.65
Muscle weakness*	11 (85)	13 (100)	0.48
Myalgias*	8 (62)	5 (38)	0.43
Arthralgias*	10 (77)	3 (23)	**0.017**
Arthritis*	6 (46)	1 (8)	0.08
Raynaud's phenomenon*	4 (31)	5 (38)	1
DM related skin rash*	9 (69)	8 (62)	1
Oesophageal dysmotility*	3 (23)	2 (15)	1
EMG positive findings*	4 (31)	2 (15)	0.43
Dyspnoea*	7 (54)	0 (0)	**0.005**
Cough*	4 (31)	0 (0)	0.09
Respiratory failure*	3 (23)	0 (0)	0.22
Elevated ESR*	6 (46)	5 (38)	>0.99
Elevated CRP*	6 (46)	6 (46)	>0.99
Elevated CPK*	5 (38)	4 (31)	>0.99
ANA*	11 (85)	12 (92)	>0.99
Myositis-associated antibodies*	10 (77)	5 (38)	0.11
Myositis specific antibodies*	11 (85)	9 (69)	0.65
Antisynthetase antibodies*	9 (69)	1 (8)	**0.004**

*Data are expressed as n (%).
**Data are expressed as mean ± standard deviation.
#Active or former smokers.
ANA: antinuclear antibodies; DM: dermatomyositis; EMG: electromyography; ESR: erythrocyte sedimentation rate; CPK: creatine phosphokinase; CRP: C-reactive protein; IIM: idiopathic inflammatory myopathies; ILD: interstitial lung disease.

patients non-ILD) (Table I). Clinical, laboratory and imaging features were compared between the two groups of patients. IIM-ILD patients presented more frequently with dyspnoea (53.8% *vs*. 0%, *p*=0.005; OR = ∞, 95% CI: 3.3-∞), fever (61.5% *vs*. 7.7%, *p*=0.011; OR = 19.2, 95% CI: 1.97-226.6) and arthralgias (76.9% *vs*. 23%, *p*=0.017; OR = 11.1, 95% CI: 1.83-52.59), compared with IIM patients without ILD. Cough and arthritis were also more prevalent in IIM-ILD patients, but without reaching statistically significant difference (30.8% *vs*. 0%, *p*=0.09 and 46.2% *vs*. 7.7%, *p*=0.08 respectively). Other clinical features (including muscle, skin and oesophageal involvement), inflammation markers and serum muscle enzymes did not differ between the two groups. Ground-glass opacities were the most frequent finding (92.3%) among IIM-ILD patients, followed by reticular opacities (84.6%); 12 of 13 (92.3%) IIM-ILD patients had an imaging pattern of NSIP, while 1 patient (7.7%) had the OP pattern (Table I). The IIM-ILD group presented more frequently positive anti-synthetase antibodies than IIM-non-ILD patients (69.2% *vs*. 7.7%, *p*=0.004; OR = 27, 95% CI: 2.66-314.1). Treatment modalities for IIM-ILD patients included corticosteroids, mycophenolate mofetil, rituximab or intravenous immunoglobulin, while IIM-non-ILD patients received corticosteroids, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, rituximab or intravenous immunoglobulin (Table I and Supplementary Table S1).

Pulmonary and small airway function tests in IIM patients with and without ILD

IIM-ILD patients tended to present lower predicted FVC than IIM patients without ILD, (mean: 88.2% *vs*. 104.1%, *p*=0.09), while predicted slow vital capacity (SVC) was statistically significantly lower in IIM-ILD patients (mean: 82.7% *vs*. 102.5%, *p*=0.044). Forced expiratory volume in 1 second (FEV_1), forced expiratory flow at 25–75% of FVC (FEF_{25-75}), peak expiratory flow (PEF), maximal inspiratory and expiratory pressures (MIP, MEP) did not differ between the 2 groups. Predicted DLCO was markedly lower in IIM-ILD patients (mean: 56.3% *vs*. 78.2%, *p*=0.005). Furthermore, predicted TLC and RV measured by multiple breath nitrogen washout method (TLC_{N2WO}, RV_{N2WO}) were significantly lower in IIM-ILD patients (mean: 111.1% *vs*. 153.4%, *p*=0.034, median: 171% *vs*. 210%, *p*=0.039, respectively). On the other hand, TLC and RV measured by body plethysmography method did not differ significantly between the two groups.

Airway resistance (Raw) and specific airway conductance (sGaw) measured by body plethysmography and the impulse oscillometry parameters R20, R6-R20, X6 and Fres did not differ between IIM-ILD patients and IIM patients without ILD. Predicted respiratory resistance measured by the interrupter technique (R_{int}) tended to be higher among IIM-ILD patients, difference hardly missed statistical significance (mean: 100.5% *vs*. 76.6%, *p*=0.053). Considering that multiple breath nitrogen washout tends to underestimate lung volumes in patients with small airway obstruction due to gas trapping as compared to body plethysmography (13, 14), we chose to use the TLC nitrogen washout/TLC body plethysmography ratio (TLC_{N2WO}/TLC_{pleth}) as an indirect measure of small airway function. Indeed, IIM-ILD patients exhibit a significantly lower TLC_{N2WO}/TLC_{pleth} ratio than IIM-non-ILD patients (median: 1.28, range 1.02-1.52 *vs*. median 1.45, range 1.28-2.56, *p*=0.039). Pulmonary and small airway functional tests are shown in Table II and Supplementary Table S2.

Due to the low number of IIM-ILD patients only specific correlations could be explored. No correlation could be identified between the extent of ILD among IIM-ILD patients (defined as high exten t>20% of lung parenchyma and low extent <20%) with predicted R_{int} and sGaw, except from DLCO which showed a statistically signifi-

Table II. Pulmonary and small airway function characteristics of IIM patients with and without ILD.

	IIM-ILD patients (n=13)	IIM patients without ILD (n=13)	*p*-value
FVC (% pred)*	88.2 ± 23.4	104.1 ± 21.2	0.09
FEV1 (% pred)*	85.8 ± 18.1	101.9 ± 22.9	0.07
FEV1/FVC (%)*	82.7 ± 7.7	80.9 ± 7.7	0.57
FEF_{25-75} (% pred)*	85.7 ± 32.4	90.4 ± 36.9	0.74
PEF (% pred)*	101.6 ± 22.2	96.6 ± 17.6	0.52
Raw (cmH2O*s/L)*	2.47 ± 1	2.52 ± 1.01	0.83
sGaw (1/cmH2O/s)*	0.22 ± 0.07	0.17 ± 0.05	0.07
TLC_{pleth} (% pred)*	82.6 ± 18.1	89.9 ± 16.4	0.32
RV_{pleth} (% pred)*	83.9 ± 23.9	76.1 ± 20.2	0.40
TLC_{N2WO} (% pred)*	111.1 ± 18.7	153.4 ± 41.2	**0.034**
RV_{N2WO} (% pred)**	171 (90-190)	210 (129-379)	**0.039**
TLC_{N2WO}/TLC_{pleth}**	1.28 (1.02-1.52)	1.45 (1.28-2.56)	**0.039**
DLco (% pred)*	56.3 ± 16	78.2 ± 17.2	**0.005**
MEP (% pred)*	69 ± 27.4	62.4 ± 26	0.57
MIP (% pred)*	93.4 ± 25.2	72.5 ± 25.6	0.06
R_{int} (% pred)*	100.5 ± 23.3	76.6 ± 31.9	0.053
R6-R20 (kpa/l/sec)*	0.08 ± 0.11	0.04 ± 0.09	0.41
X6 (kpa/l/sec)*	-0.23 ± 0.11	-0.2 ± 0.11	0.49
Fres (Hz)*	19.68 ± 5.47	21.89 ± 6.15	0.41

*Data are expressed as mean ± standard deviation.
**Data are expressed as median (range).
DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume in 1 second; FEF25-75: forced expiratory flow after an expiration of 25% to 75% of forced vital capacity; Fres: resonance frequency; FVC: forced vital capacity; IIM: idiopathic inflammatory myopathies; ILD: interstitial lung disease; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; PEF: peak expiratory flow; R6: resistance at 6Hz; R20: resistance at 20Hz; Raw: airway resistance; R_{int}: respiratory resistance measured by the interrupter technique; RV: residual volume; RV_{N2WO}: residual volume measured by multiple breath nitrogen washout; RV_{pleth}: residual volume measured by body plethysmography; sGaw: specific airway conductance; TLC: total lung capacity; TLC_{N2WO}: total lung capacity measured by multiple breath nitrogen washout; TLC_{pleth}: total lung capacity measured by body plethysmography; X6: reactance at 6Hz.

cant negative relation (p=0.011, r=-0.7, Supplementary Fig. S1). Predicted R_{int} was not associated with either DLCO or FEF_{25-75} and neither was DLCO with sGaw. A weak correlation was only found between FEF_{25-75} and sGaw (p=0.045, r=0.562, Suppl. Fig. S2).

Discussion

In this prospective study, the clinical, laboratory and imaging features of a group of newly diagnosed IIM patients with and without ILD are presented, together with their conventional and contemporary pulmonary and small airway function tests. IIM-ILD patients presented more frequently with fever, arthralgias and dyspnoea and had higher prevalence of anti-synthetase antibodies, compared to IIM patients without ILD. Classic spirometric parameters did not differ between the two groups, but as expected DLCO was significantly lower among IIM-ILD patients. Most lung physiology parameters assessing small airway function did not differ between the 2 groups, including Raw, sGaw and impulse oscillometry parameters (Fres, R6-R20, X6). However, IIM-ILD patients had a significantly lower TLC_{N2WO}/TLC_{pleth} ratio while respiratory resistance measured by the interrupter technique (R_{int}) was higher in IIM-ILD patients, both suggesting at least some degree of small airway dysfunction. Interestingly, no statistically significant difference was found between the IIM-ILD patients and IIM patients without ILD, regarding smoking history (active or former).

ILD is traditionally considered a diffuse parenchymal disorder, sparing the large and small airways. However, a number of previous studies have supported small airway involvement in non-autoimmune ILD (6, 7). Fulmer *et al*. after studying patients with idiopathic pulmonary fibrosis (IPF), found peribronchiolar inflammation and fibrosis, as well as reduction of small airway diameter in lung biopsy (25). Recently two independent groups described small airway disease using multidetector CT and micro-CT in specimens of explanted lungs of IPF patients who underwent lung transplantation, by demonstrating a reduction of the number of terminal bronchioles, as well as thickening and narrowing of preterminal bronchioles in areas of the lungs with minimal fibrosis (26, 27). In another study, small airway pathology in lung biopsies of patients with both UIP and NSIP, revealed small airway remodelling, bronchiolar and peribronchiolar parenchymal inflammation and fibrosis, bronchiolar epithelial metaplasia and peribronchiolar bronchus-associated lymphoid tissue (BALT), implying expansion of inflammation from lung intersitium to terminal bronchioles. On the contrary, studying small airways in more preserved areas of the lungs without extensive fibrosis, suggested that small airways could participate directly in idiopathic interstitial pneumonia pathogenesis rather than being the result of expansion of parenchymal inflammation. Interestingly, patients in that study did not present abnormal pulmonary function parameters concerning small airway disease rather because of the inability of conventional PFTs to detect mild small airway dysfunction (5). Thus, it is possible that small airways might be the primary site of involvement in ILD driving the inflammatory process in lung interstitium. Whether small airways is the target or the initiator of the interstitial insult of the lung remains to be addressed.

Small airway involvement in ILD patients with systemic autoimmune diseases has been described only in one study, documented mainly by imaging modalities and to a lesser extent by pulmonary function testing. Patients with ILD, either idiopathic or in the context of systemic autoimmune rheumatic diseases, had findings of small airway disease on HRCT, without abnormal conventional PFTs but higher values of oscillometry parameters R5-R20, X5 and Fres (28). However, the number of ILD patients with associated systemic autoimmune rheumatic diseases was rather small and no distinc-

tion was made between ILD patients with or without systemic autoimmune rheumatic diseases or among the various systemic autoimmune rheumatic diseases.

We hypothesised that ILD involvement among IIM patients could potentially affect the small airway function as supported by the literature regarding non autoimmune UIP and NSIP cases (5-7). contemporary pulmonary function tests may reveal early changes in small airway function. Interestingly, small airway disease, when present in ILD patients, seems to participate in their symptoms and treatment with bronchodilators may help to ameliorate these symptoms. Hu *et al*. showed that IPF patients with small airway dysfunction, determined by impulse oscillometry parameters, showed significant improvement in FEV_1, FEF_{25-75} and symptoms after treatment with bronchodilators (8). Additionally, early detection of small airway disease in the context of ILD may lead to more aggressive therapeutic interventions in order to avoid irreversible tissue damage and inappropriate remodelling.

Our study is the first to describe small airway dysfunction in idiopathic inflammatory myopathies patients. Many contemporary indices of small airway dysfunction did not differ between patients with and without ILD involvement. To the extent of our knowledge, such evaluation has never been conducted before in IIM patients and according to our cohort, the TLC_{N2WO}/TLC_{pleth} ratio appears to be a sensitive index of small airway dysfunction in IIM-ILD patients.

The present study has some limitations. Firstly, the number of patients is rather small to reveal statistically significant differences between IIM patients with and without ILD at least in some pulmonary function tests, to identify associations with clinical features and to perform multivariable analysis for risk factors of ILD. Secondly, the lack of healthy controls in our study leaves unanswered the question whether there is some degree of small airway dysfunction in IIM-non-ILD patients compared to healthy individuals. Thirdly, we have introduced a new and very sensitive respiratory index (TLC_{N2WO}/TLC_{pleth} ratio) to assess small airway function without comparing with a reliable standard method, since the commonly employed index of FEF_{25-75} is not always indicative. Finally, no lung biopsy has been performed in any of these IIM-ILD patients to document the presence of small airway inflammation.

Conclusion

Small airway disease may be an early manifestation of IIM associated ILD which could be underdiagnosed with conventional PFTs. Large prospective cohorts of IIM patients with and without ILD are required to confirm this clinical observation and address the potential of early diagnosis and treatment initiation to affect the progression of the disease at the level of small airways. On the other hand, lung biopsies from selected patients are anticipated to provide insights into the underlying pathogenetic mechanisms such as inflammation and/or impaired remodelling.

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