Original Article

Increased expiratory flows identify early interstitial lung disease

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Abstract:

BACKGROUND: Most interstitial lung diseases (ILDs) manifest with a restrictive ventilatory defect as the common physiologic abnormality. Low carbon monoxide diffusing capacity (Dlco) is considered to be the earliest abnormality on pulmonary function tests (PFTs) in patients with ILD. However, its measurement requires complex and expensive equipment. Our study aimed to assess if high expiratory flows are the earliest PFT abnormality in patients with idiopathic pulmonary fibrosis (IPF) and ILD.

METHODS: In a real-world cohort of incident cases with ILD, we identified the initial PFTs on all patients newly diagnosed with ILD at Kingston Health Sciences Center (in Kingston, Ontario, Canada) between 2013 and 2017. The diagnosis of ILD, including IPF, was established as per current guidelines. Among patients with normal forced vital capacity (FVC), total lung capacity (TLC), and Dlco, we assessed the frequency of high expiratory flows defined as forced expiratory volume in 1 s (FEV_1)/FVC, FEF_{25}, FEF_{25-75}, $FEF_{75,}$ and peak expiratory flow > 95% confidence limit of normal. We adjusted for emphysema, increased airway resistance, and obesity.

RESULTS: We assessed PFTs of 289 patients with ILD; 88 (30%) of them had normal FVC, TLC, and Dlco. Among these, high FEV1/FVC was the most common abnormality in 37% of patients, in 43% of nonobese patients, and in 58% of those with no emphysema and normal airway resistance. Results were similar in the 88 patients with IPF.

CONCLUSIONS: High FEV1/FVC could allow identifying patients with ILD/IPF in the earliest stages of their disease with simple spirometry, leading to earlier diagnosis and treatment.

Keywords:

Expiratory flows, idiopathic pulmonary fibrosis, interstitial lung diseases

Interstitial lung diseases (ILDs) are a diverse group of pulmonary disorders with similar clinical, roentgenographic, physiologic, or pathologic features involving inflammation and fibrosis of the alveoli, distal airways, and interstitium of the lungs.[1,2] Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial pneumonia and the most common idiopathic interstitial pneumonia.[3] Most ILDs including IPF share a common pattern of physiologic abnormality. A restrictive ventilatory defect is typical with a downward and rightward shift of the pressure–volume curve. Lung recoil is increased over the range of the inspiratory capacity (IC) with a reduction of total lung capacity (TLC), vital capacity (VC), and carbon monoxide diffusing capacity (Dlco).[4-6] Low Dlco and a fall in PaO2 on exercise have been described as the earliest function test changes in ILD.[6] A few small studies have reported that some expiratory flows – when adjusted for volume – may be normal or high normal in ILD patients.[7-9]

However, to our knowledge, no studies have assessed if increased expiratory flows are the initial abnormality on pulmonary function tests (PFTs) in ILD.

Objective

We aimed to assess if high expiratory flows are the earliest PFT abnormality in patients with IPF and ILD.

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Methods

This was a study performed in a real-world cohort of newly diagnosed patients with any ILD at Kingston Health Sciences Center (KHSC) in Kingston, Ontario, Canada, between January 2013 and December 2017. To determine the earliest functional abnormality in these patients, we obtained the initial lung function test results available from the PFT laboratory database for all incident cases with IPF/ILD diagnosed at the KHSC-ILD clinic. We did not exclude any cases. The information on all ILD patients is stored in a dedicated ILD clinic database at KHSC, including PFTs. To ensure we obtained the earliest PFT results on these patients, we did a deterministic linkage of the ILD clinic database and the PFT laboratory database using KHSC unique patient identifier codes.

The diagnosis of ILD, including IPF, was established in the ILD clinic according to guideline criteria.[3,10] The PFTs were done using standard equipment and according to the American Thoracic Society and European Respiratory Society guidelines. We applied the Global Lung Function Initiative (GLI) reference values for spirometry, lung volumes, and Dlco. We collected information on the presence of obesity (body mass index >30 kg/m^2), emphysema (on chest computed tomography [CT]), and increased airway resistance (on plethysmography), to adjust in the analyses for the potential confounding effect of these factors on PFT results and particularly in expiratory flows. The study was approved by the Queen's University Research Ethics Board.

Analysis

We did a descriptive analysis of the patients as well as type and frequency of abnormal PFT results in the baseline PFTs in all ILD/IPF patients. We used mean and standard deviation for continuous variables and frequencies/percentages for categorical variables.

We defined abnormal PFT results as those <5% or >95% of the confidence limit of GLI reference values for the following variables: forced VC (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, FEV at 25%–75% of FVC (FEF_{25-75}), at 50% (FEF_{50}) of FVC, and at 75% of FVC (FEF_{75}), and peak expiratory flows (PEFs). TLC, VC, IC, functional residual capacity, expiratory reserve volume, and residual volume; and Dlco.

Among patients with normal FVC, TLC, and Dlco, we determined the frequency of high expiratory flows. We defined high expiratory flows as either FEV_1/FVC, FEF_{25}, FEF_{25-75}, FEF_{75}, or PEF being >95% confidence limit of the corresponding normal GLI reference values. We also applied stratified analyses to adjust for the potential confounding effect of emphysema, increased airway resistance, and obesity. We did these analyses for all ILD patients and independently for patients with IPF. Because this is a descriptive analysis of the frequency of high expiratory flows in patients with ILD with no evidence of a restrictive parenchymal abnormality on PFTs (i.e., normal FVC, TLC, and Dlco), no comparative analyses were done. We used SPSS Inc Chicago, Illinois 60606-6307, U.S.A for the analyses.

Results

We included 289 ILD patients in the study, 30% of patients had IPF, 59% were male, 43% were obese, and 28% had emphysema on chest CT [Table 1]. On their initial PFTs, 30% of patients had low FVC, 52% low TLC, and 55% low Dlco. Thirty percent of all ILD patients had normal FVC, TLC, and Dlco.

High FEV_1/FVC was the most common abnormality among patients with normal FVC, TLC, and Dlco and was present in 30% of cases [Table 2]. However, high FEV_1/FVC was present in 50% of patients with normal airway resistance and 58% of patients with no emphysema on CT. High FEF_{50} was the next most common abnormal airflow in ILD patients, found in up to 32% of patients with normal airway resistance and no emphysema. After adjusting for obesity, among ILD patients with normal FVC, TLC, and Dlco, 43% had a high FEV_1/FVC, and 29% had a high FEF_{50}. Results were similar when the analysis was done in the 88 patients with IPF.

Discussion

To our knowledge, ours is the first study to assess high expiratory flows as the initial lung function abnormality in patients with ILD. We found that high FEV_1/FVC is the earliest abnormality on PFTs in patients with ILD and IPF.

Table 1: Baseline demographic and clinical characteristics of interstitial lung disease patients (*n*=289)

Characteristic	Mean (SD) or frequency (%)
Age (years)	65 (20)
Gender	
Male	171 (59)
Female	118 (41)
Diagnosis	
IPF	86 (30)
CTD-ILD	81 (28)
HP	50 (17)
Other ILDs	103 (36)
Obese (>30 kg/m^2)	123 (43)
Emphysema on chest CT	81 (28)

Other ILDs included drug related, idiopathic NSIP, sarcoidosis, asbestosis, and unclassifiable. IPF = Idiopathic pulmonary fibrosis, CTD-ILD = Connective tissue-related interstitial lung disease, HP = Hypersensitivity pneumonitis, CT = Computed tomography, NSIP = Nonspecific interstitial pneumonia, SD = Standard deviation

Table 2: Percentage of patients with high expiratory flows (>95% confidence limit of normal Global Lung Function Initiative reference values)

	Percentage of patients with high expiratory flows				
	All cases (%)	With normal FVC, TLC, and Dlco			
		Percentage	Normal airway resistance (%)	Normal airway resistance and no emphysema (%)	Nonobese (%)
FEV_1/FVC	37	30	50	58	43
FEF_{50}	16	13	26	32	29
$FEF_{25–75}$	4	6	5	6	10
FEF_{75}	4	2	0	1	0
PEF	2	4	8	10	14

FEV_1 = Forced expiratory volume in 1 s, FEF_{50} = Forced expiratory volume at 50% of FVC, $FEF_{25–75}$ = Forced expiratory volume at 25%–75% of FVC, FEF_{75} = Forced expiratory volume at 75% of FVC, GLI = Global Lung Function Initiative, FVC = Forced vital capacity, TLC = Total lung capacity, Dlco = Carbon monoxide diffusing capacity, PEF = Peak expiratory flow

High FEV1/FVC was the only PFT abnormality in almost a third of all patients with ILD. The increase in expiratory airflows in patients with ILD/IPF is explained by the combined effects of increased elastic recoil and reduced resistance in peripheral airways.[7] A high proportion of IPF patients are smokers/ex-smokers which puts them at risk for chronic obstructive pulmonary disease (COPD). However, diagnosing COPD depends on a reduced postbronchodilator FEV_1/FVC that could be falsely normal or even high in ILD patients. Because emphysema can decrease the lung elastic recoil and increase airway resistance, we adjusted by excluding patients with these conditions from the analyses and found a high FEV1/FVC as the only PFT abnormality in more than one in two ILD patients without emphysema. On the other hand, obesity can increase chest wall elastic recoil and increase airflow; as such, we controlled for obesity and found that high FEV1/FVC was the only PFT abnormality in almost one in two nonobese patients with ILD. Hence, our findings are robust even after controlling for common causes that affect expiratory airflows.

Thus, simple spirometry could be a useful screening test for ILD patients, even before the disease becomes symptomatic. Examples are asymptomatic patients with family history of ILD, or patients with incidental fine or coarse crackles on chest auscultation, which have been reported to be the earliest clinical manifestation of ILD.[11]

For symptomatic patients, it has been widely accepted that low Dlco is the earliest abnormality in patients with ILD; however, we have shown that high expiratory flows are present even in patients with normal Dlco. Furthermore, measuring Dlco requires equipment that is not usually available in physician's offices, and it is more expensive and time-consuming than simple spirometry. Simple spirometry is frequently requested by clinicians in the diagnostic workup of patients with persistent respiratory symptoms; high expiratory flows on spirometry would allow suspecting ILD in such patients.

Thirty percent of our ILD patients had normal lung volumes and Dlco, which is a high proportion for a tertiary care referral center; however, this is because our ILD clinic receives also referrals directly from family physicians in southeastern Ontario, including patients incidentally found to have interstitial lung abnormalities on chest CT. This provided us with a unique opportunity to study patients with ILD early in their disease.

A limitation of our study is that it was performed in a single center and on PFTs performed up until 2017. As such, validation in other centers would be desirable to ensure the generalizability of results. However, the pathophysiologic mechanism by which early ILD causes an increase in expiratory flows in humans is universal; in particular, FEV1/FVC does not depend on reference values that may vary across populations and time. As such, the point prevalence of high expiratory flows in early ILD may vary among centers, but the conclusions of our study are expected to remain, despite geographic location or time.

Conclusions

High FEV1/FVC is the earliest abnormality observed on PFTs in patients with ILD/IPF. High FEV1/FVC could allow identifying patients with ILD/IPF in the earliest stages of their disease with simple spirometry, leading to early diagnosis and treatment.

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Conflicts of interest
There are no conflicts of interest.

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