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Original research article

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Expiratory flow limitation in a cohort of highly symptomatic COPD patients

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Take home message: EFL, defined by oscillometry, is a common and relatively stable component of disease pathophysiology in highly symptomatic COPD patients. EFL is associated with worse airflow obstruction, small airway resistance, worse quality of life and obesity.

Abstract

The question addressed by the study

Small airway collapse during expiration, known as expiratory flow limitation (EFL), can be detected using oscillometry and is associated with worse clinical outcomes in chronic obstructive pulmonary disease (COPD).

This study investigated the prevalence of EFL in a cohort of highly symptomatic patients, evaluated clinical and lung function characteristics of patients with EFL and studied the repeatability of EFL over 6 months.

Materials/patients and methods

Seventy patients were recruited. Clinical characteristics and lung function metrics were collected at baseline and 6 months. Impulse oscillometry (IOS) was used to detect presence of EFL. Patients were defined as EFL^{High} ($\Delta X5 \geq 0.28$ kPa/L/s); $EFL^{Intermediate}$ ($\Delta X5$ 0.1-0.27kPa/L/s) and EFL^{None} ($\Delta X5 < 0.1$ kPa/L/s).

Results

EFL^{High} was present in 47.8% of patients at baseline. $\Delta X5$ showed excellent repeatability over 6 months (rho = 0.78, $p<0.0001$, ICC = 0.88), with the best repeatability observed in EFL^{None} and EFL^{High} patients (ICC = 0.77 and 0.65 respectively). Compared to EFL^{None} patients, EFL^{High} had a higher BMI, worse health-related quality of life and increased peripheral airway resistance. $EFL^{Intermediate}$ was more variable over time with less severe physiological impairment.

Answer to the question

Overall, these data indicate that EFL^{High} is a common, and relatively stable, component of disease pathophysiology in highly symptomatic COPD patients. EFL^{High} was also associated with worse quality of life and obesity.

Introduction

Chronic obstructive pulmonary disease (COPD) is caused by the inhalation of noxious particles, resulting in airflow obstruction and respiratory symptoms including dyspnoea, cough and sputum production [1]. Small airway disease (SAD) is a key feature of COPD, characterised by immune cell infiltration, mucus hypersecretion and airway remodelling [2, 3]. These pathological changes cause narrowing of the small airways, thereby increasing resistance to airflow [2]. Incomplete emptying of the lung upon expiration due to SAD causes gas trapping, which increases the work of breathing and is associated with increased dyspnoea [4-6]. Small airway closure and collapse during expiration is known as expiratory flow limitation (EFL), which occurs due to regional choke points within the bronchial tree [6]. EFL is associated with increased gas trapping, a greater symptom burden and reduced exercise performance [6-8].

Oscillometry is a non-invasive technique that measures elements of respiratory mechanics during tidal breathing, notably resistance and reactance [5]. A marked change in reactance measured at 5 Hz during expiration compared to inspiration ($\Delta X5$) is a marker of EFL [9]. A threshold value of $\geq$0.28kPa/L/s ($\Delta X5$) has been used to define EFL, with patients above this threshold having more gas trapping and a greater symptom burden [6, 9]. A lower $\Delta X5$ value of >0.10 kPa/L/s, which likely detects less severe EFL, is also associated with greater dyspnoea [4]. Previous EFL studies have used broad COPD populations [6, 8, 10, 11], demonstrating associations between EFL and worse clinical characteristics including lower FEV_1 [6, 11], greater dyspnoea, with increased exercise limitation [4, 6], and increased exacerbation frequency [6, 8].

Dyspnoea is the most common symptom in COPD patients [12]. Airflow obstruction itself causes dyspnoea, but FEV_1 correlates poorly with dyspnoea [13, 14]. Other contributors to dyspnoea include gas trapping, cardiac dysfunction and muscle wasting [15]. The measurement of EFL, as a cause of gas trapping, may be a useful tool during the investigation of dyspnoea in

COPD patients. Furthermore, EFL can be considered to be a treatable trait [16] in COPD patients with dyspnoea, as it is a component that can be specifically targeted with inhaled treatment.

Previous EFL studies have enrolled broad COPD populations, including individuals with varying degrees of dyspnoea. This study focused on highly symptomatic COPD patients, as the investigation of EFL is most relevant in these individuals. The main aim was to determine the prevalence of EFL in this COPD subgroup. We used different EFL thresholds (≥0.28kPa/L/s and >0.10 kPa/L/s), and studied the relationships between EFL and other lung function measurements and clinical characteristics. Measurement repeatability over 6 months was evaluated.

Methods

Study cohort

Seventy COPD patients were recruited from the Medicines Evaluation Unit (Manchester University NHS Foundation Trust). Subjects were ≥40 years old, had a smoking history of ≥10 pack years, were not using maintenance antibiotics or oral corticosteroids and had no previous asthma diagnosis. Subjects were required to have a modified medical research council (mMRC) score ≥2 and COPD assessment test (CAT) score ≥15. All patients provided written informed consent using protocols approved by local Ethics Committees (16/NW/0836).

Study design

Clinical characteristics were obtained from participants during stable state, defined as no exacerbation or respiratory illness within 4 weeks of the baseline and 6 month visits.

Measurements

CAT [17], mMRC [18] and St George's Respiratory Questionnaire (SGRQ-C) [19] scores assessed symptoms and health related quality of life at both visits. The following procedures were performed at the baseline and 6 month visits; 6 minute walk test (6MWT), fat free mass assessment (BodyStat 1500, BodyStat Ltd, UK), Impulse oscillometry (IOS) (MasterScreen; Erich Jaeger, Hoechbery, DEK), spirometry with reversibility to 400µg of Salbutamol (EasyOne spirometer, NDD medical technologies, CHE), body plethysmography and diffusing capacity of the lungs for carbon monoxide (DLCO) (Vmax, CareFusion, Hoechbery, DEK). Spirometry, body plethysmography, DLCO and 6MWT were performed according to ATS/ERS guidelines [20-23]. Short acting bronchodilators were withheld for 6 hours, long-acting bronchodilators, anticholinergics, theophyllines and leukotriene receptor antagonists were withheld for up to 24 hours prior to lung function testing. IOS was performed as previously described [24], more detail provided in the supplement. ΔX5 was calculated using the multiple

breath method; mean reactance at 5Hz during inspiration (X5in) minus the mean reactance at 5Hz during expiration (X5ex). Inspiratory and expiratory data were averaged over multiple tidal breaths, which has been validated against the breath-by-breath method where differences between X5in and X5ex are calculated per breath and then averaged; the intraclass correlation coefficient (ICC) = 0.98 [4].

EFL was defined as EFL^{High} ($\Delta X5 \geq 0.28$ kPa/L/s); $EFL^{Intermediate}$ ($\Delta X5$ 0.10-0.27 kPa/L/s) and EFL^{None} ($\Delta X5 < 0.10$ kPa/L/s).

Statistical analysis

No formal sample size calculation was performed; this was a pilot study to generate findings that could be confirmed in larger datasets. Non-parametric data were analysed using the Kruskal-Wallis test with Dunn's post hoc analysis and spearman's correlations. Parametric data were analysed using a one-way ANOVA with a Tukey's post hoc test (Prism, GraphPad, 9.0, USA). Variation over time was assessed using Bland-Altman analysis (Prism, GraphPad, 9.0, USA) and ICC of log transformed data (SPSS 25.0, IBM, Armonk, USA). For ICC analysis of $\Delta X5$, log(x+1) was used to correct for zero values. ICC values were interpreted as excellent (> 0.75), fair to good (0.40–0.75), or poor (< 0.40) [25]. A p-value of <0.05 was considered significant.

Results

The baseline demography and clinical characteristics are shown in Table 1. The mean age was 64.3 years, 55.7% were male and 42.9% were current smokers. The patients were highly symptomatic with a mean SGRQ score of 53.9, and median CAT and mMRC scores of 21 and 4.0, respectively. The majority of patients (>95%) were using regular maintenance inhaled treatments, with 60% using triple therapy (inhaled corticosteroids plus two long acting bronchodilators). The mean exacerbation rate in the previous 12 months was 1.1. Most patients (94.3%) had at least one concomitant disease, with cardiovascular disease being the most prevalent (supplementary table 1).

Presence of EFL

69 and 54 patients provided technically acceptable IOS data at baseline and 6 months, respectively. Details of patients who were lost to follow up can be found in the supplement (Supplementary table 2). 33 (47.8%) patients at baseline and 19 (35.2%) at 6 months were classified as EFL^{High} (Fig. 1). 17.4% were classed as $EFL^{Intermediate}$ and 34.8% as EFL^{None} at baseline, while at 6 months these proportions were 20.4% and 44.4% respectively (Fig. 1).

54 patients provided IOS data at both baseline and 6 month visits. There was a positive correlation between $\Delta X5$ measurements at baseline and 6 months (rho=0.78, $p<0.0001$, Fig. 2A), with an ICC of 0.88 indicating excellent repeatability. Other IOS parameters showed positive correlations and excellent repeatability over 6 months (Fig. 2); R5 (rho=0.83, $p<0.0001$, ICC=0.90), R20 (rho=0.89, $p<0.0001$, ICC=0.93) and R5-20 (rho=0.76, $p<0.0001$, ICC=0.85). FEV_1 % predicted and absolute volume also showed excellent correlations between visits (rho=0.84 and 0.96, $p<0.0001$ for both, ICC=0.92 and 0.98 respectively, Fig. 2E&F).

A Bland-Altman analysis between baseline and 6 month measurements of $\Delta X5$ is presented in Figure 3. Visual inspection of the plot shows that the difference between measurements was

greater for higher EFL measurements. The differences between measurements were not normally distributed, and remained so after log transformation, therefore the mean difference and limits of agreement could not be calculated [26].

Figure 4 shows that 18 (69.2%) out of the 26 EFL^{High} patients at baseline remained EFL^{High} at 6 months, while 6 (23.1%) moved to $EFL^{Intermediate}$. The majority of EFL^{None} patients remained in the same category at 6 months (89.5%). There were significant correlations between baseline and 6 month ΔX5 measurements for EFL^{None}, and EFL^{High} patients (rho=0.75 and 0.43, $p<0.001$ and 0.03 respectively), with ICC values 0.77 and 0.65, respectively. In contrast, there was no correlation for $EFL^{Intermediate}$ (rho= -0.03, p=0.95, ICC=0.07), with only 3 out of 9 patients (33.3%) remaining in the same category at 6 months.

EFL and clinical characteristics

Table 2 shows that EFL^{High} patients at baseline had a higher BMI compared to EFL^{None} (30.2 vs 25.8kg/m^2, $p<0.01$), lower FEV_1 (56.8 vs 76.3% predicted, $p<0.0001$), lower FEV_1/FVC ratio (47.5 vs 57.8%, $p<0.001$) and higher total SGRQ score (57.7 vs 48.0, p=0.04), with increased scores in the activity and impact domains. Furthermore, a relationship was observed between change in total SGRQ score over 6 months and change in ΔX5 and R5-R20 (rho=0.42 and 0.28, p=0.002 and 0.04 respectively, Fig. 5A&B); an increase in ΔX5 or R5-R20 was associated with an increase in SGRQ score. DLCO and KCO were similar between groups. Presence of concomitant diseases were also mostly similar between groups (supplementary table 1).

EFL and other IOS measurements

Table 2 shows that X5 was more negative and R5, R5-R20 and AX were higher in EFL^{High} and $EFL^{Intermediate}$ patients compared to EFL^{None} at baseline, with measurements being higher in EFL^{High} compared to $EFL^{Intermediate}$. Similar results were observed at 6 months (supplementary

table 3). ΔX5 was positively correlated with R5-R20 at baseline and 6 months (rho=0.84 and 0.86 respectively, p<0.0001 for both, Fig. 5C&D).

EFL and lung volumes

Sixty four patients had technically acceptable data collected for IOS and body plethysmography at baseline. Table 2 shows that both EFL^{High} and $EFL^{Intermediate}$ patients at baseline displayed higher RV/TLC ratio compared to EFL^{None} patients, while EFL^{High} patients showed a significantly higher RV % predicted versus EFL^{None}. No differences in DLCO or KCO were observed between groups. Similar results were observed at 6 months (see more detail in the online supplement).

Figure 6 shows that ΔX5 was positively correlated with RV (%) and RV/ TLC at both baseline (rho=0.31 and 0.42, p=0.01 and <0.001 respectively) and 6 months (rho=0.29 and 0.39, p=0.03 and <0.01 respectively). Negative correlations were observed between ΔX5 and FEV_1 % predicted (Fig. 6A&D).

Discussion

In this cohort of highly symptomatic COPD patients, 48% were categorised as EFL^{High} at baseline. This finding highlights that EFL is relatively common amongst highly symptomatic COPD patients, and represents a potential target for treatment (a treatable trait [16]). The majority of these EFL^{High} patients (69%) remained in the same category or were classified as $EFL^{Intermediate}$ (23%) at 6 months, indicating that most EFL^{High} patients exhibit some degree of EFL (either "high" or "intermediate") during longitudinal follow up. Overall, the ΔX5 ICC of 0.88 indicated excellent repeatability, in line with the stability of EFL phenotype observed in the majority of patients.

The clinical features associated with EFL^{High} included reduced quality of life and higher BMI. Additionally, changes in ΔX5 or R5-R20 were associated with changes in quality of life over 6 months, measures of which have previously been shown as highly repeatable [27]. Previous cross-sectional analyses have shown associations between ΔX5 and clinical characteristics including dyspnoea and exacerbation rates (n=425 [8] and 147 [6]). Our 6 month longitudinal analysis provides further evidence of the clinical relevance of EFL, showing an association between changes in ΔX5 and changes in quality of life. Additionally, at baseline EFL^{High} patients had higher SGRQ scores driven by worse scores within the activity and impact domains, consistent with the potential for EFL to reduce exercise capacity. Other studies have produced similar findings for the relationship between ΔX5 and total SGRQ score (n=425 [4]) and the activity domain (n=147 [6]).

Small airways are defined as those <2mm in internal diameter, which are generally found between the 4^{th} - 12^{th} generation of the bronchial tree [2]. The clinical relevance of EFL was highlighted by worse airflow obstruction and increased small airway resistance (measured by R5-R20) in EFL^{High} patients. This finding alone highlights the usefulness of oscillometry measurements in detecting patients with flow limitation at rest which is associated with worse

disease severity [9]. R20 is considered to be a measure of proximal airway resistance [28] and was similar between those with and without EFL (0.36 and 0.39 kPa/L/s respectively, p=0.49). Dynamic collapse of the central airways (EDAC) shows similar reactance patterns to EFL reported here, although R20 was numerically lower in COPD patients versus COPD + EDAC (0.33 versus 1.07 $cmH_20/L/s$) [29]. Hence, it is likely that EFL is a continuous process that can occur throughout the airways.

The majority of EFL^{None} patients (89%) remained in the same category at 6 months, indicating that the absence of EFL is a relatively stable phenotype. EFL^{None} patients had the lowest variability over time for ΔX5 measurements when assessed using ICC (0.77). ICC is a well-accepted method for assessing repeatability over time. Bland-Altman analysis was designed to compare differences between methods, rather than repeatability of the same method [26]. Nevertheless, visual inspection of the Bland-Altman plot allows the 'widening trend' of the differences between measurements with increasing ΔX5 values to be observed. This trend has been previously been described as 'proportional difference variability' [26]. Fluctuations in COPD patients with EFL have been attributed to variation in lung volumes between visits [8]; for the EFL^{None} group, the absence of EFL and associated gas trapping or hyperinflation would lead to less variability between visits. Similarly, it has previously been noted, in a sample size of 425 COPD patients, that ΔX5 measurements show greater variation in individuals with more EFL [4] , although formal statistical analysis of reproducibility was not reported. Here, ICC analysis confirms higher variability for ΔX5 in EFL^{High} and $EFL^{Intermediate}$ patients (ICC 0.65 and 0.07 respectively) versus EFL^{None} patients (ICC 0.77).

The poor reproducibility of $EFL^{Intermediate}$ patients (ICC 0.07) was associated with only 33% remaining in the same category. This suggests that $EFL^{Intermediate}$ represents a relatively small heterogeneous group (17.4% at baseline) who, on repeated testing, are often classified into the group above or below. Using thresholds can lead to reclassification of individuals over time

due to relatively small changes. Nevertheless, our results (in highly symptomatic COPD patients) suggest that a single ΔX5 measurement can allocate the majority of patients to either EFL^{High} or EFL^{None}, with these groups being relatively stable over time. Similarly, in a broad group of COPD patients (not recruited on the basis of symptoms as in our current study), 70% within the EFL^{High} group remained in the same category after 2 years [6].

We observed no difference in dyspnoea or CAT scores between EFL groups, in contrast to previous reports [4, 6]. It has been reported that a ΔX5 threshold of 0.1kPa/L/s predicted breathlessness in COPD patients (sensitivity 64%, specificity 72%), while a threshold of 0.26 kPa/L/s provided a specificity of 95% for detecting breathlessness (area under the curve 0.70) [4]. The absence of any association between EFL and symptoms in the current study can be explained by the inclusion criteria, only allowing patients with higher mMRC and CAT scores to participate, thus reducing the potential to find differences between groups for these patient reported outcome measures. We observed a higher prevalence of EFL^{High} (48%) compared to previous studies using the same ΔX5 threshold (18-37%) [4, 6]. As EFL is known to be associated with a greater symptom burden [6, 8], the recruitment of highly symptomatic patients in this study cohort would be expected to increase the proportion of EFL^{High} patients.

There was an association between BMI and ΔX5, consistent with a previous report that noted a relationship between obesity and EFL [30]. Obesity is known to influence lung function through mechanical alterations caused by increased adipose deposition around the chest wall and abdomen [4, 30]. This causes decreased chest wall and lung compliance, increased work of breathing and reduced functionality of the diaphragm [31], culminating in a reduction in expiratory reserve volume (ERV) and thereby inducing flow limitation [32]. Other factors may also reduce ERV, thereby promoting lower flow rates and facilitating EFL; For example, chronic heart failure (due to an increase in volume of the heart, vascular engorgement and interstitial oedema) and acute respiratory distress syndrome (due to oedema and atelectasis)

[33]. The presence of comorbidities may therefore represent a source of variation in EFL in some COPD patients. Our results support previous observations in similarly sized cohorts that R5-R20 and ΔX5 are significantly associated (n=74 [34]), and that EFL^{High} (and to a lesser extent $EFL^{Intermediate}$) patients had more gas trapping and pulmonary hyperinflation (in studies with sample sizes n=55 [35], 147 [6] and 74 [34]). The associations between ΔX5 and small airway resistance, gas trapping and pulmonary hyperinflation [6, 34, 35] support concepts that small airway narrowing (measured by R5-R20) and collapse (measured by EFL) are linked to gas trapping and hyperinflation [36]. There was greater small airway resistance at ΔX5 >0.10kPa/L/s, with increasing severity from $EFL^{Intermediate}$ to EFL^{High} patients, aligning to the clinical findings showing worse SGRQ scores in EFL^{High} patients. Future studies may consider investigating the relationship between EFL and CT scanning parameters of small airway disease and emphysema to further understand our findings.

EFL^{High} patients may benefit from inhaled treatments that target the small airways. A recent clinical trial showed that the long acting bronchodilator components of an extra-fine triple therapy formulation (particle size <2μm) were able to improve R5-R20 with associated improvements in lung volumes [37]. Targeting the small airways may improve dyspnoea and quality of life [38, 39].

Devices utilising the forced oscillation technique (FOT) such as IOS (MasterScreen, DEK) and airwave oscillometry (AOS) (tremoFlow, CA) differ in airflow perturbation signal and have been directly compared in regard to parameter outputs [40]. It has been noted that resistance is typically greater and reactance more abnormal when comparing IOS to AOS, in healthy and patient populations [28, 40]. These differences were more pronounced in post-bronchodilator measurements and in those with more severe airway obstruction [28]. Therefore, it is important to consider methodologies when comparing clinical studies of oscillation mechanics.

This was an exploratory study, with a limited sample size; our findings need to be confirmed in larger datasets. A limitation of this study was patient withdrawal between visits reducing the sample size at 6 months. The thresholds of ΔX5 used here are based on mean measures of inspiratory and expiratory reactance and although this gives indication EFL presence, it cannot define the precise point(s) during the expiratory limb of tidal breathing at which EFL occurs. This, as described by Lorx et al, highlights further heterogeneity within flow-limited patients [41]. Furthermore, using the multiple breath method to define EFL and trichotomizing patients into categories may classify some patients as $EFL^{Intermediate}$ or EFL^{High} despite not meeting the ΔX5 threshold for every breath.

Conclusion

In conclusion, we report that EFL^{High} was present in approximately half of the individuals in this highly symptomatic COPD cohort. EFL^{High} and EFL^{None} were relatively stable phenotypes over time. EFL^{High} was associated with worse small airway disease, a reduced quality of life and higher BMI. Overall, these data indicate that EFL^{High} is a common, and relatively stable, component of disease pathophysiology in highly symptomatic COPD patients.

Statements

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Statement of Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of HRA, North West – Preston Research Ethics Committee (protocol code: 16/NW0836, date of approval: 13.12.2016). Written informed consent was obtained from all subjects involved in the study.

Conflict of Interest Statement

DS has received sponsorship to attend and speak at international meetings, honoraria for lecturing or attending advisory boards from the following companies: Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Teva, Theravance and Verona. AB, NJ and JD have no conflicts of interest to declare.

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Author Contributions

AB and DS were responsible for the concept and design of study. AB, NJ and DS were involved in data acquisition. AB analysed the data and DS oversaw all analyses. AB and DS were responsible for data interpretation and drafting the manuscript. JD revised the manuscript critically for intellectual content. All authors have approved the final version to be published and are jointly accountable for all aspects of the work.

Data availability statement

The datasets generated and/or analysed during the current study and additional related documents are not publicly available.

Tables

Table 1. Baseline clinical characteristics, n=70[a]

Clinical Characteristic	n=70	Lung function parameter	n=70
Age	64.3 (61.9-66.6)	**Post-BD FEV_1 (% predicted)**	65.6 (16.9)
Gender (% M)	55.7	**Post-BD FEV_1 (L)**	1.7 (0.6)
BMI (kg/m^2)	27.96 (26.54-29.38)	**Post-BD FVC (% predicted)**	100.2 (96.3-104.0)
FFMI	17.99 (16.95-19.04)	**Post-BD FVC (L)**	3.3 (3.1-3.5)
Smoking Status (% Current)	42.9	**FEV_1 reversibility (%)**	10.9 (8.2-13.6)
Pack Years	43.9 (39.3-48.6)	**FEV_1 reversibility (mls)**	143.3 (109.7-176.9)
Exacerbation (Previous 12m)	1.1 (0.8-1.4)	**Post-BD FEV_1/FVC ratio (%)**	52.6 (49.9-55.3)
0 (%)	38.6	**R5 (kPa/L/s)**	0.60 (0.56-0.65)
1 (%)	35.7	**R20 (kPa/L/s)**	0.37 [0.23-0.66]
≥2 (%)	25.7	**R5-R20 (kPa/L/s)**	0.22 (0.19-0.25)
ICS Use (% patients)	74.3	**AX**	2.96 (2.50-3.42)
LABA+LAMA+ICS (%)	60.0	**X5 (kPa/L/s)**	-0.30 [-0.92-(-0.07)]
LABA+LAMA (%)	8.6	**∆X5 (kPa/L/s)**	0.25 [-0.05-1.48]
ICS + LABA (%)	11.4	**TLC (L)**	6.04 [3.75-9.47]
ICS + LAMA (%)	1.4	**TLC (% predicted)**	101.80 [73.89-144.50]
ICS only (%)	1.4	**FRC(L)**	3.59 [1.69-6.79]
LABA only (%)	0.0	**FRC (% predicted)**	117.10 (109.70-124.60)
LAMA only (%)	12.9	**RV (L)**	2.72 [1.48-5.58]
No inhaled medication (%)	4.3	**RV (% predicted)**	122.80 [74.00-234.60]
mMRC	4.0 [2.0-4.0]	**RV:TLC**	48.61 (46.37-50.86)
CAT	21.0 [15.0-39.0]	**DLCO (mmol/min/kPa)**	4.25 [1.60-13.10]
SGRQ total	53.86 (50.15-57.57)	**DLCO (% predicted)**	49.00 [21.00-108.00]
SGRQ symptoms	67.31 (63.46-71.16)	**KCO (mmol/min/kPa/L)**	0.96 [0.33-4.26]
SGRQ activity	72.00 (67.71-76.29)	**KCO (% predicted)**	64.69 [26.00-148.00]
SGRQ impact	39.60 (35.23-43.97)	**VA (L)**	4.55 (4.29-4.80)
Chronic bronchitis (%)	77.1	**VA (%)**	76.77 (73.92-79.63)
6MWT Distance (m)	343.5 [122.0-534.0]		

Fibrinogen (g/L)	3.30 [0.00-6.55]
IgE (kIU/L)	60.00 [0.00-1297.00]
NLR	2.02 [0.92-6.79]

Data presented as mean (95% CI), median [range] or percentage as appropriate.

[a]5 patients could not produce technically acceptable results for lung volumes and 1 for IOS, 4 patients do not have data for FFMI and 4 could not complete the 6MWT.

Abbreviations: AX, reactance area; BD, bronchodilator; BMI, body mass index; CAT, COPD assessment test; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FFMI, fat free mass index; FRC, functional residual capacity; FVC, forced vital capacity; ICS, inhaled corticosteroids; IgE, immunoglobulin E; KCO, carbon monoxide transfer coefficient; LABA, long acting beta agonist; LAMA, long acting muscarinic antagonist; mMRC, modified medical research council questionnaire; NLR, neutrophil-lymphocyte ratio; RV, residual volume; R5, resistance at 5Hz; R20, resistance at 20Hz; SGRQ, St George's respiratory questionnaire; TLC, total lung capacity; VA, alveolar volume; X5, reactance at 5Hz, ΔX5, difference in total reactance between inspiration and expiration; 6MWT, 6 minute walk test.

Table 2. Baseline characteristics in different EFL groups, n=69[a]

Characteristic	EFL^{None} (n=24)	$EFL^{Intermediate}$ (n=12)	EFL^{High} (n=33)	ANOVA p-value
Age	64.9 (61.6-68.2)	63.6 (58.8-68.3)	65.9 (63.3-68.5)	0.64
Gender (% M)	58.3	66.7	51.5	0.79
BMI (kg/m^2)	25.8 (23.9-27.8)	27.93 (24.3-31.5)	[bb]30.2 (28.2-32.2)	0.01
FFMI	17.44 [12.20-24.89]	17.50 [5.52-22.90]	18.05 [13.22-31.65]	0.56
Smoking Status (% Current)	50.0	58.3	30.3	0.15
Pack Years	36.9 (30.6-43.2)	42.3 (42.6-62.0)	45.7 (37.8-53.6)	0.06
Exacerbation (Previous 12m)	1.0 [0.0-4.0]	1.0 [0.0-3.0]	0.0 [0.0-4.0]	0.06
ICS Use (% patients)	75.0	58.3	81.8	0.27
mMRC	4.0 [2.0-4.0]	4.0 [2.0-4.0]	4.0 [2.0-4.0]	0.22
CAT	20.0 [15.0-31.0]	22.50 [15.0-30.0]	21.0 [15.0-32.0]	0.47
SGRQ total	48.0 (42.1-53.9)	55.8 (46.0-65.7)	[b]57.7 (52.5-62.9)	0.05
SGRQ symptoms	66.9 (60.1-73.6)	69.7 (15.6-81.8)	66.1 (60.7-71.6)	0.80
SGRQ activity	65.8 (59.5-72.1)	68.6 (56.1-81.1)	[b] 77.1 (70.6-83.6)	0.05
SGRQ impact	31.1 (24.0-38.2)	43.3 (33.0-53.6)	[b] 43.4 (37.1-49.8)	0.02
Chronic bronchitis (%)	83.3	66.7	75.8	0.53
6MWT Distance (m)	368.5 [160.0-516.0]	336.5 [240.0-534.0]	338.0 [112.0-436.0]	0.58
Post-BD FEV1 (% predicted)	76.3 (71.5-81.1)	66.6 (56.5-76.6)	[b] [b] 56.8 (51.1-62.5)	<0.01
Post-BD FEV1 (L)	2.1 (1.8-2.3)	1.7 (1.5-2.0)	[b] [b] 1.5 (1.3-1.6)	<0.01
Post-BD FVC (% predicted)	106.2 (100.5-112.0)	96.8 (85.2-108.3)	96.6 (90.9-102.3)	0.06
Post-BD FVC (L)	3.6 (3.2-4.0)	3.2 (2.7-3.6)	3.1 (2.8-3.4)	0.08
FEV_1 reversibility (%)	8.9 (5.1-12.4)	10.7 (4.0-17.4)	12.6 (8.0-17.3)	0.72
FEV_1 reversibility (mls)	146.2 (81.82-210.5)	155.0 (33.1-276.9)	136.1 (95.1-177.0)	0.92
Post-BD FEV_1/FVC ratio (%)	57.8 (54.4-61.3)	55.8 (49.7-62.0	[b] [b] 47.5 (43.3-51.7)	<0.01

Fibrinogen (g/L)	3.21 [2.20-4.60]	3.29 [0.00-4.30]	3.42 [0.00-4.60]	0.41
IgE (kIU/L)	48.50 [0.00-1297.00]	65.00 [7.00-837.00]	66.00 [3.00-858.00]	0.64
NLR	2.00 [0.92-4.98]	1.84 [1.13-3.04]	2.26 [0.99-6.79]	0.46
R5 (kPa/L/s)	0.45 [0.21-0.74]	[c c] 0.65 [0.48-1.02]	[b b] 0.69 [0.44-1.02]	<0.01
R20 (kPa/L/s)	0.36 (0.33-0.39)	0.40 (0.32-0.48)	0.39 (0.36-0.42)	0.41
R5-R20 (kPa/L/s)	0.08 (0.06-0.11)	[c c] 0.21 (0.15-0.27)	[b b,d d] 0.33 (0.29-0.36)	<0.01
AX	0.95 [0.13-3.71]	[c] 2.38 [0.94-6.38]	[b b, d] 8.43 [1.91-8.52]	<0.01
X5 (kPa/L/s)	-0.15 [-0.34 (-0.07)]	[c] -0.28 [-0.46-(-0.21)]	[b b] -0.41 [-0.92-(-0.23)]	<0.01
∆X5 (kPa/L/s)	0.03 [-0.05-0.08]	[c] 0.20 [0.15-0.27]	[b b,d d] 0.54 [0.29-1.48]	<0.01
TLC (L)	5.90 [4.29-9.14]	6.09 [4.53-9.47]	6.00 [3.75-8.60]	0.90
TLC (% predicted)	101.50 [74.92-130.50]	99.60 [77.83-131.30]	102.80 [73.89-144.50]	0.80
FRC (L)	3.44 (3.10-3.79)	3.86 (3.14-4.59)	3.89 (3.46-4.31)	0.27
FRC (% predicted)	105.50 (96.54-114.50)	122.50 (104.00-141.10)	124.50 (111.50-137.5)	0.06
RV (L)	2.55 [1.85-4.28]	3.15 [1.93-5.58]	3.26 [1.48-5.14]	0.06
RV (% predicted)	114.80 (103.1-126.5)	132.60 (112.60-152.60)	[b] 143.60 (127.60-159.60)	0.02
RV:TLC	0.44 (0.41-0.47)	[c] 0.51 (0.46-0.55)	[b b] 0.52 (0.49-0.55)	<0.01
DLCO (mmol/min/kPa)	4.15 [1.80-9.30]	4.50 [2.70-11.50]	4.20 [1.60-13.10]	0.47
DLCO (% predicted)	53.04 (44.21-61.87)	58.74 (45.50-71.98)	51.60 (45.15-58.04)	0.56
KCO (mmol/min/kPa/L)	0.88 [0.33-1.76]	1.12 [0.71-2.14]	0.91 [0.45-4.26]	0.11
KCO (% predicted)	62.88 [26.00-124.50]	73.00 [53.00-148.00]	64.34 [33.11-115.00]	0.33
VA (L)	4.91 (4.41-5.41)	4.40 (3.92-4.88)	4.26 (3.93-4.58)	0.05
VA (% predicted)	81.02 (76.57-85.48)	75.65 (69.44-81.86)	73.52 (69.03-78.00)	0.06

Data presented as mean (95% CI), median [range] or percentage as appropriate. p-value corresponds to one way ANOVA, Kruskal-wallis or chi-squared test as appropriate. EFL defined as EFL^{High} (ΔX5 ≥0.28 kPa/L/s), $EFL^{Intermediate}$ (ΔX5 0.10-0.27 kPa/L/s) and EFL^{None} (ΔX5 <0.10 kPa/L/s).

[a] 5 patients did not produce technically acceptable results for lung volumes, 4 had no data for FFMI and 4 could not complete the 6MWT.

[b] = $p<0.05$, [b b] = $p<0.01$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs EFL^{High}

[c] = $p<0.05$, [c c] = $p<0.01$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs $EFL^{Intermediate}$

[d]= $p<0.05$, [d d] = $p<0.01$ (using Tukey's or Dunns post-hoc test) for $EFL^{Intermediate}$ vs EFL^{High}

Abbreviations: AX, reactance area; BD, bronchodilator; BMI, body mass index; CAT, COPD assessment test; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FFMI, fat free mass index; FRC, functional residual capacity; FVC, forced vital capacity; ICS, inhaled corticosteroids; IgE, immunoglobulin E; KCO, carbon monoxide transfer coefficient; LABA, long acting beta agonist; LAMA, long acting muscarinic antagonist; mMRC, modified medical research council questionnaire; NLR, neutrophil-lymphocyte ratio; RV, residual volume; R5, resistance at 5Hz; R20, resistance at 20Hz; SGRQ, St George's respiratory questionnaire; TLC, total lung capacity; VA, alveolar volume; X5, reactance at 5Hz, ΔX5, difference in total reactance between inspiration and expiration; 6MWT, 6 minute walk test.

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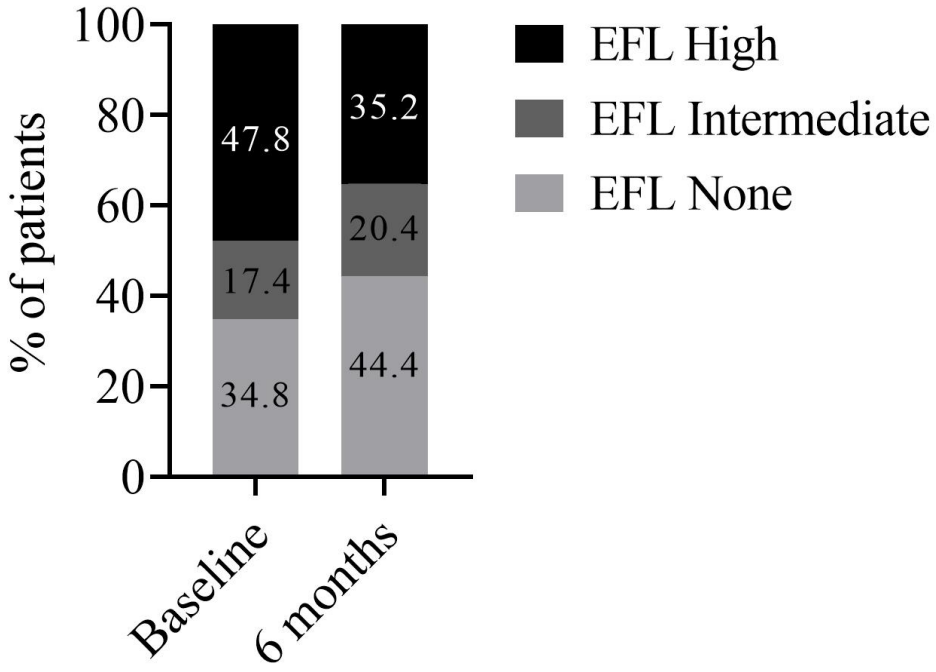

Figure 1: Proportion of patients in different EFL groups at baseline and 6 months. EFL groups defined as; ΔX5 <0.10 kPa/L/s (EFLNone), ΔX5 0.10-0.27 kPa/L/s (EFLIntermediate) and ΔX5 ≥0.28 kPa/L/s (EFLHigh), n=69 and 54 respectively. EFL, expiratory flow limitation.

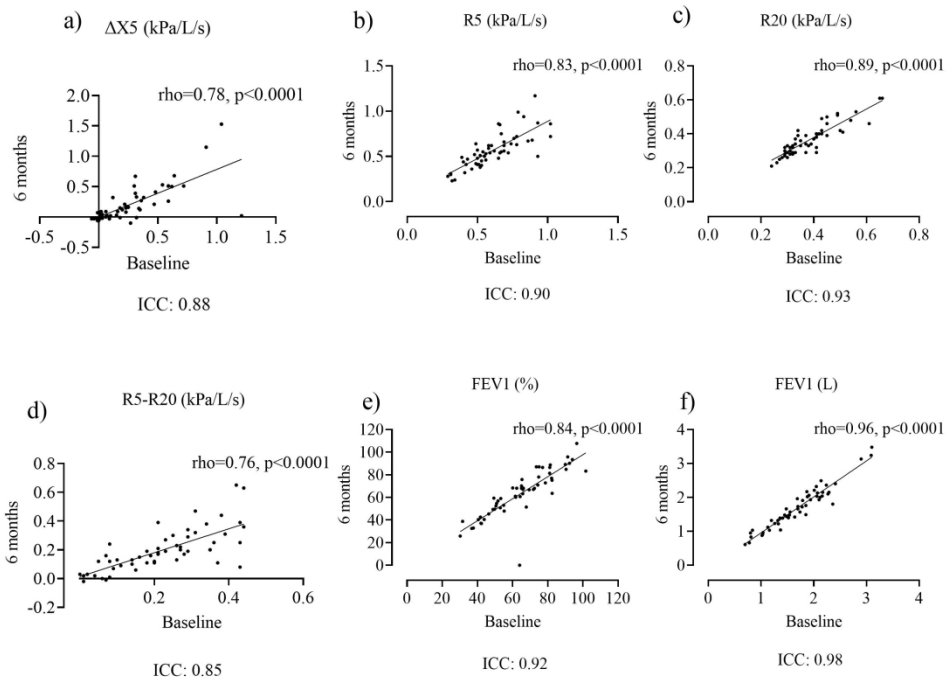

Figure 2: Association between lung function parameters over 6 months; ΔX5 (A), R5 (B), R20 (C), R5-R20 (D), FEV1 (% predicted) (D) and FEV1 (absolute) (E). n=64*. p-value corresponds to a spearman's rank test and Pearson's correlation for nonparametric and parametric data, respectively. $p<0.05$ was considered statistically significant. FEV1, forced expiratory volume in 1 second; R5, resistance at 5Hz; R20, resistance at 20Hz; ΔX5, difference in total reactance between inspiration and expiration at 5Hz*10 patients did not provide IOS data at 6 months

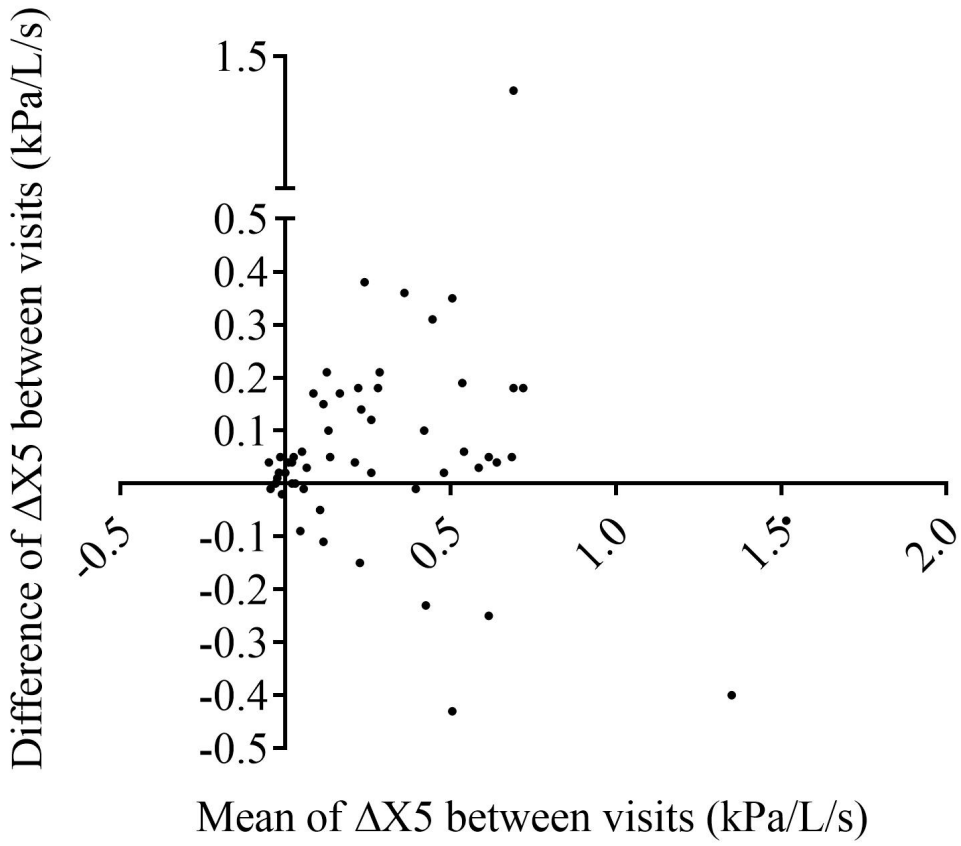

Figure 3: Bland-Altman plot of the difference versus the mean of two repeat measurements of ΔX5 over 6 months. n=54. ΔX5, difference in total reactance between inspiration and expiration at 5Hz

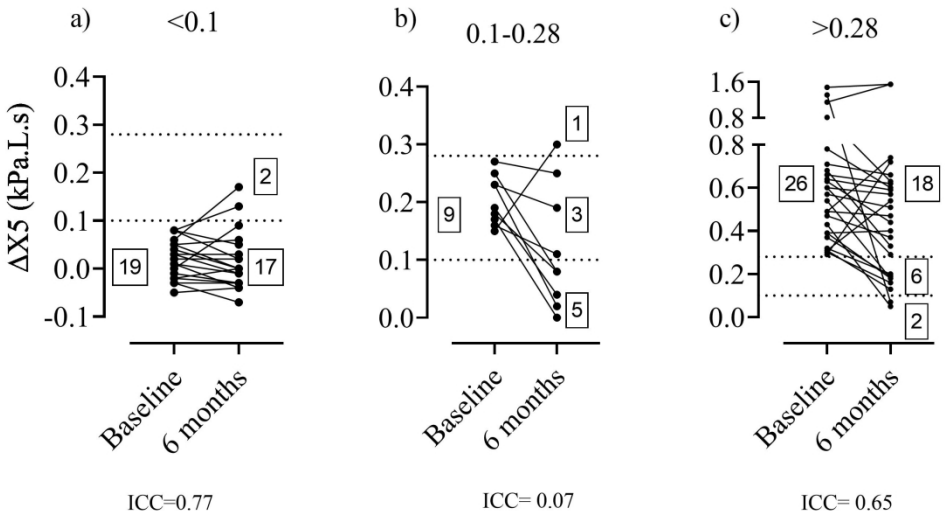

Figure 4: Repeatability of ΔX5 within different groups; EFLNone (A), EFLIntermediate (B) and EFLHigh (C). EFL groups defined as; ΔX5 <0.10 kPa/L/s (EFLNone), ΔX5 0.10-0.27 kPa/L/s (EFLIntermediate) and ΔX5 ≥0.28 kPa/L/s (EFLHigh), n=54. ICC, intraclass correlation; ΔX5, difference in total reactance between inspiration and expiration at 5Hz

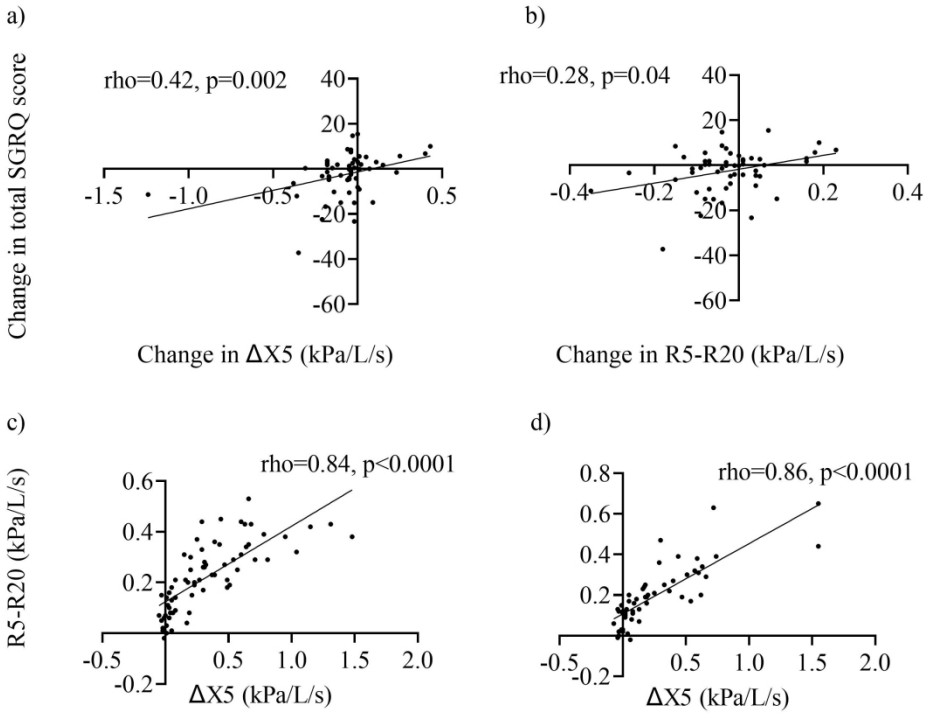

Figure 5: Change in ΔX5 (A) and R5-R20 (B) over 6 months associated with a change in total SGRQ scores, n=54 for both. Association between ΔX5 and R5-R20 at baseline (C) and 6 months (D), n=69 and 54, respectively. p-value corresponds to a spearman's rank test. $p<0.05$ was considered statistically significant. R5, resistance at 5Hz; R20, resistance at 20Hz; SGRQ, St. George's respiratory questionnaire; ΔX5, difference in total reactance between inspiration and expiration at 5Hz

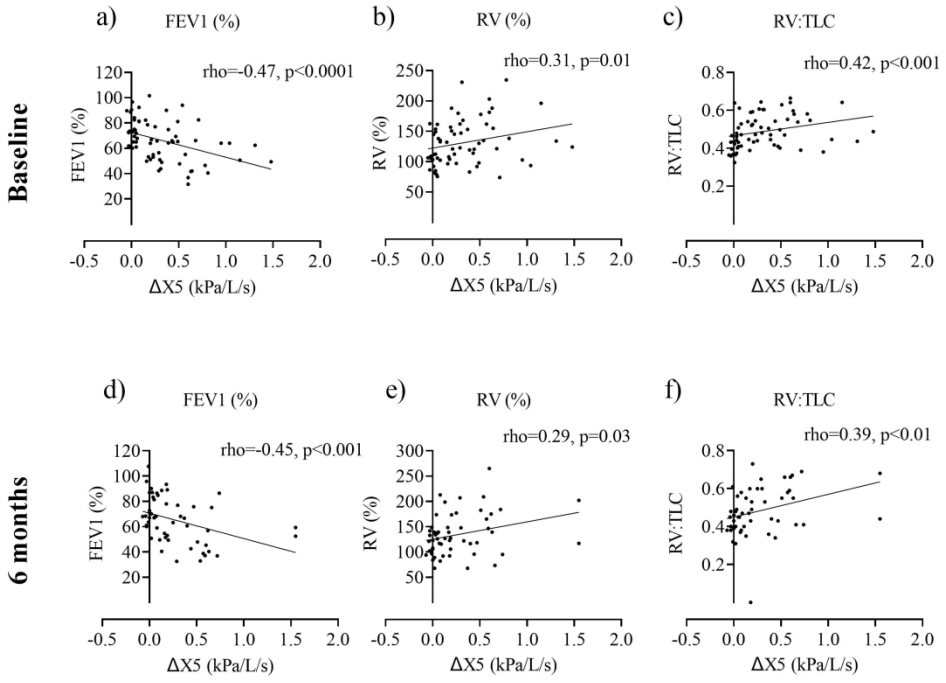

Figure 6: Association between ΔX5 and other lung function parameters at baseline; FEV1 (% predicted) (A), RV (% predicted) (B), RV:TLC ratio (C), and 6 months; FEV1 (% predicted) (D), RV (% predicted) (E), RV:TLC ratio (F). n=64 and 54* respectively. p-value corresponds to a spearman's rank test. $p<0.05$ was considered statistically significant. FEV1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; ΔX5, difference in total reactance between inspiration and expiration at 5Hz.*1 patient did not have RV data at 6 months

Online Data Supplement

Expiratory flow limitation in a cohort of highly symptomatic COPD patients

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Methods

Impulse Oscillometry (IOS)

Patients were required to support their cheeks and use a free-flow mouthpiece to depress the tongue while impulses were applied during tidal breathing for 30 seconds in a seated position - this process was repeated to achieve three technically acceptable and reproducible attempts of which the means were reported. IOS was performed prior to all other lung function measurements.

Results

EFL and other IOS measurements at 6 months

At 6 months R5 and AX were elevated in EFL^{High} patients compared to both EFL^{None} and $EFL^{Intermediate}$ (0.72 vs 0.44 and 0.56 kPa/L/s, p=0.02 and <0.0001 and 0.02. 4.48 vs 1.03 and 2.12 kPa/L/s, p<0.001 and 0.04 respectively, supplementary table 3). R5-R20 was elevated in EFL^{High} patients compared to EFL^{None} and $EFL^{Intermediate}$ (0.35 vs 0.09 and 0.19 kPa/L/s, p<0.0001 for both, supplementary table 3). R5-R20 was also higher in $EFL^{Intermediate}$ when compared to EFL^{None} (0.19 vs 0.09 kPa/L/s, p=0.01, supplementary table 3). Furthermore, X5 was more negative in EFL^{High} patients compared to both EFL^{None} patients (-0.39 vs -0.17 kPa/L/s, p<0.0001, supplementary table 3).

EFL and lung volumes at 6 months

At 6 months, 53 patients had technically acceptable data collected for both IOS and body plethysmography. RV/TLC ratio was significantly elevated in EFL^{High} compared to EFL^{None} patients (0.55 vs 0.45 respectively, p<0.01, supplementary table 3). No differences in DLCO or KCO were observed between groups.

Tables

Supplementary table 1. Baseline comorbidities, n=70

Characteristic	All (n=70) n (%)	EFL^{None} (n=24) n (%)	$EFL^{Intermediate}$ (n=12) n (%)	EFL^{High} (n=33) n (%)	p-value
Patients with at least one concomitant disease	66 (94.3)	24 (100.0)	11 (91.7)	31 (93.9)	0.41
Ischaemic heart disease	18 (25.7)	8 (33.3)	3 (25.0)	7 (21.2)	0.59
Myocardial ischaemia	13 (18.6)	4 (16.7)	2 (16.7)	7 (21.2)	0.89
Angina pectoris	7 (10.0)	4 (16.7)	0	3 (9.1)	0.28
Myocardial infarction	10 (14.3)	5 (20.8)	2 (16.7)	3 (9.1)	0.45
Cardiac failure	0	0	0	0	N/A
Cardiovascular disease	52 (74.3)	16 (66.7)	10 (83.3)	25 (75.8)	0.53
Hypertension	32 (45.7)	6 (25.0)	[b] 8 (66.7)	[a] 17 (51.5)	0.04
Hypercholesterolemia	38 (52.3)	13 (54.2)	6 (50.0)	18 (54.5)	0.96
Coronary artery disease	0	0	0	0	N/A
Pulmonary hypertension	0	0	0	0	N/A
Peripheral vascular disease	5 (7.1)	4 (16.7)	1 (8.3)	0	0.06
Cerebrovascular disease	0	0	0	0	N/A
Stroke (including transient ischaemic attack)	9 (12.9)	2 (8.3)	3 (25.0)	4 (12.1)	0.37
Irregular heartbeat	3 (4.3)	1 (4.2)	0	2 (6.1)	0.68
Diabetes	8 (11.4)	1 (4.2)	3 (25.0)	4 (12.1)	0.09
Obesity	23 (32.9)	4 (16.7)	5 (41.7)	14 (42.4)	0.10
Obstructive sleep apnoea	1 (1.4)	0	0	1 (3.0)	0.57
Anaemia	4 (5.7)	3 (12.5)	0	1 (3.0)	0.20

Osteoarthritis, osteopenia or osteoporosis	27 (38.6)	9 (37.5)	3 (25.0)	14 (42.4)	0.57
Gastro-oesophageal reflux disease	17 (24.3)	6 (25.0)	2 (16.7)	9 (27.3)	0.77
Psychological disturbances	23 (32.9)	8 (33.3)	5 (41.7)	10 (30.3)	0.79
Depression	19 (27.1)	7 (29.2)	4 (33.3)	8 (24.2)	0.81
Anxiety	9 12.9)	3 (12.5)	2 (16.7)	4 (12.1)	0.92
Insomnia	1 (1.4)	0	1 (8.3)	0	0.09

Data presented as n (%). p-value corresponds to a chi-squared test. EFL defined as EFL^{High} ($\Delta X5 \geq 0.28$ kPa/L/s), $EFL^{Intermediate}$ ($\Delta X5$ 0.10-0.27 kPa/L/s) and $\geq EFL^{None}$ ($\Delta X5 < 0.10$ kPa/L/s).

[a] = $p<0.05$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs EFL^{High}

[b] = $p<0.05$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs $EFL^{Intermediate}$

Supplementary table 2. Summary of patients that were lost to follow-up between baseline and 6 month visits (n=15)

Reason for loss of follow up	**Number of patients, n (%)**
Not contactable	10 (66.6)
Unable to produce technically acceptable oscillometry results	1 (6.7)
Withdrawn due toa change in medical circumstances	4 (26.7)

Supplementary table 3. 6 month characteristics in different EFL groups, n=54 [a]

Characteristic	EFL^{None} (n=24)	$EFL^{Intermediate}$ (n=11)	EFL^{High} (n=19)	ANOVA p-value
Post-BD FEV1 (% predicted)	74.8 (68.9-80.7)	64.7 (51.9-77.5)	[b] [b] 54.4 (46.3-62.5	<0.01
Post-BD FEV1 (L)	2.0 (1.8-2.2)	1.7 (1.3-2.1)	[b] [b] 1.4 (1.1-1.6)	<0.01
Post-BD FVC (% predicted)	102.7 (92.3-114.1)	99.8 (87.0-112.5)	95.0 (84.0-106.1)	0.60
Post-BD FVC (L)	3.4 (2.9-3.9)	3.3 (2.7-3.9)	3.1 (2.7-3.6)	0.66
FEV_1 reversibility (%)	10.0 (6.6-13.3)	11.9 (5.3-18.4)	17.6 (9.2-26.0)	0.14
FEV_1 reversibility (mls)	165.8 (112.4-219.3)	159.1 (90.8-227.4)	194.2 (110.0-278.4)	0.75
FEV_1/FVC ratio (%)	54.5 (48.3-60.6)	52.4 (45.5-59.3)	[b] 43.8 (37.5-50.2)	0.04
R5 (kPa/L/s)	0.44 (0.39-0.49)	0.56 (0.47-0.65)	[b] [b], [d] 0.72 (0.63-0.81)	<0.01
R20 (kPa/L/s)	0.36 (0.32-0.40)	0.37 (0.31-0.44)	0.38 (0.33-0.42)	0.77
R5-R20 (kPa/L/s)	0.09 (0.06-0.11)	[c] 0.19 (0.15-0.22)	[b] [b, d] [d] 0.35 (0.28-0.41)	<0.01
AX	1.03 [0.10-2.64]	[c] 2.12 [0.62-4.22]	[b] [b, d] 4.48 [1.76-11.69]	<0.01
X5 (kPa/L/s)	-0.17 [-0.27-(-0.07)]	-0.24 [-0.41-(-0.11)]	[b] [b] -0.39 (-1.00(--0.07)]	<0.01
ΔX5 (kPa/L/s)	0.01 [-0.07-0.09]	[c] [c] 0.18 [0.11-0.25]	[b] [b] 0.57 [0.29-1.55]	<0.01
TLC (L)	6.16 (5.56-6.76)	5.99 (5.08-6.90)	6.25 (5.58-6.91)	0.89
TLC (% predicted)	103.00 (77.32-136.8)	98.26 (65.05-130.08)	99.85 (74.63-149.00)	0.64
FRC (L)	3.43 [2.06-7.79]	3.78 [2.24-5.23]	4.25 [1.96-6.41]	0.11
FRC (% predicted)	109.30 [74.00-196.80]	124.80 [69.14-160.60]	133.60 [69.00-266.00]	0.08
RV(L)	2.61 [1.62-5.81]	3.08 [1.92-4.34]	3.61 [1.49-5.59]	0.08
RV (% predicted)	121.10 [68.00-213.00]	127.50 [92.00-106.80]	146.60 [68.00-265.00]	0.10
RV:TLC	0.45 [0.31-0.61]	0.49 [0.35-0.73]	[b] 0.55 [0.34-0.69]	0.03
DLCO (mmol/min/kPa)	4.50 [1.80-9.80]	3.90 [2.80-7.0]	4.0 [2.0-6.90]	0.67
DLCO (% predicted)	55.0 [25.0-92.0]	42.0 [34.0-90.0]	48.0 [31.0-86.3]	0.48
KCO (mmol/min/kPa/L)	0.96 [0.00-1.50]	0.95 [0.53-1.54]	0.85 [0.47-1.44]	0.86
KCO (% predicted)	64.86 [54.31-75.41]	71.39 [55.10-87.68]	68.72 [58.00-79.45]	0.73
VA (L)	4.61 [3.95-5.27]	4.51 [3.62-5.40]	4.41 [3.94-4.87]	0.88

VA (% predicted)	81.0 [0.0-103.0]	76.0 [58.0-106.0]	76.0 [54.0-96.0]	0.40

Data presented as mean (95% CI), median [range] or percentage as appropriate. p-value corresponds to one way ANOVA, Kruskal-wallis or chi-squared test as appropriate. EFL defined as EFL^{High} (ΔX5 ≥0.28 kPa/L/s), $EFL^{Intermediate}$ (ΔX5 0.10-0.27 kPa/L/s) and EFL^{None} (ΔX5 <0.10 kPa/L/s).

[a] 1 patient did not produce technically acceptable results for lung volumes or spirometry

[b] = $p<0.05$, [b b] = $p<0.01$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs EFL^{High}

[c] = $p<0.05$, [c c] = $p<0.01$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs $EFL^{Intermediate}$

[d] = $p<0.05$, [d d] = $p<0.01$ (using Tukey's or Dunns post-hoc test) for $EFL^{Intermediate}$ vs EFL^{High}

Abbreviations: AX, reactance area; BD, bronchodilator; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; KCO, carbon monoxide transfer coefficient; RV, residual volume; R5, resistance at 5Hz; R20, resistance at 20Hz; TLC, total lung capacity; VA, alveolar volume; X5, reactance at 5Hz, ΔX5, difference in total reactance between inspiration and expiration;