Expiratory flow limitation in a cohort of highly symptomatic COPD patients

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Shareable abstract (@ERSpublications)
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. https://bit.ly/3AMRjjL

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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 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 70 patients were recruited. Clinical characteristics and lung function metrics were collected at baseline and 6 months. Impulse oscillometry was used to detect the presence of EFL. Patients were defined as EFL^{High} (change in reactance measured at 5 Hz (ΔX_5) $\geqslant 0.28$ kPa·L^{-1}·s^{-1}); $EFL^{Intermediate}$ (ΔX_5 0.1–0.27 kPa·L^{-1}·s^{-1}) and EFL^{None} (ΔX_5 <0.1 kPa·L^{-1}·s^{-1}).

Results EFL^{High} was present in 47.8% of patients at baseline. ΔX_5 showed excellent repeatability over 6 months (ρ=0.78, p<0.0001, intraclass correlation coefficient (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 body mass index, 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

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 noninvasive 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 (ΔX_5) is a marker of EFL [9]. A threshold value of $\geqslant 0.28$ kPa·L^{-1}·s^{-1} (ΔX_5) has been used to define EFL, with patients above this threshold having more gas trapping and a

greater symptom burden [6, 9]. A lower ΔX_5 value of >0.10 kPa·L^{-1}·s^{-1}, which probably 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 forced expiratory volume in 1 s (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 this symptom [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 targeted specifically 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 (⩾0.28 kPa·L^{-1}·s^{-1} and >0.10 kPa·L^{-1}·s^{-1}), and studied the relationships between EFL and other lung function measurements and clinical characteristics. Measurement repeatability over 6 months was evaluated.

Methods

Study cohort

70 COPD patients were recruited from the Medicines Evaluation Unit (Manchester University NHS Foundation Trust, Manchester, UK). Subjects were aged ⩾40 years, 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-min walk test (6MWT), fat-free mass assessment (BodyStat 1500; BodyStat, UK), impulse oscillometry (IOS) (MasterScreen; Erich Jaeger, Hoechbery, Germany), spirometry with reversibility to 400 µg salbutamol (EasyOne spirometer; NDD Medical Technologies, Switzerland), body plethysmography and diffusing capacity of the lungs for carbon monoxide (D_{LCO}) (Vmax; CareFusion, Hoechbery, Germany). Spirometry, body plethysmography, D_{LCO} and 6MWT were performed according to American Thoracic Society/European Respiratory Society guidelines [20–23]. Short-acting bronchodilators were withheld for 6 h, long-acting bronchodilators, anticholinergics, theophyllines and leukotriene receptor antagonists were withheld for up to 24 h prior to lung function testing. IOS was performed as described previously [24]; more detail is provided in the supplementary material. ΔX_5 was calculated using the multiple-breath method; mean reactance at 5 Hz during inspiration (X_{5in}) minus the mean reactance at 5 Hz during expiration (X_{5ex}). Inspiratory and expiratory data were averaged over multiple tidal breaths, which has been validated against the breath-by-breath method where differences between X_{5in} and X_{5ex} are calculated per breath and then averaged; the intraclass correlation coefficient (ICC) was 0.98 [4].

EFL was defined as EFL^{High} (ΔX_5 ⩾0.28 kPa·L^{-1}·s^{-1}), $EFL^{Intermediate}$ (ΔX_5 0.10–0.27 kPa·L^{-1}·s^{-1}) and EFL^{None} (ΔX_5 <0.10 kPa·L^{-1}·s^{-1}).

Statistical analysis

No formal sample size calculation was performed; this was a pilot study to generate findings that could be confirmed in larger datasets. Nonparametric 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 Tukey's *post hoc* test (Prism 9.0; GraphPad, USA). Variation over time was assessed using Bland–Altman analysis (Prism 9.0) and ICC of log-transformed data (SPSS 25.0; IBM, USA). For ICC analysis of ΔX_5, 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 demographic 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 S1).

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 are presented in supplementary table S2. 33 (47.8%) patients at baseline and 19 (35.2%) at 6 months were classified as EFL^{High} (figure 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 (figure 1).

54 patients provided IOS data at both baseline and 6-month visits. There was a positive correlation between ΔX_5 measurements at baseline and 6 months (ρ=0.78, p<0.0001; figure 2a), with an ICC of 0.88 indicating excellent repeatability. Other IOS parameters showed positive correlations and excellent repeatability over 6 months (figure 2); resistance at 5 Hz (R_5) (ρ=0.83, p<0.0001, ICC=0.90), resistance at 20 Hz (R_{20}) (ρ=0.89, p<0.0001, ICC=0.93) and $R_{5–20}$ (ρ=0.76, p<0.0001, ICC=0.85). FEV_1 % predicted and absolute volume also showed excellent correlations between visits (ρ=0.84 and 0.96, p<0.0001 for both, ICC 0.92 and 0.98, respectively; figure 2e and f).

A Bland–Altman analysis between baseline and 6-month measurements of ΔX_5 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 six (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 ΔX_5 measurements for EFL^{None} and EFL^{High} patients (ρ=0.75 and ρ=0.43, p<0.001 and p=0.03, respectively), with ICC values 0.77 and 0.65, respectively. In contrast, there was no correlation for $EFL^{Intermediate}$ (ρ= −0.03, p=0.95, ICC 0.07), with only three out of nine 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 body mass index (BMI) compared to EFL^{None} (30.2 *versus* 25.8 $kg \cdot m^{-2}$, p<0.01); lower FEV_1 (56.8% pred *versus* 76.3% pred, p<0.0001); lower FEV_1/forced vital capacity ratio (47.5% *versus* 57.8%, p<0.001); and higher total SGRQ score (57.7 *versus* 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 ΔX_5 and $R_5–R_{20}$ (ρ=0.42 and ρ=0.28, p=0.002 and p=0.04, respectively; figure 5a and b); an increase in ΔX_5 or $R_5–R_{20}$ was associated with an increase in SGRQ score. D_{LCO} and transfer coefficient of the lung for carbon monoxide (K_{CO}) were similar between groups. Presence of concomitant diseases were mostly similar between groups (supplementary table S1).

EFL and other IOS measurements

Table 2 shows that X_5 was more negative and R_5, $R_5–R_{20}$ and reactance area 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 S3). ΔX_5 was positively correlated with $R_5–R_{20}$ at baseline and 6 months (ρ=0.84 and ρ=0.86, respectively, p<0.0001 for both; figure 5c and d).

EFL and lung volumes

64 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 residual volume (RV)/total lung capacity (TLC) ratio compared to EFL^{None} patients, while EFL^{High} patients showed a significantly higher RV % predicted *versus* EFL^{None}. No differences in D_{LCO} or K_{CO} were observed between groups. Similar results were observed at 6 months (supplementary material).

TABLE 1 Baseline clinical characteristics[#]

Patients (n)	70
Clinical characteristics	
Age (years)	64.3 (61.9–66.6)
Male (%)	55.7
BMI (kg·m^{-2})	27.96 (26.54–29.38)
FFMI	17.99 (16.95–19.04)
Current smoking (%)	42.9
Smoking (pack-years)	43.9 (39.3–48.6)
Exacerbations (previous 12 months)	1.1 (0.8–1.4)
0 (%)	38.6
1 (%)	35.7
⩾2 (%)	25.7
ICS use (%)	74.3
LABA + LAMA + ICS (%)	60.0
LABA + LAMA (%)	8.6
ICS + LABA (%)	11.4
ICS + LAMA (%)	1.4
ICS only (%)	1.4
LABA only (%)	0.0
LAMA only (%)	12.9
No inhaled medication (%)	4.3
mMRC[¶]	4.0 (2.0–4.0)
CAT[¶]	21.0 (15.0–39.0)
SGRQ total	53.86 (50.15–57.57)
SGRQ symptoms	67.31 (63.46–71.16)
SGRQ activity	72.00 (67.71–76.29)
SGRQ impact	39.60 (35.23–43.97)
Chronic bronchitis (%)	77.1
6-min walk distance (m)[¶]	343.5 (122.0–534.0)
Fibrinogen (g·L^{-1})[¶]	3.30 (0.00–6.55)
IgE (kIU·L^{-1})[¶]	60.00 (0.00–1297.00)
Neutrophil–lymphocyte ratio[¶]	2.02 (0.92–6.79)
Lung function parameters	
Post-BD FEV_1 (% pred)	65.6 (61.5–69.6)
Post-BD FEV_1 (L)	1.7 (1.6–1.9)
Post-BD FVC (% pred)	100.2 (96.3–104.0)
Post-BD FVC (L)	3.3 (3.1–3.5)
FEV_1 reversibility (%)	10.9 (8.2–13.6)
FEV_1 reversibility (mL)	143.3 (109.7–176.9)
Post-BD FEV_1/FVC ratio (%)	52.6 (49.9–55.3)
R_5 (kPa·L^{-1}·s^{-1})	0.60 (0.56–0.65)
R_{20} (kPa·L^{-1}·s^{-1})[¶]	0.37 (0.23–0.66)
R_5–R_{20} (kPa·L^{-1}·s^{-1})	0.22 (0.19–0.25)
AX	2.96 (2.50–3.42)
X_5 (kPa·L^{-1}·s^{-1})[¶]	−0.30 (−0.92–0.07)
ΔX_5 (kPa·L^{-1}·s^{-1})[¶]	0.25 (−0.05–1.48)
TLC (L)[¶]	6.04 (3.75–9.47)
TLC (% pred)[¶]	101.80 (73.89–144.50)
FRC (L)[¶]	3.59 (1.69–6.79)
FRC (% pred)	117.10 (109.70–124.60)
RV (L)[¶]	2.72 (1.48–5.58)
RV (% pred)[¶]	122.80 (74.00–234.60)
RV:TLC	48.61 (46.37–50.86)
D_{LCO} (mmol·min^{-1}·kPa^{-1})[¶]	4.25 (1.60–13.10)
D_{LCO} (% pred)[¶]	49.00 (21.00–108.00)
K_{CO} (mmol·min^{-1}·kPa^{-1}·L^{-1})[¶]	0.96 (0.33–4.26)
K_{CO} (% pred)[¶]	64.69 (26.00–148.00)
V_A (L)	4.55 (4.29–4.80)
V_A (%)	76.77 (73.92–79.63)

Data are presented as mean (95% CI), unless otherwise stated. BMI: body mass index; FFMI: fat-free mass index; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council questionnaire; CAT: COPD Assessment Test; SGRQ: St George's Respiratory Questionnaire; Ig: immunoglobulin; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; *AX*: reactance area; X_5: reactance at 5 Hz; ΔX_5: difference in total reactance between inspiration and expiration; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; V_A: alveolar volume. [#]: did not produce technically acceptable results for lung volumes (n=5); did not produce technically acceptable results for impulse oscillometry (n=1); no data for FFMI (n=4); did not complete 6-min walk test (n=4). [¶]: data are presented as median (range).

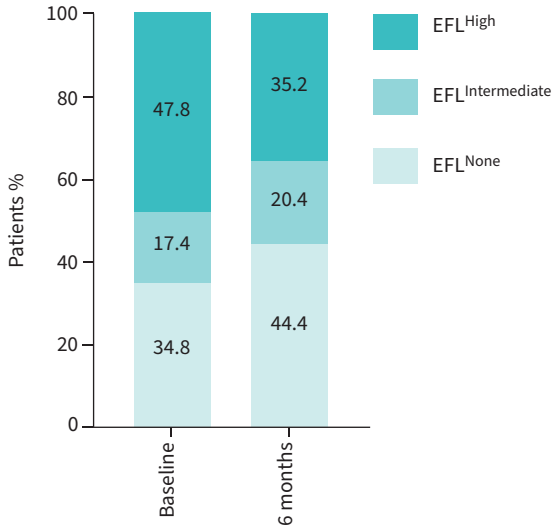

FIGURE 1 Proportion of patients in different expiratory flow limitation (EFL) groups at baseline and 6 months. EFL groups defined as difference in total reactance between inspiration and expiration (ΔX_5) <0.10 kPa·L^{-1}·s^{-1} (EFL^{None}), ΔX_5 0.10–0.27 kPa·L^{-1}·s^{-1} (EFL^{Intermediate}) and ΔX_5 ⩾0.28 kPa·L^{-1}·s^{-1} (EFL^{High}). n=69 at baseline and n=54 at 6 months.

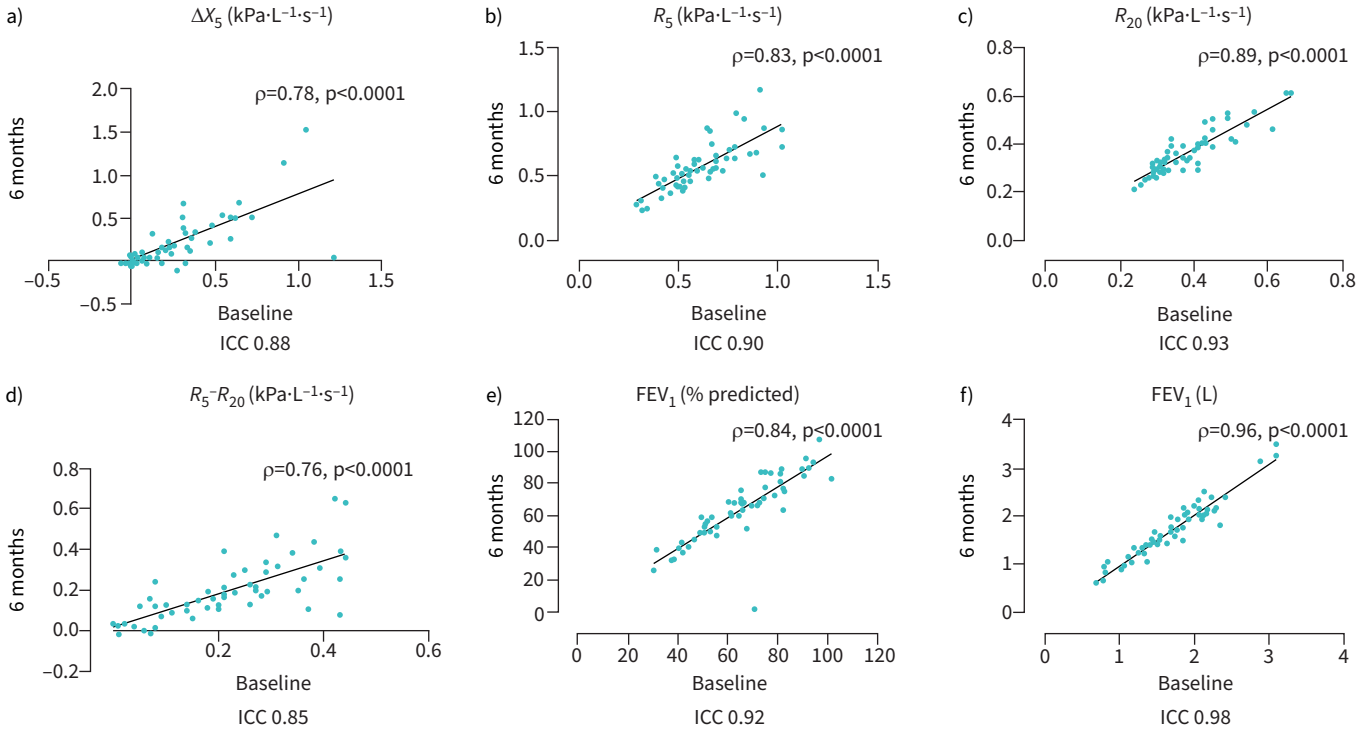

FIGURE 2 Association between lung function parameters over 6 months. a) Difference in total reactance between inspiration and expiration at 5 Hz (ΔX_5); b) resistance at 5 Hz (R_5); c) resistance at 20 Hz (R_{20}); d) R_5–R_{20}; e) forced expiratory volume in 1 s (FEV_1) (% predicted); and f) FEV_1 (absolute). n=64 (10 patients did not provide impulse oscillometry data at 6 months). ICC: intraclass correlation coefficient. 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.

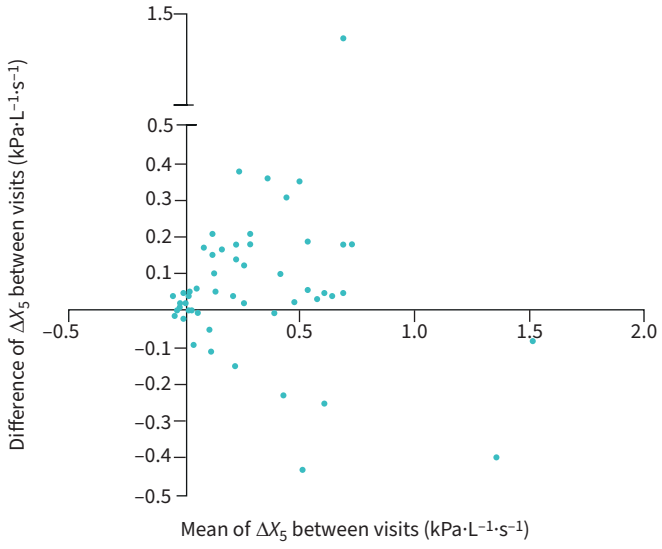

FIGURE 3 Bland–Altman plot of the difference *versus* the mean of two repeat measurements of the difference in total reactance between inspiration and expiration at 5 Hz (ΔX_5) over 6 months. n=54.

Figure 6 shows that ΔX_5 was positively correlated with RV (%) and RV/TLC at both baseline (ρ=0.31 and ρ=0.42, p=0.01 and p<0.001, respectively) and 6 months (ρ=0.29 and ρ=0.39, p=0.03 and p<0.01, respectively). Negative correlations were observed between ΔX_5 and FEV_1 % predicted (figure 6a and 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 among highly symptomatic COPD patients, and

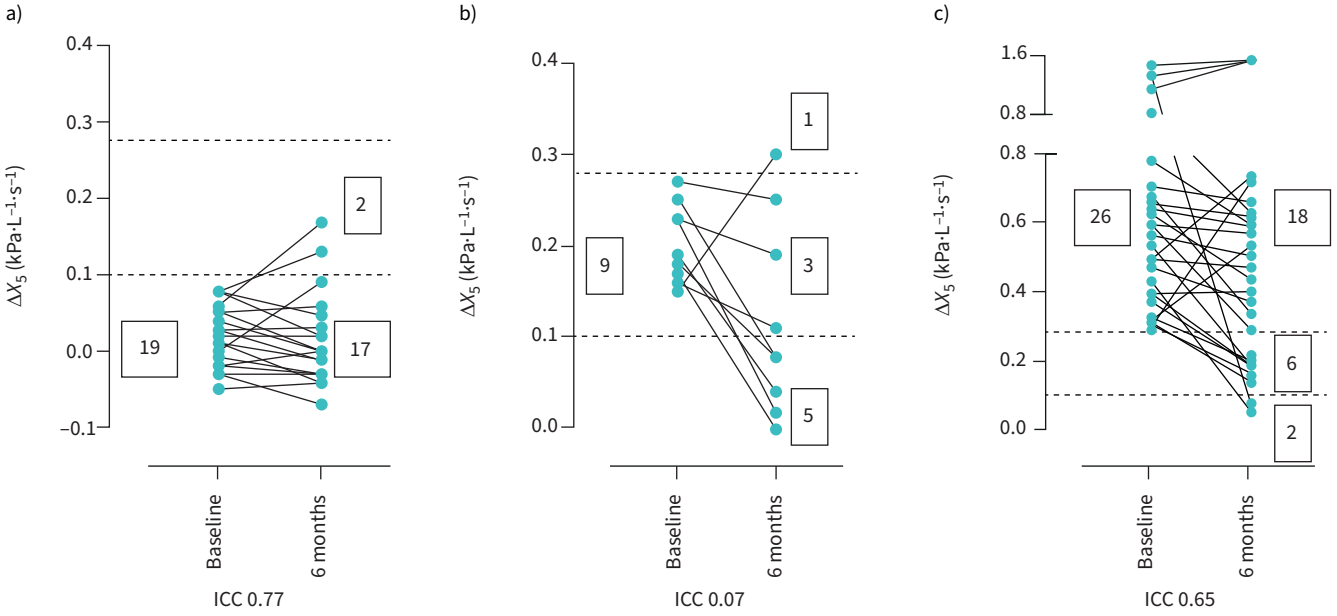

FIGURE 4 Repeatability of difference in total reactance between inspiration and expiration at 5 Hz (ΔX_5) within different groups; expiratory flow limitation (EFL). a) EFL^{None} (ΔX_5 <0.10 kPa·L^{-1}·s^{-1}), b) EFL^{Intermediate} (ΔX_5 0.10–0.27 kPa·L^{-1}·s^{-1}) and c) EFL^{High} (ΔX_5 ⩾0.28 kPa·L^{-1}·s^{-1}). n=54. ICC: intraclass correlation. Dotted lines represent thresholds of X_5 for EFL^{Intermediate} and EFL^{High} groups. Number of patients in different groups at each time point are presented in boxes.

TABLE 2 Baseline characteristics in different expiratory flow limitation (EFL)[#] groups (n=69)[¶]

	EFL^{None}	$EFL^{Intermediate}$	EFL^{High}	ANOVA p-value
Patients (n)	24	12	33	
Age (years)	64.9 (61.6–68.2)	63.6 (58.8–68.3)	65.9 (63.3–68.5)	0.64
Male (%)	58.3	66.7	51.5	0.79
BMI ($kg \cdot m^{-2}$)	25.8 (23.9–27.8)	27.93 (24.3–31.5)	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
Current smoking (%)	50.0	58.3	30.3	0.15
Smoking pack-years	36.9 (30.6–43.2)	42.3 (42.6–62.0)	45.7 (37.8–53.6)	0.06
Exacerbation in previous 12 months[+]	1.0 (0.0–4.0)	1.0 (0.0–3.0)	0.0 (0.0–4.0)	0.06
ICS use (%)	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)	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)	77.1 (70.6–83.6)*	0.05
SGRQ impact	31.1 (24.0–38.2)	43.3 (33.0–53.6)	43.4 (37.1–49.8)*	0.02
Chronic bronchitis (%)	83.3	66.7	75.8	0.53
6-min walk distance (m)[+]	368.5 (160.0–516.0)	336.5 (240.0–534.0)	338.0 (112.0–436.0)	0.58
Post-BD FEV_1 (% pred)	76.3 (71.5–81.1)	66.6 (56.5–76.6)	56.8 (51.1–62.5)**	<0.01
Post-BD FEV_1 (L)	2.1 (1.8–2.3)	1.7 (1.5–2.0)	1.5 (1.3–1.6)**	<0.01
Post-BD FVC (% pred)	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 (mL)	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)	47.5 (43.3–51.7)**	<0.01
Fibrinogen ($g \cdot L^{-1}$)[+]	3.21 (2.20–4.60)	3.29 (0.00–4.30)	3.42 (0.00–4.60)	0.41
IgE ($kIU \cdot L^{-1}$)[+]	48.50 (0.00–1297.00)	65.00 (7.00–837.00)	66.00 (3.00–858.00)	0.64
Neutrophil–lymphocyte ratio[+]	2.00 (0.92–4.98)	1.84 (1.13–3.04)	2.26 (0.99–6.79)	0.46
R_5 ($kPa \cdot L^{-1} \cdot s^{-1}$)[+]	0.45 (0.21–0.74)	0.65 (0.48–1.02)[§§]	0.69 (0.44–1.02)**	<0.01
R_{20} ($kPa \cdot L^{-1} \cdot s^{-1}$)	0.36 (0.33–0.39)	0.40 (0.32–0.48)	0.39 (0.36–0.42)	0.41
R_5–R_{20} ($kPa \cdot L^{-1} \cdot s^{-1}$)	0.08 (0.06–0.11)	0.21 (0.15–0.27)[§§]	0.33 (0.29–0.36)**,ff	<0.01
AX[+]	0.95 (0.13–3.71)	2.38 (0.94–6.38)[§]	8.43 (1.91–8.52)**,f	<0.01
X_5 ($kPa \cdot L^{-1} \cdot s^{-1}$)[+]	−0.15 (−0.34 (−0.07))	−0.28 (−0.46– −0.21)[§]	−0.41 (−0.92– −0.23)**	<0.01
ΔX_5 ($kPa \cdot L^{-1} \cdot s^{-1}$)[+]	0.03 (−0.05–0.08)	0.20 (0.15–0.27)[§]	0.54 (0.29–1.48)**,ff	<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 (% pred)[+]	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 (% pred)	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 (% pred)	114.80 (103.1–126.5)	132.60 (112.60–152.60)	143.60 (127.60–159.60)*	0.02
RV:TLC	0.44 (0.41–0.47)	0.51 (0.46–0.55)[§]	0.52 (0.49–0.55)**	<0.01
D_{LCO} ($mmol \cdot min^{-1} \cdot kPa^{-1}$)[+]	4.15 (1.80–9.30)	4.50 (2.70–11.50)	4.20 (1.60–13.10)	0.47
D_{LCO} (% pred)	53.04 (44.21–61.87)	58.74 (45.50–71.98)	51.60 (45.15–58.04)	0.56
K_{CO} ($mmol \cdot min^{-1} \cdot kPa^{-1} \cdot L^{-1}$)[+]	0.88 (0.33–1.76)	1.12 (0.71–2.14)	0.91 (0.45–4.26)	0.11
K_{CO} (% pred)[+]	62.88 (26.00–124.50)	73.00 (53.00–148.00)	64.34 (33.11–115.00)	0.33
V_A (L)	4.91 (4.41–5.41)	4.40 (3.92–4.88)	4.26 (3.93–4.58)	0.05
V_A (% pred)	81.02 (76.57–85.48)	75.65 (69.44–81.86)	73.52 (69.03–78.00)	0.06

Data are presented as mean (95% CI), unless otherwise stated. BMI: body mass index; FFMI: fat-free mass index; ICS: inhaled corticosteroid; mMRC: modified Medical Research Council questionnaire; CAT: COPD Assessment Test; SGRQ: St George's Respiratory Questionnaire; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; Ig: immunoglobulin; R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; AX: reactance area; X_5: reactance at 5 Hz; ΔX_5: difference in total reactance between inspiration and expiration; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; V_A: alveolar volume. [#]: EFL^{High} ($\Delta X_5 \geqslant 0.28$ $kPa \cdot L^{-1} \cdot s^{-1}$), $EFL^{Intermediate}$ (ΔX_5 0.10–0.27 $kPa \cdot L^{-1} \cdot s^{-1}$), EFL^{None} (ΔX_5 <0.10 $kPa \cdot L^{-1} \cdot s^{-1}$); [¶]: did not produce technically acceptable results for lung volumes (n=5), no data for FFMI (n=4), did not complete 6-min walk test (n=4); [+]: data are presented as median (range). p-value corresponds to one-way ANOVA, Kruskal–Wallis or Chi-squared test, as appropriate. *: p<0.05; **: p<0.01 (using Tukey's or Dunn's *post hoc* test) for EFL^{None} *versus* EFL^{High}. [§]: p<0.05; [§§]: p<0.01 (using Tukey's or Dunn's *post hoc* test) for EFL^{None} *versus* $EFL^{Intermediate}$. [f]: p<0.05; [ff]: p<0.01 (using Tukey's or Dunn's *post hoc* test) for $EFL^{Intermediate}$ *versus* EFL^{High}.

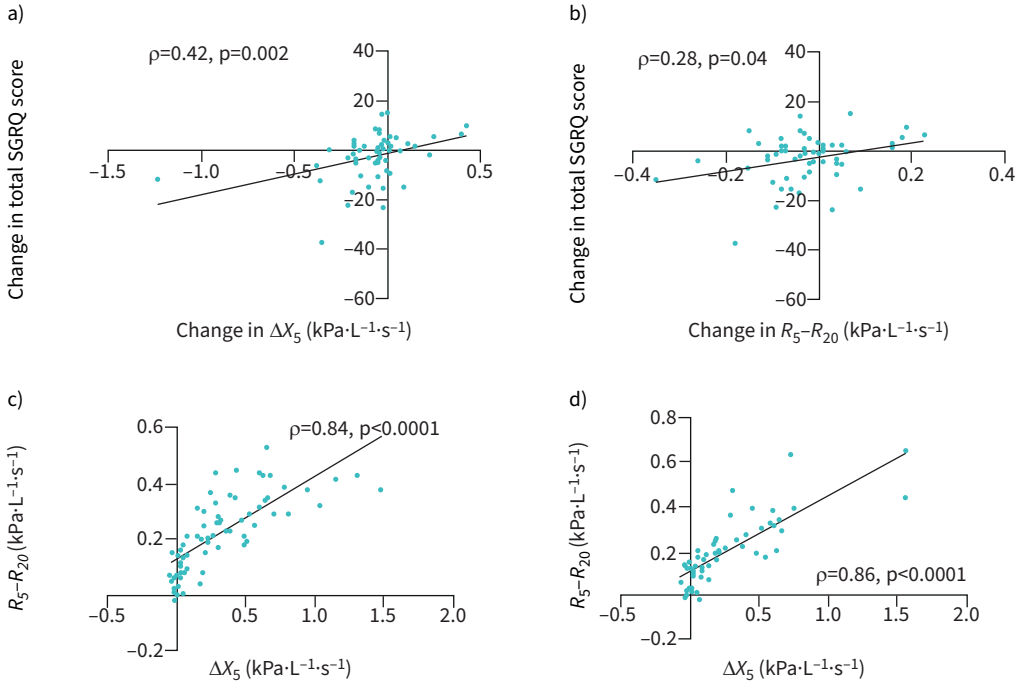

FIGURE 5 Change in a) difference in total reactance between inspiration and expiration at 5 Hz (ΔX_5) and b) R_5–R_{20} over 6 months associated with a change in total St George's Respiratory Questionnaire (SGRQ) scores, n=54 for both. Association between ΔX_5 and R_5–R_{20} at c) baseline and d) 6 months, n=69 and 54, respectively. R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz. p-value corresponds to a Spearman's rank test. p<0.05 was considered statistically significant.

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 ΔX_5 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 ΔX_5 or R_5–R_{20} 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 ΔX_5 and clinical characteristics including dyspnoea and exacerbation rates (n=425 [8] and n=147 [6]). Our 6-month longitudinal analysis provides further evidence of the clinical relevance of EFL, showing an association between changes in ΔX_5 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 ΔX_5 and total SGRQ score (n=425 [4]) and the activity domain (n=147 [6]).

Small airways are defined as those <2 mm in internal diameter, which are generally found between the 4th and 12th generation of the bronchial tree [2]. The clinical relevance of EFL was highlighted by worse airflow obstruction and increased small airway resistance (measured by R_5–R_{20}) 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]. R_{20} 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^{-1}·s^{-1}, respectively; p=0.49). Expiratory dynamic airways collapse (EDAC) shows similar reactance patterns to EFL reported here, although R_{20} was numerically lower in COPD patients *versus* COPD + EDAC (0.33 *versus* 1.07 cmH_2O·L^{-1}·s^{-1}) [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

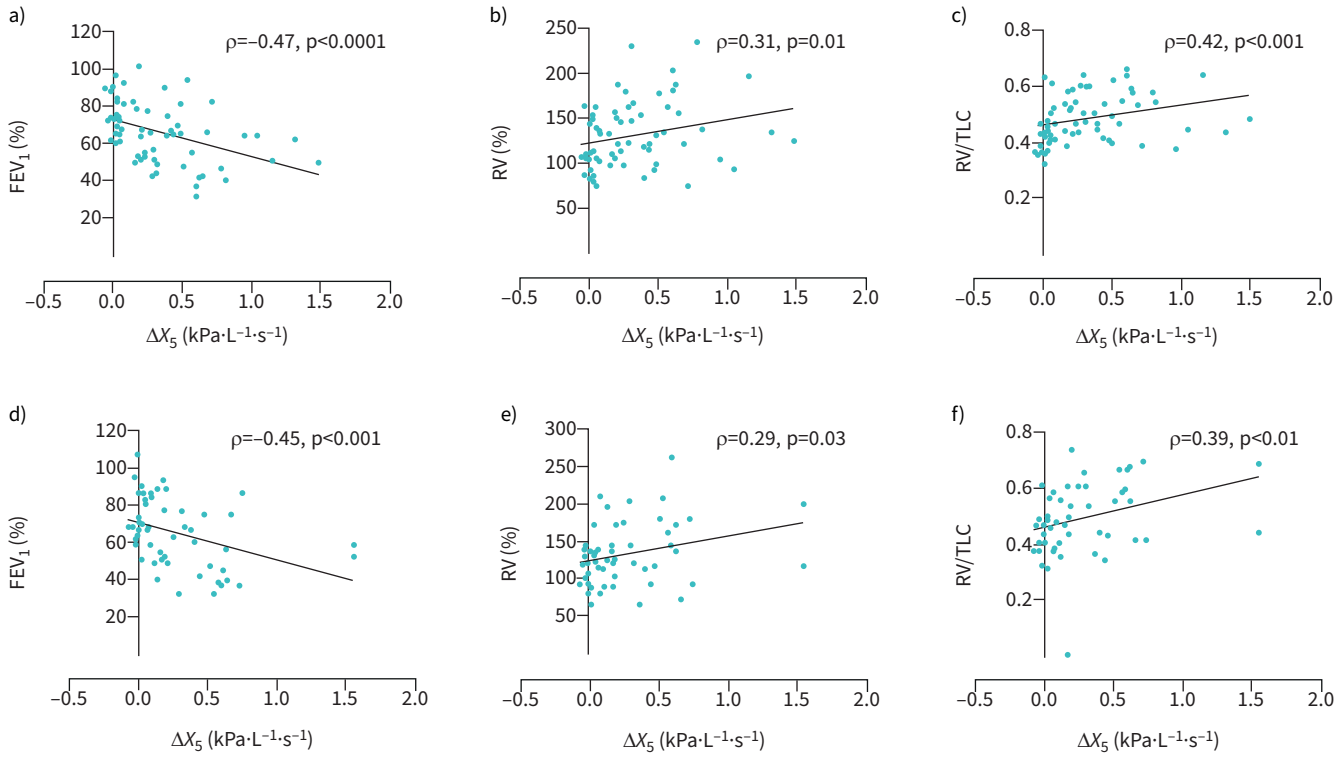

FIGURE 6 Association between difference in total reactance between inspiration and expiration at 5 Hz (ΔX_5) and other lung function parameters a–c) at baseline: a) forced expiratory volume in 1 s (FEV_1) (% predicted), b) residual volume (RV) (% predicted), c) RV/total lung capacity (TLC) ratio; and d–f) 6 months: d) FEV_1 (% predicted), e) RV (% predicted), f) RV/TLC ratio. n=64 and 54, respectively (one patient did not have RV data at 6 months). p-value corresponds to a Spearman's rank test. p<0.05 was considered statistically significant.

ΔX_5 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 ΔX_5 values to be observed. This trend has been described previously 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 was noted, in a sample size of 425 COPD patients, that ΔX_5 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 ΔX_5 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 ΔX_5 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 ΔX_5 threshold of 0.1 $kPa \cdot L^{-1} \cdot s^{-1}$ predicted breathlessness in COPD patients (sensitivity 64%, specificity 72%), while a threshold of 0.26 $kPa \cdot L^{-1} \cdot s^{-1}$ 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 ΔX_5 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 ΔX_5, 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]. Therefore, the presence of comorbidities may represent a source of variation in EFL in some COPD patients. Our results support previous observations in similarly sized cohorts that R_5–R_{20} and ΔX_5 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], n=147 [6] and n=74 [34]). The associations between ΔX_5 and small airway resistance, gas trapping and pulmonary hyperinflation [6, 34, 35] support the concepts that small airway narrowing (measured by R_5–R_{20}) and collapse (measured by EFL) are linked to gas trapping and hyperinflation [36]. There was greater small airway resistance at ΔX_5 >0.10 $kPa \cdot L^{-1} \cdot s^{-1}$, 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 computed tomography 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 <2 µm) were able to improve R_5–R_{20} 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 such as IOS and airwave oscillometry (AOS) (tremoFlo, USA) 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 ΔX_5 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. As described by Lorx *et al.* [41], this highlights further heterogeneity within flow-limited patients. Furthermore, using the multiple-breath method to define EFL and trichotomising patients into categories may classify some patients as $EFL^{Intermediate}$ or EFL^{High}, despite not meeting the ΔX_5 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.

Provenance: Submitted article, peer reviewed.

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Ethics statement: 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.

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

Author contributions: A. Beech and D. Singh were responsible for the concept and design of the study. A. Beech, N. Jackson and D. Singh were involved in data acquisition. A. Beech analysed the data and D. Singh oversaw all analyses. A. Beech and D. Singh were responsible for data interpretation and drafting the manuscript. J. Dean 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.

Conflict of interest: D. Singh 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. A. Beech, N. Jackson and J. Dean have no conflicts of interest to declare.

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