

# Clinical characteristics of COPD patients with tidal expiratory flow limitation

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**Abstract:** We have used impulse oscillometry to identify COPD patients with tidal expiratory flow limitation (EFL), which is a measurement related to small airway disease. We report that 37.4% of COPD patients had EFL; these patients had multiple clinical characteristics of more severe disease including lower forced expiratory volume in 1 second values, greater hyperinflation, reduced exercise performance, and increased small airway impairment. We highlight that EFL can be used to identify a subgroup of COPD patients with distinct characteristics associated with small airway disease.

**Keywords:** COPD, expiratory flow limitation, IOS, small airway, reactance

## Introduction

COPD is a heterogeneous condition, with pathophysiological abnormalities that vary in severity between patients.<sup>1</sup> Small airway inflammation is a common feature of COPD,<sup>2</sup> causing a reduction of the cross-sectional area of the small airway lumen. Small airway narrowing and collapse can cause gas trapping on expiration and hyperinflation.<sup>3</sup> The presence of hyperinflation is associated with greater dyspnea and reduced exercise tolerance.<sup>4</sup>

Impulse oscillometry (IOS) measures respiratory resistance and reactance during tidal breathing using sound waves of different frequencies.<sup>5</sup> Resistance is the loss of energy arising from friction or turbulence, while reactance is the capacity for energy storage, which is dependent on the elastic properties of the lungs. COPD patients typically have increased total airway resistance and a greater negative reactance compared to healthy subjects.<sup>6</sup>

Small airway narrowing and closure during expiration can prevent low-frequency oscillometric signals from traveling to the distal lung.<sup>6</sup> These regional “choke points” within the airway tree are present during expiration but not during inspiration, and cause expiratory flow limitation (EFL). EFL can be detected by a marked change in reactance during tidal breathing. Dellacà et al<sup>7</sup> used within-breath analysis to show that the difference between inspiratory and expiratory reactance at 5 Hz (known as  $\Delta X_5$ ) identifies EFL during tidal breathing in COPD patients;  $\Delta X_5$  of 0.28 kPa/L/s has a high specificity and sensitivity for detecting EFL. COPD patients with higher  $\Delta X_5$  values have greater dyspnea.<sup>6</sup>

The aim of this study was to quantify the proportion of COPD patients with EFL, and to further characterize the clinical characteristics of patients with EFL. We also studied whether the presence of EFL is stable after 2 years of follow-up.

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## Methods

A total of 147 COPD patients were recruited (75 from the COPD-MAP cohort) with 45 patients attending for follow-up at 2 years. Patients were aged >40 years, with post-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) ratio of <0.7, ≥10 pack-year smoking history, and had no history of asthma. Patients experiencing an exacerbation within the preceding 6 weeks were excluded. The study was approved by the Greater Manchester Ethics Committees (ref: 10/H1003/108) and all patients provided written informed consent.

COPD patients performed the following procedures at baseline and 2-year visit: St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), dyspnea visual analog scale (VAS), spirometry with reversibility, IOS (MasterScreen; Erich Jaeger, Hoechberg, Germany), plethysmography, diffusing capacity of the lungs for carbon monoxide (DLCO), and the 6-minute walk test, as previously described.<sup>8</sup> Plethysmography, DLCO, and spirometry (Vmax, CareFusion, Hoechberg, Germany) were performed according to the ATS/ERS guidelines.<sup>9–11</sup> ΔX5 was calculated as mean inspiratory reactance at 5 Hz (X5<sub>in</sub>) minus the mean expiratory reactance at 5 Hz (X5<sub>ex</sub>). EFL was defined as ΔX5 of ≥0.28 kPa/L/s.

Statistical analysis was performed using unpaired *t*-tests or Mann–Whitney *U* tests for comparison between groups at baseline; paired *t*-test or Wilcoxon matched pair tests for within patient comparisons at 2 years; and chi-square tests for categorical data. Pearson's correlation or Spearman's rank tests were used to assess associations. Analysis was performed using Prism 5 (Graphpad, La Jolla, CA, USA); *P*<0.05 was considered statistically significant.

## Results

In all, 55 (37.4%) of the 147 COPD patients had EFL; see Table 1 for clinical characteristics. Patients with EFL were more likely to be current smokers (*P*=0.01), have worse airflow obstruction (mean 42 versus 59 FEV<sub>1</sub>% predicted; *P*<0.0001); and have more gas trapping with a higher RV (median 166 versus 121% predicted; *P*<0.0001) and FRC (mean 144 versus 122% predicted; *P*<0.0003). The EFL group had worse SGRQ activity and symptom component scores and lower 6-minute walk distance.

There were significant differences between groups for all IOS measurements; notably, R5–R20 was greater in the EFL group. ΔX5 was significantly associated with R5–R20 (*r*=0.87, *P*<0.0001), FEV<sub>1</sub>% predicted (*r*=–0.49, *P*<0.0001), FEV<sub>1</sub>/FVC (*r*=–0.27, *P*=0.001), hyperinflation

(RV% predicted: *r*=0.37, *P*<0.0001; FRC% predicted: *r*=0.33, *P*=0.0003), CAT score (*r*=0.21, *P*=0.011), and SGRQ total score (*r*=0.22, *P*=0.009) including all the SGRQ domains (symptoms, impact, and activity). There was no association between ΔX5 and the VAS dyspnea scale (*r*=0.11, *P*=0.22).

A total of 45 patients returned at 2 years. In all, 20 patients had EFL at baseline, of which 14 (70%) had EFL at 2 years. For the remaining 6 patients without EFL at 2 years, the median ΔX5 changed from 0.44 kPa/L/s at baseline to 0.24 kPa/L/s after 2 years (*P*=0.031). A total of 25 patients did not have EFL at baseline; 21 (82%) remained without EFL at 2 years. Overall, there were no significant changes in ΔX5 values between baseline and 2 years for both the EFL and non-EFL groups. FEV<sub>1</sub> decreased in both the groups (mean changes: EFL: –66.5 mL/year, *P*=0.003; non-EFL: –71 mL/year, *P*=0.0005).

## Discussion

EFL was a common finding in COPD patients, being present in over a third of the cohort. EFL patients had a lower FEV<sub>1</sub>% predicted and more hyperinflation and gas trapping, with reduced exercise performance. R5–R20 is recognized as a measurement of small airway resistance<sup>5</sup>; EFL was associated with greater small airway impairment. This association is compatible with the cause of EFL, namely small airway narrowing and collapse.

Dellacà et al<sup>7</sup> proposed the ΔX5 threshold value of 0.28 kPa/L/s for EFL using results from forced oscillometry data during individual breathing cycles. We used mean data from multiple breathing cycles during IOS, which may categorize some patients with EFL despite not all cycles reaching the EFL threshold. Nevertheless, using this method to define EFL we identified a subgroup of patients with marked small airway disease, gas trapping, and hyperinflation. Furthermore, the identification of EFL was reproducible in the majority of cases at the 2-year follow-up.

Aarli et al<sup>6</sup> used IOS to measure EFL in COPD patients, and also found that EFL was associated with lower FEV<sub>1</sub> values and greater hyperinflation. In common with our findings, a significant association with worse health status and symptom scores was also reported. While there were some differences in the patient-reported outcome tools used, the overall interpretation of these two studies is that the presence of EFL is associated with a greater symptom burden in COPD patients.

Aarli et al<sup>6</sup> reported that COPD patients with ΔX5 ≥0.1 kPa/L/s experienced greater dyspnea. Healthy

**Table 1** Baseline clinical characteristics of patients with and without EFL

Clinical characteristics	EFL, n=55	Non-EFL, n=92	P-value
Sex (% male)	67	65	0.80
Age (years)	66 (64–68)	66 (64–67)	0.73
Current smokers (%)	38	20	0.015
Smoking (pack-years)	45 (29–59)	47 (35–67)	0.23
ICS (%)	80	78	0.80
LABA (%)	82	83	0.90
LAMA (%)	75	78	0.61
12-month exacerbation prior to study entry (number/year)	1.9 (1.5–2.3)	1.6 (1.2–2.0)	0.10
Pre-BD FEV <sub>1</sub> % predicted	42 (37–46)	59 (54–63)	<0.0001
Pre-BD FEV <sub>1</sub> /FVC (%)	38 (33–45)	47 (40–57)	<0.0001
Post-BD FEV <sub>1</sub> % predicted	47 (43–52)	64 (60–68)	<0.0001
Post-BD FEV <sub>1</sub> /FVC (%)	39 (34–45)	48 (41–56)	<0.0001
SGRQ activity	68 (59–92)	67 (37–83)	0.049
SGRQ impact	35 (29–42)	32 (27–36)	0.33
SGRQ symptoms	67 (52–81)	57 (35–71)	0.008
SGRQ total	53 (29–67)	45 (21–61)	0.12
CAT score	21 (15–26)	17 (11–25)	0.07
VAS dyspnea score	44 (21–63)	38 (18–59)	0.44
6MWD (min)	343 (324–363)	393 (371–415)	0.002
DLCO% predicted	54 (49–60)	59 (55–64)	0.14
KCO% predicted	76 (57–91)	69 (55–95)	0.49
VA% predicted	72 (69–87)	82 (71–88)	0.06
TLC% predicted	113 (108–117)	105 (101–109)	0.015
RV% predicted	166 (128–187)	121 (101–153)	<0.0001
RV/TLC (%)	61 (55–67)	47 (39–55)	<0.0001
FRC% predicted	144 (134–154)	122 (115–129)	0.0003
R5 (kPa/L/s)	0.77 (0.66–0.93)	0.49 (0.42–0.59)	<0.0001
R20 (kPa/L/s)	0.38 (0.32–0.42)	0.34 (0.30–0.41)	0.040
R5–R20 (kPa/L/s)	0.41 (0.38–0.45)	0.15 (0.13–0.17)	<0.0001
R5insp–R20insp (kPa/L/s)	0.25 (0.19–0.35)	0.10 (0.05–0.18)	<0.0001
X5 (kPa/L/s)	–0.53 (–0.59 to –0.43)	–0.22 (–31 to –0.15)	<0.0001
$\Delta$ X5 (kPa/L/s)	0.51 (0.42–0.77)	0.05 (0.00–0.19)	<0.0001
AX (kPa/L)	5.49 (4.43–6.81)	1.78 (1.07–2.88)	<0.0001
Fres (Hz)	30.6 (27.3–34.3)	22.9 (20.0–25.2)	<0.0001
R5exp (kPa/L/s)	0.79 (0.68–0.94)	0.52 (0.46–0.63)	<0.0001
R5insp (kPa/L/s)	0.64 (0.56–0.76)	0.44 (0.38–0.54)	<0.0001
X5exp (kPa/L/s)	–0.78 (–1.02 to –0.70)	–0.23 (–0.40 to –0.16)	<0.0001
X5insp (kPa/L/s)	–0.26 (–0.34 to –0.19)	–0.19 (–0.23 to –0.14)	<0.0001

**Note:** Data are presented as mean (95% CI), median (interquartile range), and percentages as appropriate.

**Abbreviations:** EFL, expiratory flow limitation; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; BD, bronchodilator; FEV<sub>1</sub>, forced expired volume in 1 second; FVC, forced vital capacity; SGRQ, St George's Respiratory Questionnaire; CAT, COPD Assessment Test; VAS, visual analog scale (dyspnea); 6MWD, 6-minute walk distance; DLCO, diffusing capacity of the lungs for carbon monoxide; KCO, carbon monoxide transfer coefficient; VA, alveolar volume; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; R5, total resistance; R20, central resistance; R5–R20, peripheral resistance; R5insp–R20insp, peripheral resistance during inspiration; X5, total reactance;  $\Delta$ X5, difference in total reactance between inspiration and expiration; AX, reactance area; Fres, resonance frequency; R5exp, total expiratory resistance; R5insp, total inspiratory resistance; X5exp, total expiratory reactance; X5insp, total inspiratory reactance; CI, confidence interval.

subjects have  $\Delta$ X5 values around zero. The  $\Delta$ X5  $\geq$ 0.1 kPa/L/s threshold value is obviously lower than that used in the current study, and is likely to identify patients with less severe EFL. The higher  $\Delta$ X5 threshold value used in this study identified a group with greater EFL that was associated with more severe disease manifestations.

It has been reported that  $\Delta$ X5 is associated with the level of symptoms and duration of hospitalization during COPD

exacerbations.<sup>12</sup> Treatment with an inhaled corticosteroid/long-acting beta-agonist combination for 3 months improved  $\Delta$ X5.<sup>13</sup> The identification of small airway disease and EFL in COPD patients using oscillometry methods may allow individualized targeting of drugs to treat these pathophysiological abnormalities. For example, inhalers with a greater proportion of extra-fine particles<sup>14</sup> could be targeted to COPD patients with EFL.

We recruited a reasonable size cohort that was clinically characterized in detail at baseline. There was limited follow-up at 2 years, and larger cohort studies are needed to build on the observations here about the long-term clinical implications of EFL.

## Conclusion

We have long recognized that small airway disease<sup>2</sup> and EFL<sup>6,7</sup> are features of COPD. We show that IOS can identify patients with EFL, and that EFL is associated with more severe airflow obstruction, hyperinflation, and symptoms. We suggest that EFL is a “treatable trait”,<sup>15</sup> and may provide an opportunity for therapeutic intervention.

## Disclosure

Dave Singh has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards, and research grants from various pharmaceutical companies including Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GlaxoSmithKline, Glenmark, Merck, NAPP, Novartis, Pfizer, Respivert, SkyePharma, Takeda, Teva, Therevance, and Verona. The other authors report no conflicts of interest in this work.

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