The clinical utility of forced oscillation technique during hospitalisation in patients with exacerbation of COPD

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Abstract

Background Forced Oscillation Technique (FOT) is an innovative tool to measure within-breath reactance at 5 Hz (ΔXrs_{5Hz}) but its feasibility and utility in acute exacerbations of COPD (AECOPD) is understudied.

Methods A prospective observational study was conducted in 82 COPD patients admitted due to AECOPD. FOT indices were measured and the association between these indices and spirometry, peak inspiratory flow rate, blood inflammatory biomarkers and patient-reported outcomes including assessment of dyspnoea, quality of life, anxiety and depression and frailty at admission and discharge were explored.

Results All patients were able to perform FOT in both sitting and supine position. The prevalence of expiratory flow limitation (EFL) in the upright position was 39% (32 out of 82) and increased to 50% (41 out of 82) in the supine position. EFL (measured by ΔXrs_{5Hz}) and resistance at 5 Hz (Rrs_{5Hz}) negatively correlated with forced expiratory volume in 1 s (FEV_1); those with EFL had lower FEV_1 (0.74±0.30 *versus* 0.94±0.36 L, p = 0.01) and forced vital capacity (1.7±0.55 *versus* 2.1±0.63 L, p = 0.009) and higher body mass index (27 (21–36) *versus* 23 (19–26) kg·m^{-2}, p = 0.03) compared to those without EFL. During recovery from AECOPD, changes in EFL were observed in association with improvement in breathlessness.

Conclusion FOT was easily used to detect EFL during hospitalisation due to AECOPD. The prevalence of EFL increased when patients moved from a seated to a supine position and EFL was negatively correlated with airflow limitation. Improvements in EFL were associated with a reduction in breathlessness. FOT is of potential clinical value by providing a noninvasive, objective and effort-independent technique to measure lung function parameters during AECOPD requiring hospital admission.

Introduction

Pulmonary function testing has a vital role in the clinical assessment of COPD including diagnosis, monitoring and management. Thus far, spirometry remains the gold standard test of lung function to assess airflow limitation [1]. COPD severity is defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) based on persistent airflow limitation demonstrated on spirometry [2].

Nevertheless, spirometry has drawbacks which limit its use in clinical practice. First, there is only a weak relationship between spirometry indices and patient-reported symptoms [3]. Second, it has limited value in detecting early disease [1, 4]. This is likely because spirometry assesses larger airway flows. Although it has been established that COPD arises from small airways [5], COPD affects both small and large airways [6].

Furthermore, spirometry is effort-dependent and requires patients to forcefully exhale, which can be challenging to perform in children, frail and elderly patients, and patients who are acutely unwell for example at the time of an exacerbation.

Forced Oscillation Technique (FOT) is a noninvasive, objective and effort-independent lung function test to assess respiratory impedance (resistance and reactance) [7]. DELLACÀ *et al.* [7] used FOT to detect expiratory limitation (EFL) in COPD patients and found that within-breath reactance (ΔXrs_{5Hz}) provides an accurate, reliable and noninvasive technique to identify EFL. This technique is particularly useful in COPD to evaluate response to interventions such as bronchodilators and offers monitoring of disease progression [8]. FOT has also been found to be feasible as a home telemonitoring tool to detect COPD exacerbations [9, 10]. However, the clinical value of FOT for the assessment of EFL and other pulmonary mechanics in hospitalised COPD exacerbations is limited [11–13]. Previous studies were conducted on a small number of patients and did not assess inflammatory biomarkers, peak inspiratory flow rates and other patient-reported outcomes such as depression, anxiety and frailty [11–13]. A recent systematic review of the use of physiological tests (including FOT) in COPD exacerbations recommended additional research to evaluate the value of such measures in COPD exacerbations to monitor progress and treatment response [14]. Therefore, this paper aims to holistically investigate the clinical utility of FOT in a COPD population admitted to hospital due to exacerbation and identify whether there is an association between COPD airflow severity using spirometry and FOT indices, as well as comparing the characteristics of patients who do and do not have EFL.

Methods

This was a single centre prospective cohort study conducted on respiratory wards at the Royal Free London NHS Foundation Trust, UK. Ethical approval was obtained from the health research authority (HRA) and Health and Care Research Wales (HCRW) (reference 19/EM/0080). Written informed consent was obtained for each participant before participating in the study.

Participants

Consecutive patients with a confirmed COPD diagnosis (post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.7) and an appropriate exposure history, admitted to hospital due to acute exacerbation of COPD (AECOPD) were recruited between June 2019 and March 2020. In March 2020 study recruitment was stopped due to coronavirus pandemic restrictions. We excluded any patient with a predominant history of asthma or bronchiectasis, patients with mental health disorders preventing compliance with the trial protocol and those in whom an initial diagnosis of an AECOPD was revised to an alternative at a later phase of their admission.

Outcome measures

- The prevalence and change over time of EFL during hospitalised exacerbation of COPD, in both the upright and supine positions using FOT. EFL was defined as ΔXrs_{5Hz} of $\geqslant$2.8 cmH$_2$O·L^{-1}·s.
- Relationship between FEV_1 and respiratory impedance including within-breath reactance (ΔXrs_{5Hz}) and resistance.
- Differences in clinical characteristics of patients with COPD exacerbations who do and do not have EFL.

Recruitment assessment

At enrolment, demographic and relevant clinical data including smoking and exacerbation history, medication use, and blood inflammatory biomarkers were gathered from the patients and their medical record. Patient-reported outcomes were measured, including assessment of dyspnoea (modified Medical Research Council, mMRC) [15]; quality of life using the COPD Assessment Test (CAT) [16]; and anxiety and depression questionnaire (HADS) [17]. Frailty was assessed using the Reported Edmonton Frail Scale (REFS) [18].

Quality assured spirometry using ndd EasyOne® Air was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria [19]. COPD was confirmed when the post-bronchodilator FEV_1/FVC was <0.70 in the context of an appropriate exposure history.

A FOT device (ResmonPro; ResTech, Milan, Italy) was used to measure the patients' respiratory impedance: resistance (Rrs) and reactance (Xrs) at 5 Hz [20]. The EFL was measured by within-breath difference in reactance at 5 Hz (ΔXrs_{5Hz}) and can thus detect flow-limited breaths with high sensitivity and specificity [7]. This test was conducted according to standard recommendations [20]. For the upright

measurement, patients were instructed to be in a sitting position with the head in a neutral or slightly extended position to perform the test. The patients' cheeks and base of the mouth were firmly supported using both hands to prevent mouth leaks. A nose clip was placed to eliminate leak. Each patient was instructed to breathe in and out normally for 10–20 breaths into the ResmonPro. FOT measurements were also taken in the supine position to compare them with the upright position.

Patients were asked about their preference for spirometry or FOT.

Peak inspiratory flow rate (PIFR) was measured using the InCheckTM DIAL (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical, Granbury, TX, USA). This tool is well validated and can measure inspiratory flow rates between 15 and 120 $L·min^{-1}$ [21, 22].

All the above measurements were conducted at the recruitment assessment during admission (within the first 48 h) and within 2 days before discharge from hospital. All assessments were conducted during the morning to have consistent timepoints for all patients.

Analysis

Data were inspected using histograms to look for outliers and tested for normality using a Kolmogorov–Smirnov test. If normally distributed (parametric), data were expressed as mean±SD and if not normally distributed, were expressed as median (inter-quartile range, IQR) (non-parametric) as appropriate. Categorical variables were compared using the Chi-squared test or the Fisher exact test. For other comparisons, Wilcoxon signed-rank was used for non-parametric paired data and t-test (paired test) was used for parametric data. Relationships between variables were analysed using Spearman rank correlation coefficient test for non-parametric variables, and for normally distributed variables we used the Pearson correlation. For the purposes of comparison, we divided patients into two groups according to their within-breath reactance (ΔXrs_{5Hz}) value (a marker of EFL) in the upright position. EFL was defined as ΔXrs_{5Hz} of $\geqslant 2.8$ $cmH_2O·L^{-1}·s$ [7]. We analysed our data using the software Statistical Package for the Social Sciences (SPSS), version 26 (IBM, Armonk, NY, USA). Data from this cohort examining factors predicting readmission to hospital have been previously published [23].

Results

A total of 82 patients were recruited to the study and included in the main analysis (figure 1). The patients had a mean±SD age of 71±10.4 years. Most were ex-smokers (58 (71%)) with a median pack-year of
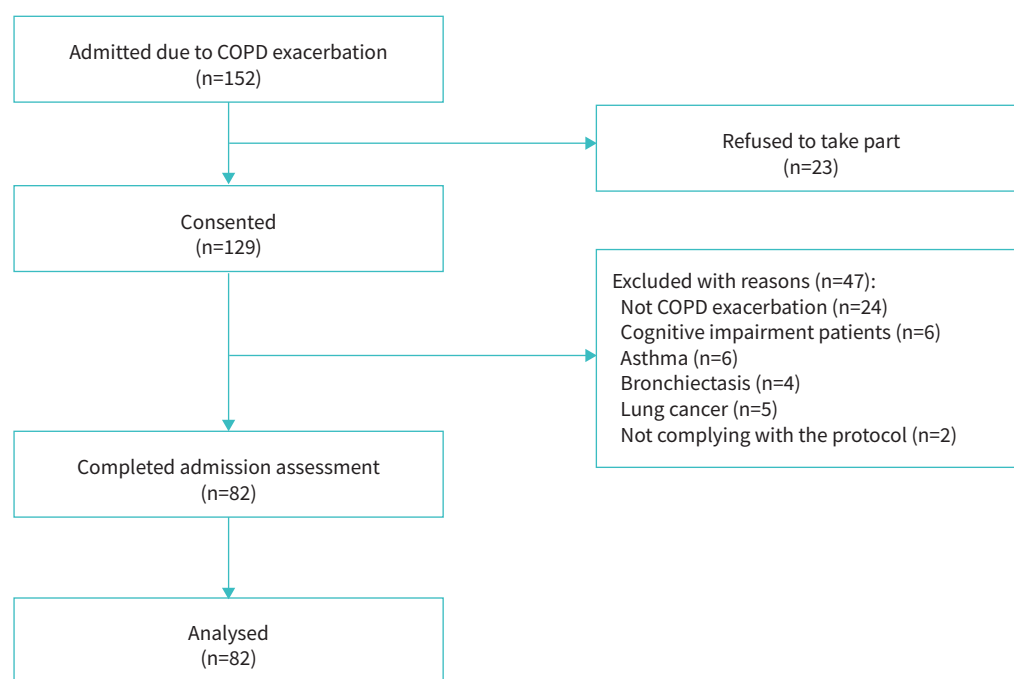

FIGURE 1 CONSORT diagram.

42 (29–56). The admission characteristics of the patients are reported in table 1. The time from admission to initial assessment ranged between 24 and 48 h. All patients preferred FOT over spirometry.

Prevalence of EFL at hospitalised COPD exacerbation

The prevalence of EFL in the upright position was 39% (32 out of 82), and this increased to 50% (41 out of 82) when the measurement was taken supine. Median ΔXrs_{5Hz} in the upright position was 2.1 (0.4–5.1) $cmH_2O \cdot L^{-1} \cdot s$ with a percentage of flow limitation breaths (FL%) of 20%; this increased to 3 (0.9–7) $cmH_2O \cdot L^{-1} \cdot s$ in the supine position with FL% of 50%. Rrs_{5Hz} in the upright position was 4.7 (3.2–6.2) $cmH_2O \cdot L^{-1} \cdot s$, and this increased to 5.3 (3.7–7.2) $cmH_2O \cdot L^{-1} \cdot s$ in the supine position. At discharge, EFL had resolved in six out of the 39 (15.4%) subjects with flow-limited breaths in the upright position on admission, while EFL had resolved in nine out of 41 patients with flow-limited breaths in the supine position on admission.

The measurements of FOT are presented in table 2. There were no significant changes in ΔXrs_{5Hz} in upright and supine positions from admission to discharge (2.1 (0.4–5.1) *versus* 2.7 (0.82–5.2) $cmH_2O \cdot L^{-1} \cdot s$, p = 0.51) and (3 (0.9–7) *versus* 3.4 (1.3–7.3) $cmH_2O \cdot L^{-1} \cdot s$ p = 0.53), respectively.

Relationship between COPD airflow severity and FOT indices

We explored the relation between FEV_1 and ΔXrs_{5Hz} in upright and supine positions and found weak but statistically significant negative correlations (r = −0.25, p = 0.03; r = −0.30, p = 0.01, respectively). Figure 2 illustrates that those with more severe airflow limitation (lower FEV_1) have greater EFL. We also investigated the relationship between FEV_1 and Rrs_{5Hz} in the upright and supine positions, and again there

TABLE 1 Characteristics of the index admission between those with expiratory flow limitation and those without, in the upright position

Characteristics	All patients	Patients with EFL	Patients with no EFL	p-value
Subjects n	82	32	50	
Male	40 (49)	13 (41)	27 (54)	0.31
Female	42 (51)	19 (59)	23 (46)	
Age years	71±10.4	70.2±10.2	72±10.6	0.49
BMI kg·m^{-2}	24 (20–29)	27 (21–36)	23 (19–26)	**0.03**
Current smoker	24 (29)	10 (31)	14 (28)	0.68
Ex-smoker	58 (71)	22 (69)	36 (72)	
Smoking history (pack-years)	42 (29–56)	38 (27.5–53)	42.5 (29–61)	0.84
Number of exacerbations (within past 12 months)	2 (1–4)	3 (1–4)	2 (1–4)	0.92
Number of hospitalised exacerbations (<12 months)	2 (1–3)	1 (1–3)	2 (1–3)	0.61
Pulmonary rehabilitation (<12 months)	28 (34)	16 (50)	12 (24)	**0.02**
Charlson Comorbidity Index	4.3±1.6	4.1±1.3	4.4±1.7	0.23
FEV$_1$ L	0.86±0.34	0.74±0.30	0.94±0.36	**0.01**
FEV$_1$%	34.3±12.4	32±12	36±13	0.25
FVC L	2.2±2.3	1.7 ±0.55	2.1 0.63	**0.009**
FVC %	61±16.7	59 ±16.1	63 ±17.5	0.45
FEV$_1$/FVC %	43.5±11	42±11	44±11	0.52
IC L	1.3 (1–1.8)	1.2 (1–1.8)	1.4 (1–1.8)	0.84
PIFR L/m	60 (50–85)	60 (50–88)	62 (50–85)	0.72
Length of stay in days	7 (4–10.3)	7.5 (4.2–11.5)	8 (5–10.7)	0.93
CAT score	31 (27.7–34)	31 (27–34)	32 (28.5–34)	0.52
mMRC	4 (3.7–4)	4 (4–4)	4 (3–4)	0.54
REFS	10 (9–12.2)	10 (10–12)	10.5 (9–12)	0.54
Depression	11 (7–14)	8 (5.2–12.7)	11.5 (7.2–14)	0.08
Anxiety	9 (6.7–11)	9 (6.2–12)	9 (6.2–11)	0.82
WBCs (10^9/L)	10.6 (7.9–14.5)	10.5 (8–15)	11 (7.8–14)	0.70
Eosinophils (10^9/L)	0.07 (0.02–0.24)	0.06 (0.02–0.17)	0.1 (0.01–0.40)	0.43
Neutrophils (10^9/L)	8 (5.1–11.6)	8 (5–12)	8 (6–11)	0.75
CRP mg·L^{-1}	20 (6–62)	15 (6–70)	21 (5–70)	0.61
eGFR mL·min^{-1}	85 (65–90)	70.5 (60–90)	90 (68–90)	0.06

Data are presented as n (%), mean±SD or median (IQR). BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV$_1$/FVC: calculated ratio between both measurements; IC: inspiratory capacity; PIFR: peak inspiratory flow rate; CAT: COPD Assessment Test; mMRC: modified Medical Research Council dyspnoea scale; REFS: Reported Edmonton Frail Scale; WBCs: white blood cells; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate. Data in bold: p<0.05.

TABLE 2 Changes from admission to discharge between those who do and do not have expiratory flow limitation (EFL)

Outcomes	Patients with EFL[#]				Patients with no EFL[¶]				p-value[+]
	Admission	Discharge	Median difference	p-value	Admission	Discharge	Median difference	p-value	
ΔXrs_{5Hz} at upright position $cmH_2O \cdot L^{-1} \cdot s$	6.1 (4.4–8.1)	5.1 (3.9–6.5)	−0.35 (−2.4–0.96)	0.10	0.9 (0.07–1.75)	1 (0.23–2.7)	0.27 (−0.3–1.7)	0.02	0.009
FL% at upright position	100 (85–100)	91 (63–100)	0 (−22–0.9)	0.07	0 (0–20)	10 (0–53)	0 (−20–51)	0.04	0.02
ΔXrs_{5Hz} at supine position $cmH_2O \cdot L^{-1} \cdot s$	8.2 (4.3–11.3)	7.4 (4.2–10.3)	0.1 (−2.1–1.7)	0.72	2.1 (0.7–3)	2 (0.5–4.2)	0.3 (−1.1–1.5)	0.58	0.29
FL% at supine position	100 (78–100)	91 (66–100)	0 (0–1.8)	0.86	27 (0–60)	27 (0–80)	0 (−21–18)	0.98	0.71
Rrs_{5Hz} at upright position $cmH_2O \cdot L^{-1} \cdot s$	6.1 (4.8–8.1)	6.2 (5.1–8.3)	0.05 (−1.1–0.6)	0.53	3.9 (2.5–5.3)	4.1 (3.2–5.4)	0.4 (−0.4–1.3)	0.08	0.13
Rrs_{5Hz} at supine position $cmH_2O \cdot L^{-1} \cdot s$	6. 5 (5.2–8.1)	7.3 (5.5–8.8)	−0. 1 (−0.9–1.7)	0.56	4.8 (3.2–6.5)	5.1 (3.8–6.2)	−0.2 (−0.9–11.3)	0.61	0.96
PIFR (L/m)	60 (50–88)	75 (50–100)	10 (−1.5–14.5)	0.002	60 (50–85)	75 (55–100)	10 (−2.5–20)	0.001	0.56
IC L	1.2 (0.9–1.7)	1.3 (1–1.7)	0.04 (−0.14–0.19)	0.55	1.2 (0.9–1.7)	1.4 (1–1.7)	0.08 (−0.05–0.28)	0.02	0.23
mMRC	4 (4–4)	3 (2–3)	−1 (−1–0)	0.001	4 (3–4)	2 (2–3)	−1 (−1–0)	0.001	0.26
CAT score	31 (27–34)	17.5 (14.2–22.7)	−10.5 (−15– −6)	0.001	32 (28.5–34)	21 (17–25)	−10 (−13– −5)	0.001	0.27
WBCs (10^9/L)	10.5 (8–15)	8.5 (7–12)	−1.7 (−5.7–0.6)	0.01	11 (7.8–14)	10 (8–12)	−1.1 (−3.8–0.9)	0.005	0.48
Eosinophils (10^9/L)	0.06 (0.02–0.17)	0.13 (0.05–0.25)	0.04 (−0.01–0.1)	0.05	0.1 (0.01–0.40)	0.13 (0.03–0.21)	0.01 (−0.11–0.14)	0.91	0.39
Neutrophils (10^9/L)	8 (5–12)	5.5 (5–8	−0.7 (−5.1–0.42)	0.009	8 (6–11)	7 (5–8)	−1.5 (−4.6–0.91)	0.002	0.76
CRP $mg \cdot L^{-1}$	15 (6–70)	7 (4–47)	−5 (−47–1)	0.01	21 (5–70)	11 (4–28)	−8 (−52–1.5)	0.003	0.89
eGFR $mL \cdot min^{-1}$	70.5 (60–90)	84 (63–90)	0 (−1.5–19)	0.03	90 (68–90)	90 (78–90)	0 (0–1)	0.25	0.23

Data are presented as median (IQR). ΔXrs_{5Hz}: within-breath reactance at 5 Hz; FL%: flow limitation percentage; Rrs_{5Hz}: resistance at 5 Hz; PIFR: peak inspiratory flow rate; IC: inspiratory capacity; mMRC: modified Medical Research Council dyspnoea scale; CAT: COPD Assessment Test; WBCs: white blood cells; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate.[#]: n = 32; [¶]: n = 50; [+]: median difference between groups.

were statistically significant negative correlations (r = −0.35, p = 0.003; −0.31, p = 0.01, respectively) (figure 3.).

Relationship between baseline characteristics and FOT indices

There were significant negative correlations between FVC and ΔXrs_{5Hz} in the upright and supine positions (r = −0.33, p = 0.005; r = −0.36, p = 0.002, respectively) (figure 4). Further, there were statistically significant positive correlations between body mass index (BMI) and ΔXrs_{5Hz} in the upright and supine positions (r = 0.27, p = 0.01; r = 0.30, p = 0.008, respectively) in which those with higher BMI have greater
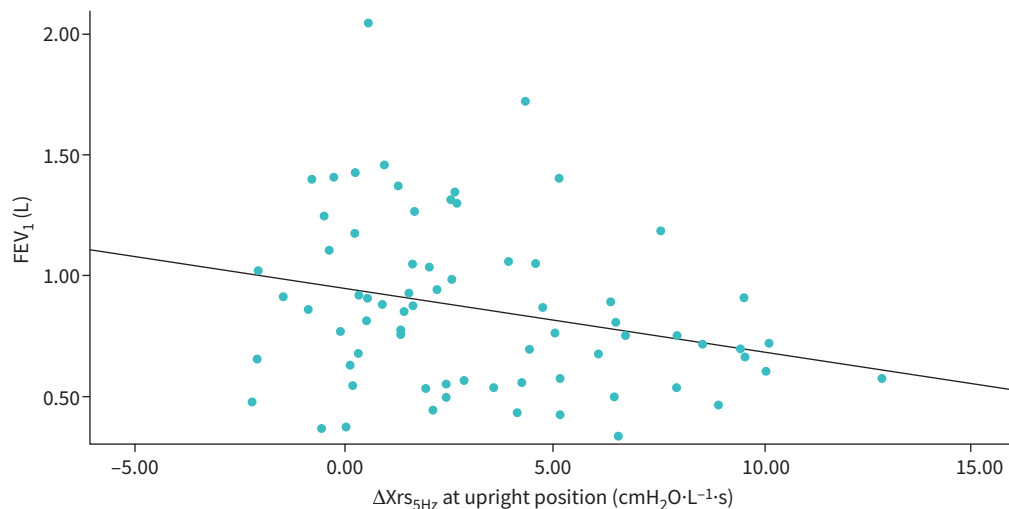

FIGURE 2 Correlation between forced expiratory volume in 1 s (FEV_1) and expiratory flow limitation (EFL) at admission assessment (r = −0.25, p = 0.03). Xrs_{5Hz}: reactance of the respiratory system measured at 5 Hz.

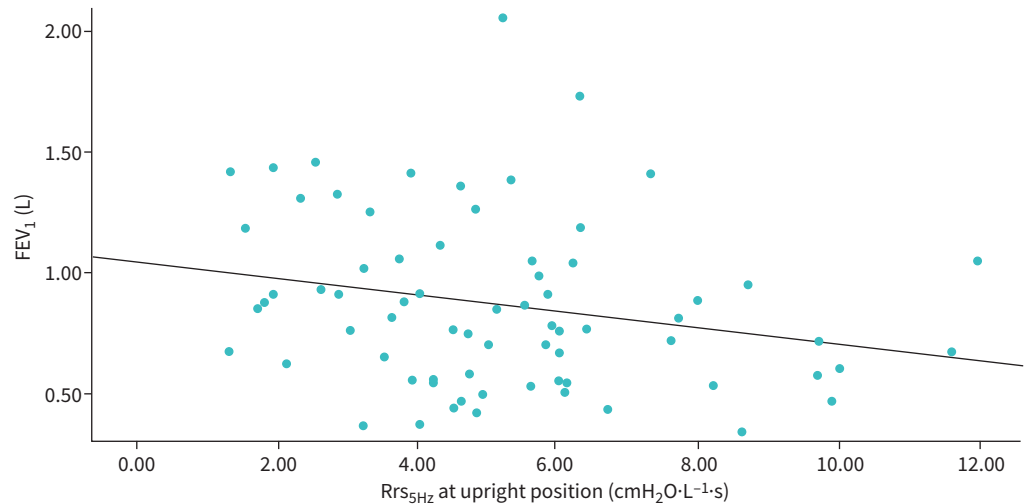FIGURE 3 Correlation between forced expiratory volume in 1 s (FEV_1) and resistance of the respiratory system measured at 5 Hz (Rrs_{5Hz}) at admission assessment (r = −0.35, p = 0.003).

EFL (figure 4). There were no significant correlations between FOT indices and other clinical variables including age, smoking history, prior exacerbation and hospitalisation history, length of stay, comorbidity index, blood biomarkers and self-reported patient outcomes.

Clinical characteristics between those who do and do not have EFL

There were no significant differences between those with and without EFL in sex, age, smoking history, comorbidity index and previous exacerbation and hospitalisation rates. However, subjects who have EFL at admission had higher BMI (27 (21–36) versus 23 (19–26) kg·m^{-2}, p = 0.03). There were significant differences between the two groups in FEV_1 (0.74±0.30 versus 0.94±0.36 L; p = 0.01) and FVC (1.7±0.55 versus 2.1±0.63 L; p = 0.009), respectively; those with EFL had lower FEV_1 and FVC compared to those without. The results, as shown in table 1, indicate no statistically significant differences between groups in self-reported patient outcomes (breathlessness scale, CAT, HAD and frailty score), length of stay and blood biomarkers.

Comparing the two groups, it can be seen from table 2 that ΔXrs_{5Hz} in the upright and supine positions of the group with EFL was significantly higher than those with no EFL (6.1 (4.4–8.1) versus 0.9 (0.07–1.75),
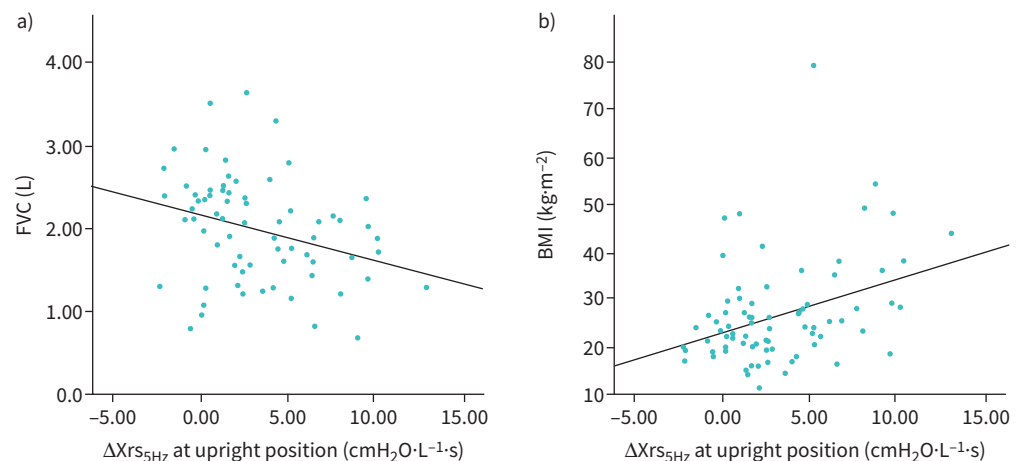

FIGURE 4 Correlation between forced vital capacity (FVC), body mass index (BMI) and expiratory flow limitation (EFL) at admission assessment. a) Negative correlation between FVC and EFL (r = −0.33, p = 0.005). b) Positive association between BMI and EFL (r = 0.27, p = 0.01). Xrs_{5Hz}: reactance of the respiratory system measured at 5 Hz.

8.2 (4.3–11.3) *versus* 2.1 (0.7–3) (cmH$_2$O·L^{-1}·s), p⩽0.001), respectively. This was associated with significant differences in FL% in the upright and supine positions between groups: 100 (85–100) *versus* 0 (0–20); 100 (76–100) *versus* 29 (0–61) %, p⩽0.001, respectively. When we compared Rrs$_{5Hz}$ in the upright and supine positions between groups, statistically significant differences were found, in which the EFL group have a greater resistance than those with no EFL: 6.1 (4.8–8.1) *versus* 3.9 (2.5–5.3), 6.4 (5.1–8.1) *versus* 4.8 (3.4–6.6) (cmH$_2$O·L^{-1}·s), p⩽0.001), respectively.

Recovery during hospitalisation in flow-limited patients

Table 2 shows the differences within and between groups between the initial and pre-discharge assessments. There were no significant differences between the groups in FOT indices except for ΔXrs$_{5Hz}$ and FL% in the upright position (−35 (−2.4–0.96) *versus* 0.27 (−0.3–1.7) cmH$_2$O·L^{-1}·s, p = 0.009; 0 (−22–0.9) *versus* 0 (−20–51) %, p = 0.02), respectively. Within the EFL group, there were no statistically significant differences found in FOT indices, while there were significant differences in ΔXrs$_{5Hz}$ and FL% in the upright position within patients in the group with no EFL.

There were statistically significant increases in PIFR between admission and discharge in the groups both with and without EFL (60 (50–88) *versus* 75 (50–100) L/m, p = 0.002; 60 (50–85) *versus* 75 (55–100) L/m, p = 0.001), respectively, while no difference was found between groups. Although there was an improvement trend in inspiratory capacity within the EFL group, no significant change was found, whereas in patients with no EFL there was a significant change (1.2 (0.9–1.7) *versus* 1.4 (1–1.7) L, p = 0.02). Generally, there were statistically significant differences in mMRC and CAT scores within both groups (p = 0.001), but these changes were not significant between groups. Table 2 shows that there has been a significant improvement in most blood biomarkers within both groups from admission to discharge, with no statistically significant differences between the groups. When we assessed correlations in the EFL group, there were statistically positive correlations between difference of EFL in upright and supine positions and difference in mMRC (r = 0.41, p = 0.03; r = 0.47, p = 0.01), respectively (figures 5 and 6).

Discussion

In patients hospitalised due to COPD exacerbation: 1) all patients were able to easily perform FOT during hospitalisation in both upright and supine positions and preferred FOT to spirometry; 2) EFL measured by ΔXrs$_{5Hz}$ was prevalent in both upright and supine positions, 39% and 50% respectively; 3) EFL and resistance negatively correlated with FEV$_1$, a marker of airflow limitation; 4) those with EFL had lower FEV$_1$ and FVC, and higher resistance and BMI compared to those without EFL; and 5) during recovery
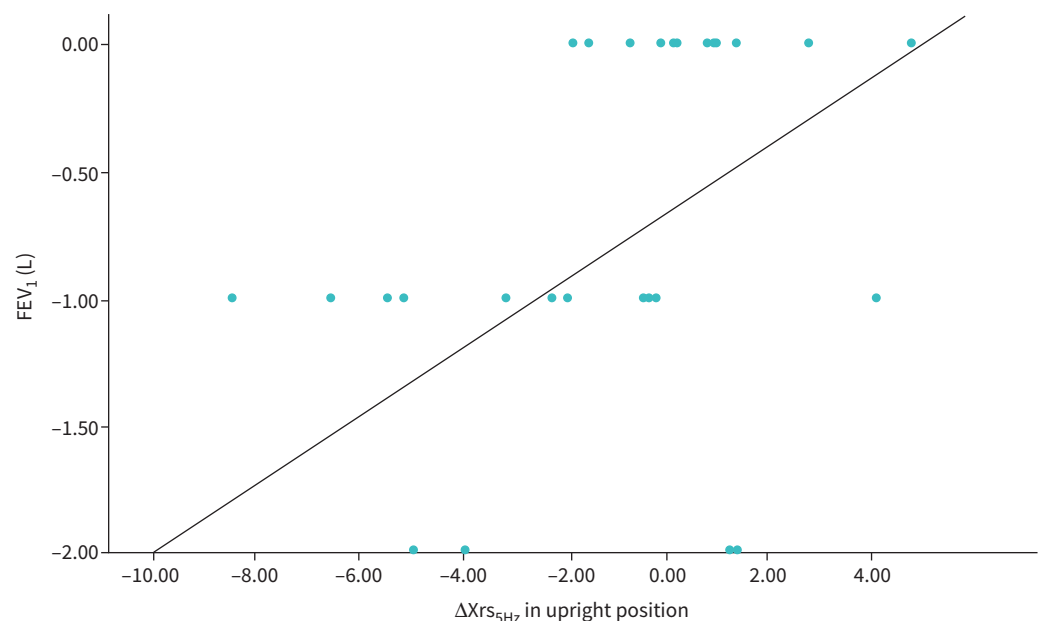

FIGURE 5 Correlation between change in modified Medical Research Council (mMRC) and change in expiratory flow limitation (EFL) in the upright position (r = 0.41, p = 0.03). Xrs$_{5Hz}$: reactance of the respiratory system measured at 5 Hz.
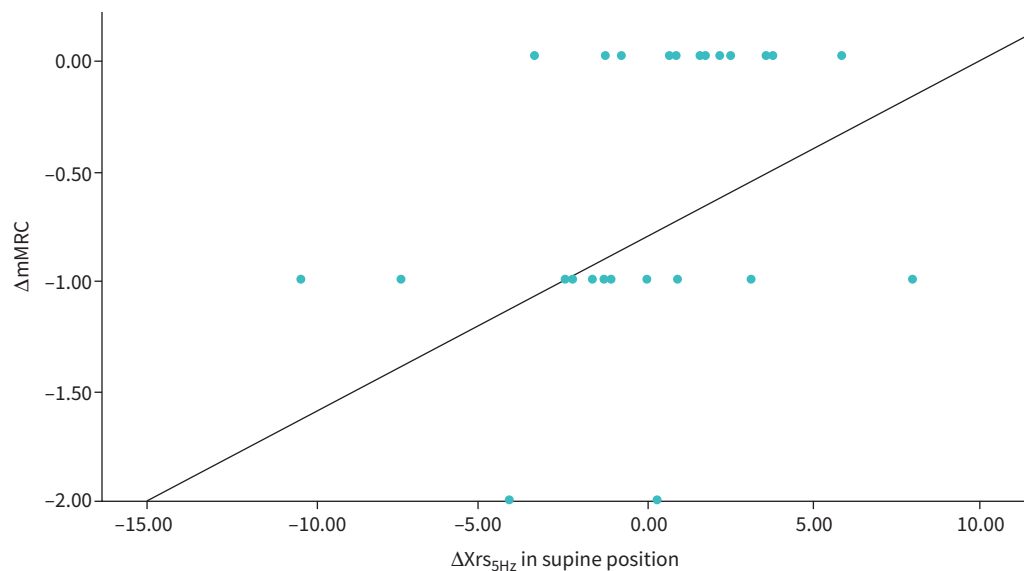
FIGURE 6 Correlation between change in modified Medical Research Council (mMRC) and change in expiratory flow limitation (EFL) in the supine position ($r = 0.47$, $p = 0.01$). Xrs_{5Hz}: reactance of the respiratory system measured at 5 Hz.

from acute exacerbations, changes in EFL were observed in association with improvement in breathlessness. Our results support the feasibility and utility of FOT as a routine part of patient assessment and monitoring at hospitalised exacerbation of COPD.

This study has demonstrated that it is feasible to use FOT to measure EFL during AECOPD. In a real-world clinical setting, it has been reported that around 15% of patients failed to perform high-quality spirometry at baseline that met the ATS/ERS standards [24]. We would expect a higher failure percentage at exacerbation. Our patients' experience of performing both spirometry and FOT, preferring the latter, suggest FOT may be a useful tool in the context of exacerbations where it may be difficult to undertake reliable spirometry due to breathlessness.

We found a higher prevalence of EFL during hospitalised COPD exacerbations in the supine position of 50% (41 out of 82) compared to the upright position of 39% (32 out of 82). This might be expected as the relaxation volume and end expiratory lung volume are reduced due to gravitational forces associated with recumbency [25]. Previous work in this area found a lower prevalence of EFL in a seated position in which 31% (9 out of 29) of patients hospitalised due to exacerbation had EFL [11]. However, this study was carried out on a small number of patients and did not present lung volume and inflammatory biomarkers measures. Our reported prevalence of EFL in the seated position is consistent with that of STEVENSON *et al.* [13] who found that 41% (9 out of 22) of COPD patients showed EFL at admission. However, this was measured using negative expiratory pressure (NEP) and conducted on only 22 patients. In our cohort there were general improvements in those with EFL at discharge, but complete resolution, defined as ΔXrs_{5Hz} of <2.8 (cmH$_2$O·L^{-1}·s), was only observed in 15% (6 out of 29) in the upright position and 22% (9 out of 42) in the supine position. This finding contrasts with JETMALANI *et al.* [11] and STEVENSON *et al.* [13] in which 44% of the patients in each study had complete resolution from EFL at discharge. This could be attributed to different factors including severity of COPD, demographic data and use of NEP. Such findings indicate that when COPD patients recover from exacerbations, improvement in EFL occurs but complete resolution from EFL is not universal at the point of discharge. Recently, EFL at discharge was found to be associated with 90-day readmission following COPD exacerbation (OR 3.02, 95% CI 1.17–7.83) [23]. This highlights the value of using EFL as a physiological biomarker to predict COPD readmission and lessen its burden [26, 27].

We have provided detailed data demonstrating that those with severe airflow limitation (lower FEV$_1$) have greater EFL and resistance at hospital admission for exacerbation of COPD, in keeping with expected physiological changes during an acute exacerbation such as suboptimal peak expiratory flow rates and lung hyperinflation [28, 29]. EFL results from the effects of permanent parenchymal destruction caused by

emphysema and airway dysfunction in COPD. FEV_1 airflow severity reflects a reduction in driving pressure for expiratory flow caused by constricted airways that ultimately lead to an increase in resistance. As a result, EFL is increasing [30, 31]. It has been found that EFL can predict patient-reported symptoms better than FEV_1 [32, 33]. In stable COPD, EFL was associated with more severe airflow limitation and hyperinflation with reduced functional performance [34, 35]. Indeed, the observed increase in ΔXrs_{5Hz} and Rrs_{5Hz} at exacerbation can be attributed to several physiological changes that have poor correlation with spirometry. Further, respiratory reactance measured by FOT correlates with FEV_1 and can predict the rate of change in FEV_1 over time [36]. Given the ease with which EFL can be measured by FOT in patients hospitalised due to COPD exacerbation, measuring EFL is both more convenient and clinically relevant than spirometry to track disease recovery.

Concerning the relationship between baseline characteristics and FOT indices, we found significant negative correlations between FVC and EFL (ΔXrs_{5Hz}) in the upright and supine positions. This could be explained by the presence of EFL and due to hyperinflation changing operating lung volumes and increasing functional residual capacity, which decreases lung operating volumes [12]. Those with higher BMI had higher EFL, and this was expected because those patients usually breathe at low lung volume, with the closing capacity increases above expiratory residual volume, therefore resulting in EFL [37, 38]. There were no significant correlations between FOT indices and age, smoking history, exacerbation and hospitalisation history, length of stay, comorbidity index, inflammatory biomarkers and self-reported patient outcomes. A possible explanation for this might be that FOT measurements reflect the current respiratory compliance and inertial properties of the respiratory system, rather than disease severity.

When we compared the EFL group to those with no EFL, there were no statistically significant differences between groups in sex, age, smoking history, comorbidity index and previous exacerbation and hospitalisation rates and length of stay. This result agrees with a previous study conducted with hospitalised COPD exacerbation patients [11]. Nevertheless, YAMAGAMI et al. [39] showed significant differences in respiratory impedance between those with frequent exacerbations and those with no exacerbation in the last 2 years. However, this study was limited by its retrospective design. There were significant differences between the two groups in FEV_1 and FVC ($p = 0.01$ and $p = 0.009$, respectively), in which those with EFL have lower FEV_1 and FVC compared to those without EFL. This outcome is contrary to that of JETMALANI et al. [11] who found similar spirometry values between those with EFL and those with no limitation; this could be due to their small sample size. Our findings show that there were significant differences between both groups in all FOT indices (ΔXrs_{5Hz}, FL%, Rrs_{5Hz}), whereby the EFL group had greater values compared to those with no EFL. We present, for the first time, the relationship between COPD patients with and without EFL and inflammatory biomarkers. Our results show no association in FOT indices and blood biomarkers between the groups. The reason for this is not clear but it might be because FOT measurements reflect the current degree of airflow limitation and air trapping not exacerbation severity, and more studies are needed to explore this.

The most important clinically relevant finding was that the improvement in EFL index values from admission to discharge was associated with an improvement in mMRC in COPD patients. Indeed, the impairment in lung mechanics gradually resolves as exacerbations are treated but was not completely resolved at the time of discharge [13]. Such findings have important clinical and research implications. Detecting EFL at COPD exacerbation could be used to identify those with more severe physiological disturbance and to assess their response to treatment during recovery. This could have clinical value for patient monitoring and personalised treatment, by providing an effort-independent, objective test to measure lung function parameters during a COPD exacerbation requiring hospital admission. This would help prevent further COPD exacerbations, identified as one of the 10 top research priorities in a shared patient–clinician research prioritisation exercise [40]. These findings also raise intriguing research questions regarding the nature and extent of EFL impact on the patient's recovery from COPD exacerbation and reducing hospital readmission, aiming to improve clinical outcomes.

The findings from this study make several contributions to the current literature. Firstly, we are the first to measure EFL in both upright and supine positions at hospital admission and discharge, utilising a larger sample size than prior research. Secondly, we conducted the first comprehensive assessment in hospitalised COPD exacerbation that includes patient-reported outcomes, flow and lung volume measures, inflammatory blood biomarkers and FOT indices. Thirdly, our study can be used to inform power calculations for future studies. Lastly, based on our hospitalised COPD patients' experience, FOT is a preferable option when assessment of respiratory physiology is required, and it provides an objective measurement that could help to track recovery from exacerbation.

This study has some limitations. Firstly, we did incorporate serial measurements, but not at standardised timepoints, so additional measurements would have been valuable to look at recovery trajectory. Secondly, as we made measurements at admission and discharge only, it would have been useful to look at follow-up, but this was beyond the scope of the study. Thirdly, as recruitment was stopped early due to the global pandemic, the study may be under-powered for some analyses. Fourthly, the device used to measure FOT produces results that might not be directly comparable to other FOT devices.

Conclusion

Our study shows that during hospitalisation due to COPD exacerbation, FOT was feasible to detect EFL. The severity of EFL increased when patients moved from a seated to a supine position, and this negatively correlated with airflow limitation. Improvements in EFL were associated with a reduction in breathlessness. FOT can be utilised to detect EFL during hospitalised COPD exacerbation, and potentially could be used to identify those with more severe physiological disturbance and to track their recovery. FOT has potential clinical value by providing a noninvasive, objective and effort-independent technique to measure lung function parameters during a COPD exacerbation requiring hospital admission.

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