

# The association of tidal EFL with exercise performance, exacerbations, and death in COPD

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**Background:** Tidal expiratory flow limitation (EFL<sub>T</sub>) is frequently found in patients with COPD and can be detected by forced oscillations when within-breath reactance of a single-breath is  $\geq 0.28$  kPa·s·L<sup>-1</sup>. The present study explored the association of within-breath reactance measured over multiple breaths and EFL<sub>T</sub> with 6-minute walk distance (6MWD), exacerbations, and mortality.

**Methods:** In 425 patients, spirometry and forced oscillation technique measurements were obtained on eight occasions over 3 years. 6MWD was assessed at baseline and at the 3-year visit. Respiratory symptoms, exacerbations, and hospitalizations were recorded. A total of 5-year mortality statistics were retrieved retrospectively. We grouped patients according to the mean within-breath reactance ( $\overline{\Delta Xrs}$ ), measured over several breaths at baseline, calculated as mean inspiratory–mean expiratory reactance over the sampling period. In addition to the established threshold of EFL<sub>T</sub>, an upper limit of normal (ULN) was defined using the 97.5th percentile of  $\overline{\Delta Xrs}$  of the healthy controls in the study; 6MWDs were compared according to  $\overline{\Delta Xrs}$ , as normal,  $\geq ULN < EFL_T$ , or  $\geq EFL_T$ . Annual exacerbation rates were analyzed using a negative binomial model in the three groups, supplemented by time to first exacerbation analysis, and dichotomizing patients at the ULN.

**Results:** In patients with COPD and baseline  $\overline{\Delta Xrs}$  below the ULN (0.09 kPa·s·L<sup>-1</sup>), 6MWD was stable. 6MWD declined significantly in patients with  $\overline{\Delta Xrs} \geq ULN$ . Worse lung function and more exacerbations were found in patients with COPD with  $\overline{\Delta Xrs} \geq ULN$ , and patients with  $\overline{\Delta Xrs} \geq ULN$  had shorter time to first exacerbation and hospitalization. A significantly higher mortality was found in patients with  $\overline{\Delta Xrs} \geq ULN$  and FEV<sub>1</sub> >50%.

**Conclusion:** Patients with baseline  $\overline{\Delta Xrs} \geq ULN$  had a deterioration in exercise performance, more exacerbations, and greater hospitalizations, and, among those with moderate airway obstruction, a higher mortality.  $\overline{\Delta Xrs}$  is a novel independent marker of outcome in COPD.

**Keywords:** forced oscillation technique, reactance, COPD, exacerbations, 6-minute walk test, mortality

## Introduction

COPD is a major cause of morbidity and mortality, leading to an estimated 3.1 million deaths globally in 2012.<sup>1</sup> Although symptoms and exacerbation rate have been added to our assessment system of COPD,<sup>2</sup> spirometry remains an important tool in assessing severity and prognosis in this disease. Changes in the forced expiratory volume in 1 second (FEV<sub>1</sub>) are still the best indicator of disease progression and the risk of dying from COPD.<sup>2,3</sup> Yet, on an individual level, FEV<sub>1</sub> is an unreliable marker of morbidity, especially in early disease,<sup>4-6</sup> and there is a need to identify alternative objective tests that can aid in stratifying the risk of further patient deterioration.

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Patients who exhibit tidal expiratory flow limitation (EFL<sub>T</sub>) might be such a subgroup. EFL<sub>T</sub> occurs when increases in driving pressure fail to increase expiratory flow during resting tidal breathing and is most often seen in patients with severe COPD,<sup>7,8</sup> although it can occur with only moderate airway obstruction. Previous studies of EFL<sub>T</sub> in COPD have focused on its association with operating lung volume, exercise tolerance,<sup>9,10</sup> and its relation to breathlessness.<sup>11–13</sup> It is not known whether EFL<sub>T</sub> can provide longer-term prognostic information in COPD.

EFL<sub>T</sub> can be detected by the forced oscillation technique (FOT).<sup>14,15</sup> When peripheral airways collapse on expiration, oscillatory pressure signals are prevented from reaching the alveoli. As this happens, the oscillatory compliance is reduced. Consequently, expiratory reactance ( $X_{rs\_exp}$ ) becomes more negative than the inspiratory reactance ( $X_{rs\_insp}$ ), leading to a within-breath reactance difference ( $\Delta Xrs$ ). In the absence of EFL<sub>T</sub>, reactance measured in inspiration and in expiration is almost identical. The within-breath reactance difference ( $\Delta Xrs$ ) cut-off of 0.28 kPa·s·L<sup>-1</sup> has been defined and validated to identify flow-limited breaths.<sup>14,15</sup> EFL<sub>T</sub> is not only linked to dyspnea in COPD,<sup>11,16</sup> but also to COPD exacerbations, where  $\Delta Xrs$  have been found to increase at the onset of COPD exacerbations and decrease when the exacerbation resolves.<sup>17</sup>

In this study, we used forced oscillation technique to define EFL<sub>T</sub> in 425 patients with COPD. We hypothesized that the presence of EFL<sub>T</sub>, assessed by increased mean  $\Delta Xrs$  ( $\overline{\Delta Xrs}$ ), would relate to changes in 6MWD, the risk of COPD exacerbations, and, possibly, mortality. We explored these hypotheses using baseline  $\overline{\Delta Xrs}$  as a predictor for future events. Patients with COPD with abnormally high  $\overline{\Delta Xrs}$ , both above the upper limit of normal (ULN) and above the established threshold of EFL<sub>T</sub>, were investigated to determine whether they differed from those without evidence of tidal expiratory flow limitation.

## Methods

### Study design and patients

The current data derive from the Bergen cohort of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study,<sup>18</sup> with additional patients enrolled from our clinical catchment area. Written informed consent was obtained from all study subjects. The study was approved by the regional ethics committee, REK vest (REK 165.08), and performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines ([ClinicalTrials.gov](http://www.ClinicalTrials.gov); No: NTC00292552; [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)).<sup>39</sup>

Inclusion criteria for patients with COPD were: age 40–75 years, FEV<sub>1</sub> <80% predicted, FEV<sub>1</sub>/FVC <0.7, and a smoking history of ≥10 pack-years. Study patients were evaluated every 6 months for 3 years with an additional visit at 3 months after baseline, totaling eight visits. The American Thoracic Society-Division of Lung Disease (ATS-DLD-78) questionnaire and the modified Medical Research Council dyspnea scale score (mMRC) were used to record respiratory symptoms.<sup>19,20</sup>

Post-bronchodilator spirometry and oscillatory lung mechanics during tidal breathing were performed after inhalation of 0.4 mg salbutamol (GlaxoSmithKline, Ventolin, London, UK) according to American Thoracic Society/European Respiratory Society (ATS/ERS) international standards at each visit using a Jaeger MasterScope CT Impulse Oscillation System (Jaeger, Hoechberg, Germany).<sup>21,22</sup> Local reference values were used to determine the FEV<sub>1</sub>% predicted.<sup>23</sup> The FOT measurements were performed with the patient seated, cheeks supported, and wearing a nose clip. We performed three continuous measurements of 30 seconds, totaling 90 seconds of tidal volume breathing. Acceptability of measurements was determined using the ERS 2003 task force recommendations.<sup>22</sup>

$\overline{\Delta Xrs}$  reactance was averaged over the 90-second sample, containing several breaths, and was calculated as follows:  $\overline{\Delta Xrs} = \text{mean } X_{rs\_insp} \text{ at } 5 \text{ Hz} - \text{mean } X_{rs\_exp} \text{ at } 5 \text{ Hz}$ . Two cut-offs were investigated: the ULN defined as the 97.5th percentile of healthy controls in the Bergen cohort of the ECLIPSE study ( $\overline{\Delta Xrs} \geq 0.09 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$ ; Figure S1),<sup>13</sup> and at the established EFL<sub>T</sub> defining threshold for within-breath reactance, 0.28 kPa·s·L<sup>-1</sup>, derived from single-breath analysis.<sup>14,15</sup> To illustrate the variability of our multiple-breath measurement,  $\overline{\Delta Xrs}$  was plotted against time in a subset of the patients defined EFL<sub>T</sub> at baseline with complete visits (N=20).

### Study outcomes

Distance walked during the 6-minute walk test (6MWT) was used to assess exercise performance. The 6MWT was supervised by a trained technician and performed in a 30-m, straight hospital corridor according to agreed standards at baseline and at the end of the study, at the 3-year visit.<sup>24</sup>

Exacerbations were defined as a worsening of respiratory symptoms over 2 days or more that required systemic corticosteroids or antibiotics, alone or in combination (“moderate exacerbations”), or exacerbations resulting in hospitalization (“severe exacerbations”). Assessment of exacerbations was performed retrospectively by the study physician at the half-yearly visits, over the 3-year study period.

Mortality statistics were retrieved on August 25, 2011, approximately 5 years after the conclusion of the baseline

visit by checking vital status in our local patient file system, which is linked to the Norwegian Causes of Death Registry. The Causes of Death Registry includes deaths of all residents, regardless of whether they die in Norway or abroad, and is assumed to have information on >98% of all deaths.<sup>25</sup>

## Statistics

IBM SPSS version 22, Stata 13.1, and R 3.2.3 GUI 1.66 were used for different aspects of statistical analyses. Data are presented as mean  $\pm$  standard deviation, median (quartiles), mean (95% confidence interval), and absolute count or percentage. Means were compared using independent samples *t*-tests, paired samples *t*-tests, or Mann–Whitney *U* test when appropriate.

Patients were categorized into three groups according to  $\Delta\bar{X}_{rs}$ : normal,  $\geq \text{ULN} < \text{EFL}_T$ , and  $\geq \text{EFL}_T$  at baseline. We report the change in the 6-minute walk distance in these three groups from baseline to the 3-year visit in notched boxplots. Differences in walking distance between baseline and the end of the study were compared using paired samples *t*-test, grouping the patients according to the  $\Delta\bar{X}_{rs}$  and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade.<sup>2</sup>

The rate of exacerbations in the three groups was analyzed as suggested by Keene et al using a negative binomial regression model, accounting for the yearly variability among test subjects in the exacerbation rate over the 3-year study period, adjusting for FEV<sub>1</sub>, age, sex, and a binary classifier

identifying frequent exacerbators in the year prior to inclusion.<sup>26</sup> Parameter effects of the baseline explanatory variables are reported as annual rate ratios (RRs), 95% confidence interval (CI), and *P*-values. Moderate and severe exacerbations requiring hospitalization were also investigated on the basis of the occurrence of  $\Delta\bar{X}_{rs} \geq \text{ULN}$  at baseline by time to first event analysis. Groups were compared using a log-rank test. Results are displayed as 1-minus-survival plots.

Survival analysis was performed with Kaplan–Meier survival analysis, comparing distributions with the log-rank test, grouping patients by the occurrence of  $\Delta\bar{X}_{rs} \geq \text{ULN}$  at baseline, and by dichotomizing FEV<sub>1</sub> at 50% of that predicted.

## Results

### Baseline characteristics

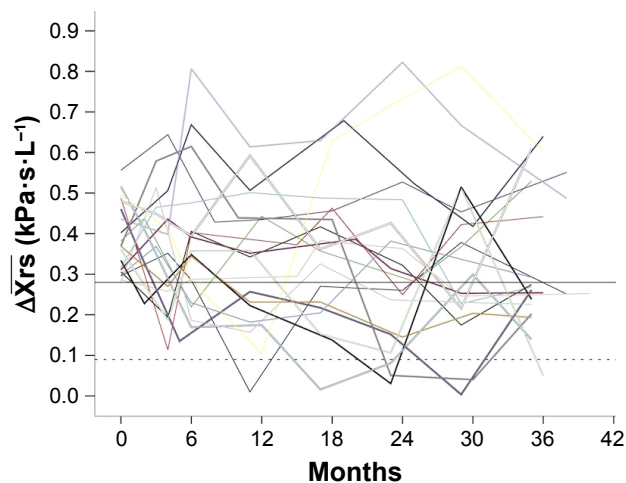
In this population of patients with COPD, 60% were men and had moderate to very severe airway obstruction. Women were, on average, 2 years younger and had lower tobacco exposure (Table S1); 50% of patients with COPD had normal  $\Delta\bar{X}_{rs}$ , 31% were classified as being abnormal with  $\Delta\bar{X}_{rs} \geq \text{ULN} < \text{EFL}_T$ , and 18% had  $\Delta\bar{X}_{rs}$  above the threshold of  $\text{EFL}_T$  (Table 1). From the normal to the abnormal group, lung function worsened with a decline in FEV<sub>1</sub> and FVC, and an increase in body mass index (BMI) and mMRC. This difference was most marked between the normal and  $\text{EFL}_T$  group. For IC, we only found a significant difference between the normal and the  $\text{EFL}_T$  group.

**Table 1** Baseline characteristics in COPD patients with different levels of  $\Delta\bar{X}_{rs}$  (N=425)

Subject characteristics	Normal	Abnormal	$\text{EFL}_T$
	$\Delta\bar{X}_{rs} < \text{ULN}$	$\text{ULN} \geq \Delta\bar{X}_{rs} < \text{EFL}_T$	$\Delta\bar{X}_{rs} > 0.28 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$
Subjects (n)	213 (50%)	134 (32%)	78 (18%)
Women	40%	36%	49%
Age (years)	63 (7)	64 (7)	63 (6)
BMI kg/m <sup>2</sup>	24 (5) <sup>c,d</sup>	26 (5) <sup>c,e</sup>	28 (6) <sup>d,e</sup>
Pack-years (years)	40 (24)	43 (22)	39 (22)
Frequent exacerbators (%)	13%	20%	35%
mMRC	1.2 (0, 2) <sup>c,d</sup>	1.8 (0.25, 2) <sup>c,e</sup>	2.3 (1, 2) <sup>d,e</sup>
FEV <sub>1</sub> (L)	1.7 (0.5) <sup>c,d</sup>	1.3 (0.5) <sup>c,e</sup>	1.1 (0.4) <sup>d,e</sup>
FEV <sub>1</sub> (%)	52 (11) <sup>c,d</sup>	42 (12) <sup>c</sup>	38 (13) <sup>d</sup>
FVC (L)	3.5 (0.9) <sup>c,d</sup>	3.2 (0.8) <sup>c,e</sup>	2.8 (0.9) <sup>d,e</sup>
IC (L)	2.6 (0.8) <sup>d</sup>	2.5 (0.7)	2.3 (0.7) <sup>d</sup>
IC (%)	88 (19)	85 (20)	84 (21)
6MWD (meters)	455 (102) <sup>c,d</sup>	410 (109) <sup>c,e</sup>	363 (110) <sup>d,e</sup>
Estimated exacerbations per year <sup>a</sup>	0.7	1.3	1.6
Deaths <sup>b</sup>	25 (12) <sup>c,d</sup>	28 (21) <sup>c</sup>	18 (23) <sup>d</sup>

**Notes:** Data presented as mean  $\pm$  standard deviation unless otherwise stated. <sup>a</sup>Estimated exacerbation rate by negative binomial model. <sup>b</sup>Number of deaths at the 5-year census (%). Significant differences at the 5% level are marked as <sup>c</sup>between normal and abnormal, <sup>d</sup>between normal and  $\text{EFL}_T$ , and <sup>e</sup>between abnormal and  $\text{EFL}_T$ . pack-years: packs of 20 cigarettes smoked per day  $\times$  years as a smoker; Frequent exacerbators: percentage with  $\geq 2$  exacerbations the year prior to inclusion.

**Abbreviations:** ULN, upper limit of normal 0.09 kPa·s·L<sup>-1</sup>;  $\text{EFL}_T$ , tidal expiratory flow limitation; BMI, body mass index; mMRC, modified Medical Research Council dyspnea scale score – mean (quartiles); FEV<sub>1</sub>, forced expiratory volume in 1 second; FEV<sub>1</sub> (%), FEV<sub>1</sub> percentage of predicted; FVC, forced vital capacity; IC, inspiratory capacity; IC (%), IC percentage of predicted;  $\Delta\bar{X}_{rs}$ , difference between mean inspiratory and mean expiratory reactance at 5 Hz over multiple breaths; 6MWD, 6-minute walk distance.



**Figure 1** Timeplot illustrating the variability of  $\Delta\overline{Xrs}$  measurements (splines) over the course of the study shown in the first 20 patients with COPD with complete visits, defined as having  $EFL_T$  at baseline ( $\Delta\overline{Xrs} \geq 0.28 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$ ). The dotted line is set at  $0.09 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$ , the upper limit of normal and the solid line at  $EFL_T$ .

$\Delta\overline{Xrs}$  was not a stable measurement. Many patients defined as  $EFL_T$  at baseline fell below the  $EFL_T$  threshold during the course of the study (Figure 1). Six percent of the consequent  $\Delta\overline{Xrs}$  measurements were found to be normal; 23% of the patients dropped out of the study before the final visit, the main reason being death during the study period (Table 2).

### Relationship of $EFL_T$ to study outcomes

$\Delta\overline{Xrs}$  was as poorly correlated with baseline 6-minute walking distance as  $FEV_1$  (Figure 2A and B). On a group level, 6MWD declined with increasing  $\Delta\overline{Xrs}$ , being 455 m in the normal, 410 m in the abnormal, and 363 m in the  $EFL_T$  group (Table 1). In patients who completed both the baseline and the final visit, changes in 6MWD were compared. No significant change between the baseline and the final 3-year visit was seen in the 6MWD of patients with normal  $\Delta\overline{Xrs}$ . Patients with  $\Delta\overline{Xrs} \geq \text{ULN}$  declined by a mean of 37 m (95% CI 15–58),  $P=0.001$ , and patients with  $EFL_T$  declined by 63 m (95% CI 31–95),  $P<0.001$  (Figure 2C).

**Table 2** Deaths and dropouts during the 3-year study period (N=96)

Reason	N	%
Died	41	10
FOT not performed at the final visit	16	4
Refused further participation	8	2
Excluded due to use of oral steroids	8	2
Excluded after being diagnosed with pulmonary cancer	5	1
Other causes	18	4
Total	96	23

**Abbreviation:** FOT, forced oscillation technique.

Grouping by GOLD grade produced similar boxplots. GOLD 2 patients remained stable whereas a significant decline was seen in GOLD 3–4 grades (Figure 2D).

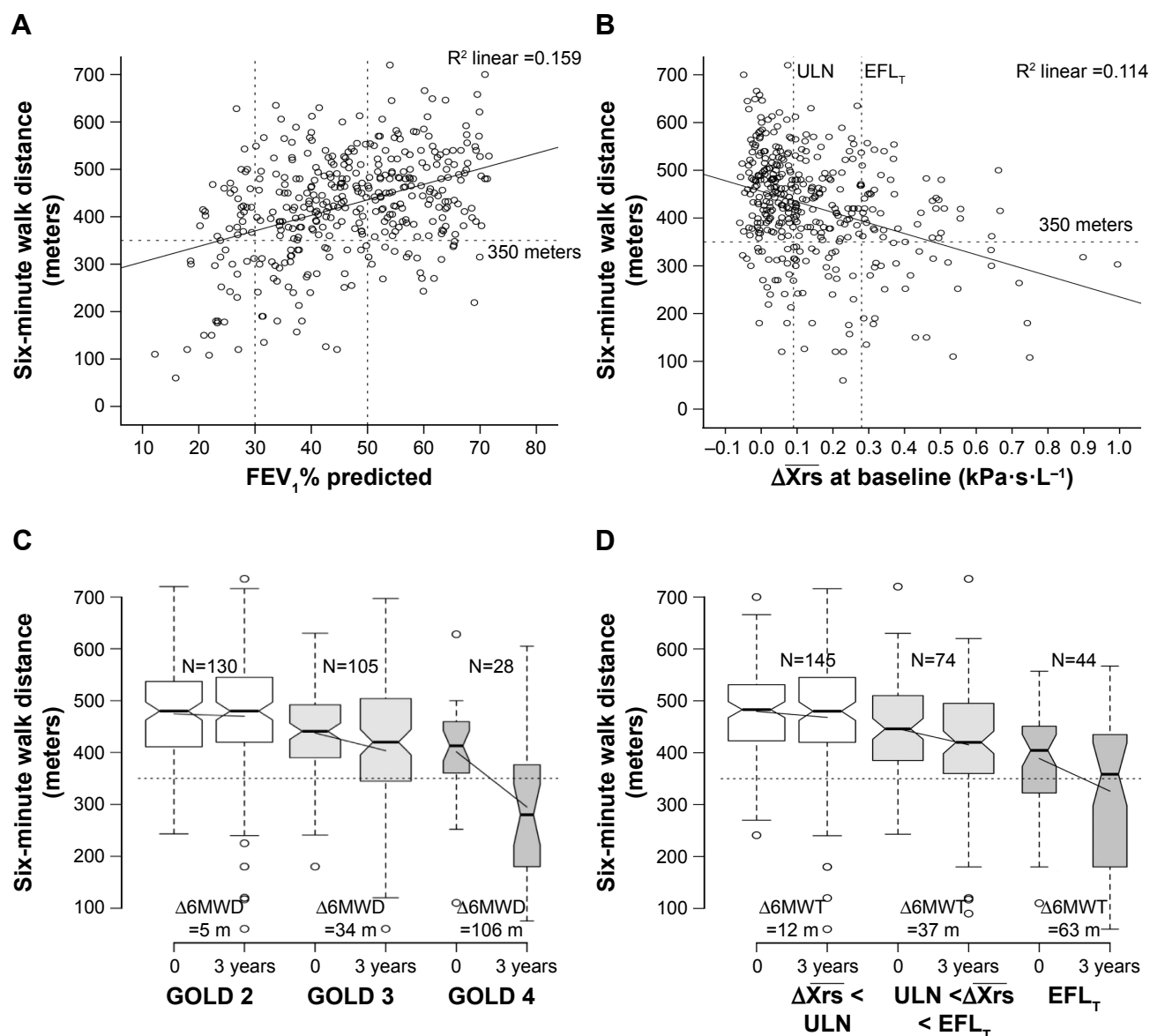
A total of 1,289 moderate to severe exacerbations were recorded throughout the study. By negative binomial regression, estimated annual exacerbations rates were 0.7 in patients with normal  $\Delta\overline{Xrs}$ , 1.3 in patients with COPD with  $\Delta\overline{Xrs} \geq \text{ULN}$ , and 1.6 in patients with  $EFL_T$ . Annual exacerbation RR compared to the normal group was 1.28 for ULN patients and 1.30 for  $EFL_T$  patients (Table 3). A time to first exacerbation analysis was performed in patients with COPD with and without evidence of  $\Delta\overline{Xrs} \geq \text{ULN}$  at baseline. Significant differences were found in both time to first exacerbation ( $P=0.009$ ) and in time to first hospitalization ( $P=0.017$ ; Figure 3A). Median time to first moderate or severe exacerbation was 76 weeks in patients with COPD with normal  $\Delta\overline{Xrs}$ , compared with only 55 weeks in COPD patients with  $\Delta\overline{Xrs} \geq \text{ULN}$  at baseline (Table 4). The time until 25% of the patients were hospitalized was 126 weeks in patients with normal  $\Delta\overline{Xrs}$  and 72 weeks in patients with  $\Delta\overline{Xrs} \geq \text{ULN}$ .

### Mortality

At the 5-year census, 72 (17%) of the 425 patients with COPD had died. Deaths were significantly more frequent in patients with  $\geq \text{ULN}$  than in patients with normal  $\Delta\overline{Xrs}$ , but not significantly different between the  $\geq \text{ULN}$  and the  $EFL_T$  groups (Table 1). Mortality was higher in patients with  $FEV_1 < 50\%$  (Figure 4). The difference in mortality between patients with  $\Delta\overline{Xrs}$  in the normal range and  $\geq \text{ULN}$  was driven by increased mortality in patients with  $FEV_1 > 50\%$  (Figure 4). Mortality was 17% in  $\Delta\overline{Xrs} \geq \text{ULN}$  patients with  $FEV_1 > 50\%$ , compared to 5% in patients with normal  $\Delta\overline{Xrs}$  ( $P<0.001$ ; Figure 4). Mortality in patients with  $\Delta\overline{Xrs} \geq \text{ULN}$  was similar to what was found in patients with COPD with much more advanced airway obstruction.

### Discussion

Using data from the ECLIPSE study, we investigated associations between increased  $\Delta\overline{Xrs}$  at the ULN and at the threshold of  $EFL_T$  with decline in 6MWD, risk of later exacerbations, and all-cause mortality. No change in 6MWD was found in patients with COPD with  $\Delta\overline{Xrs}$  in the normal range. All patients with COPD with  $\Delta\overline{Xrs} \geq \text{ULN}$  deteriorated significantly in 6MWD. Patients with COPD with  $\Delta\overline{Xrs} \geq \text{ULN}$  had increased risk for both moderate and severe exacerbations, and, in the patients with only moderate airway obstruction,  $FEV_1 > 50\%$ , a significantly higher mortality. This study



**Figure 2** (A) Six-minute walk distance (6MWD) in patients with COPD ( $N=388$ ) at different levels of  $FEV_1\%$  predicted (A) and  $\Delta\bar{Xrs}$  (B) at baseline. Dotted lines set at 350 m (horizontal) and at  $\Delta\bar{Xrs} = 0.09$  kPa·s·L<sup>-1</sup>, upper limit of normal (ULN), and  $\Delta\bar{Xrs} = 0.28$  kPa·s·L<sup>-1</sup>, the threshold for tidal expiratory flow limitation ( $EFL_T$ ). The solid lines represent the regression lines. (C) 6MWT at baseline and the 3-year visit presented by notchplots with quartiles, 95% central range and outliers among COPD patients of GOLD II–IV grades and categorized according to  $\Delta\bar{Xrs}$  (D) as normal (white), below  $EFL_T$ , but above ULN (light gray), and  $> EFL_T$  threshold (gray). Non-overlapping notched areas are likely to represent significant differences between groups. Solid lines are drawn between the mean 6MWD at baseline and the 3-year visit.

demonstrates that  $\Delta\bar{Xrs}$  provides valuable extra information in addition to  $FEV_1$  when characterizing the effects of small-airway obstruction on key COPD outcomes.

We defined the ULN at the 97.5th percentile of healthy controls included in our study. Data describing the control group have previously been published.<sup>13,18</sup> The FOT threshold identifying a single flow-limited breath has been defined when within-breath reactance was  $>0.28$  kPa·s·L<sup>-1</sup>.<sup>14,15</sup> We interpreted our continuous spectrum measurements performed over several breaths as showing evidence of flow limitation when measurements between the ULN

and the threshold of  $EFL_T$  were found. These borderline measurements are thought to represent a mixture of normal and flow-limited breaths.

Exercise limitation is extremely common in COPD, and even small decreases in the 6MWD over time identify patients with increased risks of dying.<sup>27</sup> When  $EFL_T$  is present, patients can only increase their minute ventilation during exercise by increasing breathing frequency or by dynamic hyperinflation, allowing end-expiratory lung volume to rise.<sup>28</sup> Dynamic hyperinflation can be induced by self-paced walking exercise. This is usually assessed by changes in

**Table 3** Annual rate ratios estimated by negative binomial regression (N=395)

Baseline explanatory variables	RR	95% CI	P-value
$\overline{\Delta Xrs}$			
$\geq ULN$ (0.09 kPa·s·L <sup>-1</sup> ) and $< EFL_T$	1.28	1.05, 1.55	0.011
$\geq EFL_T$ (0.28 kPa·s·L <sup>-1</sup> )	1.30	1.05, 1.64	0.009
FEV <sub>1</sub> % predicted	0.07	0.04, 0.14	<0.001
Age in decades	1.36	1.06, 1.34	0.009
Sex (male)	0.85	0.72, 1.00	0.048
Exacerbation in the year prior to inclusion			
$\geq 2$	1.99	1.64, 2.41	<0.001
Intercept	0.98	0.42, 2.27	0.965

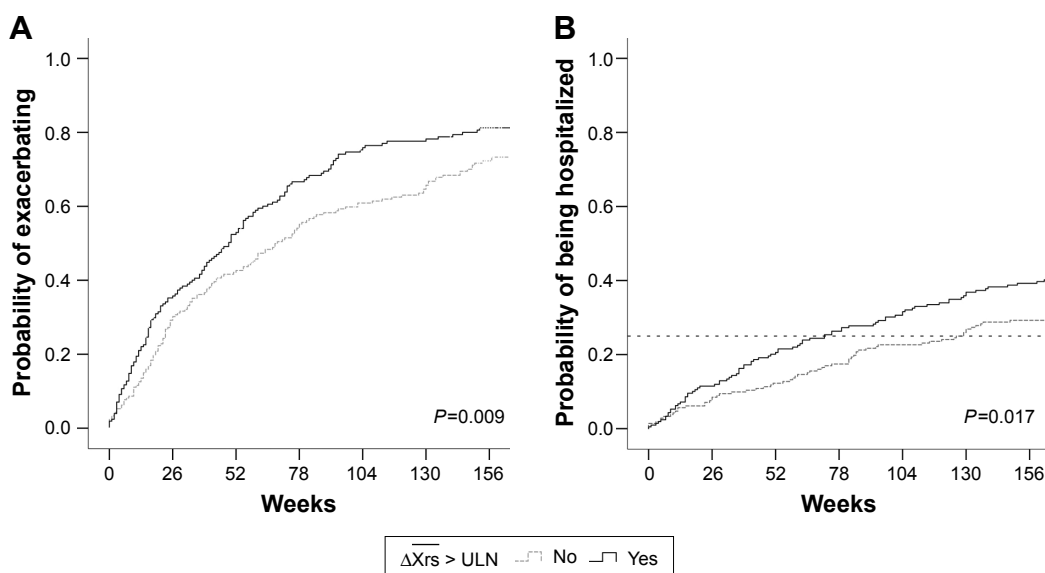
**Abbreviations:** RR, estimated rate ratio; 95% CI, confidence interval; ULN, upper limit of normal 0.09 kPa·s·L<sup>-1</sup>; EFL<sub>T</sub>, tidal expiratory flow limitation; FEV<sub>1</sub>, forced expiratory volume in 1 second; FEV<sub>1</sub> (%), FEV<sub>1</sub> percentage of predicted.

operating lung volume.<sup>12,29</sup> We did not measure lung volume during the 6MWT, but reasoned that patients with COPD showing evidence of flow limitation at baseline, either as having  $\overline{\Delta Xrs} \geq ULN$  or the threshold of EFL<sub>T</sub>, were more likely to have a worse exercise tolerance at the same visit. This was true on a group level. The EFL<sub>T</sub> group had the lowest 6MWD, but neither FEV<sub>1</sub> % predicted nor any cut-off level of  $\overline{\Delta Xrs}$  could identify patients with COPD with a short walking distance (<350 m), as proposed by Spruit et al.<sup>30</sup> No significant decline was seen in patients with  $\overline{\Delta Xrs}$  in the normal range; in patients with COPD with  $\overline{\Delta Xrs} \geq ULN$ , it declined 37 m, and in patients with EFL<sub>T</sub>, it declined by 63 m. The minimal clinically important difference on an individual level has been suggested to be 30 m in an ERS/ATS systematic review;<sup>31</sup> consequently, the differences seen

over time between our subgroups defined by  $\overline{\Delta Xrs} \geq ULN$  and EFL<sub>T</sub> are likely to be clinically important.

Exacerbation and hospitalization rates at our site were similar to those reported in the completed ECLIPSE study and in the TORCH study.<sup>32,33</sup> By negative binomial regression, the  $\overline{\Delta Xrs}$  cut-offs  $\geq ULN$  and EFL<sub>T</sub> were both significant predictors for higher rates of exacerbations with very similar RR, demonstrating that the increased risk of exacerbations by EFL<sub>T</sub> is identified already at ULN. In the time to first event analysis of patients with  $\overline{\Delta Xrs} \geq ULN$ , we found a shorter time to first exacerbation and a shorter time to first hospitalization than that of the COPD patients with  $\overline{\Delta Xrs}$  in the normal range. A previous study on hospitalized patients showed that many, but not all, have FOT-defined EFL<sub>T</sub> during a COPD exacerbation.<sup>17</sup> FOT measurements performed during hospitalized COPD exacerbations show that  $\overline{\Delta Xrs}$  measurements improve during resolution of an exacerbation, although many patients remain EFL<sub>T</sub> at discharge.<sup>17</sup> At present, there is a shortage of readily measurable biomarkers that can predict the risk of future exacerbations. Our data suggest that, after adjusting for lung function and exacerbation history, EFL<sub>T</sub> measurement can identify patients who are more likely to develop exacerbations. Further prospective studies to confirm these observations and explore their mechanism are merited.

Patients with COPD with an FEV<sub>1</sub> >50% predicted and evidence of EFL<sub>T</sub>, defined as baseline  $\overline{\Delta Xrs} \geq ULN$ , had significantly higher risk of dying within the 5-year follow-up. Similar associations were not found in the patients with more advanced



**Figure 3** Time to first moderate or severe exacerbation (A) and to the first hospitalization (B) in COPD patients with  $\overline{\Delta Xrs}$  measurements above the upper limit of normal (ULN), 0.9 kPa·s·L<sup>-1</sup> (solid line), and below the ULN at the baseline visit. Dashed line at 25%.

**Table 4** Exacerbations, hospitalizations, and deaths in COPD patients with and without  $\overline{\Delta Xrs} \geq \text{ULN}$  at baseline (N=425)

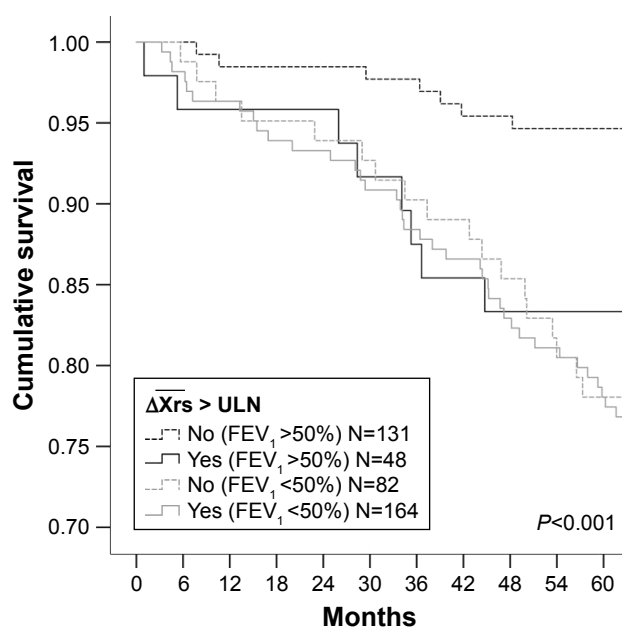
Parameter	$\overline{\Delta Xrs} < \text{ULN}$	$\overline{\Delta Xrs} \geq \text{ULN}$
<b>Total N</b>	213	212
N patients (%) with exacerbation	144 (68%)	152 (72%)
Median time (weeks) to first exacerbation (95% CI)	76 (57, 95)	55 (42, 68)
Log-rank test	P=0.009	
N patients (%) hospitalized	62 (29%)	84 (40%)
Time (weeks) until 25% of the patients were hospitalized	126	72
Log-rank test	P=0.017	
N dead at 5-year follow-up	25 (12%)	46 (22%)
Log-rank test	P=0.011	

**Note:** ULN defined at  $\overline{\Delta Xrs} \geq 0.09 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$ .

**Abbreviations:** ULN, upper limit of normal  $0.09 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$ ; 95% CI, 95% confidence interval.

airway obstruction and  $\text{FEV}_1 < 50\%$ . However, COPD is a complex, heterogeneous disease, and respiratory impairment is associated with higher incidence of comorbidities, such as hypertension, cardiovascular disease, and diabetes.<sup>34</sup> If there is an association between  $\overline{\Delta Xrs}$  and mortality, the higher risk of adverse outcomes associated with comorbid disease could mask such an association with advanced disease. Although the association between death and  $\overline{\Delta Xrs}$  was highly significant, this sub-analysis should be interpreted with caution due to the relatively small number of deaths in patients with  $\text{FEV}_1 > 50\%$  predicted (Table 1).

There are certain limitations of this study. The FOT threshold identifying a single flow-limited breath has been



**Figure 4** Kaplan-Meier survival curves in COPD patients with normal  $\overline{\Delta Xrs}$  and in COPD patients with  $\overline{\Delta Xrs}$  measurements above the upper limit of normal (ULN). Test of equality of survival distributions was performed using log-rank test.

defined at  $\overline{\Delta Xrs} > 0.28 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$ .<sup>14,15</sup> It is not known whether the use of this threshold may lead to different results when applied to values measured over a continuous spectrum of several breaths. Previously published data show that the end-expiratory lung volume varies from breath-to-breath, affecting the prevalence of  $\text{EFL}_T$ .<sup>8,15</sup> Although the prevalence of  $\text{EFL}_T$  increased as the  $\text{FEV}_1\%$  predicted declined, not all patients with very severe airway obstruction were found to have  $\text{EFL}_T$ . In previous studies on elderly and COPD with the NEP technique, higher prevalence of  $\text{EFL}_T$  have been reported than in the present study.<sup>11,35,36</sup> Different inclusion criteria and differences in sensitivity between the NEP and the FOT technique, together with the possibility that in borderline patients the application of a NEP per se could lead to development of  $\text{EFL}_T$ , are likely explanations. The wide reference range of  $\text{FEV}_1$  inevitably may also lead to an overestimation of the suspected lung function decline in many patients.<sup>23</sup>

As previously noted,  $\text{EFL}_T$  varies between breaths in many patients with COPD and varies with repeat testing, likely reflecting differences in the end-expiratory lung volume on different test days.<sup>13</sup> Physiological variability in these measurements might require the repetition of this test in different periods to increase the sensitivity of our test. Despite this limitation, important relationships related to the presence of tidal flow limitation were seen, even when the data were controlled for severity of airflow obstruction measured by  $\text{FEV}_1$ . The data reflect results from the largest recruiting center in the ECLIPSE study, in which patients were carefully characterized using standardized methodologies including oscillatory mechanics.<sup>18,37</sup>

## Conclusion

Consistent differences in clinically relevant outcomes were found, such as exercise capability, exacerbations, hospitalizations, and death in COPD patients with baseline  $\overline{\Delta Xrs}$  beyond the ULN. This is below the established threshold for  $\text{EFL}_T$ . Our data support previous studies showing that patients with  $\text{EFL}_T$  have worse lung mechanics than is evident from  $\text{FEV}_1$  measurement alone.<sup>11,38</sup> The present study suggests that evidence of  $\text{EFL}_T$ , measured during tidal breathing in an effort-independent fashion, can identify a subgroup of COPD patients with worse clinical outcomes.

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## Author contributions

The corresponding author BBA wrote the manuscript, had access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. PMAC was in the ECLIPSE Scientific Committee and PSB in the ECLIPSE Steering Committee. They both contributed to the development of the research design. PSB, JAH, and TMLE also contributed in the data collection. All authors, including RLJ and RD, contributed to the data analysis, the clinical interpretation of the data, and to reviewing the final submission.

## Disclosure

The authors report no conflicts of interest in this work.

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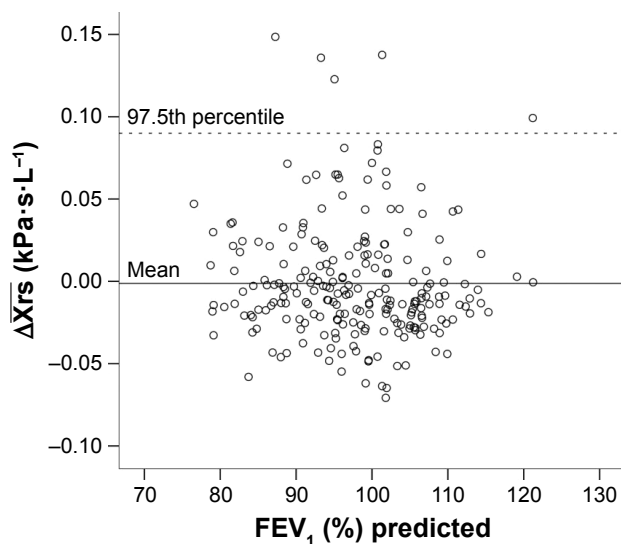
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## Supplementary materials



**Figure S1** Scatterplot of  $\Delta\bar{X}_{rs}$  plotted against  $FEV_1$  % predicted in healthy controls (N=229). Mean represented by the solid line. The dashed line represents the 97.5th percentile, the upper limit of normal (ULN).

**Table S1** Baseline characteristics in men and women (N=425)

Subject characteristics	Total	Men	Women	P-value
Subjects (n)	425	254	171	
Age (years)	63 (7)	64 (7)	62 (7)	0.014
BMI kg/m <sup>2</sup>	25 (5)	26 (5)	25 (6)	ns
Pack-years (years)	41 (23)	45 (24)	33 (18)	<0.001
mMRC	1.6 (1, 2)	1.6 (1, 2)	1.7 (1, 2)	ns
$FEV_1$ (L)	1.5 (0.5)	1.6 (0.6)	1.3 (0.4)	<0.001
$FEV_1$ (%)	46 (14)	45 (14)	48 (13)	0.007
FVC (L)	3.3 (0.9)	3.7 (0.8)	2.6 (0.6)	<0.001
$\Delta\bar{X}_{rs}$ (kPa·s·L <sup>-1</sup> )	0.14 (0.17)	0.13 (0.14)	0.16 (0.20)	ns

**Note:** Data presented as mean (standard deviation) unless otherwise stated.

**Abbreviations:** ULN, upper limit of normal 0.09 kPa·s·L<sup>-1</sup>;  $EFL_{T}$ , tidal expiratory flow limitation; BMI, body mass index; Pack-years, packs of 20 cigarettes smoked per day × years as a smoker; Frequent exacerbators, percentage with  $\geq 2$  exacerbations the year the prior to inclusion; mMRC, modified Medical Research Council dyspnea scale score – mean (quartiles);  $FEV_1$ , forced expiratory volume in 1 second;  $FEV_1$  (%),  $FEV_1$  percentage of predicted; FVC, forced vital capacity; IC, inspiratory capacity; IC (%), IC percentage of predicted;  $\Delta\bar{X}_{rs}$ , difference between mean inspiratory and mean expiratory reactance at 5 Hz over multiple breaths; 6MWD, 6-minute walk distance.