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Tidal Expiratory Flow Limitation

A new method for evaluating pulmonary function in elderly and patients with Chronic Obstructive Pulmonary Disease

Bernt Bøgvald Aarli

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Scientific environment

The Bergen Respiratory Research Cluster (BRRC), Department of Clinical Medicine, University of Bergen conducted the study in cooperation with the Department of Thoracic Medicine, Haukeland University Hospital.

The group currently consists of 8 professors, 4 post docs, and 9 PhD fellows. In the last decade alone, 19 doctoral theses have been brought forth by the BRRC. The group was awarded "Best research group" at the Medical Faculty and Dentistry, University of Bergen in 2007, and in the latest evaluation from the Norwegian Research Council in 2011 the research group was rated "very good to excellent".

International collaborators

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Prof. Frank L. Powell, Division of Physiology.
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Acknowledgements

Time is up! Roll up your sleeves and get a real job. That's the problem. Nobody considers what I have been doing the last few years a real job. I used to have one, living a lulled, happy clinician existence. Then one day I took the elevator instead of the stairs on my way to the wards, mostly not to spill coffee. That's when it happened.

-"Bernt! Would you, by any chance, be interested in research?" The assistant chief at the Department Per Bakke squeezed in before the door shut. He could have asked for anything. I just wanted to stay on. Research? Hadn't given it a single thought.

-"Yes! Very much so!" I replied without hesitation.

-"Excellent, I have just the perfect project for you…"

It was settled. I had no idea what I was getting myself into. A brief talk in the elevator leading to instant regrets and years of hard work, or as a wise man once told me (professor emeritus Amund Gulsvik): The PhD is a road paved with disappointments.

Here I am, at the final frontier. It opened my eyes to a new world, and at the journey's end, I would like to acknowledge the outstanding individuals who have inspired, supported, assisted, encouraged, and sacrificed themselves to help me in this involuntary pursuit of a higher education degree.

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Tomas Eagan, you paved the way for my research stay in San Diego. Per Bakke, thank you for recruiting me to this amazing research group. Thanks to both of you for supervising me, and for your friendship. Peter Calverley, your guidance and help have been invaluable. I can't thank you enough for your brilliant comments, support, and help co-authoring most of my work.

The data retrieval did not come easy. We performed two studies, where in hindsight the key parameters were missing from our records even though it had been measured. Cracking the not so user-friendly Jaeger SQL database was the logic solution. Assistance provided by the manufacturer Hans-Jürgen Smith in CareFusion, and Torgeir Langholen in Akumed was greatly appreciated, and even more so, the help from Robert Jensen with the SQL export and reorganization of the data. He also helped co-author many of my papers and posters.

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Thank you, professor Raffaele Dellaca at the Politecnico di Milano University for inviting me to Milano. What a beautiful city. The small addition we discussed in London ended up being a separate paper. It's been inspiring working with you. Thanks to professor Frank Powell for inviting me to UCSD, and to my supervisor there, assistant professor Xavier Soler, and to the chief of the Division, professor Atul Malhotra for inviting me into your stimulating research environment. I also would like to thank professor Douglas Conrad with whom I am still collaborating on a side project, not directly related to the current project. You all made my research stay in USA great. Thank you for all your constructive feedback, and for the work we did

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Finally, my good colleagues of hard working clinicians who have come here to support me at the defence feel free to take a copy of this book even if you're not planning on reading past the acknowledgements. My final warning to you: If you want to stay on the narrow path in the clinic, take the stairs.

I'll dedicate the thesis to my family, my loving parents, to Karin and my wonderful children Malin and Ulrik. Thanks to my dear friends Ragnar & Anne, Frode & Ingvild, Frode & Anna Mette, Trond Erik & Ingelin, Arve & Janka, Bjarte, Sverre, and Kjell. I love you all very much. Will life bless me with more time for family and friends after the completion of the project? Maybe, and maybe not, only one thing is certain, if you read this, I'm in front of the auditorium defending my thesis. I'm prepared and choose to ignore my professor in emeritus's ominous advice. Just to be on the safe side, I'll walk the stairs.

Abstract

Background: Lung function declines with old age and is further accelerated by exposure to noxious particles. As our society ages, expected lifespan increases, and prevalence of chronic obstructive pulmonary disease (COPD) is on the rise. Spirometry is used both to diagnose and to grade the degree of airway obstruction, but many elderly fail to perform this procedure satisfactory. More tools are needed to evaluate this large patient group. The present study explores the use of forced oscillation technique (FOT) in healthy elderly and in a longitudinal case-control study of COPD patients and controls.

Aims:

- Generate reference values for FOT using impulse oscillations in healthy elderly.
- Evaluate the agreement between two methods: sinusoidal pressure oscillations and impulse oscillations.
- Evaluate variability of whole-breath and within-breath FOT measurements, examine factors influencing tidal expiratory flow limitation, and describe its impact on morbidity and mortality.

Materials and Methods: regional ethics committees have approved all studies. In the first study, predictive equations were generated for FOT parameters in 75 subjects with normal spirometry who were drawn in an age and sex stratified sample from healthy, non-smoking responders of a health questionnaire in elderly, aged >70 years. The second study examined the agreement between sinusoidal pressure oscillations and impulse oscillations in 20 patients in a rehabilitation hospital. The final study followed 425 COPD and 229 controls over 3 years/8 visits with FOT and spirometry. Six-minute walk distance (6MWD) was assessed at baseline and at the final visit, respiratory symptoms, exacerbations, and hospitalizations were recorded, and mortality statistics retrieved retrospectively.

Results: Reference values for whole-breath and within-breath FOT parameters were generated in healthy elderly. In non flow-limited patients, good agreement between sinusoidal and impulse pressure oscillations was found. Flow-limited patients had higher variability than the expected biological variability and significantly higher resistance values. Healthy controls had little variability in the FOT measurements. A higher variability was found in COPD patients. COPD patients with mean within-breath reactance, $\Delta\overline{Xrs}$ >0.1 kPa·s·L^{-1} were more breathless. The upper limit of normal (ULN), defined at the 97.5 percentile of $\Delta\overline{Xrs}$, in healthy controls was 0.09 kPa·s·L^{-1}. COPD patients with $\Delta\overline{Xrs}$ ≥ULN had a significant decline in 6MWD from baseline to the final visit, more exacerbations and more hospitalizations than COPD patients with $\Delta\overline{Xrs}$ in the normal range. COPD patients with FEV_1 >50% and $\Delta\overline{Xrs}$ ≥ULN also had a significantly higher mortality.

Conclusions: Reference equations generated in healthy elderly yielded higher resistance measurements than what was found when simply extrapolating existing reference equations generated in a younger population. When examining agreement between sinusoidal pressure oscillations and impulse oscillations, impulse oscillations overestimated resistance in patients with flow-limitation. We describe a new method to assess flow-limitation in COPD patients by averaging measurements over several breaths. The COPD patients with $\Delta\overline{Xrs}$ >0.1 kPa·s·L^{-1}, just above the ULN were more likely to report dyspnea. $\Delta\overline{Xrs}$ ≥ULN in COPD was associated with a significant decline in 6MWD, more moderate and severe exacerbations, and in patients with moderate airway obstruction, a significantly higher mortality.

List of publications

Paper I

Aarli BB, Eagan TM, Ellingsen I, Bakke PS, Hardie JA. Reference values for within-breath pulmonary impedance parameters in asymptomatic elderly, Clin Respir J. 2013 Jul; 7(3): 245-52. doi: 10.1111/j.1752-699X.2012.00312.x. Epub 2012 Aug 20.

PMID: 22822726

Paper II

Aarli BB, Govani L, Pompilio PP, Simonetta Valdi, Hardie JA, Dellaca R. Agreement between sinusoidal and impulse oscillations when measuring pulmonary impedance.

In manuscript: To be submitted to the journal of Respiratory Physiology & Neurobiology in 2017.

Paper III

Aarli BB, Calverley PMA, Jensen RL, Eagan TM, Bakke PS, Hardie JA. Variability of within-breath reactance in COPD patients and its association with dyspnea. Eur Resp J. 2015. Mar; 45(3): 625-34. Oct 30.

PMID: 25359342

Paper IV

Aarli BB, Calverley PMA, Jensen RL, R Dellaca, Eagan TM, Bakke PS, Hardie JA. The association of tidal EFL with exercise performance, exacerbations, and death in COPD: A COPD Cohort Study. International Journal of Chronic Obstructive Pulmonary Disease. In press 2017.

Abbreviations

ΔXrs	Within-breath reactance at 5 Hertz (mean $Xrs5_{inspiration}$ – mean $Xrs5_{expiration}$)
$\Delta\overline{Xrs}$	Mean ΔXrs measured over multiple-breaths
6MWD	Six-minute walk distance (meters)
6MWT	Six-minute walk test
ATS/DLD-78	American Thoracic Society and the Division of Lung Diseases questionnaire
AX	Area of reactance
BCCS	Bergen COPD Cohort Study
BMI	Body Mass Index
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
DX5	Within-breath reactance at 5 Hertz (mean $Xrs5_{inspiration}$ – mean $Xrs5_{expiration}$)
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
EELV	End-expiratory lung volume
EFL	Expiratory flow limitation
EFL_T	Tidal expiratory flow limitation
FEV_1	Forced expiratory volume in 1 second
FEV_1 (%)	Forced expiratory volume in 1 second in % of the predicted value
FOT	Forced oscillation technique
FRC	Functional residual capacity
FVC	Forced vital capacity
*f*res	Resonance frequency
GOLD	Global Initiative for or Chronic Obstructive Lung Disease
IC	Inspiratory capacity
ICC	Intra-class correlation coefficient
IOS	Impulse oscillation system
Ln	Natural logarithm
MCID	Minimal Clinical Important Difference
MMRC	Modified Medical Research Council dyspnoea scale score

P	Impulse oscillations
P_{AO}	Pressure at the airway opening
Pack-years	Smoking 20 cigarettes per day for 1 year
PaO2	Arterial oxygen partial pressure
PRN	Pseudo random noise
R	Pulmonary resistance
R_{insp}	Inspiratory resistance
R_{exp}	Expiratory resistance
R5	Resistance at 5 Hertz
RR	Incidence rate ratios
Rrs_5	Resistance at 5 Hertz
RV	Residual volume
S	Sinusoidal pressure oscillations
SD	Standard deviation
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
TLC	Total lung capacity
ULN	Upper limit of normal
V'_{AO}	Flow at the airway opening
V_T	Tidal volume
X	Pulmonary reactance
X_{exp}	Expiratory reactance
X_{insp}	Inspiratory reactance
X5	Reactance at 5 Hertz
Xrs_5	Reactance at 5 Hertz
Z	Pulmonary impedance
Zrs	Pulmonary impedance

Contents

1. Introduction

"Life and respiration are complimentary. There is nothing living which does not breathe nor anything breathing which does not live."

William Harvey (1653)

Measuring of breath by spirometry is the most common pulmonary function test. We use it to diagnose obstructive pulmonary disease. We use it to track disease progression, and we use it to measure the effect of a given treatment [1, 2]. Additionally, when lung volumes decline, they are not only markers of pulmonary disease, but also some of our most powerful predictors of cardiovascular disease and death [3, 4]. Simply put, in pulmonary medicine, spirometry is the most important test. Even so, it is not without limitations.

Spirometry depends highly on cooperation and on the effort involved, and an adequate spirometry procedure may be difficult to obtain in some patients [5, 6]. Spirometry alone does not capture dynamic changes occurring during tidal volume breathing, such as the changes in end-expiratory lung volume seen in patients with dynamic hyperinflation, and spirometry cannot be used to detect flow limitation during tidal volume breathing. These are only some of the reasons why alternative ways to evaluate lung function, requiring less patient cooperation, are needed.

The following study explores a new method to evaluate lung function in healthy elderly and in people with chronic obstructive pulmonary disease.

1.1 The aging population

Since the mid-twentieth century an unprecedented aging of the world population has occurred, driven not only by a decrease in child mortality, but also by considerable increase in longevity. Globally, the number of elderly aged 60 years and older is expected to more than double by 2050 to an estimated 2 billion people [7].

A similar trend is seen in Norway where our elderly population >70 years is projected to double within the next 30 years, and our proportion of elderly to increase from today's 11% to 19% of the total population by 2060 [8].

This reshaping of the population brings challenges to clinical and epidemiological research. As disability, co-morbidities, and multiple-medication increase with age, healthy norm populations used as reference are increasingly difficult to recruit. At the same time, the number of volunteers in elderly populations is often small, and further diminishes when the asymptomatic individuals without pre-existing conditions are identified.

All the same, elderly are overrepresented in our hospital wards, particularly in the departments of thoracic medicine. According to Statistics Norway, 54% of the 20.916 patients admitted to hospital in 2016 with the diagnose of chronic obstructive pulmonary disease (COPD) were aged 70 years and older, highlighting the importance of reliable reference studies in elderly [9].

1.2 Pulmonary function in the elderly

Aging brings visible changes. Our skin becomes lined and less elastic and wrinkles appear. Height is often reduced, and postural changes may influence the movement of our rib cage. Similar changes affect our internal organs. The most prominent physiological change to our lungs, is the loss of elastic recoil caused

by decrease and alteration in the cross-linkage of elastic fibers and collagen [10]. Skeletal changes such as osteoarthritis of the costovertebral junctions and calcification of the sternocostal joints, increase the stiffness of the chest wall and leads to increased rigidity [11]. Kyphosis may reduce the maximal lung volume. The pulmonary vasculature also becomes stiffer, and the pulmonary arterial pressure increases [12, 13]. Even healthy aging brings enlargement of the alveolar airspaces and reduction in the total number of alveoli, leading to a reduced surface area for gas diffusion [14-16]. Consequently, pulmonary gas exchange declines with age [17]. In addition, weakening of respiratory muscle strength due to atrophy, and age related decrease in type II, fast twitch fibers, may aggravate the effect of these morphological changes on breathing [18].

As a consequence, decrease in lung function with age is expected. This is reflected in our reference equations for spirometry [19, 20]. Inhaled particles, particularly those of cigarette smoke accelerate this decline. In a hallmark study by Fletcher and Peto the natural decline in lung function and the accelerated decline associated with smoking was illustrated, Figure 1 [21].

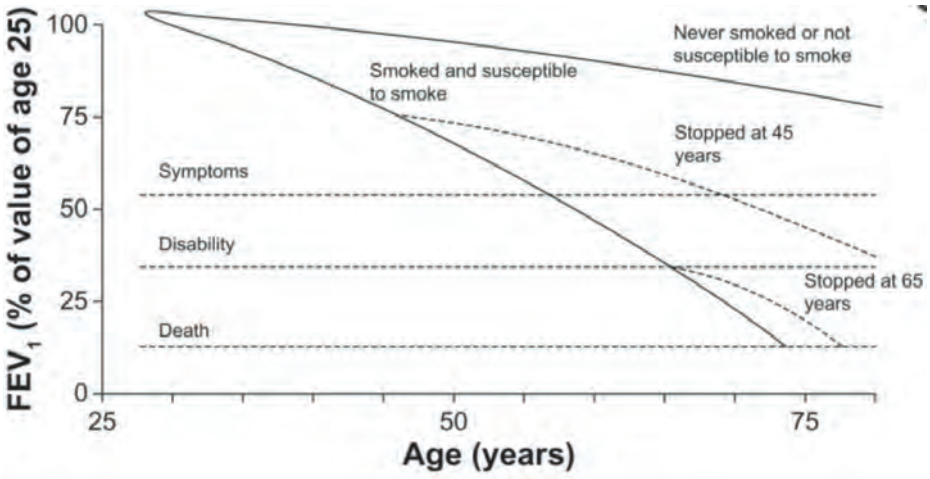

Figure 1. The Fletcher and Peto's curve illustrates the natural decline in Forced Expiratory Volume in 1 second (FEV_1) [21]. Reproduced with permission from BMJ Publishing Group Ltd.

1.3 Chronic Obstructive Pulmonary Disease

The 2017 update of the Global Initiative for Chronic Obstructive Lung Disease report defines COPD as follows:

"*Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."*[1]

In spite of the trend towards longer, healthier lives, a longer life expectancy also expands our lifetime exposure to risk factors, and chronic degenerative diseases becomes more common[1, 7]. We have seen considerable reduction in daily smokers in most western countries [22]. A 50% reduction in daily smokers has been noted in Norway since the 1980s [22]. Still, the smoking epidemic of the 20th century left a heavy burden, and we may not have reached the peak prevalence of COPD yet. COPD was rated the 3rd leading cause of death in 2012, with an estimated 3 million deaths worldwide. In Norway the prevalence is estimated at 14% of the adult population, or approximately 400.000 people. Only a fraction has been diagnosed [23]. As our population ages, we expect the number of people living with COPD to rise. While spirometry is used to diagnose and to grade the degree of airway obstruction, the ability to perform spirometry satisfactory falls with age [6, 24, 25]. New tools to help assess this huge patient group, are welcomed

1.4 Spirometry

Spirometry assesses lung function by measuring the amount of air a test subject can exhale after a maximal inhalation [26]. While some measurements can be retrieved unforced, the most common procedure is the forced expiration

maneuver. Key parameters are the forced expiration in 1 second (FEV_1) and the forced vital capacity (FVC). The measurement depends on the test subject blowing the air out as fast and forcibly as possible and that he or she continues to do so until the lungs are fully emptied (to the residual volume). FEV_1 is the volume of air exhaled in the first second of the blow. In COPD FEV_1 is used to assess the severity of the airflow obstruction by comparing the measured volumes against a reference value based on age, height, sex, and ethnicity [1]. Forced vital capacity (FVC) is the total volume of air that forcibly can be expired in one breath. The fraction of air expelled in the first second relative to the total volume exhaled, the FEV_1/FVC ratio is used to confirm presence of airway obstruction. This ratio is independent of ethnicity, which allows for a universal definition of airway obstruction [20]. In COPD the fixed ratio of 0.7 is recommended to verify the presence of airway obstruction [1]. Due to a natural decline in the FEV_1/FVC ratio with age, this may lead to an overestimation of airway obstruction in the elderly [27]. Alternately, the lower limit of normal (LLN) can be used, classifying the lower 5% as abnormal to reduce misclassification of airway obstruction in the elderly [1, 20].

1.5 Forced oscillation technique

Recent discoveries using forced oscillation technique (FOT) show promise in the evaluation of COPD patients. FOT detects early respiratory changes due to smoking [28]. In addition FOT accurately detects tidal expiratory flow limitation (EFL_T), and a high correlation between improvement in symptoms and changes in certain FOT parameters have been found during resolution of COPD exacerbations [29-31].

FOT superimposes sound waves from a loudspeaker to spontaneous breathing. The pulmonary impedance (Zrs) is then calculated from the resultant pressure/flow signals measured at the mouthpiece. Zrs describes the total

mechanical load of the respiratory system and is further subdivided into resistance (Rrs) describing the frictional forces on the airflow moving through airways, and reactance (Xrs) reflecting storage and release of energy cause by the elasticity of the tissue. Their relation is expressed in Equation 1 [32]:

Equation 1. $$Pulmonary\ impedance\ (Zrs) = \frac{\Delta\ Pressure}{\Delta\ Flow} = \sqrt{Rrs^2 + Xrs^2}$$

The first attempts to measure lung function using forced oscillations were made already in the 1950s [33]. At that time calculations had to be performed by hand, and only single frequency sinusoidal pressure signals were used in order to simplify calculations. It took decades before advances in microprocessor technology made commercial apparatuses available. Today oscillatory forcing signals can be either mono- or multi-frequency, applied continuously or as a train of impulses.

In the following studies we used impulse oscillations to measure oscillatory lung mechanics [34-37]. FOT measures airway mechanics non-invasively during resting breathing. It is effort independent and does not requiring complex breathing manoeuvres. In elderly higher feasibility have been found for FOT than for spirometry [6, 24].

1.6 Reference values for whole-breath and within breath FOT parameters

When we started this study, reference values for oscillation mechanics in adults were limited, and the number of elderly participating in these studies low, Table 1 [32, 35, 38-46]. Although respiratory impedance is age dependent, only one reference study reported reference values in elderly using continuous

pseudorandom noise (PRN) [41]. However, one report has documented systematic differences in resistance measurements between devices using different forcing signals, a continuous PRN device and an impulse oscillation system (IOS) [47]. This finding calls for verification. If different forcing signals yield different results, device specific reference values are needed.

For the IOS, the software reports normal values based on unpublished reference equations generated from 506 healthy subjects in Erfurd, Germany aged 18-69 [32]. If older patient are tested, the software extrapolates normal values from these equations, generated from a younger population. Japanese and Australian normal values had also been published. Both studies contained few elderly [44, 46].

Respiratory impedance measurements vary within the breathing cycle. Resistance (Rrs) measurements are higher during expiration than in the inspiratory phase [48-54]. The variability of the measurements is lower in inspiration than expiration, and in patients with COPD, the differences between inspiration and expiration is larger than in healthy subjects [49]. Reactance (Xrs) decreases in expiration both in healthy subjects and in patients with COPD with the largest difference in the COPD patients [30, 49, 51, 53]. Similar changes have also been reported for other FOT parameters, such as the resonant frequency and the area of reactance [49].

Pulmonary impedance (Zrs) changes in the respiratory cycle have been studied in a wide range of conditions, including patients on mechanical ventilation [55-59], while using nasal CPAP [60], in sleep studies [61, 62], in patients with interstitial lung disease [63], and in patients with obstructive lung disease [29-31, 64]. Normal values for within-breath impedance parameters would make interpretation easier. We have only found 1 study reporting within-breath reference equations for FOT [42]. This study reported reference equations for men and women, calculating inspiratory and expiratory Rrs based on the end-

expiratory thoracic gas volume. Due to small sample size (n=65), and the use of only one predictor, these equations have limited precision. Reference equations are also easier to use if based on demographic data rather than a plethysmographic parameter like the end-expiratory thoracic gas volume. Normal values for other within-breath impedance measurements have yet to be published.

These are some of the reasons why device specific reference values for IOS in elderly are needed. Existing reference values for within-breath FOT parameters are incomplete, only reporting respiratory Rrs. In addition, more studies are needed comparing different devices.

Table 1. Reference values for forced oscillation technique (FOT) in adults

					Age		
Study	**Year**	**Participants**	**Signal**	**Men**	Mean	Range	**N**
Jiemsripong [42]	1976	Healthy subjects, USA	SIN	47 %	40	21-64	76
Landsér [43]	1982	Healthy subjects, Belgian Air Force	PRN	100%	26	15-57	224
Clemént [65]	1983	Healthy subjects, Belgian Air Force	PRN	100%	29	15-57	442
Vogel [32]	1994	Healthy subjects, Germany	IOS	59 %		18-69	506
Goevarts 24	1994	Healthy subjects	PRN		51		60
Pasker [45]	1996	Healthy subjects, Belgium	PRN	49 %	56	21-83	277
Guo [41]	2005	Lunge healthy inpatients, Switzerland	PRN	35 %	83	65-100	223
Shiota [46]	2005	Healthy subjects, Japan	IOS	60 %	39	20-83	299
Newbury	2008	Healthy subjects, Australia	IOS	47 %	49	25-74	125
Brown [38]	2010	Healthy subjects, Australia	PRN	38 %	55	18-92	904
Aarli [35]	2013	Healthy elderly, Norway	IOS	53 %	79	70-98	75
Schulz [66]	2013	Never smoking lung healthy, Germany	IOS	39 %		45-89	397

Year: year of publication. SIN: Sinusoidal pressure oscillations. PRN: Pseudo random noise. IOS: impulse oscillations. N: number of subjects.

1.7 Tidal expiratory flow limitation

Chronic airway obstruction is a diagnostic criterion in COPD, defined when repeatedly, no more 70% of the vital capacity can be exhaled within the first second of a forced expiration manoeuvre [67]. At advanced disease, flow limitation often presents at exercise, and frequently even when sitting still, breathing at rest [68-70]. When this occurs and maximal flow is reached at tidal

volume breathing, tidal expiratory flow limitation, EFL_T is said to be present [71].

At extreme exercise, the mechanical limits of breathing may even cause expiratory flow limitation during in healthy subjects [72]. As demands for ventilation increase during progressive exercise, this is achieved either by increasing the tidal volume or the respiratory rate. The tidal volume is increased by encroaching both on the inspiratory and the expiratory reserve volumes, Figure 2 [73].

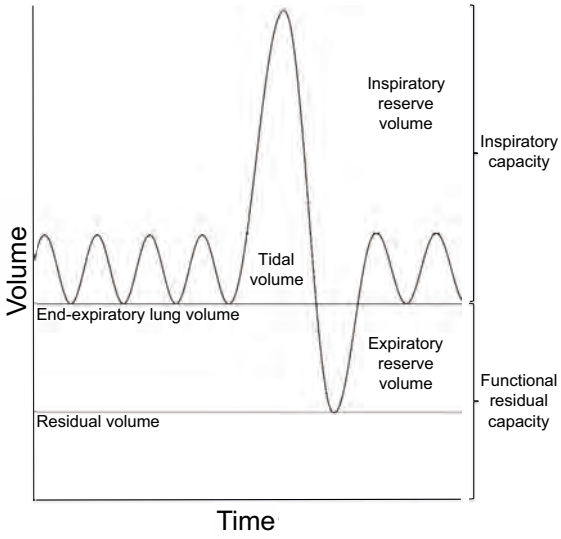

Figure 2. Lung volumes. The image shows 4 tidal volume breaths, which is the volume of air inhaled in a single breath, followed by a maximal inspiration reaching the total lung capacity (TLC) and a maximal expiration reaching the residual volume. The inspiratory capacity is the volume from TLC to the end-expiratory lung volume.

In healthy lungs, the lung volume at relaxed end-expiration lung volume is determined by the balancing forces between the outward recoil pressure of the chest wall and the inward elastic pressure of the lungs [74]. During maximal exercise, end-expiratory lung volume (EELV) may decrease to the point where pleural pressure is only slightly positive, approaching the flow limiting pressures

at low lung volumes. To avoid expiratory flow limitation, EELV is increased at high intensity exercise, and further increases in tidal volumes are derived from the inspiratory reserve volume alone. At the same time, the time for lung emptying at this flow rate may be insufficient for the lungs to reach their normal relaxation EELV, resulting in an increasing degree of air-trapping. This has been termed dynamic hyperinflation, Figure 3. With loss of the elastic recoil in lungs in elderly and in patients with COPD, residual volume and closing capacity are at higher lung volumes then in younger subjects [10]. These effects reduce the ranges of the operating lung volumes. Dynamic hyperinflation occurs at lower intensity exercise in elderly and in patients with COPD than in younger healthy subjects, and patients with COPD commonly resort to a static hyperinflation, breathing at higher lung volumes then healthy subjects already at rest in order to avoid EFL_T.

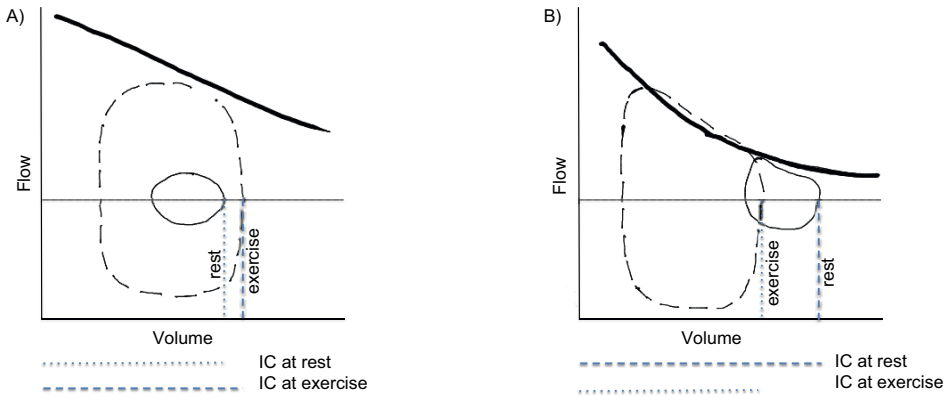

Figure 3. Changes in tidal volume loops from rest to exercise. A) In a healthy subject inspiratory capacity (IC). In COPD patients the end-expiratory lung volume frequently shifts to the left due to insufficient time for lung emptying, leading to a reduction in the IC at exercise (B).

1.8 Methods for EFL_T detection

Direct assessment of EFL_T requires the demonstration that an increase in the transpulmonary pressure fails to increase expiratory flow. Measuring transpulmonary pressure directly in the pleura is impractical and involves the risk of pneumothorax. For this reason the intrathoracic pressure measured in the esophagus is used as a substitute. The esophageal pressure is representative for the intrapleural pressure and can be measured by inserting a catheter through the mouth or nose with an air filled, thin walled balloon [75]. The Mead and Whittenberger method to detect EFL_T estimates the transpulmonary pressure using an esophageal balloon while measuring flow in a body box [76]. Figure 4 shows the flow-pressure relationship in a non-flow limited patients and in a patient with EFL_T measured with the Mead and Whittenberger method. Drawbacks of this technique are that it is invasive, technically complex, and relatively time consuming.

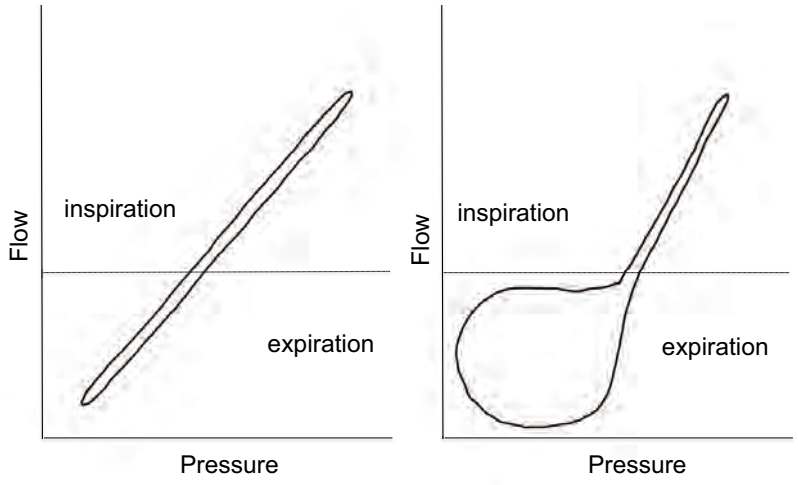

Figure 4. Mead and Whittenberger graphs plotting flow measured at the airway opening plotted against the pressure drop during a tidal volume breath in a COPD patient without flow limitation (A) and in a COPD patient with EFL_T (B).

A non-invasive method to detect EFL_T was proposed by Hyatt in 1961 by superimposing a tidal breath flow-volume curve on a maximal expiratory flow volume (MEFV) curve [77]. By this technique, EFL_T is defined to be present if the flow-volume trace of a tidal volume breath is along or higher than the MEFV, and not present if the breath is below the MEFV curve, Figure 5. The technique requires volume to be measured in a body box in order to avoid gas compression artifacts and patient cooperation is necessary to produce the MEFV curves. Aligning and comparing the flow-volume curves correctly may be difficult [78, 79].

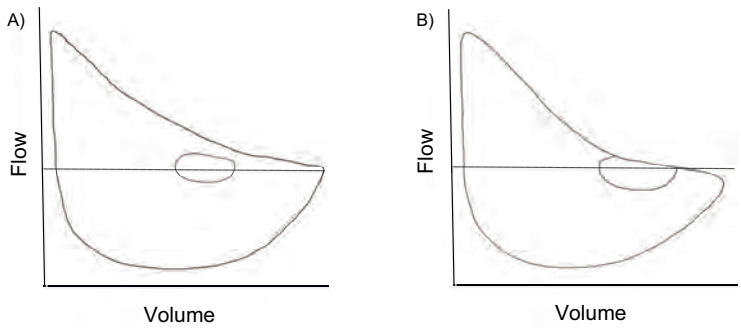

Figure 5. Tidal volume flow-volume curve superimposed on a maximal expiratory flow volume curve in a patient with no EFL_T (A) and in a patient with EFL_T (B)

The negative expiratory pressure (NEP) technique simplifies EFL_T detection by not requiring patient cooperation, FVC maneuvers, or use of a body box [80]. When a negative pressure is applied to the breathing circuit at the beginning of expiration, either by a vacuum cleaner or a venturi device, the increased pressure gradient between the airway opening and the alveoli leads to an increase in flow unless the test subject already is breathing at maximal flow at tidal volume breathing. When EFL_T is present, NEP fails to increase the flow, Figure 6. EFL_T detection involves visual inspection and interpretation of flow-volume curves.

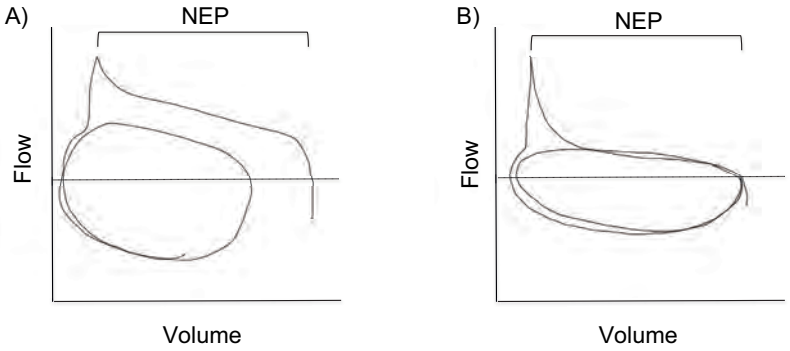

Figure 6. Tidal volume flow-volume curves during the negative expiratory pressure (NEP) technique. In COPD patients without EFL_T, NEP induces an increased flow (A). In EFL_T COPD patients the NEP fails to increase flow compared with the previous tidal volume curve (B).

EFL_T may also be detected by FOT. When EFL_T occurs, the peripheral airways collapse during expiration, obstructing the oscillatory pressure signals from reaching the alveoli. Instead they are reflected from the airway walls proximal to the site of obstruction, Figure 7. The resulting reactance, estimated by measuring the pressure-flow relationship at the airway opening will be more negative during expiration than during inspiration, creating a within-breath reactance difference, ΔXrs. In two small studies, the ΔXrs cut-off 0.28 $kPa \cdot s \cdot L^{-1}$ was found accurately to detect EFL_T validated against the Mead and Whittenberger and the NEP technique [29, 30].

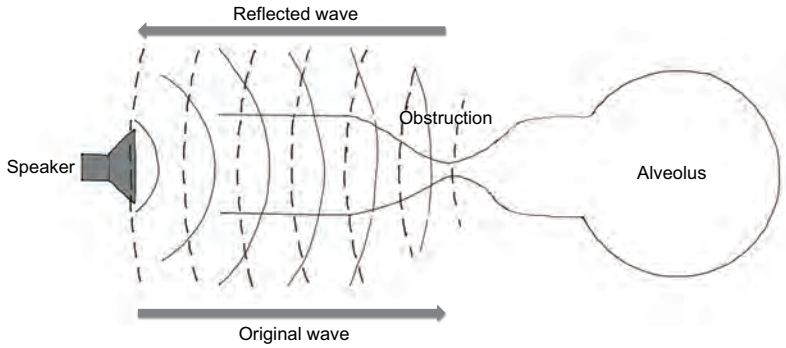

Figure 7. Detecting EFL_T by the FOT technique: Pressure oscillations are reflected from the sites of obstruction during expiration, while they travel all the way to the alveoli during inspiration, generating a within-breath difference in the impedance parameters.

1.9 Clinical significance of EFL_T

Ventilation can increase to meet the demands of exercise by either increasing the respiratory rate and/or by increasing the tidal volume. In COPD patients with expiratory flow limitation, tidal volume is unable to expand by encroaching on the expiratory reserve volume. All increments must come from the inspiratory capacity, leading to a gradual dynamic hyperinflation at progressing exercise. When hyper inflating the lungs, the respiratory muscles are shortened and have to work at much less favorable force-length relationships, thus increasing the work of breathing [81]. At the same time the end-expiratory lung volume increases, increasing the number of poorly ventilated alveoli [82]. This increased alveolar dead space may cause ventilation/perfusion abnormalities, and lead to retention of CO_2. Airway obstruction also leads to an increased intra-thoracic pressure which in turn may reduce the cardiac output [83].

EFL_T and dynamic hyperinflation have strong associations to the sensation of dyspnea. Although many factors contribute to this subjective sensation, the mechanical constraint of EFL_T with loss of the ability to control the operating

lung volume is thought to be a major contributor [74]. The combined negative effects of dynamic hyperinflation and exertional dyspnea reduce the exercise capacity of patients with EFL_T.

EFL_T has also been proposed as a stage in the development to symptomatic COPD in smokers where the airway closure during tidal volume breathing may cause mechanical injury leading to disease progression [84]. And there is a strong association between COPD and exacerbations. As airflow limitation increases with an exacerbation the prevalence of EFL_T increases, and as the exacerbation resolves, the EFL_T index, ΔXrs has been shown to decrease [85]. It is not known if the presence of EFL_T by itself actually increases the risk of COPD exacerbations, but there are mechanisms indicating that this might be the case. Coughing plays an important role in maintaining the airways by removing excess secretions from the respiratory tract [86]. Under normal circumstances a cough creates an increase in the airflow velocity within an airway. This is commonly intense enough to move mucus and secretions. But if maximal velocity within that airway is reached already at tidal volume breathing, coughing may be less efficient in eliminating mucus [87]. An inefficient cough mechanism might lead to increased mucus retention, increasing the risk of pulmonary infections, hereby increasing the risk of COPD exacerbations. EFL_T is thought to be associated with an emphysematous phenotype in COPD where prognosis might differ from other COPD patients, but further studies are needed to link EFL_T to certain phenotypes [71].

Although many techniques are established to evaluate EFL_T, no gold standard exists [29, 30, 69, 75-77, 88]. We found the FOT technique attractive since it does not require complex panting maneuvers, and due to its high feasibility in the elderly [6, 24]. A selection of studies on COPD using FOT is shown in Table 2.

Table 2. Selected studies reporting FOT measurements in COPD patients and smokers

Study	Year	Participants	N	Findings
Farre [57]	1998	COPD patients	5	Measuring respiratory mechanics in mechanically ventilated COPD patients
Janssens [24]	2001	Elderly	240	FOT was found to have a higher feasibility than spirometry in elderly
Dellaca [30]	2004	COPD/controls	22	Agreement between FOT and the Mead and Whittenberger method in detecting $EFL_{T.}$
Johnson [31]	2006	COPD patients	39	FOT changes following COPD exacerbations
Dellaca [29]	2007	COPD patients		Agreement between FOT and the NEP technique method in detecting $EFL_{T.}$
Faria [28]	2009	Smokers	28	Early smoking induced respiratory changes detected by FOT
Kubota [49]	2009	COPD/controls	38	Low frequency FOT variables are less variable during inspiration than during expiration.
Ohishi [53]	2011	COPD/controls	44	IOS can be used to detect within-breath oscillatory mechanics with a high temporal resolution.

Year: year of publication. N: number of subjects.

The present study set out to examine an alternative method to assess lung function in elderly and in patients with COPD by evaluating within-breath reactance FOT measurements in sequences of tidal volume breathing. We report $\Delta\overline{Xrs}$ as mean inspiratory minus mean expiratory reactance over several breaths, Equation 2.

Equation 2. Mean within-breath reactance, $\Delta\overline{Xrs} = \overline{Xrs}_{insp} - \overline{Xrs}_{exp}$

2. Objectives

We used data from the Bergen Elderly Lung Health (BELH) study, a validation study performed on inpatients at the Salvatore Maogeri en Montescano Hospital in Milano (Milano study), and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study, with additional patients enrolled from our clinical catchment area.

The main object of the study was to evaluate a new method for evaluating pulmonary function in elderly and patients with COPD by measuring the mean within-breath reactance difference over multiple breaths, $\Delta\overline{Xrs}$.

Paper I: The aim of this cross-sectional study was to establish reference values for whole-breath and within-breath impedance measurements in elderly aged 70 years and older using IOS.

Paper II: The aim of this clinical validation study was to analyse the agreement between two different forcing signals, impulse oscillations and sinusoidal pressure oscillations when measuring pulmonary impedance.

Paper III: The aim of this case-control study was to compare the use of $\Delta\overline{Xrs}$ to the tradition breath-by-breath ΔXrs measurements used to identify EFL_T, examine within- and between-day reproducibility of $\Delta\overline{Xrs}$, examine factors affecting the size of $\Delta\overline{Xrs}$, and to examine the association between $\Delta\overline{Xrs}$ and dyspnoea.

Paper IV: The aim of this longitudinal cohort study was to describe the impact of EFL_T on morbidity and mortality in a large COPD cohort.

3. Methods

Three studies form the base of this thesis:

- The Bergen Elderly Lung Health (BELH) Study
- The Milano study
- The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study

3.1 The BELH study

The Bergen Elderly Lung Health Study was a cross-sectional study conducted from 1998 to 2000 in elderly subjects aged 70 years and older living in the municipality of Bergen [27, 89-92]. We re-examined previously unpublished forced oscillation mechanics data from this study. A sex and age stratified sample of 319 subjects were drawn from the responders of a respiratory health postal questionnaire based on the American Thoracic Society and the Division of Lung Diseases questionnaire (ATS/DLD-78) [93]. The never and ex-smoking participants, 208 were invited to the clinic to undergo further testing out of whom 161 participants showed up at the test site, see flowchart, Figure 8. Subjects with acceptable and normal spirometry and at least 2 acceptable IOS measurements were included in our analysis for paper I, N=75, Figure 3 [26, 27, 94].

3.1.1 Inclusion criteria:

- Age >69 years
- Acceptable spirometry and IOS measurements [26, 94]
- FEV_1 and FVC >80% predicted
- FEV_1/FVC >5 percentile / lower limit of normal

3.1.2 Exclusion criteria:

- Acute or chronic respiratory disease
- ATS/DLD dyspnoea grade 4 (after walking 100m on level ground)
- Heart disease
- Hypertension if complicated by ATS/DLD dyspnoea grade 3 (ever having to stop due to breathlessness on the level)
- Current-smoker status

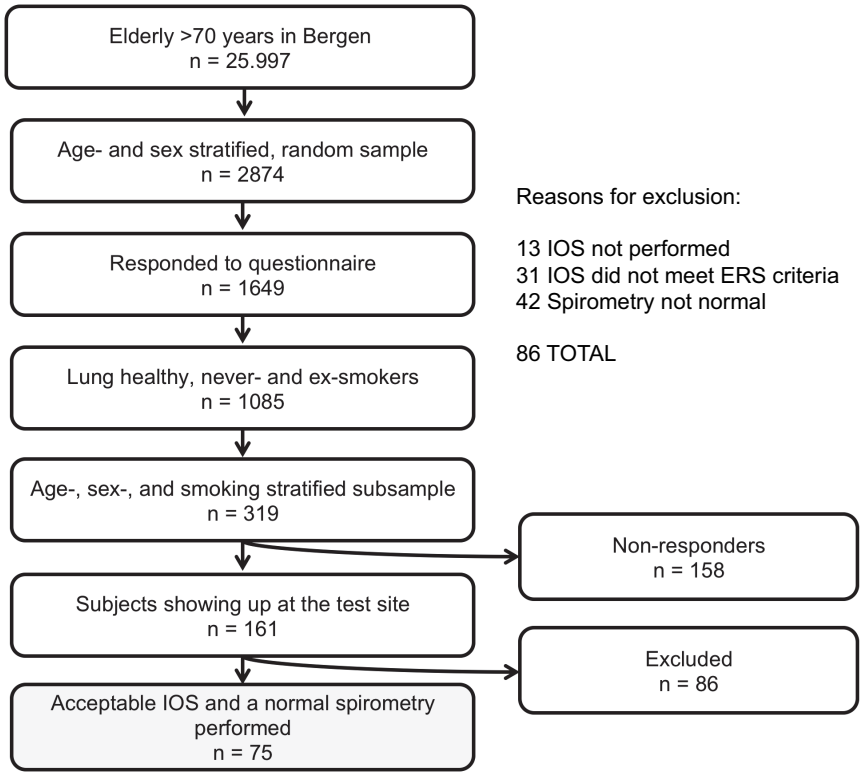

Figure 8. Flowchart of the Bergen Elderly Lung Health study

3.1.3 Assessment tools

Spirometry

Spirometry manoeuvres were performed according to ATS guidelines sitting, wearing a nose clip, using a Vitalograph dry wedge bellows (Vitalograph, Buckingham, UK) [26]. Before each session calibration was performed with a 1L syringe using repeated strokes up to 9L. The best values for FEV_1 and FVC out of 3 acceptable manoeuvres were reported. Only 119 of the original 161 participants were able to complete an acceptable spirometry [26]. Reasons for not being able to perform spirometry were: Coughing within the first second, leakage, too early termination, and not being able to follow instructions.

Forced Oscillation Technique

FOT measurements were performed on a Masterscreen IOS (Erich Jaeger Gmbh, version 4.5). At the beginning of each day a 2L syringe and a reference resistance of 0.2 $kPa \cdot s \cdot L^{-1}$ were used for volume and pressure calibration. IOS was performed sitting, wearing a nose clip, supporting cheeks with both hands, and using a cylindrical cardboard mouthpiece. Each subject performed 2-5 measurements of 30 seconds tidal volume (V_T) breathing. An on site evaluation of acceptability was performed by the technician. In addition the original recordings were reviewed retrospectively using the ERS task force recommendations, which were not available at the time of the recordings [94]. Additional 48 tests were excluded due to signs of leakage around the mouthpiece (N=4), hyperventilation (N=20), and glottis movement (N=24). 117 test subjects had at least two FOT measurements meeting the acceptance criteria.

3.1.4 Statistics

Data processing

IBM SPSS Statistics, Version 18 was used for data management and analysis.

Descriptive analysis

Data were presented as mean ± standard deviation, median (95% confidence interval), median (interquartile range), or percentage. Normal distribution was assessed by histograms, Q-Q plots, and by Kolmogorov-Smirnov and Shapiro-Wilks tests of normality [95, 96]. Repeatability of the parameters was assessed by coefficient of variation (CV) and graphically by modified Bland-Altman plots [97].

Regression analysis

Non-parametric impedance parameters were normalized using natural log (ln) transformation [98]. Predictive equations were generated using multiple linear regression for whole breath, mean inspiratory, and mean expiratory values separately for men and women examining the relationship between the IOS variables and the independent variables of height and weight [99]. Mean of IOS measurements were back-transformed from the geometric mean.

3.1.5 Ethics

Participation in the study was voluntary. Oral and written information was given, and informed consent obtained from all study subjects prior to enrolment. The study was reviewed and approved by the Western Norway Regional Committee for Medical and Health Research Ethics.

3.2 The Milano study

The Milano study (2008-2009) compared FOT measurements with different input signal waveforms. Test subjects were all inpatients at the Salvatore Maogeri en Montescano rehabilitation hospital. 20 clinically stable patients reporting respiratory symptoms were recruited. The study population consisted of 16 men and 4 women. In 13 patients COPD was verified by spirometry. 7 patients were obese with a BMI >30 kg/m^2. Pre- and post bronchodilator spirometry and FOT were performed in order to estimate the agreement between pulmonary impedance measurements obtained with sinusoidal pressure oscillations and impulse oscillations.

3.2.1 Inclusion criteria

- Inpatient at the Salvatore Maogeri en Montescano rehabilitation hospital
- Respiratory symptoms
- Being clinically stable at the time of the measurements
- Signed, and dated informed consent

3.2.2 Exclusion criteria

- Unstable disease at the time of the measurements.
- Failure to perform the measurements.

3.2.3 Assessment tools

Height and weight was measured. Pre- and post bronchodilator spirometry were performed using a body plethysmograph (Masterlab, Jaeger, Würzburg, Germany). 2 patients failed to perform acceptable spirometry, but were still kept

in the sample. FOT measurements were sampled using sinusoidal pressure signals generated with a commercial loudspeaker (HS250, Ciare, Ancona, Italy) and with impulse oscillations generated by a modified commercially available impulse oscillations system (Masterscreen IOS, Carefusion Hoechberg, Germany). Both pressure signals were measured using the pressure and flow transducers of the Masterscreen IOS, synchronized with the internal clock of the Masterscreen IOS microprocessor.

3.2.4 Statistics

Data processing

IBM SPSS Statistics, Version 23 (SPSS Inc., Chicago, Illinois, USA), R 3.3.1 GUI (The R Foundation for Statistical Computing, Vienna, Austria), and Sigmaplot 11.0 (Systat Software, San Jose, CA, USA) were used for statistical analysis.

Statistical analysis

Data were presented as mean ± standard deviation, absolute count or percentage. Normal distributions were assessed using histograms, Q-Q plots, Kolmogorov-Smirnov, and Shapiro-Wilks tests of normality [95, 96]. Non-parametric data were compared using Wilcoxon signed rank test. Coefficient of variation (CV) was used a measure of repeatability [97]. The agreement between sinusoidal pressure oscillations and impulse oscillations was shown by scatterplots and Bland-Altman plots. Measurement repeatability (or short-time variability) was calculated as the 2.5 and 97.5 percentiles of the distribution of the differences between two consecutive measurements using data from the COPD patients ECLIPSE/BCCS study [34]. Relationship between the two measurements was analysed using Deming regression. The resulting regression lines and confidence

intervals were compared with the calculated measurement repeatability.

3.2.5 Ethics

Written, informed consent was obtained from all study subjects. The institutional research ethics committee approved the study.

3.3 The ECLIPSE study

The ECLIPSE study (2006-2010) was as a large, longitudinal, non-interventional, case-control study designed to identify new markers of disease progression [100]. 46 centres in 12 countries participated in the study. Our site, Haukeland University Hospital was one of the largest contributors with 400 COPD cases and 147 smoking controls. Participants were recruited from the general population, patient out-clinics, and hospitals with a majority having participated in previous studies performed at our site, the Hordaland County Cohort Study and the GenKOLS study [101, 102]. No non-smoking controls were recruited from our site to the official ECLIPSE study, however, a local addition was added following the same entry criteria: 46 non-smoking and 36 smoking controls and 25 COPD patients. These study subjects did not attend all visits. A flowchart illustrating the patient inclusion is shown in Figure 9. The Bergen cohort with the additional study subjects is also known as the Bergen COPD Cohort Study (BCCS) [103].

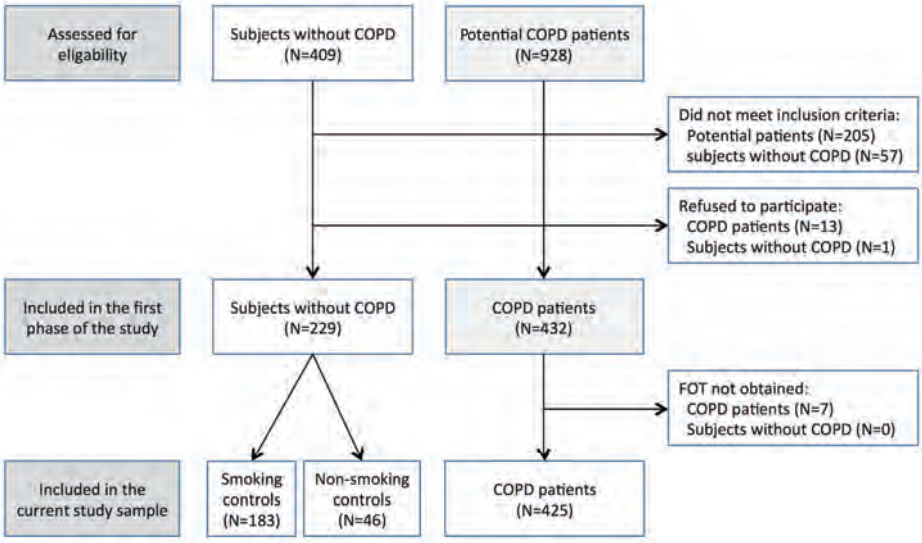

Figure 9. Flowchart illustrating the patient inclusion of the ECLIPSE/Bergen COPD Cohort Study

3.3.1 Inclusion criteria

COPD cases

- Age 40-75.
- Baseline post-bronchodilator FEV_1 <80% predicted and a $FEV_1/FVC \leq$ 70%.
- Smoking history ≥10 pack-years.
- Signed, and dated informed consent
- Being able to complete the study.

Smoking controls

- Age 40-75.
- Baseline post-bronchodilator FEV_1 >85% predicted and a FEV_1/FVC >70%
- Smoking history ≥10 pack-years.
- Signed, and dated informed consent.

- Being able to complete the study.
- Available for the duration of the study.

Non-smoking controls

- Age 40-75.
- Baseline post-bronchodilator FEV_1 >85% predicted and a FEV_1/FVC >70%
- Smoking history <1 pack-year.
- Signed, and dated informed consent.
- Being able to complete the study.
- Available for the duration of the study.

3.3.2 Exclusion criteria

Cases and controls

- Known respiratory disorders other than COPD.
- Prior medical history of significant inflammatory disease other than COPD.
- Severe α_1-antitrypsin deficiency.
- Having undergone lung surgery.
- A diagnosis of cancer within the last 5 years.
- Serious uncontrolled disease likely to interfere with the study or to likely impact subject safety.
- Taking part in a blinded drug study.
- Participation in a study with radiation exposure.
- Substance abuse.
- Blood transfusion in the 4 weeks prior to study start.
- Having a COPD exacerbation within 4 weeks of enrolment.

- Inability to walk.
- Participant, or a family member of the participant working in the study.
- Use of oral steroids for stabile COPD.

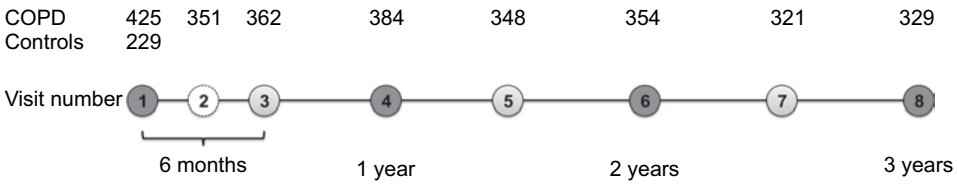

Figure 10. Timeline and number of COPD patients at each visit of the ECLIPSE/Bergen COPD Cohort Study. For the controls, the study only used baseline data. Visit 2 was performed 3 months after baseline.

3.3.3 Assessment tools

At baseline, study subjects were assessed with a physical examination, blood gas, pulmonary function tests, measurements of lung volumes, six-minute walk test, and a booklet of questionnaires, including the ATS/DLD-78, the Saint George Respiratory Questionnaire (SGRQ-C), and the modified Medical Research Council dyspnoea scale score (MMRC) [93, 104-107]. Exacerbations were widely defined as a worsening of respiratory symptoms for 2 following days or more. In the present study only exacerbations requiring the use of antibiotics or systemic corticosteroids and exacerbations requiring hospitalization were included. Exacerbation history was recorded at baseline. Test subjects were called in for a total of 8 visits: at baseline, at 3 months, and then half-yearly for a total of 3 years, Figure 10. Exacerbations were assessed retrospectively, every six months in a clinical interview. Table 3 gives an overview of the assessment tools used at the different visits, which we have referred to in paper III and IV. The questionnaires used to assess exacerbations are shown in the Appendix.

Table 3. Assessment tools in the ECLIPSE/Bergen COPD Cohort Study

	Visit number							
	1	2	3	4	5	6	7	8
Physical examination	*	#	*	*	*	*	*	*
Blood gas	*		*	*	*	*	*	*
Questionnaires								
SGRQ-C	*			*		*		*
ATS/DLD-78	*							
MMRC	*			*		*		*
Exacerbations			*	*		*		*
Spirometry	*	*	*	*	*	*	*	*
IOS	*	*	*	*	*	*	*	*
Plethysmography	*			*		*		*
Six-minute walk test	*			*				*

SGRQ-C: Saint George Respiratory Questionnaire [105]. ATS/DLD-78: American Thoracic Society and the Division of Lung Diseases questionnaire [93]. MMRC: modified Medical Research Council dyspnoea scale score [104]. IOS: Impulse Oscillometry System. *Performed. #: If needed.

3.3.4 Pulmonary function tests

Spirometry and IOS

Pre- and post- bronchodilator (0.4 mg salbutamol) spirometry and FOT measurements were performed by trained personnel each visit in accordance with agreed standards on a Masterscope CT Impulse Oscillation System (IOS) (Jaeger, Hoechberg, Germany) [26, 94]. Before each session a 3L syringe and a reference resistance of 0.2 $kPa \cdot s \cdot L^{-1}$were used for volume and pressure calibration. The highest values from at least 3 acceptable spirometry procedures were used to determine FEV_1 and FVC. FEV_1 % predicted was calculated using local reference values [19, 26]. IOS was performed sitting, wearing a nose clip, and supporting cheeks with both hands. Each subject performed 3 acceptable measurements of 30 seconds V_T breathing. Acceptability was assessed on site by visual inspection of the patient while performing the test and by a review of the recordings using the ERS task force recommendations [94]. Both whole- and within-breath (inspiratory and expiratory) values were reported for: Resistance at 5 Hz (Rrs_5), reactance at 5 Hz (Xrs_5), and resonant frequency ($f$res). Mean

within-breath reactance at 5 Hertz, $\Delta\overline{Xrs}$ was calculated for each measurement averaged over the 30-second sampling period, Equation 2.

Plethysmography

Whole-body plethysmography was performed on a Masterscreen^{TM} body plethysmograph (Jaeger, Hoechberg, Germany). Before each session, volume was calibrated, and before each individual examination, the test subject weighed, and allowed a 5 minutes rest. 3 acceptable tests were performed according to international standards [108]. Variables used in this study were residual volume (RV), total lung capacity (TLC), and inspiratory capacity (IC).

3.3.5 Six-minute walk test

Only the COPD cases performed the six-minute walk test (6MWT). The test was performed in accordance with the ATS guidelines in a straight, 30 meter hospital corridor, supervised by a trained technician [106]. The oxygen saturation was measured both before and directly after the test using a Nonin 8500 Handheld Pulse Oximeter (Nonin Medical, Inc., Plymouth, Minnesota, USA). Safety criteria for stopping the test were chest pain, intolerable dyspnoea, diaphoresis, leg cramps, if the patient started staggering, and if the patient appeared pale or ashen. If a desaturation ≤86% was found at the end of the test, the COPD patient was referred to pulmonary rehabilitation for evaluation of oxygen treatment. The level of dyspnoea and fatigue was evaluated using Borg scale in the beginning and at the end of the test [109].

3.3.6 Statistics

Data processing

IBM SPSS Statistics, Versions 20-22 (SPSS Inc., Chicago, Illinois, USA) and Stata 13.1 (StataCorp LP, College Station, Texas, USA) were used for statistical analysis.

Descriptive analysis

Data were presented as mean ± standard deviation, interquartile range, 95% confidence interval, absolute count, or percentage. Normal distributions were assessed using histograms, Q-Q plots, Kolmogorov-Smirnov, and Shapiro-Wilks tests of normality [95, 96].

Associations, binary classifiers, and grouping of cases

Dependence between variables was assessed with Pearson's correlation coefficient or Spearman's rho [110]. Means were compared using t-test or Mann-Whitney U test when appropriate [111]. In paper III receiver operating characteristic (ROC) curves were used to illustrate the performance of $\Delta\overline{Xrs}$ and FEV_1 to detect dyspnoea as their discrimination threshold were varied [112]. In line with the current GOLD guidelines, an empirical threshold of ≥2 of the modified Medical Research Council dyspnoea scale score (MMRC) was used to define dyspnoea [67, 104, 107]. The best composite specificity and sensitivity for dyspnoea (MMRC ≥2) was found at $\Delta\overline{Xrs} > 0.1$ kPa·s·L^{-1} [34]. In paper IV cases were divided into groups based on occurrence of EFL_T, at baseline.

Variability

Coefficient of variation (CV) was used a measure of repeatability [97]. Consistency between repeated measurements of $\Delta\overline{Xrs}$ with the breath-by-breath and the multiple-breath approach was tested with intraclass correlation coefficient (ICC) [113]. The within-day repeatability of $\Delta\overline{Xrs}$ was shown in a modified Bland-Altman plot, and a timeline plot was used to illustrate the reproducibility over the course of the 3-year study in cases and controls [114].

Longitudinal data and survival analysis

Negative binomial regression was used to analyse annual exacerbation rates over the 3-year study [115]. The analysis accounts for the yearly variability among test subjects. We adjusted for age, sex, FEV_1, in addition to a binary classifier identifying COPD patients with ≥2 exacerbations the year prior to inclusion. The parameter effects of the negative binomial regression were reported as rate ratios (RR), 95% confidence interval, and p-values. Exacerbations were also investigated by time to first event analysis with Kaplan-Meier survival analysis and 1-survival plots. The patients were grouped based on occurrence of $\Delta\overline{Xrs}$ >upper limit of normal at baseline and dichotomized at FEV_1 50 % predicted [67, 116, 117]. In our survival analysis Kaplan-Meier product limit estimates for patients with and without evidence of EFL_T at baseline were plotted in COPD patients with FEV_1 >50 % predicted and in COPD patients with FEV_1 <50 %, and differences between groups analysed using Log-rank test. Hazard ratios were obtained using Cox proportional hazards regression [116, 117].

3.3.7 Ethics

Participation in the study was voluntary. Oral and written information was given, and informed consent obtained from all study subjects prior to enrolment. The

ECLIPSE/BCCS was approved by the Western Norway Regional Committee for Medical and Health Research Ethics (REK 165.08) and performed in agreement with the Declaration of Helsinki and the Good Clinical Practice guidelines, ClinicalTrials.gov/NTC00292552 [118].

4. Synopsis of papers

4.1 Paper I

Reference values for within-breath pulmonary impedance parameters in asymptomatic elderly

Aarli BB, Eagan TM, Ellingsen I, Bakke PS, Hardie JA. Clin Respir J. 2013 Jul; 7(3): 245-52. doi: 10.1111/j.1752-699X.2012.00312.x. Epub 2012 Aug 20.

The forced oscillation technique measures airway mechanics non-invasively during normal tidal breathing. By evaluating variations in the pulmonary reactance in the respiratory cycle, a method has been developed which accurately detects EFL_T [29, 30]. However, at the time of the study, reference values for FOT parameters in elderly were very limited, particularly using impulse oscillations. Reference values for partitioned inspiratory and expiratory measurements used by the method were non-existent [32, 41]. The aim of this study was to present reference values for oscillatory lung mechanics in healthy elderly.

An age- and sex-stratified sample was drawn from healthy, non-smoking responders of a postal questionnaire study in elderly aged >70 years in the city of Bergen [89]. Study subjects performed both spirometry and FOT measurements on an Impulse Oscillometry System (IOS). 75 study subjects had normal and acceptable spirometry and at least two acceptable IOS measurements [26, 94].

Predictive equations were generated for whole-breath and within-breath impedance FOT parameters were created separately for men and women using multiple linear regression [99]. The paper reports reference values for whole-breath as well as within-breath FOT parameters in healthy elderly aged >70 years. In this healthy elderly population, $\Delta\overline{Xrs}$ was around zero and the 95 percentile in men and women, 0.26 and 0.24 $kPa \cdot s \cdot L^{-1}$ consecutively. Only one subject had $\Delta\overline{Xrs}$ above the defined threshold of tidal expiratory flow limitation.

4.2 Paper II

Agreement between sinusoidal and impulse oscillations when measuring pulmonary impedance

Aarli BB, Govani L, Pompilio PP, Baldi S, Hardie JA, Dellaca RL. In manuscript form: to be submitted to the Journal of Respiratory Physiology and Neurobiology in 2017.

Several different input signals are presently used to measure pulmonary impedance: sinusoidal pressure oscillations, pseudo-random noise, and impulse oscillations. In linear systems, the responding pulmonary impedance should be the same. In nonlinear systems, which may occur in pulmonary disease with airway obstruction, this might not apply. The aim of this study was to test the agreement between sinusoidal pressure oscillations and impulse oscillations.

20 patients who reported respiratory symptoms were recruited from inpatients at the Salvatore Maogeri en Montescano rehabilitation hospital. Pre- and post bronchodilator FOT and spirometry were performed with both impulse oscillations generated by an IOS commercial device, and sinusoidal pressure oscillations generated by a homemade loudspeaker system. Only the input signal was changed while transducers and breathing circuits were the same.

A wide range of spirometry and Zrs measurements was found in this mixed group of patients. EFL_T was detected in 17 out of 36 FOT measurement using the established ΔXrs threshold 2.81 $H_2O \cdot L^{-1} \cdot s$ [30]. In non-EFL_T patients, good agreement was found using the two different forcing signals. In EFL_T patients, variability of Rrs and Xrs exceeded the expected biological variability. Rrs values measured by impulse oscillations were significantly higher than the sinusoidal pressure oscillation measurements in the EFL_T patients.

Conclusion: Compared with sinusoidal pressure oscillations, impulse oscillations overestimate the Rrs measurements, but only at pathologically high impedance measurements found in EFL_T patients.

4.3 Paper III

Variability of within-breath reactance in COPD patients and its association with dyspnea

Aarli BB, Calverley PMA, Jensen RL, Eagan TM, Bakke PS, Hardie JA. Eur Resp J. 2015. Mar; 45(3): 625-34. Oct 30.

The forced oscillation technique can be used to identify EFL_T by detecting changes in reactance over the respiratory cycle [29, 30]. A cut-off in within-breath reactance, ΔXrs has been defined to identify single breaths as tidal expiratory flow limited, however, evidence suggest that presence of EFL_T varies from breath to breath [30]. This paper explores a new method to identify EFL_T using a mean multiple breath $\Delta\overline{Xrs}$ approach. We investigate the variability and reproducibility of this method and examine how $\Delta\overline{Xrs}$ relates to the sensation of dyspnea.

This study reports the results form the Bergen cohort of the ECLIPSE study, consisting of 425 stable COPD patients and 229 controls [67]. Study subjects

were called in for 8 visits over 3 years performing a wide range of tests and questionnaires, including spirometry and FOT using impulse oscillations.

Healthy controls generally had very low $\Delta\overline{Xrs}$ measurements with a median around zero, and a 95th percentile at 0.07 kPa·s·L-1 with little variation between measurements. The COPD patients had higher $\Delta\overline{Xrs}$ and more variability. Using receiver operating characteristics analysis, we found the cut-off $\Delta\overline{Xrs}$ ≥0.1 kPa·s·L^{-1} to identify patients with significant dyspnoea, defined as having a modified Medical Research Council Dyspnoea scale score ≥2 [104].

We describe a new method to assess EFL_T using a multiple breath approach and explore the variability of the method. A cut-off in $\Delta\overline{Xrs}$ ≥0.1 kPa·s·L^{-1} was found to identify test subjects more likely to report dyspnoea.

4.4 Paper IV

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

Aarli BB, Calverley PMA, Jensen RL, Eagan TM, Bakke PS, Hardie JA.

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EFL frequently presents already at tidal breathing in COPD and can be detected by FOT during a single breath when ΔXrs exceed 0.28 kPa·s·L^{-1} [30, 34, 70]. This study investigates the association of mean within-breath reactance measured over multiple breaths, $\Delta\overline{Xrs}$ with exercise performance, exacerbation rate, and mortality.

425 COPD patients were followed for 3 years/8 visits, reporting spirometry and impulse oscillation mechanics. Exercise performance was evaluated by the 6MWT and respiratory symptoms, exacerbations, and hospitalizations recorded.

The 5-year mortality statistics was retrieved retrospectively. Patients were grouped into 3 according to $\Delta\overline{Xrs}$ at baseline using the 97.5th percentile/ULN of the healthy controls and the established threshold of EFL_T as cut-offs. Annual exacerbation rates were analysed by a negative binomial model in the three groups, supplemented by time to first event analysis for exacerbations, dichotomizing at the ULN.

While COPD patients with $\Delta\overline{Xrs}$ <ULN (0.09 kPa·s·L^{-1}) had a stable 6MWD. The patients with $\Delta\overline{Xrs}$ ≥ULN declined significantly in 6MWD had lower FEV_1, more exacerbations, and a shorter time to first exacerbation and hospitalization. Patients with FEV_1 >50% and $\Delta\overline{Xrs}$ ≥ULN had significantly higher mortality.

Conclusions: Patients with $\Delta\overline{Xrs}$ ≥ULN deteriorated in exercise performance, had more exacerbations and hospitalizations, and in COPD patients with moderate airway obstruction, also a higher mortality. We propose $\Delta\overline{Xrs}$ is an independent prognostic marker in COPD.

5. Discussion

5.1 Methodological considerations

5.1.1 Study design

The papers included are based on 2 observational studies performed years apart, the BELH and the ECLIPSE, and a small validation study performed in Milano. Different study designs chosen for each paper:

- Paper I reports reference value equations generated from healthy elderly in the cross-sectional BELH study.
- Paper II is a validation study investigating the agreement between two forcing signals used in FOT: sinusoidal pressure oscillations and impulse oscillations.
- Paper III use data from the prospective, case-control ECLIPSE study. Variability of within-breath reactance was tested in cases and controls. The longitudinal design allowed for the assessment of reproducibility both at baseline and over time.
- Paper IV used a prospective cohort study design, following COPD cases only in the ECLIPSE study. It investigates the associations between presence of EFL_T and adverse outcomes such as deterioration in exercise capacity, exacerbations, hospitalizations, and death.

An overview of design and study population is shown in Table 4.

Table 4. Design and study population in the four papers

Paper	Design	N	Men	Age	Participants
I	Cross sectional BELH study	75	53 %	79 ± 7	Healthy elderly
II	Validation study	20	85 %	69 ± 10	Inpatients at a rehabilitation hospital
III	Prospective case-control 3-year follow up ECLIPSE/BCCS study	654	57 %	60 ± 9	Controls (N=229) GOLD 2 (N=179) GOLD 3 (N=186) GOLD 4 (N=60)
III	Prospective cohort study 3-year follow up ECLIPSE/BCCS study	425	60 %	63 ± 7	GOLD 2 (N=179) GOLD 3 (N=186) GOLD 4 (N=60)

Data presented as mean ± standard deviation, percentage, or absolute numbers. BELH: Bergen Elderly Lung Health Study. ECLIPSE/BCCS: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints/Bergen COPD Cohort Study. GOLD: Global Initiative for Chronic Obstructive Lung Disease [67].

5.1.2 Patient selection

The inclusion and exclusion criteria have previously been outlined in the Methods section, chapter 3. This section describes the recruitment process of the different studies. For the longitudinal ECLIPSE/BCCS the dropout rate is also discussed.

The BELH study

The BELH study participants were recruited from the municipality of Bergen. Although covering a relatively large area, 465 km^2, about 97% of the population of Bergen lives in urban areas [119]. For our target population, the Norwegian population in general, the corresponding number is 81% [120]. In 1972 the municipality of Bergen merged with four surrounding and at the time relatively rural municipalities, Arna, Fana, Laksevåg, and Åsane, increasing it's population with 90.000 people [121]. Many subjects included in our study have lived in rural areas parts of their lives, reducing possible differences derived from differences in the proportion in elderly living in rural and urban areas between

the study and the target population. The non-responders have previously been described [89].

The Milano study

The study was performed from February 2008 to June 2009. Inpatients at the Salvatore Maogeri en Montescano rehabilitation hospital with respiratory symptoms, in whom COPD was suspected, were recruited. Out of 22 patients included in the study, 2 patients were excluded due to missing data. 2 patients unable to perform spirometry, but with valid sinusoidal and IOS measurements were still kept in the sample. As results are used to make inferences on a sample of COPD patients, it is a disadvantage that only 65% of the study subjects actually had a spirometry confirmed diagnosis of COPD. However, the goal of the study was to recruit patients with a wide range of spirometric measurements and a varying degree of airway obstruction in order to have an equally large spread in the FOT measurements. Due to low sample size, the study must be regarded as hypothesis testing more than validating.

The ECLIPSE study

COPD cases were recruited from the GenKOLS study performed in 2003-2004. Screen failures from the GenKOLS study with FEV_1 80-90% at risk of developing COPD were re-examined and included if they met entry criteria. Patients were recruited from the out-clinic and the pulmonary rehabilitation referrals of the Department of Thoracic Medicine at Haukeland University Hospital, and from the to the out-clinic at the Department of Medicine at the following hospitals: Stord, Førde, Kristiansand, and Voss. In addition some patient were referred from a private pulmonology practice in Straume.

Controls were mainly recruited from the previous studies GenKOLS and the 2003 follow-up of the Hordaland County Respiratory Health Survey [122]. Only controls living in our clinical catchment area were included.

Dropout rate was approximately 23%, deaths included from baseline to the final visit, Table 5. This is lower than comparable longitudinal COPD studies [123, 124].

Table 5. Deaths and dropouts during the 3-year study period

	N	%
Died	41	10
IOS 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

5.1.3 Internal validity

Internal validity is the degree to which the results are determined by independent variables and not to some other explanations. Research designed to investigate cause-and-effect relationships may be affected by various systematic errors, which may affect the outcome.

Selection bias

The BELH study recruited randomly among the healthy responders of a respiratory questionnaire sent to the elderly in the general population of Bergen. Steps taken in the recruitment process to minimize the risk of selection bias was stratifying for age and sex

In the ECLIPSE/BCCS study the smoking controls were on average 10 years younger than the COPD patients [34]. We do not know if the $\Delta\overline{Xrs}$ 97.5th percentile used to define the ULN would have been higher in a control population more similar to the COPD cases in age. Gender differences may also have affected the results. Among COPD patients 60% were male [36]. Matching for age and sex could have secured a more uniform patient population, possibly reducing the risk of age and sex being confounders.

Information bias

In order to minimize the risk of information bias, validated questionnaires were used [93, 104, 105, 109]. A prospective design, collecting information and measurements at each visit not to long apart, reduces the risk of recall bias. Socially sensitive questions such as smoking history are often underestimated [125]. To improve our smoking history estimates, detailed registration of smoking habits were registered at baseline. Only pulmonary function tests equipment compliant with the regulations of European Medical Device Directive were used. The Erich Jaeger/Carefusion spirometer/IOS apparatuses used are certified according to the International Organization for Standardization, ISO 9001/IEC 13485. Spirometry, IOS and plethysmography were performed according to ATS/ERS standards [5, 94, 108]. The measurement and calibration procedures are reported in the methods section, Chapter 3.

Confounding

Steps taken in the BELH study to avoid confounding were restricting admission to the study by selecting a group of healthy elderly with similar levels of confounding factors. Only elderly aged >69 years with FEV_1 and FVC >80% predicted and a FEV_1/FVC >LLN with no acute or chronic respiratory disease, heart disease, hypertension if complicated by ATS/DLD dyspnea grade 3, or

ATS/DLD dyspnea grade 4. A randomized selection was chosen among the healthy responders to undergo further testing.

A consideration of confounding effects in the ECLIPSE/BCCS study was made when choosing the inclusion and exclusion criteria, i.e. restricting the study by only including COPD patients with a smoking history ≥10 pack-years, reduces the possible confounding effect caused by tobacco smoking.

Controlling for confounding was performed in the multiple regression models used in both the BELH and the ECLIPSE/BCCS studies, keeping only statistically significant variables in the models. In the Milano study the experimental setup was designed specifically to minimize confounding factors related to the FOT device and the measurement situation, i.e. measurements using sinusoidal pressure oscillations were performed in the same session as impulse oscillations changing only the forcing signal, while the sensors and circuits were the same. The order of the measurements, whether sinusoidal or impulse oscillations were performed first, was altered randomly.

Random error

The number of test subjects in the BELH study, was relatively small (N=75), lowering the precision of the reference equations generated [35]. The Milano study included 36 FOT measurements with both sinusoidal and impulse oscillations performed in only 20 patients. Due to low sample size, we cannot exclude that the overestimation of Rrs using impulse oscillations could have been caused by random error. The ECLIPSE study's sample size was considerably larger, increasing the precision of the estimates.

5.1.4 External validity

To ensure generalizability of the study population and to reduce the risk of selection bias, a randomized selection of the healthy respondents was chosen and

called in for further testing in the BELH study. A random sample of the non-responders interviewed by telephone, found only minor differences between responders and non-responders, minimizing the risk of a non-responder bias [89].

Sampling bias

A sample is biased if some members of a population or patient group are more likely to be included than others. In the ECLIPSE/BCCS study the COPD patients were recruited mainly from hospital out-clinics, a population with higher morbidity than general population [102]. At the same time the COPD patients with the most advanced disease may have been underrepresented due to inability to participate. The study required being able to meet at the hospital to participate in the visits. A considerable disability and limitations in performing activities in daily living is associated with very advanced airway obstruction, making travelling to and from the hospital more difficult. For this reason GOLD grade 4 patients may have been more reluctant to participate among potential candidates for inclusion. Thus, it is likely that the majority of included COPD cases in the study were more afflicted than the COPD population at large, yet some particularly afflicted patients were probably excluded.

The healthy controls were volunteers from previous cohort studies, and not randomly selected. There is some possibility for selection of controls particularly worried about their own health, either being very health-conscious and thus healthier than the average population, or by knowing that they have a potential for adverse health. Previous non-response studies found response rate to drop significantly with old age [89], non-responders were more likely to be smokers and to have a higher burden of respiratory symptoms [126], additional factors increasing the risk of non-response were unemployment, being a student, or being retired [127]. A high response rate counteracts response bias. The ECLIPSE/BCCS study had a response rate of 69 % [128].

In the ECLIPSE study, several facilities participated in recruitment, covering an area, which included most municipalities in Hordaland County, both urban and suburban. A few test-subjects were also added from Vest Agder County. Although study participants were mostly recruited from Hordaland County, the population of Norway is relatively homogenous, allowing us to generalize the results to a more universal population. However, being recruited mainly through hospitals, the results might be more representative of the hospital seeking COPD population rather than the COPD population found in the general population.

5.1.5 Reliability

Reliability refers to the consistency of the test results. The ECLIPSE/BCCS studied stable COPD. If the test subject was found to have a COPD exacerbation at the time of the visit, the visit was rescheduled.

Exercise capacity was estimated in the ECLIPSE/BCCS study using the well-established 6MWT [106]. The latest ERS/ATS systematic review on field walking tests in COPD reports it to be a reliable test with intra-class correlation coefficients in the range from 0.82 to 0.99 [129]. A learning effect has been reported with a mean improvement between two tests of 26 meters [129]. For this reason a practice test should be considered, but is not mandatory [106]. Due to limited resources we did not perform any practice test of the 6MWT. A learning effect could mask a decline in the 6MWD from baseline to the final visit.

5.1.6 Data retrieval

The within-breath FOT parameters were not originally transcribed in the BELH or the ECLIPSE study. In the BELH study the within-breath parameters were retrieved from the database of the IOS software linking the individual tests to the

test subjects id number and the test date. By recalculation, a new screen report was generated including the FOT parameters of interest.

In the ECLIPSE study, the vast number of measurements over the course of the visits made such an approach impractical. Instead the complete database from all IOS apparatuses used in the study were imported and merged in a computer with the newer software (JLAB 5.22), which had a structured query language (SQL) export option. Microsoft SQL server and Microsoft Access 2010 were used for database management of the JLAB 5.22 SQL export data. Each individual test was matched to the punched test in the ECLIPSE study by subject id number, test date, and by matching for the post-bronchodilator resonant frequency value. By matching for a punched number we were able to exclude the tests discarded on site by the technicians, but may have lost some tests due to punching errors.

5.2 Methodological strengths and weaknesses

5.2.1 The BELH study

Strengths

Sex and age stratification ensured a representative number of very old subjects in the study. A non-responder bias study where attempts were made to reach hard to reach groups, such as people residing in nursing homes found only minor differences between responders and non-responders [89].

Weaknesses

As a consequence of a relatively small sample size, reference values generated from this study should be interpreted with care, particularly since confidence intervals were relatively wide. In addition pulmonary impedance measurement data is not normally distributed, and natural log transformations were used.

5.2.2 The Milano study

Strengths

The experimental setup was specifically designed to eliminate confounding factors, and the agreement between measurements using different forcing signal was compared with the expected biological variability between two tests using impulse oscillations.

Weaknesses

Low sample size increases the risk of random errors affecting the results. Even though heterogeneity of the study population gave the intended wide spread of measurement outcomes, the associations may have been stronger, and more clinically relevant if the study had been restricted to COPD patients only.

5.2.3 The ECLIPSE study

Strengths

The ECLIPSE study is one of the best characterized, case-control studies performed on COPD patients [130]. The longitudinal design and the large number of patients and controls made it possible to investigate associations between baseline characteristics, disease progression, exacerbations, hospitalizations, and death rates.

Weaknesses

Our data was restricted to the Bergen cohort of the ECLIPSE study, the only site where within-breath oscillatory mechanics were retrieved. If similar data were available in the complete ECLIPSE cohort, the study would have had a higher power to test clinical endpoints. Single-breath ΔXrs measurements have been validated against both the NEP technique and the esophageal balloon technique

to identify single expiratory flow limited breaths. Our measurements represent 90 seconds samples containing several breaths. When we describe associations with breathlessness, exercise capacity, exacerbations, and death using lower $\Delta\overline{Xrs}$ cut-offs than the established threshold of EFL_T, we interpret these borderline measurements of $\Delta\overline{Xrs}$ that are beyond what is found in healthy subjects as likely to contain some flow-limited breaths. The exact number of flow-limited breaths within in each sample is not known, and further prospective studies confirming our observations is merited before clinical use is concluded.

5.3 Discussion of main results

The study was set out to evaluate a new method for evaluating pulmonary function in elderly and patients with COPD by measuring the mean within-breath reactance difference over multiple breaths, $\Delta\overline{Xrs}$.

We explored this in 4 papers where we:

I. Established reference values for whole-breath and partitioned inspiratory and expiratory pulmonary impedance parameters in elderly using IOS.
II. Evaluated the agreement between $\Delta\overline{Xrs}$ measured by sinusoidal pressure oscillations and impulse oscillations.
III. Compared the use of $\Delta\overline{Xrs}$ to the tradition breath-by-breath ΔXrs measurements used to identify EFL_T. Examined the within- and between-day reproducibility of $\Delta\overline{Xrs}$, examined the factors affecting the size of $\Delta\overline{Xrs}$, and examined the association between $\Delta\overline{Xrs}$ and dyspnea.
IV. Described the impact of EFL_T on morbidity and mortality in a large COPD cohort.

The main empirical findings are discussed separately for each study.

5.3.1 Reference values in asymptomatic elderly

Human physiology is complex, whereas reference equations used in respiratory physiology are much less so. Generally they use less than a handful predictors. With only the strongest predictors, variability is only explained in part, and relatively large confidence intervals are to be expected. Still, the references ranges found in healthy subjects are extremely useful. The reference ranges aid us in uncovering respiratory disease in individuals who fall outside these boundaries, and we compare with median values of FEV_1 when airway obstruction is graded. How a healthy reference group of elderly should be defined, on the other hand, is difficult to agree on. The WHO defines health as follows:

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[131]

This definition excludes most elderly and cannot be applied. While a homogenous reference sample would be the ideal, the elderly is a very heterogeneous group [132]. Elderly with identical lung function test may be very different with regards to respiratory symptoms, exercise capability, and chronic diseases. Differences in smoking habits, working conditions, and lifestyle cause huge differences in exposure of air pollutants and other risk factors to evolve. In this setting, it is difficult to ensure a representative norm population, and there are presently no guidelines defining how reference values should be produced in elderly. What is normal aging, and what should be considered pathology? Postural changes such as kyphosis and scoliosis with age have considerable effect on lung volumes. What is the impact of chronic illnesses? Should medication be considered?

In the absence of reliable reference values, a change in the measurements of one individual over time, is much more informative than any single measurement

validated against a reference value. This has particularly been true for IOS measurements in elderly, where reliable reference studies until recently were lacking. As a substitute, reference values for elderly aged >70 years were extrapolated from equations generated in subjects <70 years of age [32]. This approach is problematic as it assumes existing trends will continue. It disregards the large heterogeneity with regards to health and exposure history, which arise in the elderly, and it assumes that reference equations generated in younger subjects are representative for an elderly population. If reference equations are used on different populations than the one that was enrolled and tested to generate the equations, they may be misleading.

Unless elderly are targeted specifically in the design of reference studies, the proportion of elderly included may be non-existent or very small. In the recent Global Lung Function Initiative (GLI) multi-ethnic reference values for spirometry, the proportion of elderly aged >80 years was only 0.8% [20].

The BELH study supplies reference values for whole-breath and partitioned inspiratory and expiratory IOS measurements in healthy elderly aged 70 and more. FOT defined EFL_T in this sample was very rare. Only 1 out of 75 had $\Delta\overline{Xrs}$ measurements above the established threshold of EFL_T, which is in stark contrast to previous findings by Bisschop et al reporting EFL_T in almost half of the subjects, examining elderly in France [35]. Selection bias may explain some of the differences, but it is likely that the NEP technique used by Bisschop et al has a different sensitivity and specificity of detecting EFL_T than the FOT technique. While a COPD patient may dissolve EFL_T identified by FOT by starting to breath at a higher lung volume, applying a negative pressure during expiration with the NEP technique effectively cancels this possibility to dynamically regulate the operating lung volume. Breathing just above the flow limiting end-expiratory lung volume, the airway remains open, and pressure/flow signals applied at the mouth are allowed to reach the distant alveoli before they are reflected. The

flow/volume loops, however, may appear flow-limited. As a consequence, borderline breaths will be defined as flow-limited by the NEP technique and as normal by the FOT technique.

5.3.2 Forcing signals used to measure pulmonary impedance

FOT calculates pulmonary impedance at the airway opening when a forcing signal is superimposed on normal tidal volume breathing. The forcing signal can be either single- or multi-frequency. In single frequency FOT, the test subject's response to a sinusoidal pressure signals is studied. Relatively rapid changes in pulmonary impedance may be tracked, such as changes within the respiratory cycle [30]. Pulmonary impedance is calculated from the responding pressure and flow signals, providing valuable information about the airway mechanics. As the technique measures only one frequency at the time, investigating a range of frequencies by single frequency FOT would be time consuming. For this reason multi-frequency FOT is preferred when examining mechanisms of frequency dependency [94].

Multi-frequency FOT, such as pseudo-random noise and IOS measures respiratory mechanics as a function of frequency, allowing the characteristic responses from many different frequencies to be measured at the same time. This is useful because different frequencies affect the lungs differently. When examining bronchodilator effect of salbutamol in COPD patients by impedance measurements in the 4-32 Hertz range, much larger differences are found in pulmonary resistance and the reactance at low frequencies than high frequencies [133]. The low frequencies seem to penetrate the peripheral airways better, while higher frequencies better describe the central airways [134].

When multi-frequency signals are used, the complex signal is decomposed into its individual frequencies by fast Fourier transformation [32]. This allows us to

examine many frequencies in the same timeframe, and allows the use of several different signals with different qualities, such as white noise, PRN, and impulse oscillations. The calculated impedance should be the same.

IOS differs from white noise and PRN by using impulse shaped waveforms of short duration. Some patients perceive these impulses as slightly unpleasant, but in general feasibility is high. The standard IOS setup uses 5 impulses per second, which allows for intra-breath analysis comparable to single frequency FOT. As the total energy from the pressure signals is applied within a very short timeframe, there is less risk of non-linearities caused by dynamic changes in the respiratory system [134]. PRN has a poorer time resolution and is not that well suited to capture within-breath changes in pulmonary impedance.

A study by Hellinckx et al compared measurements of pulmonary impedance between an impulse oscillations apparatus and a PRN device in a selection of healthy test subjects and patients with various respiratory diseases (N=49). In this study, the IOS overestimated resistances at low frequency, Rrs_5 [47]. The differences increased with higher magnitude of the resistance measured, and was confirmed in a mechanical model using the wave tube technique. The Xrs measurements did not show any systematic differences and were very similar. Compared with sinusoidal pressure oscillations, we found similar results. A systemic overestimation of Rrs_5 by the IOS device was found, while no systematic effect was seen on the Xrs_5 measurements [37].

5.3.3 Variability of FOT measurements

Variability of FOT measurements depends on the precision of the measurement and the biological variability. The accuracy of the sensors of the IOS used in this study, the pneumotach and the pressure transducer, are reported to be ±2% by the manufacturer [135]. Biological variability is higher and can be separated into the

intra-subject variability, both within a day and the changes over time, and the inter-subject variability. The ERS task force recommends using the coefficient of variation (CV), defined as the standard deviation (σ) to the mean (μ), as the main index of FOT repeatability and variability, Equation 3 [94].

Equation 3. Coefficient of variation (CV) $= \frac{standard\ deviation}{mean} = \frac{\sigma}{\mu}$

Within-day variability

FOT measurements were performed in one session and should not be affected by circadian variation known to exist in pulmonary function [136]. Measurements are performed at tidal volume breathing, but may be influenced by the operating lung volume, i.e. the degree of hyperinflation, the distensibility at different volumes, or if the end-expiratory lung volume is close to the closing volume. Glottis closure or swallowing, leads to spikes in the impedance tracings. When such artefacts are found in the flow- or impedance tracings, that particular section of the test can be removed, calculating impedance from the remaining sample [94]. In the BELH- and the ECLIPSE/BCCS studies these individual test were discarded [34, 35]. For FOT measurements, a coherence function is normally used on site, rejecting measurements with coherence <95 %. In the BELH and the ECLIPSE/BCCS study, coherence was estimated on site. These data are not reported.

Previous reports of within-day variability of the FOT in healthy subjects and patients with obstructive pulmonary disease found a within-day variability of Rrs between 5-15 %, Table 6. It has been suggested that the short-term variability for FOT parameters should not exceed 10 % at frequencies ≥5 Hz [134]. Both the BELH and the ECLIPSE/BCCS study had Rrs_5 measurements within this boundary [34, 35]. However, the main focus of our studies, were the pulmonary reactance, including the partitioned inspiratory and expiratory components in addition to the within-breath reactance. The BELH study and also previous

reports find CVs for Xrs, Xrs_{insp}, $Xrs_{exp,}$ and ΔXrs to be higher than 10%, Table 6, but the CV is by definition unsuited to evaluate variability of pulmonary reactance. These measurements are frequently close to zero, in which case the CV becomes very high, approaches infinity, or cannot be calculated. Alternative measures include the within-subject standard deviation (SD_W), the coefficient of repeatability (CR), and the intra-class correlation coefficient (ICC) [114, 137]. The SD_W is seldom reported, but has been found quite low, 0.01-0.04 $kPa \cdot s \cdot L^{-1}$ in pulmonary reactance, with Xrs_{insp} as the most stable measurement [138, 139]. For $\Delta\overline{Xrs}$, the SDw is higher in COPD patients than in healthy control subjects, and increases with the magnitude of the measurement [34, 37].

For spirometric measurements, the optimal method of reporting the short-term variability is to estimate the coefficient of repeatability (CR) [140]. CR is calculated as 2 times the standard deviation of the differences between two measurements [114]. In a multicenter, multi-device study (5 different FOT apparatuses), CR was 0.05 $kPa \cdot s \cdot L^{-1}$ for Xrs_5 in healthy adults, N=302 [141]. The intra-class correlation coefficient (ICC) for Xrs_5, Xrs_{insp}, and ΔXrs was ≥0.94 in a study on variability of impedance parameters in COPD patients [139].

The SD_W, CR, and ICC show good within-day reproducibility for Xrs_5, including partitioned inspiratory- and expiratory components, and the ΔXrs, but variability increase with the magnitude of the measurement. We interpret an increased $\Delta\overline{Xrs}$, which is below the established threshold of EFL_T as a mixture of some normal and some flow-limited breaths [30]. The spontaneous variability of ΔXrs in COPD might be caused by a dynamic regulation of the end-expiratory lung volume in order to prevent EFL_T.

Table 6. Within-day variability of the forced oscillation technique (FOT)

					Measure of variability			
Study	Input signal	Participants	N	FOT index	SD_W	CV %	CR	ICC
Neild[142]	SIN	Healthy	25	Rrs_{10}		11.3		
Neild[142]	SIN	Asthma	28	Rrs_{10}		10.3		
Timmins[139]	SIN	COPD	10	Xrs_6	0.04	12.6		0.95
"	"	"	"	$Xrs_{6\ insp}$	0.01	10.3		0.94
"	"	"	"	ΔXrs	0.04	25.4		0.94
Robinson[138]	"	Healthy children	34	Xrs_6	0.01			0.88
"	"	Asthma	22	Xrs_6	0.02			0.71
Snashall[143]	SIN	Asthma	24	Zrs_{10}		4.9		
Guo[41]	PRN	Healthy	223	Rrs_{4-16}		7.6		
Janssens[24]	PRN	Inpatients	67	Rrs_{4-16}		7.9		
Elshout[144]	PRN	Asthma	30	Rrs_8		10.0		
"	"	"	"	Xrs_{4-52}		26.8		
Noord[145]	PRN	COPD/asthma	125	Rrs_6		15.2		
Watts[146]	PRN	COPD	302	Xrs_5				
Oostveen[141]	PRN&IOS	Healthy	302	Xrs_5			0.05	
Goldman[147]	IOS	Asthma	24	Xrs_5		12.1		
Shiota[46]	IOS	Healthy	299	Rrs_5		5.0		
"	IOS	Healthy	"	Xrs_5		13.3		
BELH[35]	IOS	Healthy	75	Rrs_5		10		
"	"	"	"	Xrs_5		18		
"	"	"	"	$Xrs_{5\ insp}$		19		
"	"	"	"	$Xrs_{5\ exp}$		25		
ECLIPSE[34]	IOS	COPD	425	Rrs_5		5.3		
ECLIPSE[148]	IOS	COPD	433	Xrs_5		10.3		

SIN: Sinusoidal pressure oscillations. PRN: pseudo random noise. IOS: impulse oscillations. SD_W: within-subject standard deviation (kPa·s·L¯1). CV: coefficient of variation. CR: coefficient of repeatability ($kPa \cdot s \cdot L^{-1}$). ICC: intra-class correlation coefficient. Rrs: Resistance, number indicates frequency used. Zrs: impedance, number indicates frequency used. Xrs: Reactance, number indicates frequency used. Exp: expiratory. Insp: inspiratory. ΔXrs: Xrs_{insp} - $Xrs_{exp.}$

Day-to-day variability

The day-to-day variability in lung function testing reflects circadian changes in airway resistance from testing on different times of the day, cyclical changes over time, such as the influence of sex hormones on asthma in women, [149], and in patients with COPD changes related to the disease itself and by bronchodilator treatment affecting lung function measurements. Day-to-day variability is larger than the within-day variability. For spirometric measurements in COPD patients, a change in FEV_1 has to exceed 13 % within a day, and 20 % from week-to-week to be regarded significant [140]. No formal recommendations for what is to be regarded as a significant change has been defined for FOT measurements. The day-to-day SD_W is larger than the within-day SD_W, Table 7. CV is poor for Xrs_5, Xrs_{insp}, and ΔXrs, but as mentioned above should not be used to reflect the

variability of these parameters. While the $\Delta\overline{Xrs}$ is close to zero with little variability in healthy controls, it is not a stable measurement in COPD patients, Figure 12.

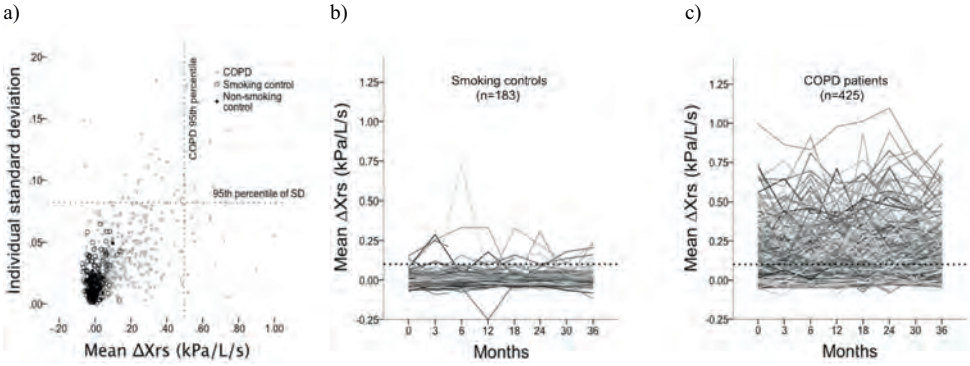

Figure 12. Within-day (a) and day-to-day (b, c) variability of ΔXrs. SD: individual standard deviation.

In COPD, ΔXrs increases during exacerbations and decreases when the exacerbation resolves, and the variability over time of this measurement reflect the variability of the disease over time [85]. While the exact value of $\Delta\overline{Xrs}$ varies over time in COPD patients with EFL_T, COPD patients with $\Delta\overline{Xrs}$ below the upper limit of normal defined by healthy subjects have relatively stable measurements over time [34, 150].

Table 7. Day-to-day variability of the forced oscillation technique (FOT)

					Measure of variability	
Study	Input signal	Participants	N	FOT index	SD_W	CV %
Timmins[139]	SIN	COPD	10	Xrs_6	0.06	24.4
"	"	"	"	$Xrs_{6\ insp}$	0.03	22.0
"	"	"	"	ΔXrs	0.07	87.1
Robinson[138]	"	Healthy children	34	Xrs_6	0.02	
"	"	Asthma	22	Xrs_6	0.02	

Abbreviations as in Table 6.

Inter-subject variability

Zrs measurements are not normally distributed. For this reason the variability of these measurements are commonly reported in interquartile range. In the

ECLIPSE/BCCS the 95th or the 5th percentiles were reported. When large inter-individual variability is found, only extreme values indicate pathology. For this reason between-session changes within one individual are usually more valuable than any single measurement compared against a reference value.

5.3.4 Associations of EFL_T with clinical endpoints

Expiratory flow limitation is not common in healthy subject, neither at rest, nor during heavy exercise [35, 72]. In COPD patients on the other hand, EFL_T is frequently found. While it is more common in COPD patients with severe airway obstruction, it is also found in patients with only moderate airway obstruction [68].

EFL_T is functionally relevant as it promotes dynamic hyperinflation and increases the positive end-expiratory pressure (PEEP), potentially reducing cardiac output [83, 151]. During hyperinflation the work of breathing increases at the same time as the diaphragm and other inspiratory muscles have to work at a less efficient part of their force-length relationship [81].

Although many factors contribute to the level of physical activity, exertional dyspnea caused by expiratory flow limitation is a major factor in patients with COPD [152]. During expiration, there may not be sufficient time for lung emptying, leading to a higher end expiratory lung volume. The resulting air-trapping during activity when ventilatory demands are increased, leads to dynamic hyperinflation, which strongly correlates with exertional dyspnea [152]. Exertional breathlessness increases when inspiratory muscle activity increases, and COPD patients with the lowest ventilatory reserve report the most exertional breathlessness for a given activity [153]. Characterizing breathlessness with the MMRC in COPD patients, EFL_T detected with NEP technique correlates better with dyspnoea than spirometry [68, 69], and with FOT, $\Delta\overline{Xrs}$ values far below

the established threshold of EFL_T, are similar to FEV_1 in its ability to identify breathlessness.

Gas exchange abnormalities with a lower diffusion capacity for carbon monoxide have been found in COPD patients with EFL_T in supine position [154]. Orthopnoea in obese subjects may partly be explained by EFL_T. Lying flat, obese subjects breathe at lower lung volumes, reducing the expiratory reserve volume. In morbidly obese, BMI >40 kg/m^2, EFL_T is frequently found as they are breathing close to the residual volume [155]. In obese subjects in contrast to COPD patients, EFL_T is a positional phenomenon and seldom observed in a sitting position [155].

In the ECLIPSE/BCCS study COPD patients with EFL_T declined significantly in 6MWD while COPD patients with normal $\Delta\overline{Xrs}$ did not. A third group with borderline $\Delta\overline{Xrs}$ measurements, defined as above the upper limit of normal, but below the threshold of EFL_T also declined significantly. We interpret these borderline measurements as showing evidence of EFL_T by containing a mixture of normal and flow-limited breaths. Physical activity is considerably reduced in patients with chronic obstructive pulmonary disease (COPD) and may lead to a downward spiral of deconditioning, Figure 13 [156].

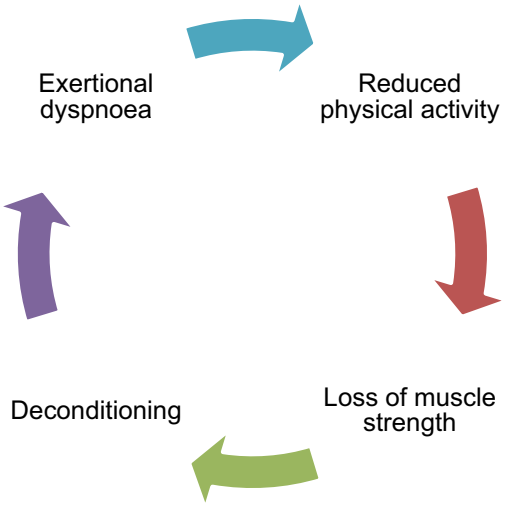

Figure 13. Downward spiral of deconditioning caused by tidal expiratory flow limitation with concomitant dynamic hyperinflation and exertional dyspnoea.

The detrimental effect of inactivity is well described. Inactivity is not only associated with muscle wasting and a poorer quality of life [157], in COPD low levels of physical activity increases the risk of hospitalizations, readmissions, and even mortality [158, 159].

EFL_T is prevalent during acute exacerbations of COPD. As exacerbations resolves, ΔXrs has been shown to decrease [85]. In the ECLIPSE study, evidence of EFL_T with $\Delta\overline{Xrs} \geq$ULN was a significant predictor for increased risk of exacerbations, and these COPD patients had a shorter time to first exacerbation and first hospitalization. COPD patients with evidence of EFL_T and a FEV_1 <50% predicted also had a significantly higher risk of dying.

5.3.5 Implications

Since our report on reference values in asymptomatic elderly, a larger study of whole-breath oscillatory mechanics have been published in adults of advanced

age which should be preferred due to larger sample size [35, 66]. However, the reference equations generated in the BELH study are presently the only normal values for partitioned within breath oscillatory indices [35].

The BELH study demonstrates that high $\Delta\overline{Xrs}$ measurements were rare in asymptomatic elderly. At the same time, a significant risk of over-diagnosing COPD in elderly never-smokers was found when the fixed 0,7 FEV_1/FVC ratio was used. 35% of these very old subjects had a lower ratio [27]. While it is acknowledged that the fixed FEV_1/FVC ratio leads to a more frequent diagnose of COPD in the elderly than using the LLN of the FEV_1/FVC ratio [160, 161], characterizing the bottom 5% of the healthy population as abnormal, the GOLD guidelines favors the fixed ratio over the LLN due to simplicity and independence of reference values [1]. In elderly characterized as having COPD by the fixed ratio where the clinical suspicion still is low, the present studies indicate that abnormal $\Delta\overline{Xrs}$ measurement should strengthen the diagnose of COPD.

Although the Milano study and the previous study by Hellinckx et al were too small to exclude existence of systemic differences in pulmonary reactance measured by different input signal waveforms, both studies found very similar Xrs measurements [37, 47]. The studies support that the threshold of EFL_T derived using sinusoidal pressure oscillations may also be used for PRN or impulse oscillations devices, and that the upper limit of normal of $\Delta\overline{Xrs}$ derived with impulse oscillations may be used for devices using sinusoidal pressure oscillations or PRN.

Most FOT parameters have good between-test reproducibility. Within-breath Xrs measurements have a higher variability in COPD patients. We interpret this to be caused by dynamic regulation of the end-expiratory lung volume in order to prevent EFL_T. When some breaths are flow-limited and others not, the ΔXrs will vary from breath to breath. The within-day variability of ΔXrs is acceptable with

an intra-class correlation coefficient of 0.94 (Table 6) [139]. The day-to-day variability is large for $\Delta\overline{Xrs}$.

Differences in symptoms and clinically relevant outcomes were found in COPD patients with baseline $\Delta\overline{Xrs}$ beyond the upper limit of normal. $\Delta\overline{Xrs}$ identifies breathlessness, defined as having a MMRC dyspnoea scale score ≥2. In addition, there were significant differences with regards to decline in 6-minute walk distance, exacerbations, and also mortality in COPD patients with $\Delta\overline{Xrs}$ ≥ULN compared with COPD patients with $\Delta\overline{Xrs}$ comparable with healthy controls. As with airway obstruction in asthma, with $\Delta\overline{Xrs}$ ≥ULN may not be present at any given evaluation of a COPD patient. Patients with EFL_T, or $\Delta\overline{Xrs}$ ≥ULN have a worse lung mechanics than is evident from spirometry measurements alone.

EFL_T have mechanical, muscular, cardiovascular, symptomatic, and prognostic consequences. With FOT, EFL_T is easily determined. The feasibility of FOT measurements makes these measurements particularly useful in COPD patients unable to perform spirometry. We suggest borderline measurements of $\Delta\overline{Xrs}$ indicating evidence of $EFL_{T,}$ may be used as marker identifying a subgroup of COPD patients with a worse prognosis.

6. Conclusions

- Healthy controls as well as elderly without respiratory complaints generally have very low $\Delta\overline{Xrs}$. FOT defined EFL_T is not common in healthy elderly.
- Impulse oscillation forcing signals overestimates Rrs_5 compared with PRN and sinusoidal pressure oscillations. Reactance measurements are similar using different devices with no systemic differences, supporting the use of the same threshold when the ULN and EFL_T are estimated using devices with different forcing signals.
- Most FOT measurements have good between-test reproducibility. The variability increases with increasing measurements. Although EFL_T may vary from breath-to-breath, variability of $\Delta\overline{Xrs}$ is acceptable when measured over multiple breaths. The day-to-day variability of $\Delta\overline{Xrs}$ is large.
- $\Delta\overline{Xrs}$ is associated with dyspnoea and clinically relevant outcomes, such as decline in the 6-minute walk test, exacerbations, hospitalizations, and death.
- We suggest that $\Delta\overline{Xrs}$ may be used as a marker to identify a subgroup of COPD patients with a worse prognosis.

7. Perspectives

The present thesis facilitates the use of FOT by supplying normal values in elderly, comparing the agreement between different forcing signals, and by examining the variability. Finally, we explored the association of $\Delta\overline{Xrs}$ with dyspnea and clinically relevant outcomes, such as decline in walking distance, exacerbations, and death. Suggestions for further research are:

- Reference values in elderly should have an expiration date. Updates are necessary to capture changes in occupational exposure to dust and noxious particles as well as different smoking habits between generations.
- Reference studies where the study population is examined by several different input forcing signals are needed if device independent reference equations are to be retrieved.
- The agreement between the $\Delta\overline{Xrs}$ and the NEP technique, has not been resolved, nor has IC maneuvers been performed in relation to the $\Delta\overline{Xrs}$ measurements.
- The clinical importance of $\Delta\overline{Xrs}$ needs further research.
    - Patients unable to perform spirometry could benefit from other means of evaluation, i.e. patients on respirators, the cognitive impaired, and children.
    - Can $\Delta\overline{Xrs}$ be used to set PEEP in ventilators, and would algorithms using $\Delta\overline{Xrs}$ have advantage over algorithms using flow? Can we use this parameter to evaluate treatment effects of bronchodilators in patients on mechanical ventilation?
    - Do patients with $\Delta\overline{Xrs}$ >ULN benefit from pulmonary rehabilitation? Can loss of walking distance in the 6MWT be prevented? Does physical exercise improve $\Delta\overline{Xrs}$ and/or the tendency of flow-limited breaths?

8. Errata

Paper I

The total number of subjects in the Phase II age-, sex-, and smoking history random subsample of the BELH study was 319. From this sample only the 208 subjects who reported to be never-smokers were called in for further testing, not 319 as stated.

Throughout the paper the measuring unit of the FOT parameters: Rrs, Xrs and ΔXrs are reported as $kPa \cdot L^{-1} \cdot s^{-1}$. The correct measuring unit is $kPa \cdot s \cdot L^{-1}$.

Paper II

Each individual part of the 6 part figure, Fig. 3 contains several graphs, a scatterplot showing the relationship between sinusoidal and impulse oscillation measurements, a Deming regression line with it's confidence intervals, and 2 dotted lines illustrating the expected biological variation derived from the 2.5 and the 97.5 percentile line derived from the 425 COPD patients in the Bergen Cohort of the ECLIPSE study.

The dotted lines representing the 2.5 and the 97.5 percentile lines have been misplaced and are too narrow in figure 3d-f. The correct position of the percentiles lines is shown in e-Fig. 1.

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Appendix

Protocol Identifier	Subject Identifier		Visit Description
SCO104960			Visit 1

ST GEORGE'S LUNGE SKJEMA FOR PASIENTER MED KRONISK OBSTRUKTIV LUNGESYKDOM (SGRQ-C)

Dette spørreskjemaet skal hjelpe oss å finne ut mer om hvordan dine luftveisproblemer påvirker deg og livet ditt. Vi bruker skjemaet til å finne ut hvilke sider ved sykdommen din som gir deg mest problemer, snarere enn hva leger og sykepleiere tror er ditt problem.

Vennligst les spørsmålene grundig. Spør hvis det er noe du ikke forstår.
Ikke bruk for lang tid til å tenke over hva du skal svare.

Før du fyller ut resten av spørreskjemaet,

ber vi deg sette kryss i den ruta som best beskriver din nåværende helse:

Meget bra	Bra	Ganske bra	Dårlig	Meget dårlig
☐	☐	☐	☐	☐

Version: 1st Sept 2005

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Protocol Identifier	Subject Identifier		Visit Description
SCO104960			Visit 1

ST. GEORGE SPØRRESKJEMA OM LUFTVEISPROBLEMER DEL 1

Spørsmål om hvor mye lungeplager du har.

Sett kun ett kryss for hvert spørsmål:

	De fleste dagene i uken [1]	Flere dager i uken [2]	Bare ved luftveis-infeksjoner [4]	Ikke i det hele tatt [5]
1. Har jeg hostet:	☐	☐	☐	☐
2. Har jeg hostet opp slim:	☐	☐	☐	☐
3. Jeg er tungpusten:	☐	☐	☐	☐
4. Jeg har anfall med piping i brystet:	☐	☐	☐	☐

5. Hvor mange anfall med lungeplager hadde du i løpet av det siste året?

3 eller flere dager ☐ [1]

1 eller 2 dager ☐ [3]

Ingen perioder ☐ [5]

6. Hvor ofte har du hatt gode dager (med lite lungeplager)?

Ingen gode dager ☐ [1]

noen gode dager ☐ [?]

de fleste dage er god ☐ [4]

Hver dag er god ☐ [5]

7. Hvis du har pipelyder i brystet, er det verst om morgenen?

Nei ☐ [N]

Ja ☐ [Y]

Protocol Identifier	Subject Identifier		Visit Description
SCO104960			Visit 1

ST. GEORGE SPØRRESKJEMA OM LUFTVEISPROBLEMER DEL 2

8. Hvordan vil du beskrive din lungetilstand?

Sett ett kryss:

Forårsaker svært mange problemer eller er det viktigste problemet jeg har	☐ [1]
Det gir meg noen få problemer	☐ [3]
Det gir meg ingen problemer	☐ [4]

9. Spørsmål om hvilke aktiviteter som vanligvis gjør deg tungpusten

*For hver setning, vennligst sett kryss **i ruten** som passer best for din situasjon **nå for tiden**:*

	Riktig [T]	Galt [F]
Vaske deg eller kle på deg	☐	☐
Gå omkring hjemme	☐	☐
Spasere utendørs på flatmark	☐	☐
Gå opp en trapp, én etasje	☐	☐
Gå i motbakke	☐	☐

10. Noen flere spørsmål om din hoste og tunge pust.

*For hver setning, vennligst sett kryss **i ruten** som passer best for din situasjon **nå for tiden**:*

	Riktig [T]	Galt [F]
Det gjør vondt når jeg hoster	☐	☐
Min hoste gjør meg sliten	☐	☐
Jeg er tung i pusten når jeg snakker	☐	☐
Jeg er tung i pusten når jeg bøyer meg	☐	☐
Min hoste eller tunge pust forstyrrer søvnen min	☐	☐
Jeg blir fort utslitt	☐	☐

Protocol Identifier	Subject Identifier		Visit Description
SCO104960			Visit 1

ST. GEORGE SPØRRESKJEMA OM LUFTVEISPROBLEMER DEL 2

11. Spørsmål om annen innvirkning på deg av dine lungeplager.

*For hver setning, vennligst sett kryss **i ruten** som passer best for din situasjon **nå for tiden**:*

	Riktig [T]	Galt [F]
Min hoste eller tunge pust gjør meg pinlig berørt når jeg er ute blant folk	☐	☐
Mine luftveisproblemer sjenerer familie, venner eller naboer	☐	☐
Jeg blir redd eller får panikk når jeg får en følelse av å ikke få nok luft	☐	☐
Jeg føler at jeg ikke har kontroll over mine luftveisproblemer	☐	☐
Jeg har blitt svekket eller ufør av mine luftveisproblemer	☐	☐
Mosjon er ikke trygt for meg	☐	☐
Alt føles altfor anstrengende	☐	☐

12. Dette er spørsmål om hvordan dine gjøremål kan bli påvirket av pusten din.

*For hvert spørsmål, vennligst sett kryss **i ruten** som passer for din situasjon, **med tanke på pusten:***

	Riktig [T]	Galt [F]
Jeg bruker lang tid på å vaske meg eller kle på meg	☐	☐
Jeg kan ikke bade eller dusje, eller må bruke lang tid på det	☐	☐
Jeg går langsommere enn andre folk, eller må stanse for å hvile meg	☐	☐
Husarbeid og andre lignende gjøremål tar lang tid, eller jeg må stanse for å hvile meg	☐	☐
Hvis jeg går opp trappa en etasje, må jeg gå langsomt eller stanse	☐	☐
Hvis jeg skynder meg eller går fort, må jeg stanse eller gå saktere	☐	☐
Pusten min gjør det vanskelig for meg å gjøre ting som å gå opp bakker, bære ting opp trapper, utføre lett hagearbeid som luking, danse, bowle eller spille golf	☐	☐
Pusten min gjør det vanskelig for meg å gjøre slike ting som å bære tungt, grave i hagen, måke snø, jogge eller gå hurtig (8 km/t), spille tennis eller svømme	☐	☐

Protocol Identifier	Subject Identifier		Visit Description
SCO104960			Visit 1

ST. GEORGE SPØRRESKJEMA OM LUFTVEISPROBLEMER DEL 2

13. Vi vil gjerne vite hvordan dine luftveisproblemer vanligvis påvirker ditt daglige liv.

*For hvert spørsmål, vennligst sett kryss **i ruten** som passer for din situasjon, **med tanke på pusten:***

	Riktig [T]	Galt [F]
Jeg kan ikke drive med sport eller idrett	☐	☐
Jeg kan ikke gå ut på underholdningstilbud eller dra hjemmefra for å drive med fritidsaktiviteter	☐	☐
Jeg kan ikke gå ut for å handle	☐	☑
Jeg kan ikke gjøre husarbeid	☐	☐
Jeg kan ikke bevege meg langt vekk fra stolen eller senga	☐	☐

14. Kan du nå sette et kryss (og bare ett) for det du synes best beskriver hvorledes dine luftveisproblemer påvirker deg:

De forhindrer meg ikke fra noe av det jeg ønsker å gjøre	☐ [1]
De forhindrer meg fra en eller to ting jeg ønsker å gjøre	☐ [2]
De forhindrer meg fra mesteparten av det jeg ønsker å gjøre	☐ [3]
De forhindrer meg fra alt jeg ønsker å gjøre	☐ [4]

Takk for at du ville fylle ut dette spørreskjemaet.

Vennligst kontroller at du har besvart alle spørsmålene.

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Disse spørsmålene omhandler stort sett brystkassen din.

1. SYMPTOMER

1A. Hoster du vanligvis?

Note: Tell et tilfelle av hosting første gang du røyker eller første gang du går utendørs. Unnta kremting for å rense halsen.

*Hvis **NEI, FORTSETT** med spørsmål 1C.*

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

1B). Hoster du vanligvis så mye som fire til seks ganger om dagen, minst fire dager i uken?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

1C). Hoster du vanligvis i det hele tatt når du står opp, eller når du våkner om morgenen?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

1D). Hoster du vanligvis i det hele tatt i løpet av resten av dagen eller om natten?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

*Hvis du svarte **NEI** på **ALLE** de ovenstående (1A, 1B, 1C og 1D), skal du merke av for "Gjelder ikke" og **FORTSETTE** med spørsmål 2.A.*

[X] ☐ Gjelder ikke

*Hvis du svarte **JA** på **MINST ETT** av ovenstående (1A, 1B, 1C eller 1D), **BESVAR** følgende spørsmål:*

1E). Hoster du vanligvis som dette de fleste dagene i minst tre måneder etter hverandre i løpet av året?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

1F). I hvor mange år har du hatt denne hosten?

☐☐ År
[U] ☐ Vet ikke

2. OPPHOSTET SLIM

2A. Får du vanligvis opp slim fra brystet?

Note: Tell antall tilfeller av opphosting av slim første gang du røyker eller første gang du går utendørs. Ikke tell slim fra nesen. Tell slim som svelges.

*Hvis **NEI, FORTSETT** med spørsmål 2C.*

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

2B. Får du vanligvis opp slim på denne måten opptil to ganger om dagen minst fire dager i uken?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

2C. Får du vanligvis opp slim i det hele tatt når du står opp, eller når du våkner om morgenen?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

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2. SLIM (forts.)

2D. Får du vanligvis opp slim i det hele tatt i løpet av resten av dagen eller om natten? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **NEI** på **ALLE** de ovenstående (2A, 2B, 2C og 2D), skal du merke av for "Gjelder ikke" og **FORTSETTE** med spørsmål 3.A.* [X] ☐ Gjelder ikke

*Hvis du svarte **JA** på **MINST ETT** av ovenstående (2A, 2B, 2C eller 2D), **BESVAR** følgende spørsmål:*

2E. Får du vanligvis opp slim på denne måten de fleste dager i minst tre måneder etter hverandre i løpet av året? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

2F. I hvor mange år har du hatt problemer med opphostet slim? ☐☐ År [U] ☐ Vet ikke

2G. Har du hatt perioder eller episoder med (økt[1]) hosting og opphosting av slim som har vart i minst tre uker hvert år? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

[1] *For enkeltpersoner som vanligvis hoster og/eller hoster opp slim.*

*Hvis du svarte **NEI** på spørsmål 2G, **FORTSETT** med spørsmål 3.A.*

*Hvis du svarte **JA** på 2G, **BESVAR** følgende spørsmål:*

2H. Hvor lenge har du hatt minst én slik episode i året? ☐☐ År [U] ☐ Vet ikke

3. HVESING

3A. Hører du noen gang hvesing eller piping i brystet? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 3A, **FORTSETT med DEL 4 (brystforkjølelser og brystsykdommer)**. Hvis du svarte **JA** på 3A, **BESVAR** følgende spørsmål:*

3B. Har brystet ditt noen gang hvese- eller pipelyd... Merk av for det *beste svaret for hvert punkt:*

1. Ved forkjølelse?	[1] ☐ Aldri	[2] ☐ Av og til	[3] ☐ De fleste
2. Når du ikke er forkjølet?	[1] ☐ Aldri	[2] ☐ Av og til	[3] ☐ De fleste
3. Ved trening eller anstrengelse?	[1] ☐ Aldri	[2] ☐ Av og til	[3] ☐ De fleste
4. Ved utsettelse for pollen?	[1] ☐ Aldri	[2] ☐ Av og til	[3] ☐ De fleste
5. Etter at du har tatt aspirin?	[1] ☐ Aldri	[2] ☐ Av og til	[3] ☐ De fleste
6. Ved utsettelse for støv?	[1] ☐ Aldri	[2] ☐ Av og til	[3] ☐ De fleste
7. Ved utsettelse for dunster?	[1] ☐ Aldri	[2] ☐ Av og til	[3] ☐ De fleste
8. Ved utsettelse for spray?	[1] ☐ Aldri	[2] ☐ Av og til	[3] ☐ De fleste

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3. HVESING (forts.)

3C. Når oppstod hvesingen eller pipelydene sist? Merk av for *én:*	[1] ☐ Den siste uken [2] ☐ For en måned siden [3] ☐ For mer enn en måned siden
3D. I hvor mange år har du hatt det?	☐☐ År [U] ☐ Vet ikke
3E. Har du noen gang hatt tilfeller av hvesing hvor du har kjent deg kortpustet?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
*Hvis du svarte **NEI,** på spørsmål 3.E. **FORTSETT** med spørsmål 4.A.* *Hvis du svarte **JA** på 3.E, **BESVAR** følgende spørsmål:*	
3F. Hvor gammel var du da du hadde ditt første anfall av denne typen?	☐☐ år gammel [U] ☐ Vet ikke
3G. Har du hatt minst to slike episoder?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
3H. Har du noensinne hatt behov for medisiner eller behandling for disse tilfellene?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

4. HOSTING FRA BRYSTET OG SYKDOM I BRYSTET

4A. Hvis du blir forkjølet, er det vanligvis i brystet? *Note: "Vanligvis" betyr mer enn 50 % av tiden.*	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke [4] ☐ Blir ikke forkjølet
4B. Har du i løpet av de siste tre årene hatt sykdom i brystet som har forhindret deg fra å gå på jobb, tvunget deg til å holde deg innendørs hjemme eller gjort deg sengeliggende?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
*Hvis du svarte **NEI** på spørsmål 4.B, **FORTSETT** med spørsmål 5.A.* *Hvis du svarte **JA** på 4.B, **BESVAR** følgende spørsmål:*	
4C. Hostet du opp slim under noen av disse tilfellene av sykdom i brystet?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
4D. I løpet av de siste tre årene, hvor mange slike sykdomstilfeller med (økt) slimdanning, har du hatt som varte minst én uke?	☐☐ Antall sykdomstilfeller [U] ☐ Vet ikke

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5. TIDLIGERE SYKDOMSTILFELLER

5A. Hadde du lungeproblemer før du var 16 år gammel?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

Angi om du noensinne har hatt noen av følgende ved å svare på nedenstående spørsmål:

5.B. Bronkittilfeller?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 5.B., **FORTSETT** med spørsmål 5.C.*

*Hvis du svarte **JA** på 5.B, **BESVAR** følgende spørsmål:*

1. Ble det bekreftet av en lege?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

2. Hvor gammel var du da det skjedde første gang?

☐☐ år gammel
[U] ☐ Vet ikke

5.C. Sinusproblemer?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 5.C., **FORTSETT** med spørsmål 5.D.*

*Hvis du svarte **JA** på 5.C, **BESVAR** følgende spørsmål:*

1. Ble det bekreftet av en lege?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

2. Hvor gammel var du da det begynte?

☐☐ år gammel
[U] ☐ Vet ikke

5.D. Lungetuberkulose?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 5.D., **FORTSETT** med spørsmål 5.E.*

*Hvis du svarte **JA** på 5.D, **BESVAR** følgende spørsmål:*

1. Ble det bekreftet av en lege?

[Y] ☐ Ja [N] ☐ Nei
[U] ☐ Vet ikke

2. Hvor gammel var du da det begynte?

☐☐ år gammel
[U] ☐ Vet ikke

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5. TIDLIGERE SYKDOMSTILFELLER (forts.)

5.E.Lungebetennelse (inkludert bronkittlungebetennelse)? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 5.E., **FORTSETT** med spørsmål 5.F.*

*Hvis du svarte **JA** på 5.E, **BESVAR** følgende spørsmål:*

1. Ble det bekreftet av en lege? [Y] ☑ Ja [N] ☐ Nei [U] ☐ Vet ikke
2. Hvor gammel var du da du først hadde det? ☐☐ år gammel [U] ☐ Vet ikke

5.F.Høysnue? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 5.F., **FORTSETT** med spørsmål 5.G.*

*Hvis du svarte **JA** på 5.F, **BESVAR** følgende spørsmål:*

1. Ble det bekreftet av en lege? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
2. Hvor gammel var du da det begynte? ☐☐ år gammel [U] ☐ Vet ikke

5G.Har du noensinne hatt astma? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 5.G., **FORTSETT** med spørsmål 5.H.*

*Hvis du svarte **JA** på 5.G, **BESVAR** følgende spørsmål:*

1. Har du det fremdeles? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
2. Ble det bekreftet av en lege? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
3. Hvor gammel var du da det begynte? ☐☐ år gammel Vet ikke
4. Hvis du ikke har det lenger, hvor gammel var du da det opphørte? ☐☐ år gammel da det opphørte [U] ☐ Vet ikke

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5. TIDLIGERE SYKDOMSTILFELLER (forts.)

5. Har du noensinne vært innlagt på sykehus natten over for astma? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

6. Har du noensinne i løpet av det siste året vært innlagt på sykehus natten over? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

5.H Har du noensinne hatt noen form for sykdom i brystet? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 5.H., **FORTSETT** med spørsmål 5.I.*

*Hvis du svarte **JA** på 5.H., angi:*_ _

5.I. Har du noensinne hatt noen form for brystoperasjon? [Y] ☐ Ja [N] ☐ Nei

*Hvis du svarte **NEI** på spørsmål 5.I., **FORTSETT** med spørsmål 5.J.*

*Hvis du svarte **JA** på 5.I., angi:* _

5.J.Har du noensinne hatt noen form for skader på brystet? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 5.J., **FORTSETT** med spørsmål 5.K.*

*Hvis du svarte **JA** på 5.J., angi:* _

5.K.Har du vært innlagt på sykehus for lungeproblemer i løpet av de siste 12 månedene? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **JA,** hvor mange ganger?* ☐☐ ganger

5.L.Har du i løpet av de siste 12 månedene fått antibiotikabehandling for sykdom i brystet? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **JA,** hvor mange ganger?* ☐☐ ganger

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6. SYSSELSETTINGSHISTORIE

6A. Har du noensinne jobbet heltid (minst 30 timer i uken) i minst seks måneder? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **NEI** på spørsmål 6.A., **FORTSETT** med spørsmål 7.A.*

*Hvis du svarte **JA** på 6.A, **BESVAR** følgende spørsmål:*

6B. Har du noensinne arbeidet i minst ett år på en støvfylt arbeidsplass? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **JA** på 6.B.,*

1. Angi jobb/bransje: _ ☐☐ Samlet antall år jobbet
2. Var utsettelsen for støv? *Merk av for én:* [1] ☐ Mild [2] ☐ Moderat [3] ☐ Alvorlig

6C. Har du noensinne vært utsatt for gass eller kjemiske dunster i jobben din? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Hvis du svarte **JA** på 6.C.,*

1. Angi jobb/bransje: _ ☐☐ Samlet antall år jobbet
2. Var utsettelsen for dunster? *Merk av for én:* [1] ☐ Mild [2] ☐ Moderat [3] ☐ Alvorlig

7. RØYKING

7.A. Har du noensinne røykt **sigaretter**? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

*Note: 'Nei' betyr mindre enn 20 pakker sigaretter eller 340 g (eller 12 oz) tobakk i **hele livet** eller mindre enn én sigarett om dagen i ett år.*

*Hvis du svarte **NEI** på spørsmål 7.A., **FORTSETT** med spørsmål 7.B.*

*Hvis du svarte **JA** på 7.A, **BESVAR** følgende spørsmål:*

1. Røyker du for tiden sigaretter (per 1 måned siden)? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
2. Hvor gammel var du da du **først** begynte å røyke sigaretter? ☐☐ år gammel [U] ☐ Vet ikke

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7. RØYKING (forts.)

3. Hvis du har sluttet helt å røyke sigaretter, hvor gammel var du da du sluttet?
   - ☐☐ I hvilken alder sluttet du?
   - [U] ☐ Vet ikke

   Merk av her hvis du fremdeles røyker sigaretter ☐

4. Hvor mange sigaretter røyker du nå per dag?
   - ☐☐ sigaretter/dag
   - [U] ☐ Vet ikke

5. Når du tar i betraktning hele tiden du røykte, hvor mange sigaretter om dagen røykte du i gjennomsnitt?
   - ☐☐ sigaretter/dag
   - [U] ☐ Vet ikke

6. Inhalerer eller inhalerte du sigarettrøyken?
   - [1] ☐ Ikke i det hele tatt
   - [2] ☐ Litt
   - [3] ☐ Moderat
   - [4] ☐ Dypt

7. I løpet av tiden du røykte sigaretter, røykte du sigaretter med filter?
   - [1] ☐ Alltid
   - [2] ☐ Mer enn halvparten av tiden
   - [3] ☐ Omtrent halvparten av tiden
   - [4] ☐ Mindre enn halvparten av tiden
   - [5] ☐ Aldri

7.B.Har du røykt sigaretter i løpet av det siste døgnet?
- [Y] ☐ Ja [N] ☐ Nei
- [U] ☐ Vet ikke

7.C.Angi om foreldrene dine noensinne var sigarettrøykere...

1. Mor?
   - [Y] ☐ Ja [N] ☐ Nei
   - [U] ☐ Vet ikke

2. Far?
   - [Y] ☐ Ja [N] ☐ Nei
   - [U] ☐ Vet ikke

7.D.Har du noensinne røykt **pipe** regelmessig?
- [Y] ☐ Ja [N] ☐ Nei
- [U] ☐ Vet ikke

Note: 'Ja' betyr mer enn 340 g (eller 12 oz) tobakk i løpet av livet.

*Hvis du svarte **NEI** på spørsmål 7.D., **FORTSETT** med spørsmål 7.E.*

*Hvis du svarte **JA** på 7.D, **BESVAR** følgende spørsmål:*

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7. RØYKING (forts.)

1. Hvor gammel var du da du begynte å røyke pipe regelmessig? ☐☐ år gammel / [U] ☐ Vet ikke

2. Hvis du har sluttet helt å røyke pipe, hvor gammel var du da du sluttet? ☐☐ I hvilken alder sluttet du? / [U] ☐ Vet ikke

   Merk av her hvis du fremdeles røyker pipe ☐

3. Når du tar i betraktning hele tiden du røykte pipe, hvor mye pipetobakk i uken røykte du i gjennomsnitt? ☐☐ g/uke / [U] ☐ Vet ikke

   Note: En standard pakke med tobakk inneholder omtrent 42,5 gram (eller 1½).

4. Hvor mye pipetobakk røyker du nå? ☐☐ g/uke / [U] ☐ Vet ikke

   Merk av her hvis du fremdeles røyker pipe ☐

5. Inhalerer eller inhalerte du piperøyken?
   - [1] ☐ Ikke i det hele tatt
   - [2] ☐ Litt
   - [3] ☐ Moderat
   - [4] ☐ Dypt

7.E. Har du noensinne røykt **sigarer** regelmessig? [Y] ☐ Ja [N] ☐ Nei / [U] ☐ Vet ikke

Note: 'Ja' betyr mer enn én sigar i uken i et år.

*Hvis du svarte **NEI** på spørsmål 7.E., **FORTSETT** med spørsmål 7.F.*

*Hvis du svarte **JA** på 7.E, **BESVAR** følgende spørsmål:*

1. Hvor gammel var du da du først begynte å røyke sigarer regelmessig? ☐☐ år gammel / [U] ☐ Vet ikke

2. Hvis du har sluttet helt å røyke sigarer, hvor gammel var du da du sluttet? ☐☐ I hvilken alder sluttet du? / [U] ☐ Vet ikke

   Merk av her hvis du fremdeles røyker sigarer ☐

3. Når du tar i betraktning hele tiden du røykte sigarer, hvor mange sigarer i uken røykte du i gjennomsnitt? ☐☐ Sigarer i uken / [U] ☐ Vet ikke

4. Hvor mange sigarer i uken røyker du nå? ☐☐ Sigarer i uken / [U] ☐ Vet ikke

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7. RØYKING (forts.)

5. Inhalerer eller inhalerte du sigarrøyken?
   - [1] ☐ Ikke i det hele tatt
   - [2] ☐ Litt
   - [3] ☐ Moderat
   - [4] ☐ Dypt

7.F.Har du noensinne røykt **sigarilloer** regelmessig?
- [Y] ☐ Ja [N] ☐ Nei
- [U] ☐ Vet ikke

Note: 'Ja' betyr mer enn én sigarillo i uken i et år.

*Hvis du svarte **NEI** på spørsmål 7.F., **FORTSETT** med spørsmål 7.G.*

*Hvis du svarte **JA** på 7.F, **BESVAR** følgende spørsmål:*

1. Hvor gammel var du da du først begynte å røyke sigarilloer regelmessig?
   - ☐☐ år gammel
   - [U] ☐ Vet ikke
2. Hvis du har sluttet helt å røyke sigarilloer, hvor gammel var du da du sluttet?
   - ☐☐ I hvilken alder stanset det
   - [U] ☐ Vet ikke

   Merk av her hvis du fremdeles røyker sigarilloer ☐
3. Når du tar i betraktning hele tiden du røykte sigarilloer, hvor mange sigarilloer i uken røykte du i gjennomsnitt?
   - ☐☐ i uken
   - [U] ☐ Vet ikke
4. Hvor mange sigarilloer i uken røyker du nå?
   - ☐☐ i uken
   - [U] ☐ Vet ikke
5. Inhalerer eller inhalerte du sigarillorøyken?
   - [1] ☐ Ikke i det hele tatt
   - [2] ☐ Litt
   - [3] ☐ Moderat
   - [4] ☐ Dypt

7.G.Har du noensinne vært **utsatt for tobakksrøyk** fra andre i omgivelsene dine i løpet av de siste 24 timene?
- [Y] ☐ Ja [N] ☐ Nei
- [U] ☐ Vet ikke

Note: Ikke inkluder deg selv.

*Hvis du svarte **NEI** på spørsmål 7.G., skal du angi hvor mye tobakksrøyk du har blitt utsatt for fra andre:*

1. I løpet av de siste 24 timene?
   - [1] ☐ Ikke i det hele tatt
   - [2] ☐ Litt
   - [3] ☐ Moderat
   - [4] ☐ Kraftig

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SCO104960			Visit 1

ATS-DLD-78-A (forts.)

7. RØYKING (forts.)

2. I løpet av de siste 2 timene?	[1] ☐ Ikke i det hele tatt [2] ☐ Litt [3] ☐ Moderat [4] ☐ Kraftig
3. I løpet av den siste halvtimen?	[1] ☐ Ikke i det hele tatt [2] ☐ Litt [3] ☐ Moderat [4] ☐ Kraftig
7.H.Er det noen andre i hjemmet ditt enn deg som røyker regelmessig? *Note: Enten de bor hos deg eller ikke. Ikke inkluder deg selv.*	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
7.I. Røykte noen andre enn deg regelmessig i hjemmet ditt under oppveksten din (før du fylte 18 år)? *Note: Enten de bor hos deg eller ikke. Ikke inkluder deg selv.*	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

8. SYKEHISTORIE

Angi om en lege noensinne har fortalt deg at du hadde noen av følgende sykdommer ved å svare på følgende spørsmål:

8.A.Hjerteproblemer?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
*Hvis du svarte **NEI** på spørsmål 8.A., **FORTSETT** med spørsmål 8.B.* *Hvis du svarte **JA** på 8.A, **BESVAR** følgende spørsmål:* 1. Har du noensinne i løpet av de siste 10 årene fått behandling for hjerteproblemer.	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.B.Høyt blodtrykk (hypertensjon)?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
*Hvis du svarte **NEI** på spørsmål 8.B., **FORTSETT** med spørsmål 8.C.* *Hvis du svarte **JA** på 8.B, **BESVAR** følgende spørsmål:* 1. Har du i løpet av de siste ti årene noensinne fått behandling for høyt blodtrykk?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.C.Angina?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

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ATS-DLD-78-A (forts.)

8. SYKEHISTORIE (forts.)	
8.D.Har du noensinne hatt hjerteinfarkt / myokarditt?	[Y] ☐ Ja [N] ☐ Nei [U] ☑ Vet ikke
8.E.Slag?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.F.Hjertesvvikt?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.G.Arytmi?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.H.Osteoporose eller 'tynne' bein?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.I. Osteoartrose?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.J.Revmatisk artrose?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.K.Tarmbetennelseslidelser (Chrons sykdom, kolitt)?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.L.Sukkersyke?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
*Hvis du svarte **NEI** på spørsmål 8.L., **FORTSETT** med spørsmål 8.M.* *Hvis du svarte **JA** på 8.L, **BESVAR** følgende spørsmål:* 1. Har du type 1-sukkersyke?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
2. Har du type 2-sukkersyke?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke
8.M.Peptisk magesår?	[Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

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ATS-DLD-78-A (forts.)

8. SYKEHISTORIE (forts.)

8.N.Gastroøsofageal refluks / halsbrann? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

8.O.Depresjon som må behandles? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

8.P.Angst eller panikkanfall? [Y] ☐ Ja [N] ☐ Nei [U] ☐ Vet ikke

9. SOSIOØKONOMISK STATUS

9.A.Hva er det siste året eller graden av skolegang du har fullført?

Merk av for *bare ett av følgende alternativer:*

[1] ☐ Ingen grunnskole eller ikke fullført
[2] ☐ Fullført grunnskolen
[3] ☐ Noe videregående skole
[4] ☐ Fullført 3-årig videregående skole
[5] ☐ Teknisk fagskole / annen skolegang under høyskolenivå
[6] ☐ Universitets-/høyskolegrad
[7] ☐ Høyere grad fra universitet/høyskole

Protocol Identifier	Subject Identifier		Visit Description
SCO104960			Visit 1

MRC-DYSPNÉSKALA

*Oppgi det **ene** svaret som gjelder for deg.*

Merk av for bare én:

[0] ☐ Jeg blir bare andpusten når jeg trener hardt.

[1] ☐ Jeg blir kortpustet når jeg skynder meg på flat mark eller når jeg går opp en slakk bakke.

[2] ☐ Jeg går saktere enn folk på samme alder som meg på flat mark på grunn av andpustenhet, eller jeg må stanse opp for å ta en pust i bakken når jeg går i mitt eget tempo på flat mark.

[3] ☐ Jeg stanser for å ta en pust i bakken etter å ha gått omtrent 100 meter eller etter noen få minutter på flat mark.

[4] ☐ Jeg blir for andpusten til å gå ut av huset eller jeg blir andpusten når jeg kler av eller på meg.

NO:NOR (Norway/Norwegian)

MRC-DYSPNÉSKALA

INVESTIGATOR INSTRUCTIONS

- The MRC Dyspnea Scale is to be completed by the study subject.
- If the subject's perception is not quite Grade 2 or if the subject is somewhat unsure if their breathlessness is Grade 2, have the subject rate Grade 2.
- If the subject insists on rating less than Grade 2, even if you have no doubts that the subject should be rating at or above Grade 2, the subject's rating of less than Grade 2 must stand.

GRADERINGSBESKRIVELSER

Gradering 0	Ikke plaget unntatt under anstrengende trening (denne graden er vanlig for eldre enkeltpersoner som er I FORM).
Gradering 1	Plaget når forsøkspersonen skynder seg på flat mark eller opp en slakk bakke (denne graderingen er vanlig for de FLESTE SUNNE OG FRISKE enkeltpersoner).
Gradering 2	Går saktere enn folk i samme alder eller stanser for å ta en pust i bakken ved gange på flat mark (forsøkspersonen må stanse for å ta en pust etter å ha gått om lag halvannen kilometer eller etter å ha gått i OMTRENT 30 MINUTTER).
Gradering 3	Stanser for å ta en pust i bakken etter å ha gått omtrent 100 meter eller etter noen få minutter på flat mark.
Gradering 4	For andpusten til å gå ut av huset eller andpusten av- og påkledning.

HELSE BERGEN
Haukeland Universitetssjukehus

Visitt 1
Skjema 1
Anamnese
versjon 8

OPPFØLGING AV DELTAKERE FRA GENKOLS OG HORDALANDSSTUDIEN 2006 - 2009

A. Personalia

Subject ID nr.: _____

Visitt nr. _____ Dato for undersøkelse (dd.mm.yyyy) _____

Kjønn
❑ Mann ❑ Kvinne

Fødselsdato (dd.mm.yyyy) _____

Deltakerstatus: ❑ KOLS ❑ Røykende kontroll ❑ Ikke-røykende kontroll

Var deltaker med i GenKOLS? ❑ Ja ❑ Nei

Var deltaker med i Hordalandsstudien?
❑ Ja ❑ Nei

Hvis ja, GenKOLS id# _____

Sivilstand
❑ Gift
❑ Samboende
❑ Enke/enkemann
❑ Skilt
❑ Separert
❑ Ugift

Etnisitet
❑ Hispanic/latino ❑ Ikke hispanic/latino

Rase
❑ Hvit (kaukasisk) ❑ Svart
❑ Asiatisk ❑ Annen

Hvis annen rase, beskriv: _____

Antall søsken (ekskl. deg selv): _____

Deltakers plassering i søsken-flokken (førstefødt = 1) _____ Søsken i GenKOLS? ❑ Ja ❑ Nei

Søsken i ECLIPSE? ❑ Ja ❑ Nei Antall biologiske barn: _____

Yrke: _____

Arbeisdgiver, navn: _____ Adresse: _____

Fastlege, navn: _____ Adresse: _____

B. Sykdommer i familien

Både nåværende og tidligere sykdommer medregnes.

1. KRONISK BRONKITT

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

2. EMFYSEM

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

3. ASTMA

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

4. ATOPISK DERMATITT

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

5. HØYSNUE

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

6. LUNGEKREFT

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

7. ANNEN LUNGESYKDOM

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

Hvilke(n) lungesykdom(mer)? _____

8. ANGINA PECTORIS / KORONAR HJERTESYKDOM

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

9. ANNEN HJERTESYKDOM

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

Hvilke(n) hjertesykdom(mer)? _____

10. BEHANDLINGSTRENGENDE HØYT KOLESTEROL

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

11. BEHANDLINGSTRENGENDE HØYT BLODTRYKK

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

12. HJERNESLAG

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

13. DIABETES TYPE 1

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

14. DIABETES TYPE 2

a) Far ❑ Ja ❑ Nei ❑ Ukjent b) Mor ❑ Ja ❑ Nei ❑ Ukjent

c) Søsken ❑ Ja ❑ Nei ❑ Ukjent d) Barn ❑ Ja ❑ Nei ❑ Ukjent

Antall søsken med sykdommen _____ Antall barn med sykdommen _____

C. Egne tidligere og nåværende sykdommer

Tidligere innlagt på sykehus? ❑ Ja ❑ Nei

2. LUNGESYKDOM

Obstruktiv ❑ Nei ❑ Ja, før ❑ Ja, nå Sarkoidose ❑ Nei ❑ Ja, før ❑ Ja, nå

Lungefibrose ❑ Nei ❑ Ja, før ❑ Ja, nå Lungetuberkulose ❑ Nei ❑ Ja, før ❑ Ja, nå

Annen lungesykdom ❑ Nei ❑ Ja, før ❑ Ja, nå

Hvilken lungesykdom? _____

3. KOLS

Hvis deltaker har KOLS:

Årstall for sykdomsdebut KOLS _____ Antall eksaserbasjoner siste 12 mnd. _____

For eksaserbasjon 1, registrer:

Fra dato _____ til _____

Antibiotika: ❑ Nei ❑ Ja

Prednisolon/medrol: ❑ Nei ❑ Ja

Sykehusinnleggelse: ❑ Nei ❑ Ja

For eksaserbasjon 2, registrer:

Fra dato _____ til _____

Antibiotika: ❑ Nei ❑ Ja

Prednisolon/medrol: ❑ Nei ❑ Ja

Sykehusinnleggelse: ❑ Nei ❑ Ja

For eksaserbasjon 3, registrer:

Fra dato _____ til _____

Antibiotika: ❑ Nei ❑ Ja

Prednisolon/medrol: ❑ Nei ❑ Ja

Sykehusinnleggelse: ❑ Nei ❑ Ja

For eksaserbasjon 4, registrer:

Fra dato _____ til _____

Antibiotika: ❑ Nei ❑ Ja

Prednisolon/medrol: ❑ Nei ❑ Ja

Sykehusinnleggelse: ❑ Nei ❑ Ja

For eksaserbasjon 5, registrer:

Fra dato _____ til _____

Antibiotika: ❑ Nei ❑ Ja

Prednisolon/medrol: ❑ Nei ❑ Ja

Sykehusinnleggelse: ❑ Nei ❑ Ja

4. HJERTESYKDOM

Angina pectoris/koronar ❑ Nei ❑ Ja Hjertesvikt ❑ Nei ❑ Ja

Rytmeforstyrrelse ❑ Nei ❑ Ja, før ❑ Ja, nå Hypertensjon ❑ Nei ❑ Ja, før ❑ Ja, nå

Hjerneslag ❑ Nei ❑ Ja

5. KREFT

Lunge ❑ Nei ❑ Ja, før ❑ Ja, nå Tarm ❑ Nei ❑ Ja, før ❑ Ja, nå

Bryst ❑ Nei ❑ Ja, før ❑ Ja, nå Prostata ❑ Nei ❑ Ja, før ❑ Ja, nå

Annen kreftsykdom ❑ Nei ❑ Ja, før ❑ Ja, nå

Hvilken kreftsykdom? _____

6. DIABETES

Diabetes type 1 ❑ Nei ❑ Ja Diabetes type 2 ❑ Nei ❑ Ja

7. OBSTRUKTIVT SØVN APNOE SYNDROM

OSAS ❑ Nei ❑ Ja, før ❑ Ja, nå

8. ALLERGIER

Atopisk dermatitt ❑ Nei ❑ Ja, før ❑ Ja, nå Høysnue ❑ Nei ❑ Ja, før ❑ Ja, nå

Matallergi ❑ Nei ❑ Ja, før ❑ Ja, nå Medikamentallergi ❑ Nei ❑ Ja, før ❑ Ja, nå

Hvilke(t) medikament(er)? _____

Tidligere anafylaksi ❑ Nei ❑ Ja

9. HYPEREOSINOFILT SYNDROM

Hypereosinofilt syndrom ❑ Nei ❑ Ja, før ❑ Ja, nå

10. PSORIASIS

Psoriasis ❑ Nei ❑ Ja

11. ORGANSVIKT

Nyresvikt ❑ Nei ❑ Ja Leversvikt ❑ Nei ❑ Ja

Skade / traume / forgiftning ❑ Nei ❑ Ja, før ❑ Ja, nå

Hva / hvilken? _____

12. BEHANDLINGSTRENGENDE PSYKISK LIDELSE

Depresjon ❑ Nei ❑ Ja, før ❑ Ja, nå Psykose ❑ Nei ❑ Ja, før ❑ Ja, nå

13. HEMATOLOGISK SYKDOM

DVT ❑ Nei ❑ Ja, før ❑ Ja, nå Lungeemboli ❑ Nei ❑ Ja, før ❑ Ja, nå

14. ANNEN SYKDOM

Annen sykdom ❑ Nei ❑ Ja, før ❑ Ja, nå

Hvilken annen sykdom? _____

D. Bruk av faste medikamenter

Bruker medisiner fast ❑ Nei ❑ Ja

Har sluttet tidligere med medikamenter på grunn av bivirkninger ❑ Nei ❑ Ja

I tilfelle ja, hvilke? _____

Har tatt influensavaksine sist sesong ❑ Nei ❑ Ja

Bruker følgende medikamenter fast:

1. Navn _____ Dosering: _____ Start år: _____
2. Navn _____ Dosering: _____ Start år: _____
3. Navn _____ Dosering: _____ Start år: _____
4. Navn _____ Dosering: _____ Start år: _____
5. Navn _____ Dosering: _____ Start år: _____
6. Navn _____ Dosering: _____ Start år: _____

7. Navn _____ Dosering: _____ Start år: _____

8. Navn _____ Dosering: _____ Start år: _____

9. Navn _____ Dosering: _____ Start år: _____

10. Navn _____ Dosering: _____ Start år: _____

E. Røykevaner

Røyker du for tiden?

❑ Nei, har aldri røykt ❑ Nei, men røykte før

❑ Ja, daglig ❑ Ja, av og til

Aldri røykt defineres som mindre enn en sigarett daglig i ett år

Startet å røyke

Dag Måned År

____ ____ _____

Sluttet å røyke

Dag Måned År

____ ____ _____

Hvis ikke deltaker vet dag/mnd for start og/eller slutt, la det stå åpent, men prøv å tvinge frem et årstall - eventuelt hjelp til med å regne ut fra alder på start- og/eller slutt-tidspunkt

Har du hatt perioder der du ikke har røykt? I så fall, hvor mange røykfrie år utgjør disse periodene til sammen? _____

Hvis du røyker eller har røykt daglig, røyker/røykte du sigaretter daglig?

❑ Ja, fabrikkfremstilte ❑ Ja, håndrullede ❑ Nei, ikke sigaretter

Hvis du røyker/røykte fabrikkfremstilte sigaretter: hvor mange sigaretter røyker/røykte du daglig? _____

Hvis du røyker/røykte håndrullede sigaretter: hvor mange pakker (50 g) tobakk røyker/røykte du pr. uke? (husk å punsje med 1 desimal, slik at f. eks 3 pakker punsjes 3,0) _____

Bruker snus:

❑ Nei ❑ Ja, før ❑ Ja, nå

Bruker nikotin substitusjon:

❑ Nei ❑ Ja, før ❑ Ja, nå

F. Status presens

Klokkeslett _____ Puls _____

Systolisk BT _____ Diastolisk BT _____

Respirasjonsfrekvens (pr. min.) _____

Bruker pasienten kontinuerlig oksygen? ❑ Ja ❑ Nei

Hvis ja, oksygentilførsel siste 30 minutter før prøvetaking (l/min): _____

O2 metning _____

pH _____ pCO2 _____

pO2 _____ HCO3 _____

aBE _____

Høyde (m) _____ Vekt (kg) _____

Auskultasjon Cor.:

Bilyd ❑ Nei ❑ Ja

Hvis ja:

❑ Systolisk grad 2 ❑ Systolisk grad 3 ❑ Systolisk grad 4 ❑ Diastolisk

Auskultasjon pulm.:

Pipelyder ❑ Nei ❑ Ja Knatrelyder ❑ Nei ❑ Ja

Hvis knatrelyder, lokalisering av disse (kryss alle som gjelder):

Høyre	*Venstre*
❑ Apikalt	❑ Apikalt
❑ Midtfelt	❑ Midtfelt
❑ Basalt	❑ Basalt

Ankelhevelse? ❑ Nei ❑ Ja

Tatt nasopharynx prøve til Virus Ag påvisning? ❑ Nei ❑ Ja

CO (ppm) _____ CO (%) _____

Lege (4kode): _____ Punchet av: _____

Slutt

I

The Clinical Respiratory Journal ORIGINAL ARTICLE

Reference values for within-breath pulmonary impedance parameters in asymptomatic elderly

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2 Glittreklinikken, Hakadal, Norway
3 Institute of Medicine, University of Bergen, Bergen, Norway

Abstract

Introduction: A new application for the forced oscillation technique (FOT) has been described by Dellaca *et al.* using sinusoidal pressure variations at 5 Hz to detect expiratory flow limitation by measuring the within-breath reactance [termed difference between inspiratory and expiratory X5 (DX5)]. Few studies have been performed on respiratory phase differences in the elderly.

Objective: Our aim was to present reference values for within-breath impedance measurements and to examine how the earlier mentioned method performs in a study population of asymptomatic elderly.

Methods: An age- and sex-stratified random sample was drawn from the elderly population of Bergen, Norway. Among the healthy non-smoking responders from a postal questionnaire study, 148 were selected to perform FOT measurements using an impulse oscillometry system (IOS). Seventy five of these participants had a normal spirometry and were able to perform at least two valid FOT measurements. Predictive equations for men and women were created for FOT parameters by linear multiple regression analysis. DX5 was calculated from the within-breath variation of reactance at 5 Hz.

Results/Conclusion: This study presents reference values for whole-breath and within-breath impedance parameters in asymptomatic elderly aged >70 years using the IOS method. We found higher resistance measurements than what is reported in previous studies and significantly larger frequency dependence.

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Key words
elderly – oscillometry – reference values – reproducibility – respiratory function test

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Authorship and contributorship
Bernt B. Aarli analyzed the data and wrote the paper. Tomas M.L. Eagan helped with analysis and writing of the paper. Ivar Ellingsen and Per S. Bakke designed the study. Jon A. Hardie designed the study, analyzed the data and helped in writing the paper.

Ethics
Informed written consent was given from all test subjects prior to their inclusion in the study. The study was reviewed and approved by the Western Norway regional committee on medical research ethics.

Conflicts of interests
The authors have stated explicitly that there are no conflicts of interest in connection with the article.

The forced oscillation technique (FOT) allows us to measure airway mechanics, including resistance and reactance, non-invasively during normal tidal breathing. In contrast with most other pulmonary function tests (PFTs), the FOT does not use the respiratory muscles as the source of force but instead superimposes flow oscillations to spontaneous breathing by the means of an external loudspeaker (1, 2). The advantages of this technique are that it does not require complex panting maneuvers, it is less subject-

Table 1. Different methods of the forced oscillation technique

Method	Frequency	Applied pressure	Signal	Advantage of technique
Monofrequent	Single	Continuous	Sinusoidal	Simple calculation
Pseudorandom	Multiple	Continuous	Generated signal	Yields more information
Impulse oscillometry system	Multiple	Short impulses	Squared electrical signal	Better time resolution

dependent and it can be applied to patients who for various reasons are unable to cooperate during forced spirometry or plethysmography. In the elderly, it has been found to have a higher feasibility rate than spirometry, especially in the presence of cognitive impairment, and it provides us with information about lung mechanics that cannot be obtained using spirometry alone (3, 4). Consequently, FOT could provide a valuable tool for evaluation of subjects unable to perform other PFT. Recently, several studies have focused on within-breath FOT variation. In chronic obstructive pulmonary disease (COPD) patients, a significant difference has been observed between inspiratory and expiratory reactance (5, 6). This is not present in asthmatics or healthy subjects during normal tidal breathing but manifests at closing volume if end-expiratory reactance is measured during slow vital capacity maneuvers (7). These within-breath reactance differences are believed to be caused by choke points of collapsing airways in expiration. As a further application of this phenomenon, Dellaca *et al.* have demonstrated that it is possible to accurately detect expiratory flow limitation (EFL) by measuring the within-breath difference of reactance using sinusoidal pressure variations at 5 Hz in COPD patients (2, 8, 9). Few studies have been performed on within-breath FOT measurements (i.e. inspiration vs expiration), and normal values for these parameters are yet to be established.

In 2003, the European Respiratory Society (ERS) published recommendations for FOT measurements in a task force report where reference studies on adults are summarized (10). Guo *et al.* later published the first FOT reference values for older subjects (11). These recommendations and reference values were based on the pseudorandom noise (PRN) method of FOT. The impulse oscillometry system (IOS) applies short FOT pressure pulses rather than continuous PRN. The technique has a better time resolution than PRN, which is particularly useful when analyzing intrabreath variation of airway impedance (1). However, the IOS may render higher measures of resistance than PRN FOT at lower frequencies, as shown in the comparison study performed by Hellinckx *et al.* (12). Hellinckx *et al.* suggested that the IOS overestimated the true resistance in low frequencies, but this has not been confirmed by later studies. In the meantime, reference values established for the IOS method of FOT are needed as the IOS system is currently used in clinical research and practice at many centers. Table 1 summarizes a comparison of different FOT techniques.

We have performed FOT measurements using the IOS. The aim of our study was to present reference values for average and within-breath measurements for pulmonary impedance measurements in asymptomatic elderly subjects aged >70 years.

Materials and Methods

Study design

In 1998/1999, a postal questionnaire study was performed on the elderly population in the city of Bergen, Norway, population approximately 209 000 at the time (13–17). An age- and sex-stratified random sample was drawn from all subjects aged above 69 years ($n = 25\,997$). The total initial sample was 2871 persons, of which 1649 responded. The response rate fell considerably with increasing age and was lower among subjects living in nursing home than among those living at home (14). The questionnaire concerned respiratory health and was based on the American Thoracic Society (ATS)/Division of Lung Disease (DLD) respiratory questionnaire (18). An age- and sex-stratified sample of 319 subjects was drawn from the healthy responders to undergo PFTs and blood gas analyses. Exclusion criteria were chronic or current acute respiratory disease, ATS/DLD dyspnea grade 4 (after walking 100 m on level ground), heart disease or hypertension if complicated by ATS/DLD dyspnea grade 3 (ever having to stop because of breathlessness on the level), or current-smoker status. Ex-smokers were included, and their smoking history was noted. Never-smokers were defined as those who had smoked less than 20 packs/lifetime or less than 1 cigarette/day for 1 year. PFTs were performed in the department. Out of the 161 participants who showed up at the test site to perform PFTs, 148 test subjects performed IOS measurements. Spirometry and blood gas sampling

was also performed, and the results have been published previously (16, 17).

Measurements

The FOT measurements were performed on a Masterscreen IOS (version 4.5; Erich Jaeger Gmbh, Würzburg, Germany). Each patient performed 2–5 measurements while seated and wearing a nose clip. Each measurement lasted 30 s of resting tidal breathing. A cylindrical cardboard mouthpiece was used with the subject firmly supporting their cheeks with their hands. The IOS pneumotachometer was calibrated with a 2-L syringe, and in addition, quality control was performed against a reference impedance of 0.2 kPa/L/s at the beginning of each day and after 4 h of use. The 148 test subjects performed a total of 334 individual FOT measurements. Only one test subject was unable to perform the test because of an anxiety attack. Two test subjects had to be excluded due to incomplete data. The measurement acceptance criteria proposed by the ERS task force in 2003 states that tests are to be discarded if there is sign of swallowing, glottis closure, leak around the mouthpiece, improper seal with the noseclip, irregular breathing or hyperventilation (10). The primary data were reviewed, and individual measurements were excluded if there were signs of leakage on the volume graph, downward drift for inspiratory leaks and upward drift for expiratory leaks ($n = 4$), if the patient hyperventilated as defined as breathing faster than 25 breaths per minute ($n = 20$) and if there were large spikes on the impedance 5 Hz tracing (Z5) believed to be caused by glottis movement or swallowing ($n = 24$). Only measurements from subjects with at least two technically valid tests were included. Altogether, 117 test subjects performed at least two FOT measurements that met the acceptance criteria.

Spirometry

Spirometry was performed with a Vitalograph dry wedge bellows. The spirometer was calibrated at the beginning of each day using a 1-L syringe with repeated strokes up to 9 L. Measurements were performed and reported according to ATS guidelines. Difficulties in test cooperation resulted in only 119 of the total original 161 participants having completed spirometric tests by ATS criteria. The most common reasons for not being able to perform spirometry were coughing within the first second, too early termination, leakage and not being able to follow instructions. The participants with valid spirometry measurements were not identical with those who were able to perform FOT measurements on the IOS. Of the 117 participants with acceptable FOT measurements, 95 had acceptable spirometric measurements (19). We excluded test subjects with pathology in the spirometry results, defined as having a forced expiratory volume in 1 s (FEV1) or forced vital capacity (FVC) of less than 80% of predicted or having a FEV1/FVC ratio less than the 5 percentile (16). Altogether, 75 subjects had both a normal and acceptable spirometry and acceptable FOT measurements by these criteria.

Statistical analysis

Statistical Package for Social Sciences (SPSS) software version 18.0 (SPSS Inc., Chicago, IL, USA) was used for data management and analysis. The impedance parameters did not have a normal distribution but were sufficiently normalized using natural log transformation. Parameter mean was back-transformed from geometric mean, while the 95th percentile [or 5th percentile in the case of reactance at 5 Hz (X5)] was established empirically and reported for whole-breath, inspiratory and expiratory values for resistance at 5 Hz (R5), resistance at 20 Hz (R20), X5, resonant frequency (*f*res) and area of reactance (AX), the area between the reactance zero axis, and the negative values of reactance at all frequencies from 5 Hz to the *f*res. Thus, the AX is an integration of the *f*res and the frequency dependency of the reactance. In effect, it functions to amplify the signal of reactance at lower frequencies. The within-breath X5 difference was estimated as mean inspiratory X5 − mean expiratory X5 = difference between inspiratory and expiratory X5 (DX5). Repeatability of the parameters was calculated from the raw data and is reported as mean individual coefficient of variation (CV). On the transformed data, multiple linear regression was performed using the enter method where dependent variables for the impedance data were entered separately along with the independent variables of height and weight. Predictive equations were generated for men and women for the mean of all whole-breath FOT parameters, as well as separately for the mean of all inspiratory and expiratory measurements (Table 2). To estimate the upper and lower limits of normal, the standard deviation (SD) of residuals was calculated as SD (actual value − predicted value) = residual SD (RSD). As we are only interested in pathology resulting in high resistances, AX or *f*res, the upper limit of normal can thus be estimated as predicted + 1.65 × RSD. Conversely, for X5, where we are interested in pathology resulting in low X5, the lower limit of normal can be estimated as predicted − 1.65 RSD. Wilcoxon–Mann–Whitney test was

Table 2. Predictive equations for impedance parameters in asymptomatic elderly

Men	*n* = 40	R^2	RSD	Women	*n* = 35	R^2	RSD
Ln R5	3.02 – 0.023H	0.19	0.056	Ln R5	2.68 – 0.026H + 0.012W	0.30	0.047
Insp	2.37 – 0.020H	0.17	0.043	Insp	2.49 – 0.025H + 0.011W	0.29	0.039
Exp	3.62 – 0.026H	0.17	0.080	Exp	2.75 – 0.026H + 0.013W	0.26	0.069
Ln R20	1.52 – 0.016H	0.12	0.041	Ln R20	1.26 – 0.017H + 0.009W	0.25	0.031
Insp	1.43 – 0.016H	0.14	0.034	Insp	0.96 – 0.015H + 0.007W	0.18	0.027
Exp	1.42 – 0.015H	0.09	0.049	Exp	1.49 – 0.019H + 0.010W	0.27	0.035
Ln (–X5)	3.57 – 0.033H	0.19	0.023	Ln (–X5)	3.85 – 0.041H + 0.014W	0.31	0.027
Insp	1.64 – 0.022H	0.13	0.026	Insp	4.23 – 0.043H + 0.013W	0.45	0.024
Exp	5.91 – 0.047H	0.20	0.034	Exp	1.12 – 0.019H*	0.03	0.043
Ln AX	12.0 – 0.074H	0.22	0.19	Ln AX	10.8 – 0.074H	0.21	0.46
Insp	8.4 – 0.054H	0.21	0.15	Insp	10.7 – 0.069H	0.32	0.37
Exp	15.1 – 0.030H	0.20	0.33	Exp	9.06 – 0.059H*	0.08	0.77
Ln fres	6.72 – 0.023H	0.18	1.8	Ln fres	7.12 – 0.027H	0.22	2.4
Insp	6.50 – 0.022H	0.22	1.5	Insp	7.08 – 0.027H	0.29	1.9
Exp	7.35 – 0.026H	0.16	2.2	Exp	6.71 – 0.024H	0.13	2.6

Impedance parameters were normalized for computation of multivariate linear regression. Antilog of the result of the equations will give individual's predicted value. The 95th percentile for R5, R20, AX and fres can thus be calculated by adding, and the 5th percentile for X5 by subtracting 1.65 × RSD to the predicted value.

*Not significant contribution of height to equation, $P > 0.05$.

Ln, natural log; insp, ln of the inspiratory value; exp, ln of the expiratory value; H, height (cm); W, weight (kg); RSD, residual standard deviation; R2, variability; AX, area of reactance; R5, resistance at 5 Hz; R20, resistance at 20 Hz; X5, reactance at 5 Hz; fres, resonant frequency.

performed to examine group differences between men/women and smokers/ex-smokers.

Results

The 75 subjects in the study ranged from 70 to 98 years of age, with a mean age of 79 (Table 3). There were 11 male ex-smokers (28%) with an average estimated smoking burden of 20 pack years (20 cigarettes/day/year) and 16 female ex-smokers (46%) with an average of 4 pack years. In women, mean FEV1 was 1.88 L, mean FVC was 2.56 L, and mean FEV1/FVC ratio was <73.4%. For men, mean FEV1 was 2.82 L, mean was FVC 3.89, and mean FEV1/FVC ratio was <72.4% (Table 3). The subjects who failed to produce acceptable measurements were similar in age, height and weight, and there was no sex difference. They had a nonsignificant higher smoking burden and poorer spirometry results (data not shown).

FOT

Table 4 summarizes the impedance measurements in men and women. In women, resistance measures were higher, and reactance measures lower than in men. For the other parameters, we did not find significant differences between the sexes. The mean was not affected by smoking history. As a measure of repeatability, we have listed the mean individual CV for the different parameters. Acceptable CVs according to the ERS task force, ranging 5%–15%, were found for R5, R20 and *f*res, while the CV was poorer for X5 and AX (10). As shown in Fig. 1, the variation shows some dependency on the magnitude of the measurements. Repeatability was poorer with higher resistance measurements and

Table 3. Anthropometric data and pulmonary function tests

	Men	Women
Subject (*n*)	40	35
Age (years)	79.4 ± 6.9	78.8 ± 6.3
70–74	11	12
75–79	13	8
80–84	6	9
85+	10	6
Height (cm)	173 ± 6	159 ± 6
Weight (kg)	76.4 ± 12.7	65.5 ± 10.8
BMI (kg/m^2)	25.3 ± 3.5	25.9 ± 3.9
Spirometry		
FEV1 (L)	2.82 ± 0.62	1.88 ± 0.48
FEV1 % predicted*	102	110
FVC (L)	3.89 ± 0.77	2.56 ± 0.65
FEV1/FVC (%)	72.4 ± 5.6	73.4 ± 6.4
Ex-smokers	11(28%)	16(46%)
Pack years	20	4

Data presented as mean ± standard deviation.

*Reference values by Hardie *et al*. (16).

BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 4. Impulse oscillometry system measurements

Parameter	Men $n = 40$	Women $n = 35$	CV (%) $n = 75$
R5 (kPa/L/s)	0.37 (.65)	0.50 (0.85)	10
Inspiration	0.33 (0.60)	0.45 (0.73)	10
Expiration	0.40 (0.78)	0.55 (0.96)	13
R20 (kPa/L/s)	0.29 (0.56)	0.39 (0.59)	11
Inspiration	0.27 (0.50)	0.36 (0.53)	10
Expiration	0.31 (0.59)	0.42 (0.63)	12
X5 (kPa/L/s)	–0.11 (–0.28)	–0.17 (–0.31)	18
Inspiration	–0.12 (–0.19)	–0.18 (–0.30)	19
Expiration	–0.11 (–0.45)	–0.15 (–0.39)	25
DX5 (kPa/L/s)*	0.02 (0.26)	0.00 (0.24)	
AX (kPa/L)	0.45 (1.96)	0.80 (3.04)	26
Inspiration	0.41 (1.11)	0.75 (2.66)	23
Expiration	0.48 (4.35)	0.78 (4.47)	34
fres (Hz)	15.3 (26.4)	17.0 (28.6)	10
Inspiration	14.5 (24.9)	16.2 (28.0)	9
Expiration	15.8 (28.3)	17.5 (32.0)	13

Values presented as mean derived from back-transformation of the geometric mean (95th percentile of the residual).
*DX5 is derived from the raw data.
CV, mean individual coefficient of variation, DX5, difference between inspiratory and expiratory X5; AX, area of reactance; R5, resistance at 5 Hz; R20, resistance at 20 Hz; X5, reactance at 5 Hz; fres, resonant frequency.

lower reactance. Repeatability was very similar for R5 and R20. There was evidence of frequency dependence, as mean R5 was approximately 0.08–0.11 kPa/L/min higher than mean R20.

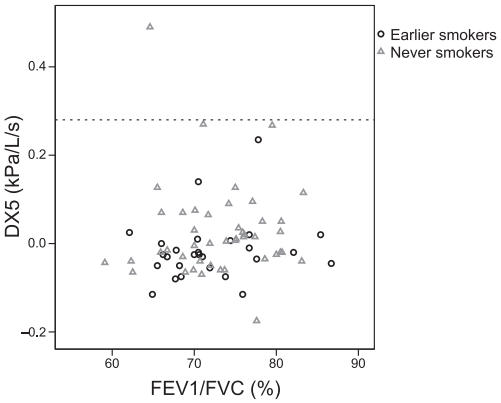

Fig. 2. The difference between reactance at 5 Hz (X5) inspiration and X5 expiration (DX5) compared with the forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC). The reference line is set at 0.28 kPa/L/s.

DX5 is presented in Table 4 and as a function of the FEV1/FVC ratio in Fig. 2. The mean difference was close to zero for both men and women. The mean for ex-smokers and never-smokers was 0.02 and 0.03, respectively. Only one subject had a DX5 over 0.28 kPa/L/s, which has been established as the threshold representing EFL (Fig. 2) (2, 8, 9). No obvious association was found between DX5 and FEV1/FVC. Predictive equations for the impedance parameters

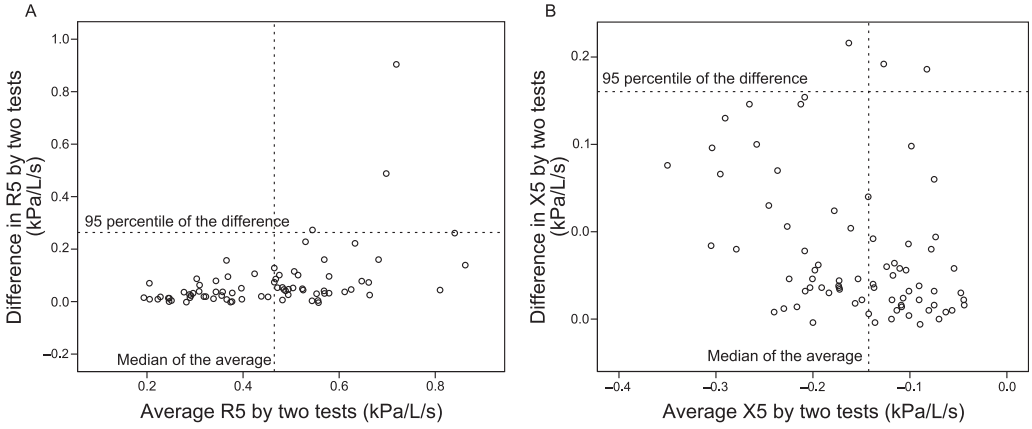

Fig. 1. (A) The difference between two resistance at 5 Hz (R5) measurements drawn against the average of the two tests demonstrating increasing variation at higher resistance measurements. (B) The difference between two reactance at 5 Hz (X5) measurements drawn against average showing increasing variation at lower reactance measurements.

were generated for men and women, and are listed in Table 2. Height was the best predictor for all respiratory impedance parameters. For X5 expiration and AX expiration in women, the contribution of height to the reported equation was found insignificant ($P > 0.05$). Weight only significantly improved the multivariate linear regression in women for the resistance parameters as well as whole-breath and inspiratory X5 ($P < 0.05$). Contribution of age was negligible.

Discussion

We present predictive equations separated by sex for whole-breath and within-breath impedance parameters in asymptomatic elderly based on height and weight. We found considerable frequency dependence, with a significantly higher R5 than R20. The mean DX5 in this reference sample was close to zero, and only one subject showed evidence of flow limitation.

For comparison, Table 5 demonstrates the resistance values according to this study compared with three previous studies. The Viasys health-care equations are the normal values supplied by the IOS software. The study population for these equations did not include elderly >70 years, and values reported by the software are extrapolated from predictive equations for younger age groups (20). The study by Guo *et al.* is the only other study presenting reference values for FOT in the elderly (11). Our study yields higher resistance values than what was found by Guo *et al.*, which excluded smokers and test subjects with less than super-normal spirometry. Mean FEV1 in the study was 104% of predicted for men and 111% of predicted for women, and for FEV1/FVC ratio, 114% and 108% of predicted, respectively. This would seemingly select a subgroup of elderly with superior lung function. In our sample, we had a large number of ex-smokers; some of them with a considerable smoking history. Because the IOS did not clearly separate the never-smokers from the ex-smokers, we have kept all in the sample. Previous studies on the same study population also failed to show any significant effect of previous smoking history on arterial blood gasses and only a small effect on FEV1 (17). Retaining the ex-smokers in the reference sample was based on a desire to avoid a super-healthy selection bias specifically in the elderly where almost all men (and a significant proportion of the women) have smoked sometime during their lifetime. We believe that reference values should depict realistic expectations representative for the generally healthy population.

Table 5. Resistance value according to predictive equations from this study and three previous studies

Reference	Men	*n*	Women	*n*
	R5		R5	
Present study	0.37	40	0.51	35
Viasys health care	0.32	298	0.43	208
	Rm		Rm	
Guo *et al*	0.22	77	0.28	146
Pasker *et al*	0.24	137	0.30	140

Values are in kPa/L/s, and are those given for men: height 174 cm, weight 77 kg, age 80 years; and for women: height 160 cm, weight 67 kg, age 80 years.
Rm, mean resistance; R5, resistance at 5 Hz.

Pasker *et al.* is the largest FOT reference value study performed among adults and elderly but contains few elderly over 70 years (21). Both Pasker *et al.* and Guo *et al.* performed FOT measurements using PRN FOT, while our study used the IOS method. These studies report mean resistance (Rm) at frequencies between 6 and 24 Hz (21), and between 4 and 16 Hz (11). Clearly, R5 is not identical to Rm, but in the study of Guo *et al.*, there was virtually no frequency dependence of resistance, and in the study of Pasker *et al.*, the frequency dependence was very small.

Ideally, the true pulmonary impedance should be reported regardless of method. However, differences have been shown between these different methods where the resistance values measured with IOS tended to be significantly higher than those measured with PRN FOT, especially at low frequencies and high resistances (12). In a comparison study by Hellinckx *et al.*, the authors were able to show in a mechanical structure model that the PRN method gave resistance results in closer agreement to the wave-tube technique than was the case for IOS (12, 22). In this study, reactance values and *f*res from PRN and IOS methods were very similar. Still, this was in a mechanical model, and which of the PRN or IOS methods gives the truest values for resistance in the human remains to be shown. In the meantime it is important to be aware of these differences and to apply reference values appropriate to the method in use.

In the present study, only one test subject had a within-breath reactance, DX5 crossing the threshold proposed by Dellaca *et al.* of 0.28 kPa/L/s (9). The importance of this finding is that few elderly without respiratory complaints would be labeled expiratory flow limited using this method if the same threshold is applicable for the IOS. We believe that the Dellaca method for measuring EFL is an important future application of the FOT, as it is simple to perform and gives information concerning a very central aspect of the pathophysiological background for dypsnea in

COPD patients (23). Reference data on the DX5 will aid in interpretation of these results in patients.

As presented in Fig. 2, it is interesting to note that there is no sign of EFL in these elderly persons without respiratory symptoms, even if several show FEV1/FVC ratios less than 0.7. This is in contrast with what one might have expected if these persons were to have been diagnosed by Global Initiative for Chronic Obstructive Lung Disease criteria as COPD patients. This finding is yet another piece of evidence that FEV1/FVC ratios between 0.6 and 0.7 need not be indication of pathologic airways and should not be defined as such based on the arbitrary cut point of 0.7 (24). The DX5 method measures flow limitation at tidal-volume breathing that is not identical to flow limitation during forced expiration; a low FEV1/FVC ratio alone does not imply EFL or a high DX5.

The most obvious limitation to the present study is the small sample size that increases the risk of statistically significant differences being false-positive, risk of real differences being falsely negative and it makes the reference equations less stable. In addition, there could be a selection bias in that subjects with superior health from the postal questionnaire study probably would be more likely to participate in the clinical study. In absence of other reference value, studies performed on elderly using the IOS our equations will form a relevant reference for clinical evaluation in the elderly. The study sample is well characterized from previous publications (16, 17). However, future larger studies for establishing more robust equations for IOS are still needed. Other limitations are that most test subjects only had two valid FOT measurements and the intersession test repeatability of the measurements was somewhat poorer than in previous studies. This is partly explained by the fact that the variation seems to depend on the magnitude of the measurements, and we found higher resistance measurements and lower reactance measurements than in the other studies. We speculate that variability may generally be higher in the elderly and that the use of a tongue positioner instead of a circular cardboard mouthpiece could have improved the measurements. The repeatability was for the most part acceptable for the resistance measurements (CV 10%–12%) and for *f*res (CV 9%–13%). For comparison, Guo *et al.* had a mean CV of 6% for Rm and *f*res. CV for these parameters were within the limits of the short-term intraindividual CV of FOT indices in healthy adults reported by the ERS task force (range 5–15%), but the repeatability of X5 and AX were poorer (10). It could be argued that CV is unsuitable to estimate variability for most of the reactance parameters, as these values commonly are close to zero. Instead, it has been suggested calculating the absolute difference values of the reactance parameters (1). By this method, we can point out that the 95th percentile of the difference between first and second test for X5 was approximately 0.13 kPa/L/s, whereas for R5, the 95th percentile of difference was approximately 0.25 kPa/L/s (Fig. 1). This also illustrates why using the CV as a measure of repeatability for X5 may not be appropriate.

This study presents the first reference values for average and within-breath impedance measurements in asymptomatic elderly aged >70 years using the IOS method. We found higher resistance measurements than what is reported in previous studies and significantly larger frequency dependence (11, 20, 21). Using the threshold proposed by Dellaca *et al.* on DX5, only one of our elderly test subjects would be labeled EFL (8, 9).

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IV

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ORIGINAL RESEARCH

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

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Background: Tidal expiratory flow limitation (EFL_T) is frequently found in patients with COPD and can be detected by forced oscillations when within-breath reactance of a single-breath is ≥0.28 kPa·s·L^{-1}. The present study explored the association of within-breath reactance measured over multiple breaths and EFL_T 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 ($\Delta\overline{Xrs}$), 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_T, an upper limit of normal (ULN) was defined using the 97.5th percentile of $\Delta\overline{Xrs}$ of the healthy controls in the study; 6MWDs were compared according to $\Delta\overline{Xrs}$, as normal, ≥ ULN < EFL_T, or ≥ 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 $\Delta\overline{Xrs}$ below the ULN (0.09 kPa·s·L^{-1}), 6MWD was stable. 6MWD declined significantly in patients with $\Delta\overline{Xrs}$ ≥ ULN. Worse lung function and more exacerbations were found in patients with COPD with $\Delta\overline{Xrs}$ ≥ ULN, and patients with $\Delta\overline{Xrs}$ ≥ ULN had shorter time to first exacerbation and hospitalization. A significantly higher mortality was found in patients with $\Delta\overline{Xrs}$ ≥ ULN and FEV_1 >50%.

Conclusion: Patients with baseline $\Delta\overline{Xrs}$ ≥ ULN had a deterioration in exercise performance, more exacerbations, and greater hospitalizations, and, among those with moderate airway obstruction, a higher mortality. $\Delta\overline{Xrs}$ 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.[1] Although symptoms and exacerbation rate have been added to our assessment system of COPD,[2] spirometry remains an important tool in assessing severity and prognosis in this disease. Changes in the forced expiratory volume in 1 second (FEV_1) are still the best indicator of disease progression and the risk of dying from COPD.[2,3] Yet, on an individual level, FEV_1 is an unreliable marker of morbidity, especially in early disease,[4–6] 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_T) might be such a subgroup. EFL_T 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,[7,8] although it can occur with only moderate airway obstruction. Previous studies of EFL_T in COPD have focused on its association with operating lung volume, exercise tolerance,[9,10] and its relation to breathlessness.[11–13] It is not known whether EFL_T can provide longer-term prognostic information in COPD.

EFL_T can be detected by the forced oscillation technique (FOT).[14,15] 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 (Xrs_{exp}) becomes more negative than the inspiratory reactance (Xrs_{insp}), leading to a within-breath reactance difference (ΔXrs). In the absence of EFL_T, reactance measured in inspiration and in expiration is almost identical. The within-breath reactance difference (ΔXrs) cut-off of 0.28 $kPa \cdot s \cdot L^{-1}$ has been defined and validated to identify flow-limited breaths.[14,15] EFL_T is not only linked to dyspnea in COPD,[11,16] but also to COPD exacerbations, where ΔXrs have been found to increase at the onset of COPD exacerbations and decrease when the exacerbation resolves.[17]

In this study, we used forced oscillation technique to define EFL_T in 425 patients with COPD. We hypothesized that the presence of EFL_T, assessed by increased mean ΔXrs ($\Delta\overline{Xrs}$), would relate to changes in 6MWD, the risk of COPD exacerbations, and, possibly, mortality. We explored these hypotheses using baseline $\Delta\overline{Xrs}$ as a predictor for future events. Patients with COPD with abnormally high $\Delta\overline{Xrs}$, both above the upper limit of normal (ULN) and above the established threshold of EFL_T, 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,[18] 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; No: NTC00292552; www.ClinicalTrials.gov).[39]

Inclusion criteria for patients with COPD were: age 40–75 years, FEV_1 <80% predicted, FEV_1/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.[19,20]

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).[21,22] Local reference values were used to determine the FEV_1% predicted.[23] 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.[22]

$\Delta\overline{Xrs}$ reactance was averaged over the 90-second sample, containing several breaths, and was calculated as follows: $\Delta\overline{Xrs}$ = mean Xrs_{insp} at 5 Hz – mean Xrs_{exp} at 5 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 ($\Delta\overline{Xrs}$ ≥0.09 $kPa \cdot s \cdot L^{-1}$; Figure S1),[13] and at the established EFL_T defining threshold for within-breath reactance, 0.28 $kPa \cdot s \cdot L^{-1}$, derived from single-breath analysis.[14,15] To illustrate the variability of our multiple-breath measurement, $\Delta\overline{Xrs}$ was plotted against time in a subset of the patients defined EFL_T 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.[24]

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.[25]

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 ± 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 $\Delta\overline{Xrs}$: normal, ≥ ULN < EFL_T, and ≥ 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 $\Delta\overline{Xrs}$ and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade.[2]

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_1, age, sex, and a binary classifier identifying frequent exacerbators in the year prior to inclusion.[26] 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 $\Delta\overline{Xrs}$ ≥ 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 $\Delta\overline{Xrs}$ ≥ ULN at baseline, and by dichotomizing FEV_1 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 $\Delta\overline{Xrs}$, 31% were classified as being abnormal with $\Delta\overline{Xrs}$ ≥ ULN < EFL_T, and 18% had $\Delta\overline{Xrs}$ above the threshold of EFL_T (Table 1). From the normal to the abnormal group, lung function worsened with a decline in FEV_1 and FVC, and an increase in body mass index (BMI) and mMRC. This difference was most marked between the normal and EFL_T group. For IC, we only found a significant difference between the normal and the EFL_T group.

Table 1 Baseline characteristics in COPD patients with different levels of $\Delta\overline{Xrs}$ (N=425)

Subject characteristics	Normal	Abnormal	EFL_T
	$\Delta\overline{Xrs}$ < ULN	ULN ≥$\Delta\overline{Xrs}$ < EFL_T	$\Delta\overline{Xrs}$ >0.28 kPa·s·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^2	24 (5)[c,d]	26 (5)[c,e]	28 (6)[d,e]
Pack-years (years)	40 (24)	43 (22)	39 (22)
Frequent exacerbators (%)	13%	20%	35%
mMRC	1.2 (0, 2)[c,d]	1.8 (0.25, 2)[c,e]	2.3 (1, 2)[d,e]
FEV_1 (L)	1.7 (0.5)[c,d]	1.3 (0.5)[c,e]	1.1 (0.4)[d,e]
FEV_1 (%)	52 (11)[c,d]	42 (12)[c]	38 (13)[d]
FVC (L)	3.5 (0.9)[c,d]	3.2 (0.8)[c,e]	2.8 (0.9)[d,e]
IC (L)	2.6 (0.8)[d]	2.5 (0.7)	2.3 (0.7)[d]
IC (%)	88 (19)	85 (20)	84 (21)
6MWD (meters)	455 (102)[c,d]	410 (109)[c,e]	363 (110)[d,e]
Estimated exacerbations per year[a]	0.7	1.3	1.6
Deaths[b]	25 (12)[c,d]	28 (21)[c]	18 (23)[d]

Notes: Data presented as mean ± standard deviation unless otherwise stated. [a]Estimated exacerbation rate by negative binomial model. [b]Number of deaths at the 5-year census (%). Significant differences at the 5% level are marked as [c]between normal and abnormal, [d]between normal and EFL_T, and [e]between abnormal and EFL_T. pack-years: packs of 20 cigarettes smoked per day × years as a smoker; Frequent exacerbators: percentage with ≥2 exacerbations the year the prior to inclusion.

Abbreviations: ULN, upper limit of normal 0.09 kPa·s·L^{-1}; EFL_T, tidal expiratory flow limitation; BMI, body mass index; 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; $\Delta\overline{Xrs}$, difference between mean inspiratory and mean expiratory reactance at 5 Hz over multiple breaths; 6MWD, 6-minute walk distance.

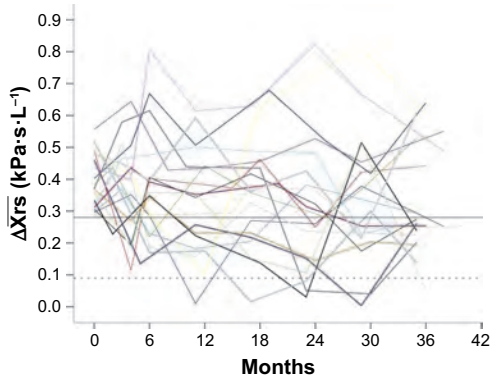

Figure 1 Timeplot illustrating the variability of $\Delta\overline{Xrs}$ measurements (splines) over the course of the study shown in the first 20 patients with COPD with complete visits, defined as having EFL_T at baseline ($\Delta\overline{Xrs} \geq 0.28$ kPa·s·L^{-1}). The dotted line is set at 0.09 kPa·s·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 $\Delta\overline{Xrs} \geq$ 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 $\Delta\overline{Xrs} \geq$ 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 $\Delta\overline{Xrs} \geq$ 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 $\Delta\overline{Xrs} \geq$ 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 $\Delta\overline{Xrs} \geq$ 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 $\geq$ ULN than in patients with normal $\Delta\overline{Xrs}$, but not significantly different between the $\geq$ 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 $\geq$ ULN was driven by increased mortality in patients with FEV_1 >50% (Figure 4). Mortality was 17% in $\Delta\overline{Xrs} \geq$ ULN patients with FEV_1 >50%, compared to 5% in patients with normal ΔXrs (P<0.001; Figure 4). Mortality in patients with ΔXrs $\geq$ 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 $\Delta\overline{Xrs} \geq$ ULN deteriorated significantly in 6MWD. Patients with COPD with $\Delta\overline{Xrs} \geq$ 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

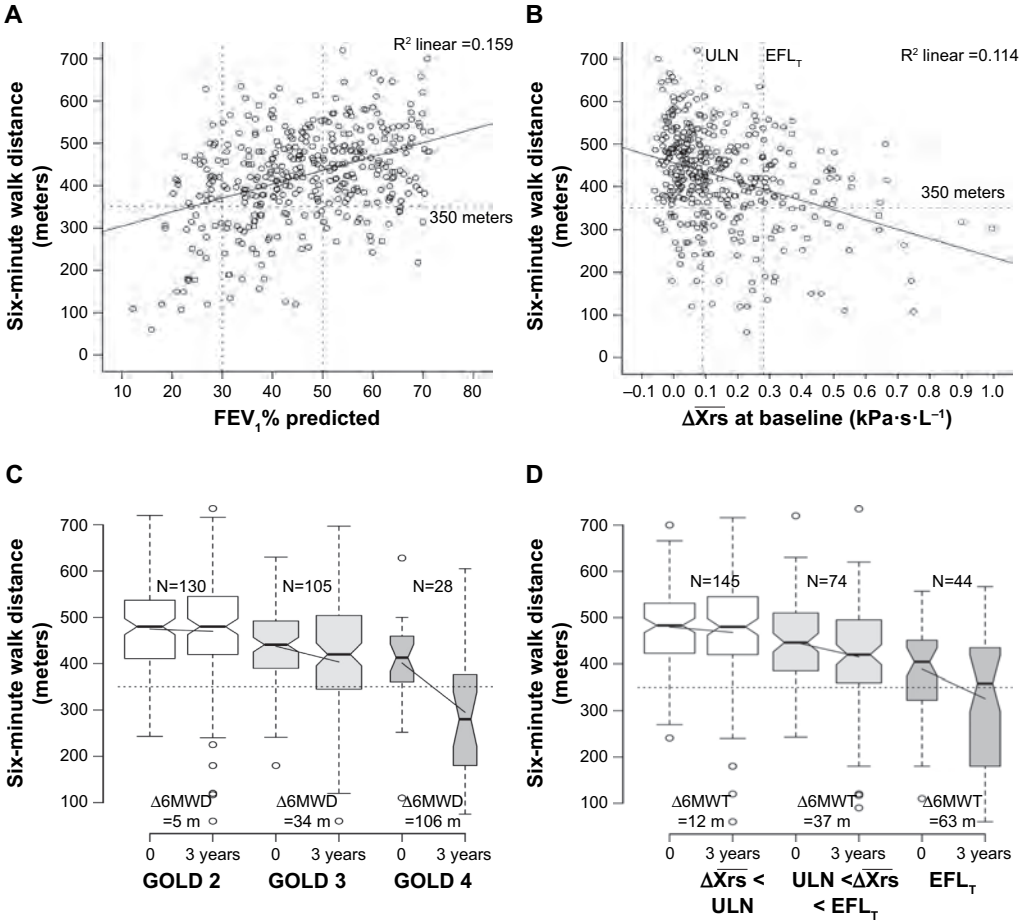

Figure 2 (**A**) Six-minute walk distance (6MWD) in patients with COPD (N=388) at different levels of FEV_1% predicted (**A**) and $\Delta\overline{Xrs}$ (**B**) at baseline. Dotted lines set at 350 m (horizontal) and at $\Delta\overline{Xrs}$ =0.09 kPa·s·L^{-1}, upper limit of normal (ULN), and $\Delta\overline{Xrs}$ =0.28 kPa·s·L^{-1}, 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 $\Delta\overline{Xrs}$ (**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 $\Delta\overline{Xrs}$ 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.[13,18] The FOT threshold identifying a single flow-limited breath has been defined when within-breath reactance was >0.28 kPa·s·L^{-1}.[14,15] 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.[27] 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.[28] 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
$\Delta\overline{Xrs}$			
≥ULN (0.09 kPa·s·L^{-1}) and <EFL_T	1.28	1.05, 1.55	0.011
≥EFL_T (0.28 kPa·s·L^{-1})	1.30	1.05, 1.64	0.009
FEV_1 % 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			
≥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^{-1}; EFL_T, tidal expiratory flow limitation; FEV_1, forced expiratory volume in 1 second; FEV_1 (%), FEV_1 percentage of predicted.

operating lung volume.[12,29] 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 $\Delta\overline{Xrs}$ ≥ ULN or the threshold of EFL_T, were more likely to have a worse exercise tolerance at the same visit. This was true on a group level. The EFL_T group had the lowest 6MWD, but neither FEV_1 % predicted nor any cut-off level of $\Delta\overline{Xrs}$ could identify patients with COPD with a short walking distance (<350 m), as proposed by Spruit et al.[30] No significant decline was seen in patients with $\Delta\overline{Xrs}$ in the normal range; in patients with COPD with $\Delta\overline{Xrs}$ ≥ ULN, it declined 37 m, and in patients with EFL_T, 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;[31] consequently, the differences seen over time between our subgroups defined by $\Delta\overline{Xrs}$ ≥ ULN and EFL_T 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.[32,33] By negative binomial regression, the $\Delta\overline{Xrs}$ cut-offs ≥ ULN and EFL_T were both significant predictors for higher rates of exacerbations with very similar RR, demonstrating that the increased risk of exacerbations by EFL_T is identified already at ULN. In the time to first event analysis of patients with $\Delta\overline{Xrs}$ ≥ ULN, we found a shorter time to first exacerbation and a shorter time to first hospitalization than that of the COPD patients with $\Delta\overline{Xrs}$ in the normal range. A previous study on hospitalized patients showed that many, but not all, have FOT-defined EFL_T during a COPD exacerbation.[17] FOT measurements performed during hospitalized COPD exacerbations show that $\Delta\overline{Xrs}$ measurements improve during resolution of an exacerbation, although many patients remain EFL_T at discharge.[17] 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_T 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_1 >50% predicted and evidence of EFL_T, defined as baseline ΔXrs ≥ ULN, had significantly higher risk of dying within the 5-year follow-up. Similar associations were not found in the patients with more advanced

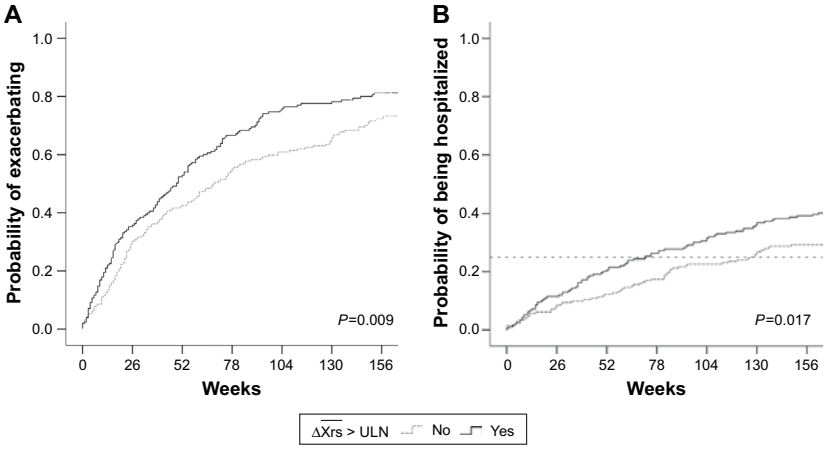

Figure 3 Time to first moderate or severe exacerbation (**A**) and to the first hospitalization (**B**) in COPD patients with $\Delta\overline{Xrs}$ measurements above the upper limit of normal (ULN), 0.9 kPa·s·L^{-1} (solid line), and below the ULN at the baseline visit. Dashed line at 25%.

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

Parameter	$\Delta\overline{Xrs} <$ ULN	$\Delta\overline{Xrs} \geq$ ULN
Total N	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 $\Delta\overline{Xrs} \geq$0.09 kPa·s·L^{-1}.
Abbreviations: ULN, upper limit of normal 0.09 kPa·s·L^{-1}; 95% CI, 95% confidence interval.

airway obstruction and 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.[34] If there is an association between $\Delta\overline{Xrs}$ 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 $\Delta\overline{Xrs}$ was highly significant, this sub-analysis should be interpreted with caution due to the relatively small number of deaths in patients with FEV_1 >50% predicted (Table 1).

There are certain limitations of this study. The FOT threshold identifying a single flow-limited breath has been defined at $\Delta\overline{Xrs}$ >0.28 kPa·s·L^{-1}.[14,15] 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 EFL_T.[8,15] Although the prevalence of EFL_T increased as the FEV_1% predicted declined, not all patients with very severe airway obstruction were found to have EFL_T. In previous studies on elderly and COPD with the NEP technique, higher prevalence of EFL_T have been reported than in the present study.[11,35,36] 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 EFL_T, are likely explanations. The wide reference range of FEV_1 inevitably may also lead to an overestimation of the suspected lung function decline in many patients.[23]

As previously noted, 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.[13] 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 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.[18,37]

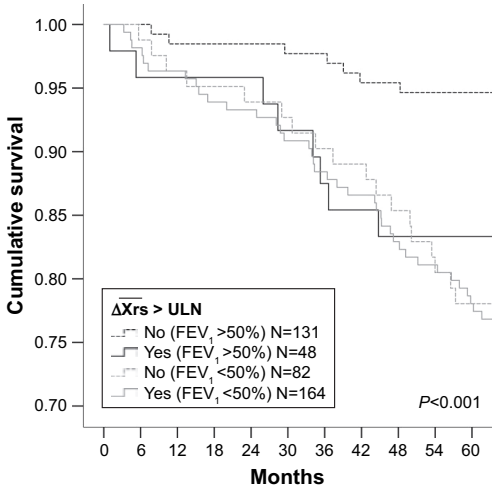

Figure 4 Kaplan–Meier survival curves in COPD patients with normal $\Delta\overline{Xrs}$ and in COPD patients with $\Delta\overline{Xrs}$ measurements above the upper limit of normal (ULN). Test of equality of survival distributions was performed using log-rank test.

Conclusion

Consistent differences in clinically relevant outcomes were found, such as exercise capability, exacerbations, hospitalizations, and death in COPD patients with baseline $\Delta\overline{Xrs}$ beyond the ULN. This is below the established threshold for EFL_T. Our data support previous studies showing that patients with EFL_T have worse lung mechanics than is evident from FEV_1 measurement alone.[11,38] The present study suggests that evidence of 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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Supplementary materials

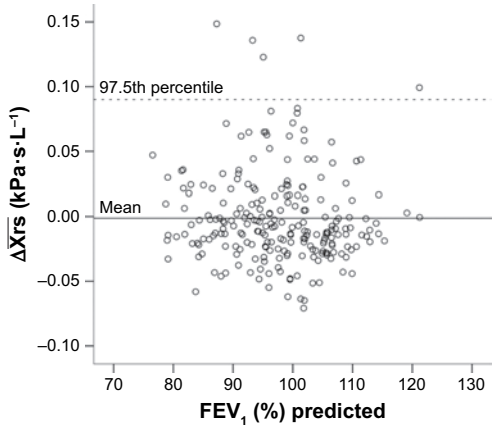

Figure S1 Scatterplot of $\Delta\overline{Xrs}$ plotted against FEV_1 % predicted in healthy controls (N=229). Mean represented by the solid line. The dashed line represents the 97.5th percentile, the upper limit of normal (ULN).

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^2	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
$\Delta\overline{Xrs}$ (kPa·s·L^{-1})	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^{-1}; 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 ≥2 exacerbations the year 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; $\Delta\overline{Xrs}$, difference between mean inspiratory and mean expiratory reactance at 5 Hz over multiple breaths; 6MWD, 6-minute walk distance.