Journal Pre-proof

Upper airway symptoms and small airways disease in Chronic Obstructive Pulmonary Disease, COPD

Nicolai Obling, Bojidar Rangelov, Vibeke Backer, John R. Hurst, Uffe Bodtger

PII: S0954-6111(21)00418-2

DOI: https://doi.org/10.1016/j.rmed.2021.106710

Reference: YRMED 106710

To appear in: *Respiratory Medicine*

Received Date: 5 May 2021

Revised Date: 28 November 2021

Accepted Date: 30 November 2021

Please cite this article as: Obling N, Rangelov B, Backer V, Hurst JR, Bodtger U, Upper airway symptoms and small airways disease in Chronic Obstructive Pulmonary Disease, COPD, *Respiratory Medicine* (2022), doi: https://doi.org/10.1016/j.rmed.2021.106710.

Upper Airway Symptoms and Small Airways Disease in Chronic Obstructive Pulmonary Disease, COPD.

Authors credits:

Nicolai Obling [1,2], M.D, (ORCID ID 0000-0003-4926-5897)

Designed the study, undertook main patient recruitment, performed data analysis and prepared main manuscript

Bojidar Rangelov[3], MPhil, Meng, (ORCID ID 0000-0001-7017-1575)

Assisted in data analysis and editing main manuscript

Vibeke Backer[4,5], MD, DMsci (ORCID ID 0000-0002-7806-7219)

Designed the study, data analysis and editing main manuscript

John R Hurst[6], MD, PhD, FHEA (ORCID ID 0000-0002-7246-6040)

Designed the study, data analysis and editing main manuscript

Uffe Bodtger[1,2], M.D, PhD (ORCID ID 0000-0002-1231-9209)

Designed the study, assisted in patient recruitment, data analysis and editing main manuscript

Upper Airway Symptoms and Small Airways Disease in Chronic Obstructive Pulmonary Disease, COPD.

Authors:

Nicolai Obling [1,2], M.D, (ORCID ID 0000-0003-4926-5897)

Bojidar Rangelov[3], MPhil, Meng, (ORCID ID 0000-0001-7017-1575)

Vibeke Backer[4,5], MD, DMsci (ORCID ID 0000-0002-7806-7219)

John R Hurst[6], MD, PhD, FHEA (ORCID ID 0000-0002-7246-6040)

Uffe Bodtger[1,2], M.D, PhD (ORCID ID 0000-0002-1231-9209)

Affiliation:

[1]Department of Respiratory Medicine, Zealand University Hospital Næstved, Denmark

[2]Institute for Regional Health Research, University of Southern Denmark

[3]Centre for Medical Image Computing, Department of Medical Physics and Biomedical Engineering, University College London, London, UK

[4]Center for Physical Activity Research, Rigshospitalet, Copenhagen University, Denmark

[5]Department of ENT, Rigshospitalet, Copenhagen University, Denmark

[6]UCL Respiratory, University College London, London United Kingdom

Corresponding author:

Nicolai Obling, MD

Email: nao@dadlnet.dk

Address: Skolevænget 12, Dk-2800, Kongens Lyngby, Denmark

Abstract: 257 words

Article: 3173 words

References: 31

Tables/ figures: 5 + 1 supplementary table.

Keywords: COPD, Small Airways Disease, Upper Airway Symptoms, United Airway, Impulse Oscillometry, Parametric Response Mapping.

Abstract

Background:

Small Airways Disease (SAD) is a recognised part of the pathology in Chronic Obstructive Pulmonary Disease (COPD) and contributes to the symptom burden in the disease. Upper airway symptoms in COPD is an emerging field of study, and in this study, we sought to examine the co-existence of SAD and upper airways symptoms in a cohort of COPD patients

Methods:

We investigated a cohort of patients with COPD for the presence of SAD with three different modalities. We performed High-Resolution CT (HRCT) with Parametric Response Mapping (PRM) analysis and recorded distribution of emphysema (PRM^{Emph}) and functional Small Airways Disease (PRM^{fSAD}). We measured central and peripheral lung resistance using Impulse Oscillometry (IOS) and recorded R5Hz, R20Hz, R5-R20Hz, X5, Fres and Ax. Static lung function parameters were obtained using Body Plethysmography.

Data on upper and lower airway symptoms were evaluated using the Upper Airway subdomain of the 22 items Sino Nasal Outcome Test ($SNOT22_{nasal}$) and the COPD Assessment Test (CAT), respectively.

Findings

We recruited a total of 112 patients. (female sex: 58%, Age 68 (±8) years, FEV1%predicted: 53% (±16%), GOLD stage: A: 23%, B: 55%, C:1% D: 21%). Forty-five (40%) were classified as having high upper airway symptoms (UAS), defined as $SNOT22_{nasal} \geq 6$. Eighty-seven per cent showed signs of SAD using IOS (R5-R20Hz > 0.07 kPa/L/s). No significant differences were found between UAS groups in IOS, PRM or Body Plethysmography parameters.

Conclusion:

In patients with COPD, the prevalence of small airways disease was very high, but no association between upper airway symptoms and small airways disease was demonstrated.

Introduction

The pathology behind Chronic Obstructive Pulmonary Disease (COPD) is complex and display a wide degree of heterogeneity between different individuals resulting in various clinical phenotypes with chronic bronchitis and emphysema dominant phenotypes being the more well-recognised [1]. A ubiquitous feature of the disease is, as the name suggests, the presence of poorly reversible airway obstruction. The cause of this obstruction is predominately due to effects in the small airways (<2mm in diameter), where both the loss of and narrowing of these airways results in a significant increase in peripheral lung resistance and to dynamic airway collapse during expiration leading to airway obstruction [2]. This "small airways disease" (SAD) is a well-established feature of COPD and was first described in the 19th century [3]. SAD is associated with increased symptom burden in patients with COPD and is regarded as a precursor of the development of emphysema [4]. Several studies have demonstrated an increased prevalence of SAD as the disease progresses [5, 6].

A less well-established feature of COPD is the presence of symptoms from the upper airways. This aspect of the disease was first hypothesised in the late 1990s and later substantiated in several other studies [7–9]. We recently reported the prevalence of upper airway symptoms in a cohort of patients with COPD from Denmark and Sweden [10]. We found that these symptoms were common, and that patients with higher upper airway symptom burden also reported more symptoms from their lower airway (CAT score) despite more preserved lung function. The cause of this increased lower airway symptom burden is not known and requires further examinations. Since SAD is a known driver of symptoms in COPD, we hypothesised that the increased CAT scores reported by COPD patients with upper airway symptoms could be due to a higher degree of SAD, and we investigated this in the current study using a multi-modality approach with impulse oscillometry, body plethysmography and parametric response mapping algorithms on high-resolution CT scan. The aim has been to illustrate co-existence of upper airway dysfunction and SAD in patients suffering from COPD.

Methods

This study was conducted as a sub-study of the cross-sectional study, "BREATHE" [11], conducted between February 2017 and February 2019. Ethical approval was granted by the local ethics committees in Denmark and Sweden (H-16047428, SJ-668, DNR 2016/1069) and by the Danish Data Protection Agency.

Patients were recruited from two specialist respiratory outpatient clinics at Næstved Hospital in Denmark and Lund in Sweden

Patients were included in the study according to the following inclusion criteria: age ≥ 40 years, a history of smoking ≥ ten pack-years of tobacco, and a post-bronchodilator Forced Expiratory Volume 1 second (FEV1) /Forced Vital Capacity (FVC) index < 0.70.

Exclusion criteria were defined as self-reported or physician-diagnosed asthma and reversibility for beta2 agonist above 400 ml and 15% from baseline FEV1. [12, 13]. We described a suspicion of asthma as early onset of symptoms (before the age of 40) or a history of persistent respiratory symptoms in childhood or adolescence. We also excluded patients with or suspected of other respiratory diseases such as sarcoidosis, pulmonary fibrosis, or lung cancer.

Medical history

Medical history included information on upper and lower airway symptoms, history of exacerbations, hospital, or emergency department admissions, and other comorbidities such as heart disease and current medication use. Smoking history was quantified using pack-years of tobacco.

Acute exacerbations of COPD (AECOPD) were defined as self-reported worsening of respiratory symptoms requiring additional treatment with oral antibiotics and/or corticosteroids or admission to hospital equivalent to moderate and severe COPD exacerbations.

Questionnaires

All patients completed the following questionnaires on airway symptoms:

The COPD Assessment Test (CAT) is an eight-item questionnaire validated to assess COPD symptom burden [14]. Patients score each item on a Likert scale from 0 ("I never cough") to 5 ("I cough all the time") with a maximum score of 40 points and a minimal clinical important difference (MCID) of 2 points [15].

The 22-item Sino Nasal Outcome Test (SNOT22) assesses chronic rhinosinusitis symptoms and includes nasal symptoms and more general symptoms such as fatigue [16]. Each item is scored on a Likert scale from 0 ("no problem") to 5 ("problem as bad as it can be"). The maximum score is 110, with an MCID of 9 points [17].

The SNOT22 nasal subdomain ($SNOT22_{nasal}$) consists of seven items (no. 1-5 + 7-8), which include: "need to blow nose", "sneezing", "runny nose", "nasal obstruction", "loss of smell or taste", "post-nasal discharge" and "thick nasal discharge". A cut-off for normality (or MCID) for the subdomain is not validated, but one study found a median overall SNOT22 score of 7 points in healthy volunteers[18].

Definition of high upper airways symptoms (UAS)

We defined high upper airway symptoms, as in our previous studies [10], as $SNOT22_{nasal} \geq 6$. We chose this cut-off value as a score of 6 implies having either mild symptoms in almost all items or moderate-severe symptoms in one or two items.

Pulmonary Function Tests

Spirometry and bronchodilator responsiveness testing for beta2-agonist were performed according to ERS/ATS guidelines using a Jaeger Spirometer (Intramedic®, Gentofte, Denmark) with the recording of FEV1, FVC, and FEV1/FVC ratio [19].

Patients underwent body plethysmography using a Jaeger Box (Intramedic®, Gentofte, Denmark) to obtain static lung volumes and with single-breath, carbon monoxide uptake measurements and RV, TLC, DLCO were recorded [20].

Impulse Oscillometry

Central and peripheral lung resistance was evaluated with Forced Impulse Oscillometry (FOT/IOS)[21, 22] using Resmon Pro (MGC Diagnostics) in Lund and the Carefusion Vyntys APS with IOS, (Intramedic, Denmark) in Næstved.

All measurements were conducted after a minimum of 72 hours pause from regular inhaled medications except for short-acting bronchodilators (SABA), which were paused a minimum of six hours before measurements. Patients performed a minimum of three measurements, and the mean of the three best attempts was calculated. We registered resistance at 5 Hz (R5Hz) and 20 Hz (R20Hz), reactance at 5 Hz (X5), area of reactance (Ax) and frequency of resonance (Fres). All measurements are reported in kilopascal per litre per second (kPa/L/s) except Fres which is measured in Hz. Resistance at 5Hz is a measure for the resistance from the mouth to the distal airway whereas resistance at 20 Hz is a measure for the resistance in the proximal airways. Small airways disease (SAD) was defined as a R5-R20Hz above 0.07 kPa/L/s [5].

Radiological evaluation:

Patients from Næstved (n=59) were scanned with a volumetric high-resolution CT (HRCT) scan of the thorax in both inspiratory (120 kV) and expiratory (100 kV) phases. The scans were performed with a slice thickness of 0.9 mm. A staff radiologist evaluated all scans for differential diagnoses.

Parametric Response Mapping

The HRCT scans were analysed using the technique of Parametric Response Mapping, where the lung parenchyma is categorised voxel-wise according to the changes in attenuation of the voxels between the inspiratory and expiratory phases.

From this analysis, the lung parenchyma was classified either as “normal” (PRM^{Normal}), functional small airways disease (PRM^{fSAD}) or emphysema (PRM^{Emph}). Details of the technical aspects of the analysis have been published elsewhere.

[23]. From this analysis, the lung parenchyma was classified either as "normal" (PRM^{Normal}), functional small airways disease (PRM^{fSAD}) or emphysema (PRM^{Emph}). Details of the technical aspects of the analysis have been published elsewhere. [23].

Briefly, the PRM analysis pipeline first segmented the lung regions from every pair of inspiration-expiration scans (removing tissues outside the lung fields). Then, the airway tree was segmented out, leaving only the lung parenchyma. The expiration scan was registered to the inspiration scan so that every voxel in the inspiration scan had a corresponding voxel in the expiration scan. The scans were clipped to the -1024 to -500 Hounsfield Units (HU) window. The PRM algorithm then proceeded by classifying every voxel according to its values on the inspiration and expiration scan, per the scheme below:

	PRM^{Emph}	PRM^{fSAD}	PRM^{Normal}
Inspiration scan (HU)	< -950	> -950	> -950
Expiration scan (HU)	< -856	< -856	> -856

Statistical analyses

Data were analysed using SPSS version 27 (IBM, Chicago, USA). Skewed data are presented as the median and interquartile range (IQR). Normally distributed data are presented with mean ± standard deviation (SD). Categorical variables are presented as a count (*n*) and percentage (%).

Normally distributed data were analysed using Independent Samples T-test. For skewed data, group comparisons were calculated using the Mann-Whitney U test. Categorical data were compared using the Chi-square test. Correlations were calculated using Pearson's correlation for normally distributed data (if both variables were normally distributed) and Spearman Rank Correlation for skewed or partially skewed data. The significance level was set at < 0.05, and all p-values are reported as two-tailed. We did not perform a pre-study sample size calculation since no prior studies have looked at the association between upper airway symptoms and small airways disease and therefore the required parameters like prevalence and statistical variance were not known.

Results

We included a total of 112 patient, of which the majority (58%) were female, and most were former smokers (74%) Details of the clinical characteristics can be seen in Table 1.

The cohort was divided into two groups according to the pre-defined threshold of upper airway symptom score ($SNOT22_{nasal} \geq 6$), and the comparison of these groups are detailed in Table 1. A total of 45 patients (40%) were classified as having high upper airway symptoms (high UAS).

Body Plethysmography:

No differences between static lung volumes were observed between upper airway symptom groups, including in the ratio between residual volume and total lung capacity (RV/TLC%). (Table 1+2)

Parametric Response Mapping:

PRM analysis showed that the levels of both emphysema and functional small airways disease (fSAD) were high in both UAS groups with a mean degree of emphysema of 25% in both groups and fSAD of 38% and 40%, respectively. There was, however, no difference between groups (Table 3).

Impulse Oscillometry:

Patients with high upper airways symptoms (high UAS) displayed significantly lower levels of overall lung resistance assessed by R5Hz – median 0.52 vs 0.63, p-value 0.040. No other differences in individual impulse oscillometry parameters were found between groups. The presence of SAD using a threshold of deltaR5R20Hz ≥ 0.07 [5] was present in most patients, 84 and 88% respectively (87% in the combined cohort), but with no differences between upper airway symptom groups.

Correlations between Impulse Oscillometry (IOS) and clinical parameters:

Table 3 outlines the relationships between IOS, symptoms scores and dynamic and static lung functions tests and shows, among other findings, that the IOS markers for SAD, R5-R20Hz and Ax, were significantly correlated with CAT score and hyperinflation (RV, TLC) and inversely correlated with FEV1 and DLCO. R5-R20 and Ax also displayed strong correlations with the RV/TLC ratio. UAS correlated inversely with R5Hz and Fres but did not show any other correlations other IOS parameters or with SAD markers.

Correlations between PRM and clinical parameters:

Table 4 shows that neither PRM measurements (PRM^{Emph} or PRM^{fSAD}) displayed any significant correlations with upper airway symptom score or CAT score. In contrast, PRM^{Emp} did show, as expected, strong correlations with both dynamic and static lung parameters. PRM^{fSAD} correlated only with TLC (%predicted).

Correlations between SAD measurements:

The three different measurements reflecting the degree of SAD in patients showed varying levels of correlation. R5-R20Hz correlated significantly with both RV/TLC% and PRM^{fSAD} (rho = 0.451, p<0.001 and r = 0.335, p = 0.014 respectively) whereas PRM^{fSAD} did not show any significant correlation with RV/TLC (r = 0.175, p = 0.194). (Details in Table 5).

Discussion

In the current study, we investigated the presence of small airways disease (SAD) in a cohort of patients with COPD and explored its association with symptoms from the upper airways. To our knowledge, our study is the first to look at this association and the first to employ these three different modalities in the assessment of SAD in COPD. We found that SAD is a widespread feature in these patients, with 87% of patients fulfilling the criterion for SAD (R5-R20Hz > 0.07). This prevalence of SAD is noticeably higher than results from prior studies looking at SAD using our chosen threshold with a Italian study reporting a prevalence of 74% and a Korean study reporting 80% [5, 24]. These studies were, however, conducted on patients with lower levels of disease severity than our cohort, which could explain the observed differences.

We also found that COPD symptom burden in the form of CAT scores correlated with increased levels of SAD. We did not, however, find any difference in the presence of SAD between patients with or without high levels of upper airway symptoms. One explanation of why we do not uncover any differences between groups could be the possibility of a type 2 error – i.e., that we overlook a real difference. This is because the threshold used for SAD classifies almost all our cohort as having SAD. This leaves just 15 patients without SAD, and the small numbers could mean that we fail to reject the null hypothesis. However, this is not likely since we also did not find a difference in the absolute values of R5-R20Hz or Ax between groups, and the tendency was identical across the three different modalities used in our study. We found that patients with high UAS had significantly lower lower lung resistance (R5Hz), but this did not result in significant differences in R5-R20Hz or Ax, which are the IOS measurements for SAD. There were also no correlations between the reported UAS score and R5-R20Hz or Ax.

Since our study is the first to look at UAS and SAD, it is not possible to compare this part of our finding to existing literature, and it motivates further studies. Regardless, our findings do carry some weight on its own. We employed three different modalities in the assessment of SAD, and although these did not show perfect consistency, there was some degree of correlation between these different measurements of SAD. Some of the variation could result from the different approaches of each modality. Body Plethysmography which provides the static lung volumes in the form of RV and TLC (and hence the RV/TLC ratio) can be a challenging procedure for patients, especially elderly or frail patients, to perform correctly. Body plethysmography also requires highly skilled personal. Although used by some studies as a measurement for SAD [25], it could be argued that the RV/TLC ratio is more a measurement of pulmonary hyperinflation due to emphysema and not specifically small airways disease. This is supported by our findings of a strong correlation between PRM^{Emph} and RV/TLC as well as a strong inverse correlation between RV/TLC and DLCO (rho

= -0,588, $p < 0.001$, data not shown). We did also not find a correlation between RV/TLC and PRM^{fSAD}. This could be unique for our study since other studies have found this association [22], and the very wide accessibility of the measurement in both clinical practice and clinical trials support its use for assessing SAD [27].

Impulse Oscillometry offers advantages over the RV/TLC ratio in accessing SAD in patients. Firstly, it is a patient-friendly modality since it requires minimal effort on the side of the patients since it is performed during tidal breathing – in contrast to spirometry which is effort dependent. The measurement during tidal breathing is also more physiological in nature than the forced manoeuvres in spirometry which can produce dynamic airway collapse not present in tidal breathing.

The observed levels of overall lung resistance (R5Hz), reactance (X5) and the degree of SAD (R5-R20Hz +Ax) in our study are very similar to those reported by others and support the external validity of our results [28, 29].

Our third modality for assessing SAD was the Parametric Response Mapping technique which is a novel approach for evaluating lung pathology on HRCT. It is unique in its ability to spatial align voxels of the lung between inspiratory and expiratory phases to assess air trapping and emphysema. This air trapping is classified as "functional small airways disease" (fSAD), and both PRM^{Emph} and PRM^{fSAD} have been shown to be increased in patients with COPD compared with both young and older smokers without COPD [26]. Both parameters were also inversely correlated with dynamic lung functions and positively correlated with hyperinflation markers including RV/TLC and TLC. However, only PRM^{Emph} significantly displayed a correlation with COPD symptoms score (SGRQ and BODE index).

In our study, we confirm that PRM^{Emph} correlated with a wide array of both static and dynamic lung function parameters (table 5), but we were unable to reproduce previous studies result on PRM^{fSAD} with only TLC predicted showing a significant correlation. The PRM analysis is performed on a CT scan in full or near-full expiration which, like in spirometry and body plethysmography, could induce airway collapse not present in tidal breathing, and this could explain some of the variation in PRM^{fSAD} with IOS measurements for SAD.

All three modalities in our study are surrogate markers or indirect measurements for SAD. The gold standard for diagnosing SAD are autopsy or micro-CT analysis of excised lung sections [2](e.g., after lung reduction surgery) and are not relevant in a clinical setting. To our knowledge, no prior studies have directly compared non-invasive SAD markers like IOS or PRM with micro-CT or autopsy analysis of SAD.

Our study does have some limitations – chiefly that only patients from Næstved had HRCT, and subsequent PRM analysis, performed. This could raise the risk of bias since patients from different sites might differ in disease severity. In fact, patients from Næstved did, on average, have lower FEV1 and higher levels of hyperinflation than did patients from Lund (Supplementary Table 1). However, patients from Næstved (PRM+IOS/FOT) were also just as likely to be in the high UAS group as patients from Lund (IOS/FOT only) and were just as likely to fulfil the IOS criterion for SAD ($p = 0.230$ and 0.194 respectively). The distribution of patients across GOLD 1-4 groups was, due to the lack of randomisation, also not uniform with just around 5% of patient in GOLD 1 and 8% in GOLD 4. This could lead to increased statistical variance and the risk of type 2 errors. The relative homogeneity of patients (the high prevalence of SAD) could also lead to weaker correlations and explain some of the lack of correlations between PRM and IOS measurements.

The detection of SAD in patients with COPD could be crucial if it could lead to a shift of treatment with ultrafine particles which to a greater extent are deposited in the small airways than traditional inhaled therapies [30] and could, in theory, relieve symptoms more efficiently and reduce the risk of pneumonia in patients on ICS treatment [31] . However, from our study, it does not appear that UAS is associated with SAD.

Conclusion

Patients with COPD and high levels of upper airway symptoms did not exhibit higher degrees of small airway disease when compared to patients without upper airway symptoms.

Conflict of interest:

Authors report no conflicts of interest related to this study

Funding:

This study has received unrestricted research grants from the Region of Zealand, from Interreg Europe, The A.P. Moller Foundation and the Danish Society of Respiratory Medicine.

References:

1. Barker BL, Brightling CE. Phenotyping the heterogeneity of chronic obstructive pulmonary disease. *Clin. Sci.* [Internet] 2013; 124: 371–387Available from: http://clinsci.org/lookup/doi/10.1042/CS20120340.

2. Hogg JC, McDonough JE, Suzuki M. Small airway obstruction in COPD: New insights based on micro-CT imaging and MRI imaging. *Chest* [Internet] The American College of Chest Physicians; 2013; 143: 1436–1443Available from: http://dx.doi.org/10.1378/chest.12-1766.

3. Gairdner W. On the Pathological States of the Lung Connected with Bronchitis and Bronchial Obstruction. *Mon. J. Med. Sci.* 1851; 3.

4. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, Wright AC, Gefter WB, Litzky L, Coxson HO, Paré PD, Sin DD, Pierce RA, Woods JC, McWilliams AM, Mayo JR, Lam SC, Cooper JD, Hogg JC. Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease. *N. Engl. J. Med.* 2011; 365: 1567–1575.

5. Crisafulli E, Pisi R, Aiello M, Vigna M, Tzani P, Torres A, Bertorelli G, Chetta A. Prevalence of Small-Airway Dysfunction among COPD Patients with Different GOLD Stages and Its Role in the Impact of Disease. *Respiration* 2016; 93: 32–41.

6. Koo HK, Vasilescu DM, Booth S, Hsieh A, Katsamenis OL, Fishbane N, Elliott WM, Kirby M, Lackie P, Sinclair I, Warner JA, Cooper JD, Coxson HO, Paré PD, Hogg JC, Hackett TL. Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study. *Lancet Respir. Med.* 2018; 6: 591–602.

7. Montnémery P, Svensson C, Ädelroth E, Löfdahl CG, Andersson M, Greiff L, Persson CGA. Prevalence of nasal symptoms and their relation to self-reported asthma and chronic bronchitis/emphysema. *Eur. Respir. J.* 2001; 17: 596–603.

8. Hurst JR, Wilkinson TMA, Donaldson GC, Wedzicha JA. Upper airway symptoms and quality of life in chronic obstructive pulmonary disease (COPD). *Respir. Med.* 2004; 98: 767–770.

9. Hurst JR, Kuchai R, Michael P, Perera WR, Wilkinson TMA, Wedzicha JA. Nasal symptoms, airway obstruction and disease severity in chronic obstructive pulmonary disease. *Clin. Physiol. Funct. Imaging* 2006; 26: 251–256.

10. Obling N, Backer V, Hurst JR, Bodtger U. Upper airway symptoms associate with the eosinophilic phenotype of COPD. *ERJ Open Res.* [Internet] 2021; Available from: http://openres.ersjournals.com/lookup/doi/10.1183/23120541.00184-2021.

11. Backer V, Klein DK, Bodtger U, Romberg K, Porsbjerg C, Erjefält JS, Kristiansen K, Xu R, Silberbrandt A, Frøssing L, Hvidtfeldt M, Obling N, Jarenbäck L, Nasr A, Tufvesson E, Mori M, Winther-jensen M, Karlsson L, Nihlén U, Veje Flintegaard T, Bjermer L, Flintegaard TV, Bjermer L, Backer V, Klein DK, Bodtger U, Romberg K, Erjefält JS, Kristiansen K, Xu R, et al. Clinical characteristics of the BREATHE cohort–a real-life study on patients with

asthma and COPD. *Eur. Clin. Respir. J.* 2020; 7: 1736934.

12. Hanania NA, Sharafkhaneh A, Celli B, Decramer M, Lystig T, Kesten S, Tashkin D. Acute bronchodilator responsiveness and health outcomes in COPD patients in the UPLIFT trial. *Respir. Res.* 2011; 12.

13. Global Initiative For Asthma (GINA). Global Initiative For Asthma. 2020 Oct.

14. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur. Respir. J.* 2009; 34: 648–654.

15. Kon SSC, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, Haselden BM, Polkey MI, Man WDC. Minimum clinically important difference for the COPD Assessment Test: A prospective analysis. *Lancet Respir. Med.* [Internet] Elsevier Ltd; 2014; 2: 195–203Available from: http://dx.doi.org/10.1016/S2213-2600(14)70001-3.

16. Lange B, Thilsing T, Al-kalemji A, Baelum J, Martinussen T, Kjeldsen A. The Sino-Nasal Outcome Test 22 Validated for Danish Patients. *Dan. Med. Bull.* 2011; 58: 1–6.

17. Slack R, Hopkins C, Browne J, Gillett S. Psychometric validity of the 22 item sinonasal outcome test. *Otolaryngol. - Head Neck Surg.* [Internet] Elsevier Inc.; 2009; 141: P116–P116Available from: http://oto.sagepub.com/lookup/doi/10.1016/j.otohns.2009.06.363.

18. Gillett S, Hopkins C, Slack R, Browne JP. A pilot study of the SNOT 22 score in adults with no sinonasal disease. *Clin. Otolaryngol.* 2009; 34: 467–469.

19. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, Miller MR, Oropez CE, Rosenfeld M, Stanojevic S, Swanney MP, Thompson BR. Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. *Am. J. Respir. Crit. Care Med.* 2019; 200: E70–E88.

20. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, Macintyre NR, Thompson BR, Wanger J. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur. Respir. J.* [Internet] 2017; 49: 1–31Available from: http://dx.doi.org/10.1183/13993003.00016-2016.

21. DuBois AB, Brody AW, Lewis DH, Burgess BF. Oscillation Mechanics of Lungs and Chest in Man. *J. Appl. Physiol.* [Internet] 1956; 8: 587–594Available from: http://www.physiology.org/doi/10.1152/jappl.1956.8.6.587.

22. Liu Z, Lin L, Liu X. Clinical application value of impulse oscillometry in geriatric patients with COPD. *Int. J. COPD* 2017; 12: 897–905.

23. Galbán CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, Galbán S, Rehemtulla A, Kazerooni EA, Martinez FJ, Ross BD. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat. Med.* 2012; 18: 1711–1715.

24. Chiu HY, Hsiao YH, Su KC, Lee YC, Ko HK, Perng DW. Small Airway Dysfunction by Impulse Oscillometry in Symptomatic Patients with Preserved Pulmonary Function. *J. Allergy Clin. Immunol. Pract.* Elsevier Inc; 2020; 8:

229-235.e3.

25. Konstantinos Katsoulis K, Kostikas K, Kontakiotis T. Techniques for assessing small airways function: Possible applications in asthma and COPD. *Respir. Med.* [Internet] Elsevier Ltd; 2016; 119: e2–e9Available from: http://dx.doi.org/10.1016/j.rmed.2013.05.003.

26. Pompe E, Galbán CJ, Ross BD, Koenderman L, ten Hacken NH, Postma DS, van den Berge M, de Jong PA, Lammers JWJ, Mohamed Hoesein FA. Parametric response mapping on chest computed tomography associates with clinical and functional parameters in chronic obstructive pulmonary disease. *Respir. Med.* 2017; 123: 48–55.

27. Burgel PR. The role of small airways in obstructive airway diseases. *Eur. Respir. Rev.* 2011; 20: 23–33.

28. Williamson PA, Clearie K, Menzies D, Vaidyanathan S, Lipworth BJ. Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD. *Lung* 2011; 189: 121–129.

29. Crim C, Celli B, Edwards LD, Wouters E, Coxson HO, Tal-Singer R, Calverley PMAA. Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results. *Respir. Med.* [Internet] Elsevier Ltd; 2011; 105: 1069–1078Available from: http://dx.doi.org/10.1016/j.rmed.2011.01.010.

30. Usmani OS, Scichilone N, Mignot B, Belmans D, Van Holsbeke C, De Backer J, De Maria R, Cuoghi E, Topole E, Georges G. Airway deposition of extrafine inhaled triple therapy in patients with copd: A model approach based on functional respiratory imaging computer simulations. *Int. J. COPD* 2020; 15: 2433–2440.

31. Sonnappa S, Martin R, Israel E, Postma Di, Van Aalderen W, Burden A, Usmani OS, Price DB, Guilbert T, Grigg J, Phipatanakul W. Risk of pneumonia in obstructive lung disease: A real-life study comparing extra-fine and fine-particle inhaled corticosteroids. *PLoS One* [Internet] 2017; 12: 1–14Available from: http://dx.doi.org/10.1371/journal.pone.0178112.

TABLE 1 Comparison of clinical characteristics between patients.

	Entire cohort n = 112	High upper airway symptoms n = 45	Low upper airway symptoms n = 67	p-value*
Age (years)	68 (±8)	68 (±8)	68 (±8)	0.894
Female sex, n (%)	65 (58%)	21 (46%)	44 (66%)	**0.046**
BMI (kg/m^2)	25.8 (±5.0)	25.4 (±5.6)	26.2 (±4.6)	0.389
Smoking status: Former Smoker Current Smoker	 83 (74%) 29 (25%)	 31 (69%) 14 (31%)	 52 (78%) 15 (22%)	0.302
Tobacco Exposure (Pack Years)	42 (±17)	42(±16)	41 (±17)	0.719
SNOT22 (total score)	17 (9-27)	27 (21-37)	12 (8-17)	<0.001
SNOT22$_{nasal}$	4 (2-9)	10 (8-12)	2 (1-4)	-
CAT score	15.2 (±6.7)	16.1 (±7.7)	14.6 (±6.4)	0.240
Inhaled medication: ICS use Dual bronchodilator Triple Therapy	 57 (51%) 35 (31%) 48 (43%)	 22 (49%) 11 (27%) 19 (46%)	 35 (52%) 17 (28%) 29 (48%)	0.853
FEV1 (L)	1.37 (±0.56)	1.51 (±0.65)	1.29 (±0.49)	0.057
FEV1 (% predicted)	53 (±17)	56 (±17)	52 (±16)	0.255
DeltaFEV1 (ml)	130 (116)	132 (±109)	129 (±121)	0.877
DeltaFEV1 (%)	12 (11)	13 (±12)	12 (±10)	0.692
RV (L)	4.6 (±1.5)	4.50 (±1.53)	4.58 (±1.53)	0.848
RV (% predicted)	203 (±67)	198 (±65)	206 (±68)	0.638
TLC (L)	7.0 (±1.7)	7.29 (±1.76)	6.88 (±1.62)	0.294
TLC (% predicted)	121 (±24)	120 (±22)	122 (±25)	0.885
DLCO (mmol/min/kPa)	3.7 (±1.7)	3.84 (±1.82)	3.61 (±1.59)	0.557
DLCO (% predicted)	45 (±17)	45 (±18)	45 (±17)	0.995
GOLD stage (A-D)	A:26 (23%) B: 62 (55%) C: 1 (1%) D: 23 (21%)	A: 10 (22%) B: 26 (58%) C: 0 (0%) D: 9 (20%)	A: 16 (24%) B: 36 (54%) C: 1 (2%) D: 14 (21%)	0.851
Yearly exacerbations (≥1)	38 (34%)	12 (27%)	26 (39%)	0.183
≥2 moderate/severe AECOPD/year, n (%)	18 (16%)	9 (20)	9 (13.4)	0.354

Data is presented as mean ±standard deviation, median and IQR or count, n and percent.
BMI: Body Mass Index. SNOT22: Sino Nasal Outcome Test 22, SNOT22$_{nasal}$: Nasal domain/upper airway domain of SNOT22.
CAT score: COPD Assessment Test. ICS: Inhaled Corticosteroids, FEV1: Forced Expiratory Volume 1 second. FVC: Forced Vital Capacity, RV: Residual Volume. TLC: Total Lung Capacity. DLCO: Diffusion Capacity for Carbon Monoxide. DeltaFEV1: Increase in FEV1 from baseline. GOLD: Global Initiative for Chronic Obstructive Lung Disease. AECOPD: acute exacerbations in COPD. Triple therapy is defined as treatment with both long-acting beta2 agonist (LABA) long-acting muscarinic antagonist (LAMA) and inhaled corticosteroids.
*p-values are comparisons between the high and low upper airway symptoms groups

TABLE 2.
Markers of Small Airways Disease: PRM and IOS parameters between patients with high and low upper airway symptoms

	High upper airway symptoms n = 45	Low upper airway symptoms n = 67	p-value
R5Hz (kPa/L/s)	0.52 (0.39-0.67)	0.63 (0.47-0.74)	**0.040**
R20Hz (kPa/L/s)	0.28 (0.24-0.39)	0.33 (0.28-0.40)	0.113
R5-R20Hz (kPa/L/s)	0.24 (0.15-0.34)	0.27 (0.14-0.41)	0.187
X5 (kPa/L/s)	-0.25 (-0.38; -0.19)	-0.29 (-0.36, -0.19)	0.294
Ax (Hz x kPa/L/s)	2.48 (1.56-3.36)	3.25 (1.66-4.54)	0.313
Fres (Hz)	25.4 (±6.3)	27.3 (±7.3)	0.311
Small Airways Disease present. (R5R20Hz ≥ 0.07)	38 (84%)	59 (88%)	0.518
RV/TLC%	61 (±11)	66 (±13)	0.101
PRM^{Emph}(%)	25.0 (±15.8)	25.5 (±12.3)	0.902
PRM^{fSAD}(%)	38.3 (±4.5)	40.4 (±5.3)	0.124

R5Hz: Resistance at 5Hz (distal airways), R20Hz: Resistance at 20Hz (Proximal airway), DeltaR5R20Hz: Difference I resistance from 5Hz and 20Hz (measure for small airways disease), X5: Reactance at 5 Hz, Ax: Area of reactance, Fres: Resonance Frequency. PRM^{emp}: Parametric response mapping measure of emphysema, PRM^{fSAD}: Parametric Response Mapping measure of functional small airways disease.
RV: Residual Volume. TLC: Total Lung Capacity
kPa/L/s: Kilopascal per litre per second.

Table 3
Correlations between Impulse Oscillometry parameters and clinical scores and lung function test.

	R5Hz	R20Hz	R5-R20Hz	X5Hz	Ax	Fres
$SNOT22_{nasal}$	**rho = -0.201, p = 0.038**	rho = -0.142 p = 0.145	rho = -0.136, p = 0.163	rho = 0.072, p = 0.464	rho = -0.153, p = 0.251	**rho = -0.259, p = 0.047**
CAT score	**rho = 0.211, p = 0.029**	rho = 0.043, p = 0.661	**r = 0.300. p = 0.002**	**r = -0.295, p = 0.002**	**rho = 0.338, p = 0.010**	r = 0.245, p = 0.062
FEV1 (L)	**rho = -0.535, p < 0.001**	**rho = -0.255, p = 0.008**	**rho = -0.582, p < 0.001**	**rho = 0.566, 0 < 0.001**	**rho = -0.597, p < 0.001**	**r = -0.509, p < 0.001**
FEV1(%)	**rho = -0.308, p = 0.001**	rho = -0.011, p = 0.908	**rho = -0.409, p < 0.001**	**rho = 0.414, p < 0.001**	**rho = -0.315, p = 0.016**	**r = -0.364, p = 0.005**
RV (L)	rho = -0.076, p = 0.769	**rho = -0.359. p = 0.002**	rho = 0.140, p = 0.248	rho = -0.103, p = 0.397	rho = 0.064, p = 0.639	r = 0.086, p = 0.520
RV (%)	rho = 0.134, p = 0.267	rho = -0.099, p = 0.416	**rho = 0.259, p = 0.030**	**rho = -0.249, p = 0.038**	rho = 0.230, p = 0.085	**r = 0.259, p = 0.049**
TLC (L)	**rho = -0.392, p = 0.001**	**rho = -0.544, p < 0.001**	rho = -0.181, p = 0.134	rho = 0.183, p = 0.129	rho = -0.211, p = 0.114	r = -0.142, p = 0.288
TLC (% predicted)	rho = 0.138, p = 0.255	rho = -0.025, p = 0.836	**rho = 0.237, p = 0.048**	rho = -0.204, p = 0.091	rho = 0.229, p = 0.088	r = 0.198, p = 0.137
DLCO	**rho = -0.342, p < 0.001**	rho = -0.173, p = 0.152	**rho = -0.353, p = 0.003**	rho = 0.210, p =	**rho = -0.268, p = 0.042**	**r = -0.270, p = 0.040**
DLCO (% predicted)	rho = -0.202, p = 0.093	rho = -0.011, p = 0.930	**rho = -0.259, p = 0.030**	rho = 0.121, p = 0.318	rho = -0.182, p = 0.172	r = -0.179, p = 0.178
RV/TLC%	**rho = 0.345, p = 0.003**	rho = 0.052, p = 0.672	**rho = 0.451, p < 0.001**	**rho = -0.357, p = 0.002**	**rho = 0.461, p < 0.001**	**r = 0.418, p = 0.001**

Correlations calculated using either Pearson's R or Spearmans' Rho depending on the distribution of the data.
SNOT22: Sino Nasal Outcome Test 22, $SNOT22_{nasal}$: Nasal domain/upper airway domain of SNOT22.
CAT score: COPD Assessment Test. FEV1: Forced Expiratory Volume 1 second. RV: Residual Volume. TLC: Total Lung Capacity. DLCO: Diffusion Capacity for Carbon Monoxide.
R5Hz: Resistance at 5Hz (distal airways), R20Hz: Resistance at 20Hz (Proximal airway), R5-R20Hz: Difference in resistance from 5Hz and 20Hz (measure for small airways disease), X5: Reactance at 5 Hz, Ax: Area of reactance, Fres: Resonance Frequency.

Table 4
Correlations between PRM parameters and clinical scores and parameters.

	PRM^{Emph}	PRM^{fSAD}
$SNOT22_{nasal}$	rho = - 0.085, p = 0.525	rho = -0.208, p = 0.117
CAT score	r = 0.015, p = 0.909	r = 0.149, p = 0.264
FEV1 (L)	**r = -0.394, p = 0.002**	r = -0.230, p = 0.083
FEV1(%)	**r = - 0.566, p < 0.001**	r = -0.035, p = 0.797
RV (L)	**r = 0.690, p < 0.001**	r = 0.032, p = 0.816
RV (%)	**r = 0.575, p < 0.001**	r = 0.162, p = 0.229
TLC (L)	**r = 0.583, p < 0.001**	r = - 0.056, p = 0.678
TLC (% predicted)	**r = 0.401, p = 0.002**	**r = 0.324, p = 0.014**
DLCO	**r = - 0.511, p < 0.001**	r = -0.191, p = 0.155
DLCO (% predicted)	**r = - 0.608, p < 0.001**	r = - 0.100, p = 0.461
RV/TLC%	**r = 0.461, p < 0.001**	r = 0.175, p = 0.194

Correlations calculated using either Pearson's R or Spearman's Rho depending on the distribution of the data.
SNOT22: Sino Nasal Outcome Test 22, $SNOT22_{nasal}$: Nasal domain/upper airway domain of SNOT22.
CAT score: COPD Assessment Test. FEV1: Forced Expiratory Volume 1 second. RV: Residual Volume. TLC: Total Lung Capacity. DLCO: Diffusion Capacity for Carbon Monoxide.
R5Hz: Resistance at 5Hz (distal airways), R20Hz: Resistance at 20Hz (Proximal airway), DeltaR5R20Hz: Difference in resistance from 5Hz and 20Hz (measure for small airways disease), X5: Reactance at 5 Hz, Ax: Area of reactance, Fres: Resonance Frequency. PRM^{emp}: Parametric response mapping measure of emphysema, PRM^{fSAD}: Parametric Response Mapping measure of functional small airways disease.

Table 5
Correlations between PRM and Impulse Oscillometry parameters.

	PRM^{Emph}	PRM^{fSAD}
R5Hz	r = -0.171, p = 0.221	**r = 0.348, p = 0.011**
R20Hz	**r = -0.284, p = 0.039**	r = 0.233, p = 0.094
DeltaR5R20Hz	r = -0.068, p = 0.630	**r = 0.335, p = 0.014**
X5	r = -0.051, p = 0.714	r = -0.227, p = 0.102
Ax	r = -0.049. p = 0.731	**r = 0.322, p = 0.020**
Fres	r = 0.024, p = 0.862	r = 0.178, p = 0.201

Correlations calculated using Pearson's R
R5Hz: Resistance at 5Hz (distal airways), R20Hz: Resistance at 20Hz (Proximal airway), R5-R20Hz: Difference in resistance from 5Hz and 20Hz (measure for small airways disease), X5: Reactance at 5 Hz, Ax: Area of reactance, Fres: Resonance Frequency. PRM^{emp}: Parametric response mapping measure of emphysema, PRM^{fSAD}: Parametric Response Mapping measure of functional small airways disease.