**Systematic review of evidence for relationships between physiological and CT indices of small airways and clinical outcomes in COPD**

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**Abstract**

**Background:** Small airways disease (SAD) is considered pivotal in the pathology of COPD. There are numerous publications describing physiological and Computed Tomography (CT) imaging markers to detect SAD. However, there is no agreed gold standard and limited understanding of the clinical associations of these measures to disease outcomes.

**Methods:** We conducted a systematic review using Embase, Medline and Pubmed to explore the relationship between physiological and CT SAD measures in COPD (GOLD Stages 1-4). Furthermore, evidence linking these physiological measures with defined clinical outcomes such as health status, functional assessment and exacerbation frequency were summarised.

**Results:** The search yielded 1160 abstracts of which 19 met the search criteria. Six studies examined physiological and CT measures while 13 publications identified physiological measures and clinical outcomes. Strong correlations were seen between CT and physiological measures of SAD. Varying associations between physiological measures and defined clinical outcomes were noted.

**Conclusions:** Physiological and CT measures of SAD correlate and infer similar information. Physiological measures of SAD may offer valuable insight into clinical expression of the disease. A consensus on the standardisation and recommendation of tests to measure SAD is needed in order to better understand any clinical benefits of targeted drug therapy to the small airways.

Keywords

Small airways disease, COPD, Physiology, CT

## Introduction

As the burden of Chronic Obstructive Pulmonary Disease (COPD) increases globally, there is an expanding need to better phenotype and understand the pathophysiological mechanisms of the disease. COPD is currently the third leading cause of death worldwide and has a substantial healthcare cost with high numbers of hospital admissions1. While COPD is recognised as a heterogeneous disease with various underlying pathological processes, patients can present with a mixed picture; clinically, physiologically and radiologically. Such pathological processes include emphysema, chronic bronchitis and small airways disease (SAD). While some patients have a predominant pathological phenotype, many have a mix of these pathological processes. In 1968, studies by Hogg *et al* showed, that in health, small airways resistance accounted for only 25% of the total airways resistance, but this increased up to forty times in COPD and suggested this may affect ventilation distribution2.

The small airways are defined as those with an internal diameter of <2mm and without cartilage3. Occurring from approximately generation 8 onwards, these airways reduce in both diameter and length but increase in number exponentially leading to greater cross-sectional area with each generation4. The design of the airway tree thus results in sharp reduction in the velocity of air as it moves from central to peripheral airways. The nature of flow changes from turbulent in the large airways to laminar in the periphery, with diffusion occurring peripheral to the so called diffusion front located in the respiratory bronchioles and beyond4. Pathology in the small airways therefore manifests in physiological changes and the majority of evidence suggests the small airways to be the main contributor to airflow limitation in COPD2,5,6. Furthermore, Hogg *et al* have shown that small airways disease may precede the onset of emphysema and therefore it’s role in COPD is key7.

The small airways, due to their airway diameter and anatomical position in the lungs are difficult to assess and there is no agreed gold standard for the measurement of SAD8,9. Physiological and radiological measures are used to indirectly assess the small airways. CT is the most widely used imaging method for COPD10-13. Although there have been advances in the technology of CT imaging, the small airways are largely beyond its resolution. However, SAD can result in gas trapping and hence be estimated by several CT techniques. Analysis of expiratory scans have been used to estimate gas trapping. The percentage of voxels below -856HU on expiration has been suggested as a marker of gas trapping in asthma14. A later study in COPD, suggested the percentage of voxels between -850 and -910 HU to be a marker of gas trapping on expiratory CT15. However, these methods may incorporate low attenuation areas resulting from both gas trapping and emphysema. In order to try exclude emphysema, paired scans can be analysed. Comparison of the mean lung density between expiratory and inspiratory scans yields the ratio, MLD E/I. Another technique, Relative Volume Change (RVC) represents the change in relative lung volume between attenuation value ranges and has been suggested as a measure of SAD16. Other air trapping indices such as attenuation-volume index (AVI) have been proposed to quantify lobar air trapping17. Novel gas trapping markers include the Parametric Response Mapping (PRM) technique, which uses co-registration of paired inspiratory and expiratory scans to compare areas of low attenuation on a voxel to voxel basis18. Thus, several methods to quantify gas trapping have been described although there is no universally agreed optimal method. Furthermore, a variety of in house or commercial software analysis packages are used to compute these indices resulting in challenges for comparison across research centres.

Traditional lung function tests used to evaluate small airways function include spirometry and measurement of static lung volumes by body plethysmography 19. Spirometry is the most commonly used lung function test to diagnose and monitor lung disease progression. The Mid Expiratory Flow between 25 and 75% of the Forced Vital Capacity (FVC) (MEF25-75) is often used as an indication of SAD. Although this parameter may in part reflect the resistance in small airways, it is dependent on the FVC and if not adjusted for lung volume, has poor reproducibility, has little correlation with other small airways measures and does not provide additional information above FEV1 to clinical decision making9,20. Body plethysmography measures static lung volumes including Residual Volume (RV), Functional Residual Capacity (FRC) and Total Lung Capacity (TLC). Residual volume is a measure of gas trapping which results from airway closure due to prolonged expiratory time. The ratio of RV to TLC (RV/TLC) is a marker of gas trapping and is often used as a surrogate measure for SAD, although like CT indices it may be affected by emphysema9.

Methods such as inert gas washout and the Forced Oscillation technique (FOT) have increased in popularity recently, however their principles have been described since the 1950s19. In 1989, Dahlqvist *et al* discussed multiple and single breath washout tests in the potential detection of small airways obstruction21. The single breath washout test measures ventilation heterogeneity in large and small airways and may reflect small airways pathology22. The Multiple Breath Nitrogen Washout (MBNW) test differentiates ventilation heterogeneity that is convection dependent from that, which is diffusion convection dependent. In doing so, it differentiates ventilation heterogeneity in the conductive airways (Scond) from the acinar (Sacin) regions of the lung23. Verbanck *et al* studied these techniques further in the late 1990’s in both asthma and COPD24,25. These studies showed both Sacin andScond to be persistently abnormal in COPD24,25. The first reference to FOT dates back to 1956 where DuBois *et al*, showed the resonant frequency in health to be 6Hz at the end of a relaxed exhalation26. Respiratory system impedance to pressure oscillations is measured by superimposing these oscillations onto tidal breathing27. Impedance comprises of resistance and reactance. Resistance across frequencies may confer information about small airways resistance27. The frequency of dependence denoted R5-R20 has been shown to be a useful marker of small airways function28,29. Reactance at low frequencies and the difference between within breath inspiratory and expiratory reactance can give information about airway closure and airflow limitation23. Expiratory flow limitation is considered to occur beyond generation 7 during tidal breathing and extend more peripherally during a forced exhalation30.

Pathology in the small airways contributes to airway narrowing, expiratory flow limitation (EFL) and early airway closure, resulting in gas trapping5,31. Such mechanisms affect Inspiratory Capacity (IC) and may cause dynamic gas trapping during exercise resulting in reduced exercise tolerance and dyspnoea31. These factors together with airways resistance can increase the work of breathing in COPD and may be assessed by functional exercise tests such as the six minute walk test (6MWT) or incremental cycle exercise, among others32. Dyspnoea may be quantified by questionnaires such as the Medical Research Council (MRC), modified (mMRC), dyspnoea visual analogue or modified Borg scales33,34. In clinical practice and research, health status questionnaires such as the COPD Assessment Test (CAT) and the St George’s Respiratory Questionnaire (SGRQ) provide insight into the impact of COPD on a subject’s life35,36. The SGRQ also assesses a subject’s COPD-related symptoms and activity limitation. Inflammation in the small airways may contribute to exacerbations and in depth phenotyping may help identify patients that would benefit from fine particle inhalers37. Targeted treatment to the small airways aims to alleviate inflammation and airway narrowing37. Exacerbations are associated with a decline in lung function and impact patients’ lives and thus their underlying mechanisms and contributing factors deserve thorough investigation.

In order to improve our understanding of the utility of physiological measures and importance of small airways pathology in COPD, it is essential to review the current evidence linking physiologically measured SAD to clinical outcomes and CT measures. This will inform future discussions about which physiological and CT measures are most appropriate when assessing SAD in COPD. Standardisation would therefore enable more accurate and sensitive measurement of a therapeutic intervention, to optimise individual patient care.

### Objectives

The objective of this review is to summarise the evidence;

1. Relating physiological measures of SAD with health status, exercise tolerance and exacerbation frequency in COPD, and,
2. For the relationship between physiological and CT measure of SAD

# Methods

Bibliographic search and selection of papers

With renewed interest in physiological tests to measure SAD, we conducted a systematic literature review to ascertain the relationship between these and clinical outcomes and to explore their relationships with CT markers of SAD, in GOLD stages 1-4 COPD38. Regarding inclusion criteria; only studies in GOLD stages 1-4 COPD subjects where physiological and CT indices of SAD were compared or where physiological indices were correlated with health status, dyspnoea, exercise tolerance or exacerbation frequency, were included .Embase, Medline and Pubmed were initially searched for manuscripts published until June 2016. Database alerts then provided updates to ensure recent publications matching the search criteria were considered for inclusion, up until August 2017. Unpublished studies and manuscripts not in the English language were excluded. The reference list of articles obtained were checked for additional manuscripts. Abstracts were scanned for potential relevance by one researcher (KG) and a random 10% were checked by a second researcher (JC), to assess agreement. The authors of manuscripts were contacted if further clarity was required. Shortlisted manuscripts were independently quality assessed by two researchers using the Downs and Black quality assessment tool and any discrepancies discussed39. Data was extracted independently by two researchers with no data synthesis. Only studies that met the pre-defined selection criteria as stated in the protocol were included. The protocol and search criteria are registered on the PROSPERO register of systematic reviews, registration number 42016049849.

## Results

A diagram of the review process is detailed in Figure 1. Of the 1162 articles identified by the search, 21 had relevant content, were of acceptable quality and included in this review. Table 1 and Table 2 describe included studies with relevant details and aims.



Figure 1: Flow diagram detailing the results yielded by the bibliographic search, review process and study selection

Table : Summary of studies relating physiological and CT measures of SAD in COPD

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year,****(Country)** | **COPD Population (severity)** | **Age (SD) or [range]** | **Sample size** | **Sex (M/F)** | **Relevant Study Aim** | **Physiological method, indices** | **CT slice thickness, reconstruction interval (mm)** | **CT method, indices** |
| **Matsuoka *et al*, 2007 (Japan)40** | GOLD Stage 1-4 | 73 [57-89] | 32 | 28/4 | To explore the relationship between CT indices in the limited lung (that excludes emphysema) and lung function measures | Spirometry, FEF25-75% | 2, 10 | Paired, complete expiration, Relative area (RA)<--900-change, RA<900-950-change |
| **Matsuoka *et al*, 2008 (Japan)16** | GOLD Stage 1-4 | 71 [57-89] | 26 | 21/5 | To determine the attenuation threshold to detect and quantify air trapping using paired scans, and to compare this to pulmonary function | Spirometry, FEF25-75%, Helium dilution, RV/TLC | 1, 0.5 | Paired, complete expiration, RVC<-860, RVC860–950 |
| **O'Donnell *et al*, 2004****(UK)41** | GOLD Stage 1-4 | 54 (7) | 44 | Not stated | To relate CT small airways measures to sputum inflammatory cells and lung function small airways markers | Spirometry, FEF50%, Body plethysmography, RV/TLC | 1, 10 | Paired, complete expiration, MLD E/I |
| **Ostridge *et al*, 2016****(UK)42** | GOLD Stage 1-2 | 66 (12) | 24 | 16/8 | To explore the relationship between CT small airways markers and; BAL inflammatory markers and lung function small airway markers  | Spirometry, FEF25-75% | 0.75, 0.5 | Paired, complete expiration, MLD E/I |
| **Kim *et al*, 2015 (Republic of Korea)43** | GOLD Stage 1-4 | 65 (8.2) | 138 | 124/14 | To determine air trapping index (ATI) using non rigid registration and assess the association with small airways lung function parameters  | Spirometry, FEF25-75%, Body plethysmography, RV, RV/TLC | 0.75, 0.7 | Paired, complete expiration, ATI, EI, MLD E/I, Exp-856 |
| **Pompe *et al*, 2017 (Netherlands)12** | GOLD Stage 1-4 | 61 (7.6) | 95 | 69/26 | To explore the relationship between Parametric Response Mapping (PRM) CT measures and clinical and functional parameters | Body plethysmography, RV/TLC | <1, not stated | Paired, complete expiration, Functional SAD (PRMfSAD), MLD E/I |
| **Hartley *et al*, 2016****(United Kingdom)44** | GOLD Stage1-4 | 69 (8.2) | 81 | 54/27 | To assess the relationship between CT marker of air trapping and lung function | Method not statedRV/TLC | 0.75, 0.5 | Paired, expiration near FRC, MLD E/I |
| **Nagatani *et al*, 2015** **(Japan)17** | GOLD Stage1-3 | 70 (12.3) | 37 | 34/3 | To explore the association between CT markers, attenuation volume index (AVI) and RVC860–950  and lung function | Method not statedRV/TLC | 0.5, not stated | Paired, complete expiration, AVI, RVC860–950 (calculated from inspiration-expiration) |

GOLD: Global Initiative for Chronic Obstructive Lung Disease; CT: Computed Tomography; ATI: Air Trapping Index; BAL: Bronchoalveolar lavage; FEF25-75%: Forced Expiratory Flow between 25 and 75% of the Forced Vital Capacity; RV/TLC: Ratio of Residual volume to Total Lung Capacity; (RA)<--900-change: Change in low attenuation area below -900 HU between inspiration and expiration ; RA<900-950-change: Change in low attenuation area between -900 and -950 HU, between inspiration and expiration; RVC<-860: Change in relative lung volume below -860 HU between inspiration and expiration; RVC860–950: Change in relative lung volume between -860 and -950 HU between inspiration and expiration; MLD E/I: Mean Lung Density expiration to inspiration ratio; Exp-856: Percentage of voxels below -856HU on expiration; EI: Emphysema Index; PRM(fSAD): Parametric Response Mapping defined functional small airways disease

Table : Summary of studies relating physiological measures of SAD to health status, exercise tolerance and exacerbation frequency in COPD

| Author, year,(Country) | COPD Population (severity) | Age (SD) or [range] | Sample size | Sex (M/F) | Relevant Study Aim | Physiological method, indices | Outcome measure | Specific outcome measure |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Santus *et al*, 2014 (Italy)45 | GOLD Stage 2-4 | 72 (7) | n=60 | 48/12 | To assess the relationship between dyspnoea scores and sRAW as an indicator of peripheral airways resistance | Airways resistance by Body plethysmography, sRAW | Health status/quality of life | Dyspnoea using VAS |
| Timmins *et al*, 2014 (Australia)46 | GOLD Stage 1-2 Steroid naive | 66 (8.4) | n=14 | Not stated | To explore the relationship between health status and small airways measures  | Multiple breath washout, Scond, Sacin | Health status/quality of life | SGRQ |
| Mikamo *et al*, 2013 (Japan)47 | GOLD Stage 1-4 | 73 [60-84] | n=56 | 52/4 | To determine the predictors of SIIIN2SBW in COPD | Single breath washout tests, SIIIN2SBW (Delta N2) | Health status/quality of life | mMRC |
| Mikamo *et al*, 2014 (Japan)48 | GOLD Stage 1-4 | 73 [54-86] | n=74 | 71/3 | To determine the predictors of expiratory flow limitation in COPD | Forced oscillation technique, EFL | Health status/quality of life | mMRC |
| Haruna *et al*, 2010 (Japan)49 | GOLD Stage 1-4 | 71 (9) | n=65 | 65/0 | To identify relationships between oscillometry small airways markers and patient related outcomes in COPD | Impulse oscillometry, R5-R20, X5 | Health status/quality of life | SGRQ, mMRC |
| Anderson *et al*, 2012 (U.K)50 | GOLD Stage 1-4 | 66 [64-69] | n=57 | 33/24 | To explore the relationships and determine if IOS or spirometry indices were predictors of dyspnoea in COPD | Impulse oscillometry, R5-R20, X5, spirometry, FEF25-75 | Health status/quality of life | MRC |
| Mahut *et al*, 2012 (France)51 | GOLD Stage 1-4 | 65 (9) | n=108 | 77/31 | To compare different indices of airways resistance and then relate these with dyspnoea in COPD | Airways resistance by Body plethysmography, sRawtot, sRaweff, Forced oscillation technique, Rrsslope   | Health status/quality of life | MRC |
| Pisi *et al*, 2015(Italy)52 | GOLD Stage 1-4 | 68 (10) | n=100 | 80/20 | To explore the link between small airways dysfunction and health status in COPD | Impulse oscillometry, R5-R20 | Health status/quality of life | CAT |
| Lopes *et al*, 2014 (Brazil)53 | GOLD Stage 1-4 | 64 (7.9) | n=31 | 26/5 | To assess correlation between SBNW and other lung function parameters with 6MWD, dyspnoea and health status | Single breath washout tests, SIIIN2, static lung volumes by body plethysmography, RV, RV/TLC | Health status/quality of life and Exercise tolerance/ Functional assessment | 6MWD, mMRC, CAT |
| Boeck *et al*, 2016 (Switzerland)54 | GOLD Stage 2-3 | 69\* [60-75] | n=65 | 42/23 | To assess whether SIIIN2 and SIIIDTG washout tests are associated with important clinical end points in COPD and are independent of FEV1 | Single breath washout tests, SIIIN2, SIIIDTG | Health status/quality of life and Exercise tolerance/ Functional assessment | mMRC dyspnoea score, exercise induced desaturation during 6MWT (minimal SpO2 during 6MWT) and exercise capacity (6MWD) |
| Ofir *et al*, 2008 (Canada)55 | GOLD Stage 1Asymptomatic | 64 (7) | n=21 | 13/8 | To examine mechanisms of dyspnoea and exercise intolerance during exercise insymptomatic smokers with GOLD stage I COPD | Spirometry, FEF25-75%, Body plethysmography, RV, RV/TLC, single breath washout, CV/VC, CC/TLC | Exercise tolerance/ Functional assessment | Exertional dyspnoea during exercise at 80W |
| Chen *et al*, 2015 (China)56 | GOLD Stage 1-4 | 71 (7.9) | n=105 | 90/15 | To determine which physiological factors are responsible for dynamic hyperinflation during the 6MWT | Spirometry, FEF25-75, FEF50, FEF75 | Exercise tolerance/ Functional assessment | Dynamic hyperinflation during the 6MWT as measured by ∆IC>0.0 L |
| Incorvaia *et al*, 2008 (Italy)57 | GOLD Stage 2-3, half frequent, half infrequent exacerbators | 72 [55-88] | n=76 | 45/29 | To explore small airways dysfunction in frequent vs infrequent COPD subjects | Spirometry, FEF25-75% | Exacerbation frequency | Mean number of exacerbations/year |

\*Median; GOLD: Global Initiative for Chronic Obstructive Lung Disease; sRAW: Specific airways resistance; Scond: Ventilation heterogeneity in the conductive airways ;Sacin: Ventilation heterogeneity in the acinar region of the lungs; SBNW: Single breath nitrogen washout; EFL: Expiratory Flow Limitation; R5-R20: Peripheral airways resistance; X5: Reactance at 5 Hz as a marker of peripheral obstruction; sRawtot: Total specific airways resistance; sRaweff: Effective specific airways resistance; Rrsslope: The resistance/ frequency slope between 4 and 16 Hz as a marker of peripheral resistance; VAS: Visual Analogue Scale; SGRQ: St George’s Respiratory Questionnaire; 6MWD: 6 minute walk distance; SIIIN2: Phase III slope of nitrogen single breath washout test; SIIIDTG: Phase III slope of double tracer gas single breath washout test; FEV1:Forced expiratory volume in the first second; 6MWT: 6 minute walk test; RV: Residual volume; RV/TLC: Ratio of Residual volume to Total Lung Capacity; FEF25-75%: Forced Expiratory Flow between 25 and 75% of the Forced Vital Capacity; CV/VC: ratio of closing volume to vital capacity; CC/TLC: Ratio of closing capacity to total lung capacity; FEF50: Forced expiratory flow at 50% of the Forced Vital Capacity; mMRC: Modified Medical Research council dyspnoea scale; MRC: Medical Research council dyspnoea scale; CAT: COPD Assessment test; SpO2: Blood oxygen saturation level; ∆IC: Change in Inspiratory Capacity after exercise;

CT gas trapping markers

The relationship between physiological and CT small airways measures was explored in eight studies included in this review. Matsuoka *et al* published studies in 2007 and 2008, both of which considered CT indices derived from paired inspiratory and expiratory scans16,40. Their 2007 study showed strong correlations between Relative lung Area (RA)<--900-change and RA<900-950-change, with FEF25-75% predicted (r= -0.610 and -0.898 respectively) 40. Their later 2008 study showed RVC860–950 to have the strongest correlation with other measures; (FEF25-75% r = –0.75, p < 0.001) and RV/TLC (r = 0.70, p < 0.001), in groups with and without extensiveemphysema and therefore proposed it’s use as a marker of SAD in COPD16. Nagatani and colleagues noted correlations between air trapping indices, RVC860–950 and RV/TLC (r=-0.583) and AVI and RV/TLC (r=-0.726)17. O'Donnell *et al* found strong correlations between MLD E/I and MEF50% (r= -0.72) and RV/TLC (r=0.71)41 while Hartley *et al* noted a moderate correlation between MLD E/I and RV/TLC (r=0.510)44. Strong correlations between MLD E/I and FEF25-75% (r −0.54, p=0.03) were also noted by Ostridge *et al* 42.

Two studies investigated CT markers of SAD derived from non-rigid registration techniques12,43. Kim *et al* showed the Air trapping index of whole lung to better correlate with FEF25-75% (r=-0.66 vs. -0.50), RV (r=0.62 vs. 0.50), and RV/TLC (r=0.68 vs. 0.43), than emphysema index (EI)43. Using parametric response mapping, Pompe *et al* showed a stronger correlation between gas trapping as defined by RV/TLC and PRMfSAD compared to that with MLD E/I (spearmans rho=0.779 and spearmans rho=0.736 respectively)12. In addition, multivariate analysis showed PRMfSAD to be associated with RV (β= 6.78, p < 0.001) as well as total lung capacity (TLC) (β=7.90, p < 0.001) and alveolar volume (VA) (β=7.79, p < 0.001)12.

### Symptoms and Health status

The association between physiological small airways measures and health status was assessed in 10 of the 13 studies which considered clinical outcomes. Santus *et al*; found sRAW to be the only predictor of dyspnoea at rest45. The study by Timmins *et al*; showed SGRQ total score correlated with Scond (r-0.62, p=0.02)46, which is a marker of gas mixing in the small conducting airways23. Furthermore, the SGRQ impact score showed strong relationships with Scond (r-0.61, p=0.02) and Sacin (rs 0.53, p=0.05), a marker of gas mixing in the acinus23. Mahut *et al* found sRawtot, sRaweff and Rrsslope (FOT) correlated with MRC dyspnoea (r = 0.24, P = 0.012; r = 0.23, P = 0.017 and r= - 0.25, p=0.01 respectively).

Both studies by Mikamo *et al* examined the relationship between small airways physiological markers and the mMRC dyspnoea scale47,48. Delta N2 correlated positively with the mMRC scale (P<0.001, Rho=0.490) but did not correlate with CAT score. In the 2014 study, EFL correlated with mMRC (p=0.016 and rho=0.282) but showed no relationship with CAT. Pisi *et al* found subjects with abnormal R5-R20>0.03kPa.s/L had significantly lower CAT<10/CAT≥10 and therefore poorer health status52. Haruna and colleagues showed significant correlations of oscillometric measures of SAD and health status49. Parameters R5-R20 and X5 were significantly correlated with the three components of the SGRQ and total SGRQ score (r = 0.31-0.51, p <0.01) and the MRC (r = 0.27-0.51, p <0.01). The most significant contributing factor in predicting MRC was R5-R20 (R2 = 0.27) while X5 was the most significant contributor to SGRQ activity domain (R2 =0.26). Conversely, a primary care study by Anderson *et al* found dyspnoea was not predicted by oscillometric parameters R5-R20 (p=0.448), X5(p=0.427) or spirometric indices (FEF25-75 p=0.977) of SAD50.

Boeck *et al* looked at small airways tests in relation to both functional assessment and health status22. Results showed SIIIN2 was associated with patient reported dyspnoea, (p=0.001). Elevated SIIIN2 was also associated with mMRC dyspnoea score (p=0.004) and these associations were independent of FEV1. Lopes *et al* noted moderate correlations between SIIIN2SBW and CAT (r = 0.728; p = 0.0001). Furthermore, multivariate analyses showed SIIIN2SBW was the only independent predictor of CAT score (R2 = 0.586; p = 0.0001), and mMRC scale (relative risk = 1.14; p = 0.0001).

### Exercise tolerance/Functional assessment

Four studies included in this review assessed the relationship between SAD and exercise tolerance in COPD22,53,55,56. In a multivariate analysis, Chen *et al* showed only FEF50% to be a predictor of hyperinflation during exercise56. Boeck *et al* found SIIIN2SBW was associated with exercise induced desaturation and exercise capacity (6MWD) (p<0.001 and p=0.047 respectively) and these associations were independent of FEV154. Lopes *et al* noted a strong negative correlation between SIIIN2SBW and 6MWD (r =-0.796; p = 0.0001) and moderate correlations between 6MWD and RV (r =-0.651; p = 0.0001) and (RV/TLC) (r =-0.600; p = 0.0004)53. A multiple regression analysis by Ofir *et al*; did not implicate small airways tests (spirometry, body plethysmography, single breath washout indices) as contributors to exertional dyspnoea55.

### Exacerbation frequency and severity

Incorvaia *et al* found that frequent exacerbators had significantly lower FEF25-75 compared to infrequent exacerbators(624 ± 418 mL versus 865 ± 372 mL (p = 0.002).

## Discussion

Small airways disease (SAD) is considered a central pathological process in COPD and with evidence that it may precede the onset of emphysema it is potentially of great importance in understanding early disease58. Due to the difficulty of obtaining *in vivo* biological samples, there is limited understanding of pathological developments in real time within the small airways. Hence, other non-invasive markers of SAD such as CT and physiological indices have been developed. A comprehensive understanding of both physiological and CT markers of SAD may enable better phenotyping of COPD, mapping of severity and progression, and assessment of therapeutic interventions. With improvement in physiological and CT imaging techniques, there is significant interest in the non-invasive measurement of SAD. This systematic review is, to our knowledge, the first to summarize the evidence relating physiological measures of SAD to clinically important outcomes, in COPD. Furthermore, it is the first to collate data which explores the relationship between physiological and CT markers of SAD.

### CT gas trapping markers

The lack of standardisation of CT defined SAD is highlighted in this review with RA<900-950-change, RVC860–950 and MLD E/I all being reported. Five of the studies in this review showed moderate to strong correlations between MLD E/I and physiological indices of small airways disease. Strong correlations have also been documented between indices of SAD derived from non-rigid techniques and physiological indices, although only two studies have explored this so far. Whether these markers provide additional value beyond MLD E/I is unclear with Kim *et al* finding the association to be similar to that noted with MLD E/I43 ,whereas Pompe *et al* showed PRMfSAD to correlate better with RV/TLC than MLD E/I. For the calculation of MLD E/I, processing requirements are less demanding and analysis software more readily available compared to non-rigid registration analyses. However, the advantage of non-rigid registration techniques to differentiate between emphysema and SAD may provide clinicians with important information. Although, strong associations between various CT markers of SAD and either spirometric or lung volume measures have been documented, the appropriateness of spirometric measures of SAD is debatable59. As technology improves, it is hoped that both CT and physiological techniques will be refined, enabling more specific SAD measures and standardisation. There is mounting evidence that FOT and inert washout techniques may be more specific in the measurement of SAD than spirometry, and associate with clinical outcomes47-49,51,60,61. Studies comparing CT measures, (MLD E/I and indices derived from non-rigid techniques such as PRM) with inert gas washout and oscillometric parameters are needed. This would aid in the validation of such techniques for the measurement of SAD.

### Symptoms and Health status

This review shows correlations between physiological indices of SAD and dyspnoea, health status and exercise tolerance, range from weak to strong. However, the studies linking SAD and dyspnoea are of clinical interest and unlikely to be purely circumstantial45,47-49,51,53,54. The significant associations documented between SAD and health status in particular those noted by Lopes *et al* imply but cannot conclude that subjects with worse SAD have worse health status46-49,52,53. The strongest evidence for this association stems from studies using indices of SAD derived from both single and multiple breath inert gas washout techniques46,47,53. These techniques are therefore promising tools which require further investigation, albeit they are not used routinely in clinical practice. Collectively, the studies in this review suggest SAD impacts the lives of COPD subjects, including the symptoms experienced and activity levels reached. The opposing study by Anderson *et al*, which did not find an association between SAD and dyspnoea may highlight the heterogeneous nature of COPD and COPD populations. These populations may differ by smoking, health status, emphysema extent and treatment. The causes of decline in health status are often multifactorial and influenced by many aspects which may explain the lack of correlation between SAD and indicators of health status in both Mikamo *et al* studies47,48. Furthermore, discrepancies may arise because of the variation in tests used to measure SAD. Different tests are used which in turn vary in measurement technique and analysis, making comparison between measures and studies challenging.

### Exercise tolerance/Functional assessment and exacerbation frequency

Another important clinical question, is whether subjects with worse SAD have reduced functional ability and exercise tolerance. The studies of Boeck *et al* and Lopes linking the phase III slope of SBNW, independent of FEV1 to exercise tolerance, is of interest and warrants further research 53-56. Conversely, Ofir *et al* found physiological evidence of SAD in COPD, but these measures were not contributing factors to exertional dyspnoea in multivariate analysis55. This may be explained by the relatively small sample size55 (n=21) and highlights the need for larger cohorts to be examined to see if this finding is confirmed. Only one study by Incorvaia *et al* addressed the important question of whether COPD subjects with worse SAD experienced more exacerbations than those without57. Frequent exacerbators had significantly lower FEF25-75, a finding of clinical relevance57. However, this study reported absolute values for FEF25-75 and therefore age and gender influences have not been adjusted for. This should be considered when interpreting the results. Longitudinal studies capturing exacerbation frequency are needed to understand the relevance of the small airways tests in phenotyping COPD. Determining if subjects with an exacerbation phenotype have worse SAD may provide insight into disease mechanisms and therapeutic targets.

### Limitations

There are limitations for each of the outcome measures discussed within this systematic review. The lack of optimal methods for the assessment of SAD is a limitation when trying to understand associated relationships. All the included CT studies examined the relationship between CT and spirometry or plethysmography SAD indices16,40-42. The use of FEF25-75% as a marker of SAD is now widely considered inappropriate, and it’s limitations must be acknowledged59. Technical and analytical limitations of both CT and physiological measures exist. CT is measured supine whereas physiological tests are measured upright. Furthermore, in COPD, CT measured gas trapping cannot be considered as SAD exclusively, as its measure may reflect air in emphysemic areas and/or be influenced by changes in perfusion62. The effects of aging and obesity on the small airways should also be considered when interpreting any marker of SAD23,63. Although many studies have measured physiological tests of SAD and either CT or the defined clinical outcomes, unless the pre-defined selection criteria were met, the study was not included in our results. For example, Hersh *et al* studied the use of paired CT scans in measuring gas trapping in the COPDGene study11. Although both physiological and CT indices of SAD were measured in smokers with and without COPD, the association between these measures were not reported for the COPD subjects specifically as a separate subgroup, and therefore could not be included. Other reasons for exclusions included insufficient information, although every effort was made to contact authors and seek clarity.

### Small airways disease and disease severity and treatment

The ECLIPSE study was not included in this review because physiological and CT markers of SAD were not compared64. However, in terms of relationships between SAD and severity of disease, they found the frequency dependence of resistance (R5-R20) related to GOLD stage severity64. Pompe *et al* has shown the most severe classification of COPD (GOLD stage IV) has the highest PRMfSAD % index12. Surprisingly, in mild and moderate COPD (GOLD stage I and II), SAD as defined by PRMfsad has been shown to be the main contributor to lung function decline65. Furthermore, in subjects with early disease but without airflow obstruction (GOLD stage 0), only PRMfSAD but not PRMemph was associated with FEV1 decline65. These findings contribute to the hypothesis that SAD is an important pathological feature in both early and established COPD.

SAD measures, including FOT indices may be used to evaluate treatment response in COPD46,52,66. The finding of Timmins and colleagues that FOT indices of SAD and SGRQ scores improved with ICS/LABA treatment despite no significant change in FEV1 suggest FOT could be a clinically useful tool in measuring treatment response in the small airways in COPD66. Other studies have also used FOT to measure treatment response in the small airways52,66. However, treatment effects are difficult to interpret as there are no Minimal Important Differences (MID) published for FOT indices66. First, standardisation of techniques and methods between centres is needed. The forced oscillation technique is not routinely used in clinical practice and not yet incorporated into international guidelines which makes the interpretation of indices challenging. Secondly, the MID for the standardised indices will then need establishing.

This systematic review provides the first step in understanding the current evidence of physiological and CT measures of SAD, in COPD. It exposes the lack of standardisation of these measures of SAD and suggests a consensus opinion is needed by international respiratory societies for the measurement of radiological and physiological tests to measure SAD. With emerging evidence for the utility of FOT and inert washout techniques for assessing SAD46,47,53,54, further studies are needed to support any recommendation of such indices into routine clinical practice. In particular, studies comparing CT measures and more specific physiological markers of SAD such as FOT and washout indices, are called for. These physiological measures need inclusion in large cohort studies of established COPD and early disease, to better understand their clinical relevance in COPD and potential to detect early disease, respectively.

## Conclusion

As a central pathological process in COPD, the understanding and quantification of SAD is of critical importance. Physiological and CT measures of SAD are widely used in a bid to understand its role in COPD in terms of disease progression and therapeutic intervention. Using a systematic review we have shown CT and physiological measures of SAD correlate and seem to confer similar information. Albeit varied, there is some evidence that physiological measures of SAD are associated with dyspnoea, exercise tolerance and exacerbations in COPD, and may offer valuable insight into disease phenotype. Given the importance of SAD in COPD, more research is needed to determine the most appropriate tool to measure it and what constitutes minimal important differences, so response to targeted therapies can be evaluated. This review highlights the necessity for a consensus opinion by international respiratory societies on the standardisation and recommendation of radiological and physiological tests to measure SAD.

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