

# An overview of exacerbations of chronic obstructive pulmonary disease: Can tests of small airways' function guide diagnosis and management?

Nowaf Y. Alobaidi<sup>1,2</sup>, James A. Stockley<sup>3</sup>, Robert A. Stockley<sup>4</sup>, Elizabeth Sapey<sup>1</sup>

<sup>1</sup>Centre for Translational Inflammation Research, Institute of Inflammation and Ageing, University of Birmingham, Departments of <sup>3</sup>Lung Function and Sleep and <sup>4</sup>Respiratory Medicine, University Hospitals Birmingham, NHS Foundation Trust, Birmingham, UK, <sup>2</sup>Respiratory Therapy Department, College of Applied Medical Sciences, King Saud Bin Abdul-Aziz University for Health Sciences, Al Ahsa, Saudi Arabia

#### Address for correspondence:

Mr. Nowaf Y. Alobaidi, Centre for Translational Inflammation Research, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, B15 2GW, UK. E-mail: nya813@student.bham.ac.uk

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#### Abstract:

Chronic obstructive pulmonary disease (COPD) is common and debilitating. Most patients with COPD experience intermittent, acute deterioration in symptoms which require additional therapy, termed exacerbations. Exacerbations are prevalent in COPD and are associated with poor clinical outcomes including death, a faster decline in lung health, and a reduced quality of life. Current guidelines highlight the need to treat exacerbations promptly and then mitigate future risk. However, exacerbations are self-reported, difficult to diagnose and are treated with pharmacological therapies which have largely been unchanged over 30 years. Recent research has highlighted how exacerbations vary in their underlying cause, with specific bacteria, viruses, and cell types implicated. This variation offers the opportunity for new targeted therapies, but to develop these new therapies requires sensitive tools to reliably identify the cause, the start, and end of an exacerbation and assess the response to treatment. Currently, COPD is diagnosed and monitored using spirometric measures, principally the forced expiratory volume in 1 s and forced vital capacity, but these tests alone cannot reliably diagnose an exacerbation. Measures of small airways' function appear to be an early marker of COPD, and some studies have suggested that these tests might also provide physiological biomarkers for exacerbations. In this review, we will discuss how exacerbations of COPD are currently defined, stratified, monitored, and treated and review the current literature to determine if tests of small airways' function might improve diagnostic accuracy or the assessment of response to treatment.

#### Keywords:

Chronic obstructive pulmonary disease, diagnosis, exacerbation, monitoring, small airway dysfunction, small airway tests

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and progressive airflow limitation which is believed to be mainly the result of chronic inflammation.<sup>[1]</sup> Many patients with COPD experience acute events termed exacerbations, which are associated with additional morbidity and increased mortality. Currently, patients self-report exacerbations on the basis of a perceived deterioration in symptoms.

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In 1987, Anthonisen *et al.* defined these episodes by a deterioration of 3 key symptoms (breathlessness, sputum volume, and sputum purulence).<sup>[2]</sup> Whereas sputum volume and purulence can be observed, it is difficult to define a change in breathlessness and there are no objective biomarkers which can measure this. Small airways' dysfunction is a feature of COPD both when stable and during exacerbations. In this review, we will discuss how exacerbations of COPD are currently defined, stratified, monitored, and treated and review the

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evidence for whether tests of small airways' function might explain the change in dyspnea and hence improve diagnostic accuracy or response to treatment.

## The Importance of Chronic Obstructive Pulmonary Disease

COPD is an important, worldwide public health challenge.<sup>[3]</sup> It is the fourth leading cause of death globally<sup>[4]</sup> and is projected to be the third leading cause of death by 2020.<sup>[5]</sup> Population studies suggest COPD affects 10% of adults in Europe and the USA, but the prevalence is predicted to increase due to the continual exposure to risk factors and a globally aging population.<sup>[5]</sup> Although COPD is more common in men, recent evidence indicates the prevalence has increased in women, reflecting increases in smoking rates.<sup>[3]</sup> In the UK, one in eight emergency hospital admissions are for COPD,<sup>[3]</sup> and COPD is estimated to cost the UK economy  $\leq 1.9$  billion each year.<sup>[6]</sup>

While COPD has become an important public health issue in the Middle Eastern countries, it remains underdiagnosed and underrecognized.<sup>[7]</sup> Here, the most common risk factors for developing COPD are tobacco smoking, waterpipe smoking ("shisha"), passive smoking, biomass fuel smoke exposure, and pollution.<sup>[7]</sup> The prevalence of smoking in men and women varies but is high (reported as 20% of men and 1% of women in Iran, 48% of men and 31% of women in Lebanon, 62.0% of men and 21% of women in Syria and 43% of men and 12% of women in Turkey).<sup>[8,9]</sup> In the Middle East, approximately 25%–45% of COPD patients are never smokers but many are exposed to biomass fuel smoke.<sup>[7]</sup>

COPD is characterized by persistent respiratory symptoms and airflow limitation.<sup>[1,3]</sup> A combination of small airways' disease and parenchymal destruction causes the airflow obstruction which defines COPD,<sup>[4]</sup> but COPD is heterogeneous, encompassing several clinical/pathological conditions including chronic bronchitis, bronchiectasis, and emphysema.<sup>[3]</sup> COPD can be modified with acute acting therapies but is not curable and is usually slowly progressive.<sup>[10]</sup> In the ECLIPSE study, the mean rate of decline in forced expiratory volume in the 1 s (FEV<sub>1</sub>) was 33 ml/year, but there was substantial variability across participants and the rate of progression only exceeded the normal age-related decline in a proportion of patients.<sup>[11]</sup>

In Saudi Arabia, the diagnosis and management of COPD patients follow the Saudi Initiative for Chronic Airway Diseases (SICAD).<sup>[8]</sup> Although the SICAD panel is adapted from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), there are some differences. In the SICAD panel, COPD is classified into

three groups based on symptoms and the risk of future exacerbations, in comparison to four groups in GOLD.<sup>[4,8]</sup> Symptoms are assessed using the COPD Assessment Tool (CAT), and risk of exacerbation is assessed by the number of exacerbations in both the SICAD panel and GOLD. In SICAD, Class I is the same as GOLD Group A where Class II is equivalent to GOLD Group B, and Class III reflects both GOLD Groups C and D. The SICAD classifications of COPD are presented in Table 1.

## Exacerbation of Chronic Obstructive Pulmonary Disease: Definitions, Severity, and Importance

In many patients with COPD, periods of disease stability are punctuated with acute episodes of increased symptoms, termed exacerbations. Approximately 75% of COPD patients experienced at least one exacerbation per year,<sup>[12]</sup> with the frequent exacerbation phenotype being defined by two or more episodes per year.<sup>[13]</sup> Exacerbations are associated with substantial mortality and morbidity, a reduction in the quality of life and lung function.<sup>[14]</sup> Exacerbations are also associated with significant healthcare utilization and cost.<sup>[15]</sup>

Despite the significant cost of exacerbations, their pharmacological treatments (corticosteroids, short-acting bronchodilators (SABD) with or without antibiotics) have changed little over 30 years. This is in stark contrast to other acute deteriorations of chronic disease, where treatment advancements have revolutionized outcomes.

GOLD<sup>[4]</sup> defines exacerbation severity by the treatment or level of care needed by the patient. Mild exacerbations require an increase in SABD alone. Moderate exacerbations are treated with SABD plus oral corticosteroids with or without antibiotics. Severe exacerbations require hospitalization or an emergency room visit. There are limitations to this definition. First, exacerbations are defined by symptoms. COPD is a heterogeneous condition, and patients describe variability in their daily burden of symptoms, making acute changes sometimes difficult to identify both at onset and conclusion.<sup>[4]</sup> The symptom-based definition does not provide any insight into pathology or treatment requirements apart from sputum purulence, which has been associated with bacterial infection and a clinical improvement when treated with antibiotics.<sup>[16]</sup> Second, patients with COPD suffer from comorbidities; breathlessness and cough can be a manifestation of these other conditions, including cardiac disease, anxiety, deconditioning and pneumonia, as well as COPD. The use of treatment or place of care provision to define severity also has limitations. COPD is more common with increasing age and often co-occurs with frailty. Age, frailty, and multimorbid disease are risk factors for hospital admission, and some patients

**Table 1: SICAD Classifications of COPD**

SICAD class	Features	Number of exacerbations in the past year.	CAT score	Equivalent to GOLD
Class I	Less symptoms, low risk of exacerbation	0-1	≤ 10	Group A
Class II	More symptoms, low risk of exacerbation	0-1	≥ 10	Group B
Class III	High risk of exacerbation	≥ 2	Any score	Group C and D

may require hospital care due to a low threshold for increased support rather than severity of the respiratory event.<sup>[17]</sup>

Minimizing the effect of the current exacerbation and preventing the development of future events are major goals of most COPD guidelines.<sup>[3,4,8]</sup> The current management strategies do not usually stratify patients by potential cause. However, there is increasing evidence that not all exacerbations are the same, both in cause, inflammatory infiltrate, and response to treatment.

### Pathogenesis of Chronic Obstructive Pulmonary Disease Exacerbations

Exacerbations of COPD are associated with several potentially causative factors, including environmental changes and infections, which can be bacterial or viral. Studies indicate that 50%–70% of exacerbations are caused by respiratory infections,<sup>[18]</sup> 10% are caused by environmental-related causes<sup>[19]</sup> and approximately 30% have no identifiable cause.<sup>[20]</sup>

Potentially pathogenic bacteria have been identified in approximately 30%–50% of sputum cultures in studies during exacerbations,<sup>[21,22]</sup> and *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, and *Pseudomonas aeruginosa* are the most common isolated.<sup>[21,23]</sup> Approximately 20%–40% of exacerbations are associated with viruses.<sup>[24]</sup> Rhinovirus is implicated for the majority of these episodes<sup>[25]</sup> with a lower percentage associated with parainfluenza and adenoviruses. Of note, exacerbations caused by viral infections are associated with a protracted recovery and a greater effect on healthcare utilization.<sup>[26]</sup> This probably reflects the limited treatment options for viral infections. Approximately 9% of exacerbations are thought to be caused by environmental pollution,<sup>[19]</sup> which is an increasing global health concern.

Most studies suggest inflammation is increased during exacerbations,<sup>[27]</sup> and just as with stable disease, most studies also report an increase in neutrophil counts in the bronchial walls and bronchial secretions during exacerbations.<sup>[28,29]</sup> Airway inflammation leads to increased airway edema, increased bronchial tone, and increased mucus secretion or plugging,<sup>[30]</sup> especially of the small airways. These airway changes result in increased airway resistance, worsening expiratory flow limitation (EFL), and ventilation/perfusion mismatch.<sup>[30]</sup>

The deterioration in EFL leads to increased air trapping and hyperinflation (which increases the work of breathing), as well as insufficient time to empty the lungs between the rapid and shallow breathing patterns present during exacerbations.<sup>[31]</sup>

Studies have focused on dividing exacerbating COPD patients into those with purulent or colored sputum and those without. Although most describe a relationship with bacteria and sputum purulence, with sputum purulence having an 85% sensitivity and specificity for bacterial etiology in one study,<sup>[16,32,33]</sup> others studies have not.<sup>[34]</sup> More recently, Bafadhel *et al.*<sup>[35]</sup> phenotyped COPD exacerbation into four biological groups: 55% of exacerbations were associated with bacteria, 29% with viruses, 28% with significant sputum eosinophilia, and 14% with no inflammation (termed pauci-inflammatory). Of note, these groups did not signify differences in symptom burden or clinical presentation, including sputum purulence, which could not discriminate between causes.

### Clinical Tools used to Assess Exacerbation Responses in Trials

Exacerbations of COPD have both short-term clinical impacts and long-term clinical effects. Symptom recovery is variable: half of community-treated exacerbations recover within a week but 14% take up to 35 days, and some patients do not appear to return to baseline.<sup>[26]</sup> Assessing response to treatment or recovery is crucial both when managing COPD patients, and when evaluating novel putative therapies and symptoms, spirometry and inflammatory changes are the most commonly used methods to assess exacerbation responses.

Patient-reported outcomes validated for exacerbations include the St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and Exacerbation of Chronic Pulmonary Disease Tool (EXACT). The SGRQ can identify exacerbation and recovery;<sup>[36]</sup> but, this questionnaire is long, complex for patients to complete when acutely unwell, and requires a scoring algorithm to assess response. CAT is shorter, far easier to complete and scored using simple addition,<sup>[37]</sup> with scores associated with systemic inflammation and decline in FEV<sub>1</sub> at exacerbation.<sup>[38]</sup> EXACT is still awaiting FDA approval for exacerbations<sup>[39]</sup> but has been validated for use in this setting.<sup>[40]</sup> There are also a number of symptom diary cards which have been used in clinical studies.<sup>[26,32]</sup>

Spirometry has been used in clinical trials during exacerbations, and FEV<sub>1</sub> is commonly the primary outcome for these COPD studies. FEV<sub>1</sub> strongly correlates with recovery<sup>[41]</sup> but has only a weak association with symptoms.<sup>[42]</sup> There have been a number of negative studies assessing therapies at COPD exacerbation where FEV<sub>1</sub> was the primary endpoint, including intravenous aminophylline<sup>[43]</sup> and erdosteine.<sup>[44]</sup> In spite of the utilization of FEV<sub>1</sub> in clinical trials, FEV<sub>1</sub> has shown to have several limitations. Being a forced, effort-dependent maneuver, patients may struggle during episodes of increased breathlessness and even in the stable state, variability in measurements is common. For example, a study which only accepted measurements following three blows which technically acceptable (that is, they varied by  $<\pm 5\%$  and by  $\pm 0.1$  L)<sup>[45]</sup> described a mean change of 22 ml (standard deviation 170 ml) in FEV<sub>1</sub> repeated after a 20 min interval in health.<sup>[46]</sup>

Inspiratory capacity (IC) (the maximum volume inhaled from end-tidal exhalation) is the most common measurement of lung volume and capacity used in clinical trials of exacerbation. IC has a strong association with symptoms, response to treatment, and recovery.<sup>[47,48]</sup> Although lung volumes can be obtained using spirometry with inert gas analyzers or plethysmography, they are not similar and lung volumes in patients with moderate–severe airflow obstruction can be underestimated by dilution methods.<sup>[49]</sup> Moreover, lung volumes measured by plethysmography can be overestimated if inaccurately measured.<sup>[50]</sup>

Several inflammatory markers have been used to assess COPD exacerbations, although not as primary endpoints in clinical trials. Poor clinical outcomes have been related to persistent systemic inflammation<sup>[51]</sup> with higher levels of serum C-reactive protein present in those with no symptom recovery or those with recurrent exacerbations.<sup>[52]</sup> Fibrinogen has been proposed as putative biomarker of risk of exacerbations, with higher levels associated with increased admissions.<sup>[53]</sup> However, inflammatory mediators have limitations in clinical studies (as recently reviewed).<sup>[54]</sup> First, inflammation is not a feature of all exacerbations (the pauci-inflammatory events) and they are also extremely variable, especially in pulmonary secretions.<sup>[55]</sup> Without a “baseline” measure, it is difficult to assess whether the changes indicate exacerbation onset or recovery.

The limitations of the current tools to identify exacerbations or map recovery/response, especially when dyspnea is the only or main symptom have generated interest in other physiological tests which might provide more sensitive and specific measures, most notably tests of small airways' function.

## Small Airways' Dysfunction in Chronic Obstructive Pulmonary Disease

Although COPD is defined by airflow obstruction, there is evidence that small airways' disease (defined as airways of  $<2$  mm diameter) might be the earliest pathological manifestation.<sup>[56,57]</sup> Studies by Hogg *et al.* reported a significant loss of small airways preceding the development of airflow obstruction or emphysema in COPD patients.<sup>[57]</sup> These findings were supported by a study of small airways' function in patients with Alpha 1 Anti-trypsin Deficiency (AATD)-related COPD.<sup>[56]</sup> In this study tests of small airways dysfunction (SAD) preceded conventional spirometric evidence of COPD and all with spirometric evidence of COPD had evidence of severe small airways' dysfunction (only 17.5% of the predicted value), despite the airflow obstruction being only mild (65% of the predicted FEV<sub>1</sub> value). Other studies have shown that a reduction in small airways' diameter was present in resected lungs of smokers with airflow obstruction<sup>[58]</sup> and progressive increments in SAD in COPD correlated with health status.<sup>[59]</sup> There are a number of different tests which can be used to assess small airways' function in COPD, including physiological and imaging studies, as described below.

## Measuring Small Airways' Dysfunction

### Expiratory flows

Flow measurements obtained from the expiratory curve include maximal expiratory flow at 75% of forced vital capacity (FVC), at 50% of FVC, and at 25% of FVC, and mid-maximal expiratory flow (MMEF). MMEF is one of the most commonly studied measures of small airway function, obtained by performing forced spirometry. It is reliant on the FVC, and thus may be affected by changes in FVC and consequently has a wide normal range in clinical practice, which limits interpretation.<sup>[60]</sup> Nevertheless, a study by Tsushima *et al.*<sup>[61]</sup> showed a lower percentage predicted MMEF in GOLD stage 0 COPD (symptomatic patients with a normal FEV<sub>1</sub>/FVC) than healthy controls. More recently, Stockley *et al.*<sup>[56]</sup> assessed MMEF, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC ratio, health status, and computed tomography (CT) in AATD COPD patients and suggested MMEF may be a valuable tool in identifying early disease.

### Inert gas washout

Inert gases (especially Nitrogen) washout has a number of clinical applications and can be used to assess different lung volumes as well as ventilation heterogeneity. There are two types of nitrogen washout tests: single breath nitrogen washout (SBNW) and multiple breath nitrogen washout (MBNW).

### Single breath nitrogen washout

SBNW involves breathing in 100% oxygen from residual volume (RV) to total lung capacity and then breathing out slowly to RV.<sup>[62]</sup> Nitrogen concentration during the second expiratory phase can be divided into four stages, reflecting anatomical dead space (Phase I), the bronchial tree (Phase II), alveoli (Phase III), and airway closure (Phase IV). Closing volume (CV) is the volume of gas exhaled when small airway closure starts.<sup>[63]</sup> Validated reference ranges for SBNW parameters are available in clinical practice<sup>[64]</sup> and in obstructive lung disease, CV is increased because of the earlier closure of the airways.<sup>[65]</sup> Abnormal CV results have been described in 44% of male and 36% female smokers, whereas FEV<sub>1</sub> appeared abnormal in only 12% of these participants.<sup>[66]</sup> A new method of performing single breath inert gas washout has been established recently,<sup>[67]</sup> using the differential distribution of two inhaled tracer gases (helium and sulfur hexafluoride) and evaluating tidal Stage III slope.<sup>[68]</sup> Although it is considered as a sensitive measure in assessing small airways' dysfunction in moderate to severe COPD,<sup>[69]</sup> further evaluation will be needed before it can be used clinically.

### Multiple breath nitrogen washout

MBNW is another nitrogen washout method, performed by breathing 100% oxygen during tidal breathing. The lung clearance index (LCI) is obtained and used to evaluate the heterogeneity of ventilation. LCI rises with the severity of airflow obstruction<sup>[70]</sup> and is one of the first tests to decrease in children with cystic fibrosis, supporting its value in recognizing early anatomical change.<sup>[71]</sup> Recently, a study has also demonstrated that LCI may be useful as an indicator of early disease in AATD before spirometry becomes abnormal.<sup>[72]</sup> Moreover, MBNW allows the identification of variation of ventilation heterogeneity between the conducting airways ( $S_{\text{cond}}$ ) and the small airways in the acinar region ( $S_{\text{acin}}$ ). Recent study by Liu *et al.* has found that both  $S_{\text{cond}}$  and  $S_{\text{acin}}$  are higher in patients with established COPD.<sup>[73]</sup>

### Airway resistance by body plethysmography

Assessments of airway function can be obtained by directly measuring airway resistance (Raw). Raw is measured using body plethysmography and relates driving pressure to airflow during tidal breathing.<sup>[74]</sup> During nonvolitional tidal breathing, specific Raw (sRaw) can be measured. sRaw is obtained from the specific resistance loop using a line of best fit (sReff), the line linking the maximum variance in shift volume (sRtot), or infrequently, the line connecting expiratory flow between  $\pm 0.5$  and  $-0.5$  L/s (sR0.5). In healthy subjects, sRaw loop is linear, and these three parameters are approximately the same whereas, in airflow obstruction, hysteresis of the sRaw loop is

common and results in notable differences between sReff, sRtot and sR0.5. Recently, a study in COPD suggested that sReff and sRtot identify small airway dysfunction and relate to symptoms of dyspnea.<sup>[75]</sup> Specific airway conductance (sGaw) is the reciprocal of sRaw, and it is often recognized as a stronger measure than Raw or sRaw because of its linear relationship with lung volumes.<sup>[76]</sup> Although a study has described significant decrease in Raw and sGaw in AATD patients with airflow obstruction,<sup>[77]</sup> studies in COPD are small and sRaw does not appear to rise substantially until moderate airflow limitation is established.<sup>[78]</sup>

### Oscillometry techniques

Forced oscillation technique (FOT) and impulse oscillometry (IOS) are used to assess the respiratory impedance (resistance and reactance) in the respiratory tract noninvasively during tidal ventilation using different frequencies (between 5 and 35 Hz). They use oscillating pressure differences to identify the mechanical characteristics of the lung. At high frequencies, oscillations relate to central airways while at low frequencies, oscillations enter into peripheral lung, reflecting small airways.

FOT assesses the respiratory impedance by applying sinusoidal pressure differences through a mouthpiece. FOT may be sensitive to early small airway changes in smokers<sup>[79,80]</sup> and may be valuable in monitoring COPD patients.<sup>[81]</sup> Other studies have shown that FOT might help to distinguish between COPD and asthma<sup>[82,83]</sup> and may be more sensitive than spirometry following bronchodilator therapy<sup>[84]</sup> or bronchoprovocation tests.<sup>[85]</sup> FOT may also be a valuable tool for evaluating COPD patients during acute exacerbation.<sup>[86,87]</sup> Recently, there have been significant advancement in FOT technology, and recent FOT devices are able to evaluate EFL and separate inspiratory/expiratory resistance and reactance.

IOS is a later version of FOT, and several parameters are reported when IOS is performed. R5-R20 (the difference in the measurement of resistance at high and low frequencies) has been used as an outcome measure to identify peripheral resistance.<sup>[88]</sup> Reactance at 5 Hz (X5) is used to evaluate the structural characteristics of the lung parenchyma in the periphery and correlates with measures of spirometry.<sup>[89]</sup> Recently, studies have suggested that IOS can identify small airway dysfunction in COPD<sup>[90-92]</sup> and might be more sensitive than spirometry to early changes.<sup>[89,93]</sup>

### Computed tomography

CT scans of the lungs assess the presence and the distribution of emphysema, both visually, but more sensitively using density data from the images. Lung density, evaluated at full inspiration, decreases with

**Table 2: Test of small airways function during exacerbation of COPD**

Test	Advantages	Disadvantages
Mid-Maximal Expiratory Flow	<ol style="list-style-type: none"> <li>1. can be done at bedside</li> <li>2. Widely accessible</li> <li>3. Provide assessment of small airway dysfunction.</li> </ol>	<ol style="list-style-type: none"> <li>1. Very effort dependent</li> <li>2. May be hard to do during exacerbation.</li> <li>3. Poor reproducibility if not adjusted for lung volume</li> </ol>
Single breath washout	<ol style="list-style-type: none"> <li>1. Provide assessment of ventilation heterogeneity</li> <li>2. Quick to perform</li> <li>3. Requires only tidal breathing if double trace gases method is used.</li> <li>4. Can be done at bedside.</li> </ol>	<ol style="list-style-type: none"> <li>1. Classical method is effort dependent</li> <li>2. Double tracer gas method not fully justified</li> </ol>
Multiple breath washout	<ol style="list-style-type: none"> <li>1. Provides assessment of ventilation in the acinar and small conducting airway.</li> <li>2. Effort independent</li> <li>3. can be done at bedside</li> </ol>	<ol style="list-style-type: none"> <li>1. Time consuming</li> <li>2. It may have variabilities</li> </ol>
Plethysmography	<ol style="list-style-type: none"> <li>1. Effort independent.</li> <li>2. Quick technique to perform.</li> </ol>	<ol style="list-style-type: none"> <li>1. Method can be technically demanding when obtaining TGV</li> <li>2. Not particular to small airway function</li> <li>3. Cannot be done at bedside.</li> </ol>
Oscillation techniques	<ol style="list-style-type: none"> <li>1. Quick to perform.</li> <li>2. Effort independent.</li> <li>3. Specific to small airway function</li> <li>4. Clinically validated.</li> <li>5. Can be done at bedside.</li> </ol>	<ol style="list-style-type: none"> <li>1. Specialized equipment</li> </ol>
CT	<ol style="list-style-type: none"> <li>1. Provides direct evaluation of the presence of disease</li> <li>2. Gold standard for detecting and phenotyping emphysema</li> </ol>	<ol style="list-style-type: none"> <li>1. High exposure to radiation</li> <li>2. Costly</li> <li>3. cannot be done at bedside</li> <li>4. Achieving consistent RV is difficult</li> </ol>

Abbreviations: TGV, thoracic gas volume, RV, residual volume

the amount of emphysema and is a highly sensitive measure of emphysema progression.<sup>[94]</sup> CT images are also increasingly being used to assess the presence of small airways' disease, by studying excess gas trapping at full expiration. Here, gas trapping is assumed to be a consequence of the loss or early closure of the small airways. Parametric response mapping (PRM) analyzes inspiratory and expiratory CT data, potentially identifying gas trapping caused by small airway disease alone through subtraction of defined emphysema. Although there are studies that have utilized CT techniques (specifically PRM) to assess small airways,<sup>[94,95]</sup> they still need to be fully validated to determine their clinical utility.

### The Rationale for and Practicality of Measuring Small Airways' Tests During Exacerbations of Chronic Obstructive Pulmonary Disease

The effect of exacerbation on small airways is likely to be amplified and therefore measuring small airways' function during exacerbations may of interest in identifying both the duration of the episode and the response to treatment. However, there are potential caveats to its use. Although comprehensive testing has not been completed in COPD, all AATD patients with mild spirometric evidence of COPD had significant small

airways' dysfunction.<sup>[56]</sup> If this were true of non-AATD COPD, small airways' function would be greatly impaired even in the stable state and potentially only milder COPD may provide a detectable signal during an exacerbation.

As previously stated, the assessment of small airways' function can be carried out using a number of tests, but whether these tests are clinically useful or could be delivered during exacerbations of COPD has yet to be fully explored. To be clinically useful, tests should provide a pretreatment measure which identifies the start, end, and response to treatment of an exacerbation, is practical by the bedside and acceptable to patients. A summary of advantages and disadvantages of each test is presented in Table 2.

In general, studies utilizing small airway tests in COPD exacerbation have been limited, both in the number of studies carried out and the number of patients recruited. Furthermore, the majority of these studies have been conducted during hospitalized exacerbations. Although two studies have included moderate exacerbation in their studies, most of the others have not specified the severity of exacerbation. In general, all studies did not specify the COPD severity of patients being examined; however, by assessing at the baseline FEV<sub>1</sub>, most studies have assessed the small airways in moderate to severe COPD.

FOT and spirometry were used in an observational study to compare changes in COPD patients hospitalized with an exacerbation and demonstrated that inspiratory resistance was associated with a significant improvement in symptoms.<sup>[87]</sup> IC and reactance by FOT have been shown to relate to exacerbation recovery.<sup>[86]</sup> Tests of small airways have also been used in several interventional studies including identifying a significant decrease in airway resistance by plethysmography after 14 days of treatment with systematic corticosteroid<sup>[96]</sup> and identifying a significant improvement in MMEF (referred to as FEF 25–75 by the authors) at 10 and 30 days following treatment with erdosteine.<sup>[44]</sup> Another study compared treatment delivered via vibrating mesh nebulizer and small volume jet nebulizer using spirometry, body plethysmography, and IOS, demonstrating an improvement in spirometry, lung volume, and airway impedance with recovery.<sup>[97]</sup> Although studies using tests of small airways' dysfunction to assess exacerbation are small, there is consistent evidence that these tests offer the ability to map recovery (especially in milder disease).

### The Evidence Gap: What Research is Needed to Decide if Tests of Small Airways Should be Incorporated Into Clinical Studies and Usual Clinical Practice?

Currently, the studies exploring small airways' tests during exacerbations of COPD are limited both in number and the number of patients studied. They have utilized different tests of small airways and different definitions of an exacerbation of COPD. While this review highlights the limitations in the current evidence for the use of small airways, a formal systematic review would provide a definitive assessment of the current tests of small airways used, the bias contained within published studies and any comparison between them. If any of the tests of small airways' function appeared sensitive to changes during exacerbation, a pilot study to see if test delivery is feasible and acceptable by the patient during exacerbation of COPD in the acute setting would be of great value. This might inform larger studies to determine if tests of small airways could be validated as outcome measures in exacerbations, and which tests might be the most informative, especially in episodes where dyspnea is the sole symptom.

### Conclusion

COPD is characterized by airflow limitation that is caused by a combination of small airways' disease and parenchymal destruction.<sup>[4]</sup> Many COPD patients experience exacerbations, associated with poor health outcomes<sup>[4]</sup> that are commonly caused by viral and bacterial infections.<sup>[35]</sup> In clinical practice, recovery

is assessed using unstructured symptoms reporting, but in clinical trials, more robust and reproducible measures are needed. Here, exacerbation response is commonly assessed using spirometry (especially FEV<sub>1</sub>), symptom-based questionnaires, and sometimes an assessment of inflammation. There are limitations with these tools and therefore significant interest in developing and testing other methodologies for use in this area. Small airways' dysfunction is thought to be one of the earliest physiological changes in COPD, and tests of small airways' function have been used in experimental studies of both stable disease and during exacerbations. Thus, hypothetically tests of small airways' function may form a tool to assess exacerbations, especially in milder disease. Small airways' dysfunction can be assessed using MMEF, inert gas washout, airway resistance (by body plethysmography, FOT and IOS), and CT, but each has potential advantages and disadvantages. Some studies have used small airways' tests to evaluate COPD patients during an exacerbation and have suggested that these are sensitive measures to assess response, but studies have been few. This small body of evidence now needs to be built upon to robustly test whether tests of small airways' function can improve the diagnosis and management of COPD exacerbations. This includes assessing which tests of small airways are the most acceptable to patients, practical to deliver and have utility within clinical trials or as a tool to help improve clinical outcomes. Currently, there is insufficient evidence to support the use of small airways' tests to clinically guide the diagnosis and management of exacerbations of COPD; however, early studies suggest they have promise to improve patient care, and further research is clearly warranted.

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### Conflicts of interest

There are no conflicts of interest.

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