Dismantling airway disease with the use of new pulmonary function indices

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Spirometry is used to diagnose and manage airway disease such as asthma and COPD, but relates poorly to symptoms, lacks sensitivity and is effort dependent. FOT and MBNW are emerging clinical lung function tests that help us dismantle disease mechanisms. http://ow.ly/nM0G30nS6Ct

ABSTRACT   We are currently limited in our abilities to diagnose, monitor disease status and manage chronic airway disease like asthma and chronic obstructive pulmonary disease (COPD). Conventional lung function measures often poorly reflect patient symptoms or are insensitive to changes, particularly in the small airways where disease may originate or manifest. Novel pulmonary function tests are becoming available which help us better characterise and understand chronic airway disease, and their translation and adoption from the research arena would potentially enable individualised patient care.   In this article, we aim to describe two emerging lung function tests yielding novel pulmonary function indices, the forced oscillation technique (FOT) and multiple breath nitrogen washout (MBNW). With a particular focus on asthma and COPD, this article demonstrates how chronic airway disease mechanisms have been dismantled with the use of the FOT and MBNW. We describe their ability to assess detailed pulmonary mechanics for diagnostic and management purposes including response to bronchodilation and other treatments, relationship with symptoms, evaluation of acute exacerbations and recovery, and telemonitoring. The current limitations of both tests, as well as open questions/directions for further research, are also discussed.

Introduction

Pulmonary function testing plays an important role in the clinical assessment of chronic airway disease, ranging from diagnosis to monitoring and management. To date, the gold standard test of lung function remains spirometry. In asthma, spirometry and peak flow are part of the formal diagnosis and assessment of disease and are used to demonstrate variable airflow limitation over time, combined with clinical symptoms such as wheeze, dyspnoea, chest tightness or cough [1]. In chronic obstructive pulmonary

disease (COPD), spirometry is used to demonstrate persistent airflow limitation and define disease severity, in conjunction with respiratory symptoms like dyspnoea, cough or sputum production [2].

Despite this, spirometry has several shortcomings. For one, it often only has a weak relationship with patient-centred outcomes such as symptoms. It is also relatively insensitive in detecting early disease or people at risk of developing chronic airway disease. This is probably because spirometry primarily reflects bulk flow in the large airways. Although asthma and COPD are both highly heterogenous diseases, the small airways have been implicated in both conditions [3, 4]. In asthma, small airways dysfunction can be demonstrated in more than half of patients, including those with mild disease [5]. While established COPD is known to affect both large and small airways [6], COPD is thought to arise from the small airways [7]. There is limited functional assessment of the small airways in clinical practice to date.

In addition, spirometry is effort-dependent, requiring forced expiratory manoeuvres that can be difficult or sometimes even impossible to perform for the very young, elderly or highly obstructed patients. Effort-independent and objective markers which are sensitive to both large and small airway mechanics would be a highly desirable addition to the currently available set of lung function tools for evaluating airway disease.

This article describes new pulmonary function indices available from two lung function tests, forced oscillation technique (FOT) and multiple breath nitrogen washout (MBNW), which provide us with an opportunity to examine the small airways and dismantle disease mechanisms. These tests have contributed much to our current understanding of airway disease, in particular asthma and COPD, which will be the focus of this article. They are also emerging as clinical tests, with increasing studies examining their clinical utility as measures of disease status, targets for treatment and predictors of future risk.

Forced oscillation technique

FOT is a noninvasive, objective and effort-independent method to measure airway mechanics. The key physical quantity measured by FOT is respiratory system impedance, which describes the relationship between pressure applied at the airway opening and the resultant flow, or *vice versa*. In FOT, pressure oscillations of low amplitude, commonly generated by a loudspeaker or a piston, are superimposed at the mouth, and can be measured during resting tidal breathing. Different oscillation signals are used in practice, with the most common ones being single or combinations of non-multiple and/or pseudorandom frequencies (conventional FOT), or harmonic multiples (impulse oscillometry). This article covers work involving both types of signals. The two main components of impedance measured by FOT are respiratory system resistance (Rrs) and reactance (Xrs), respectively. Rrs represents impedance to airflow changes, primarily reflecting a measure of overall airway calibre, whereas Xrs represents impedance to volume changes, and primarily encompasses the inertial and elastic properties of the respiratory system.

These measures are dependent on the frequency of the oscillations, revealing further insight into airway and lung mechanics. In most clinical studies, Rrs and Xrs are measured at (or close to) 5 Hz, *i.e.* R5 and X5, where resistive and elastic properties dominate respectively. This is close to the resonant frequency of the respiratory system, at which point X becomes more dominated by inertial rather than elastic forces. Another frequently encountered measure in the literature is AX, which represents the sum of Xrs components at all frequencies prior to resonant frequency. Furthermore, the difference in Rrs between 5 and 20 Hz (R5–R20) is used as an attempt to quantify frequency dependence in Rrs, although the interpretation of this index is often misunderstood. While often thought of as simply peripheral airway resistance, in reality it is a complex measure which also takes into account heterogeneity in ventilation/mechanics across the airway tree and the upper airway shunt [8–10].

In addition to these two measures of "total" resistance and reactance, it is also possible to track changes in Rrs and Xrs within a breathing cycle. In doing so, FOT can be partitioned further into its inspiratory only (inspiratory resistance and reactance (Rinsp and Xinsp), respectively) and expiratory only (expiratory resistance and reactance (Rexp and Xexp), respectively) components, as well as derive a measure of expiratory flow limitation.

Detection of expiratory flow limitation

FOT has been shown to detect expiratory flow limitation (EFL), a phenomenon which occurs when increased expiratory effort and driving pressure do not result in increased corresponding flow, due to regional "choke points" from airway closure or narrowing in the distal airways. EFL can occur in asthma [11] and is a pathological hallmark in COPD, often manifesting as dynamic hyperinflation and increased exertional dyspnoea resulting in exercise limitation [6]. The presence of EFL has been found to predict the severity of breathlessness in COPD better than forced expiratory volume in 1 s (FEV1) [12, 13]. EFL may also represent a marker of disease severity and associated morbidity in terms of symptoms, functional

impairment, degree of airflow obstruction and extent of gas trapping [14]. However, conventional methods of detecting EFL have either been invasive in nature (*e.g.* oesophageal balloon technique) or involve highly specialised operator and/or large inter-operator variability (*e.g.* the negative expiratory pressure technique). DELLACÀ *et al.* [15] established a noninvasive method to detect EFL with high sensitivity and specificity, by applying within-breath FOT analyses and calculating the difference between the inspiratory and expiratory Xrs at a frequency of 5 Hz (*i.e.* $\Delta X\text{rs}=X\text{insp}-X\text{exp}$). When EFL develops, there is a sudden increase in the magnitude of $X\text{exp}$, which possibly reflects expiratory small airway closure and which does not occur during inspiration. The method has shown potential clinical utility in titrating nasal continuous positive airway pressure (CPAP) treatment in COPD patients [16]. In further work, LORX *et al.* [17] used plots of the within-breath changes of FOT measures as functions of tidal flow and volume to visualise and differentiate between partial *versus* complete EFL.

Relationship with symptoms, disease status and severity

Spirometry consistently correlates poorly with symptoms like breathlessness [18–20]. In contrast, YOUNG *et al.* [10] demonstrated that Rrs and Xrs correlated with asthma control, and R5–20 with quality of life in COPD. R5–20 was additionally related to ventilation defects measured by magnetic resonance imaging in both asthma and COPD [10]. In addition, FRANTZ *et al.* [21] showed larger Rrs and more negative Xrs values in 450 subjects with self-reported symptoms suggestive of COPD, irrespective of whether spirometry was abnormal. Thus, in addition to demonstrating relationship with symptoms, FOT may also be better than conventional measures in the early detection of disease. FOT measures are also proportional to the degree of underlying airflow obstruction in COPD [22, 23]. In early or mild disease compared to never-smoking normal subjects, these changes are predominantly characterised by an increase in Rrs parameters, and in moderate to severe airflow obstruction by increasingly negative Xrs measures.

Evaluation of bronchodilator/treatment response

FOT may also be useful in measuring response to bronchodilation, and as outcome measures in the assessment of response to pharmacological treatment in clinical trials. Studies have shown R5 and X5 to be more sensitive than spirometric measures like FEV1 in detecting a bronchodilator response to short-acting β-agonist (SABA) administration in asthma [24], and to SABA [25–27] and long-acting β-agonist (LABA) [28] in COPD. The latter is notable since COPD is conventionally thought of as a disease of irreversible airflow limitation as measured *via* spirometry. DIBA *et al.* [29] found in moderate-to-severe COPD subjects that an improvement in respiratory system conductance (the inverse of Rrs) predicted the reduction in exertional dyspnoea experienced following bronchodilator (tiotropium bromide) administration, independent of improvements in spirometry or plethysmographic measures of hyperinflation. MILNE *et al.* [30] further demonstrated that in response to the LABA indacaterol, FOT indices correlated with hyperinflation and gas trapping. Importantly, FOT measures predicted the volume responses to indacaterol, suggesting FOT may be clinically useful to determine which COPD patients might benefit from bronchodilator treatment.

Other work suggests that FOT indices are responsive to combination treatment of inhaled corticosteroids (ICS) with LABA. For example, AKAMATSU *et al.* [31] showed that FOT predicted improvement in FEV1 following 2 months of ICS/LABA therapy in untreated asthma. In patients with moderate COPD, TIMMINS *et al.* [32] demonstrated significant improvements in FOT measurements coupled with quality of life after 3 months of ICS/LABA treatment, and in the absence of changes in FEV1.

Further evaluation of airway mechanics

FOT can be extended to glean further information regarding airway mechanics. By measuring FOT during a maximal inhalation and exhalation, it is possible to evaluate airway distensibility, *i.e.* the ability of the airways to stretch over a given range of volume [33, 34]. Airway distensibility has been found to relate to airway tone [34], as well as asthma control [35]. More recently, the relationship between FOT and lung volume during a slow vital capacity manoeuvre was used to detect the onset of airway closure/lung derecruitment [36]. Furthermore, investigations into deep inspirations have informed the mechanisms behind why asthmatics fail to dilate their airways following airway constriction [37].

Changes during recovery from exacerbation

FOT may be useful to assess recovery from acute exacerbations of COPD (AECOPD). Out of 29 COPD patients, JETMALANI *et al.* [38] found that one-third admitted to hospital for an AECOPD exhibited EFL measured by FOT, which was in turn associated with improvement in symptoms and length of stay in hospital. In contrast, STEVENSON *et al.* [39] detected no change in FOT measurements during recovery from an AECOPD, and instead found increase in inspiratory capacity to be the main determinant and a useful guide of symptom improvement. However, JOHNSON *et al.* [40] showed significant improvement in Xrs

indices alongside operating lung volume in the 6 weeks following hospital admission and discharge, suggesting Xrs may be a surrogate for the volume changes occurring during recovery from AECOPD.

Home telemonitoring of chronic airway disease

FOT lends itself particularly well for telemonitoring given its effort-independent nature and ease of performance, and several studies have already demonstrated its feasibility in home telemonitoring of asthma [41] and COPD [42, 43]. In addition to providing a measure of disease status, FOT telemonitoring may further facilitate early, objective detection of exacerbations, which are currently dependent on subjective patient recall and perception of symptoms. Early detection would allow early treatment, which in COPD is known to shorten the duration of AECOPD [44], thus reducing the enormous health and economic burden they impose [2].

A recent large European randomised, interventional trial of FOT home monitoring (CHROMED (Clinical tRials fOr elderly patients with MultiplE Disease)) showed no benefit in time to first hospitalisation or quality of life, though *post hoc* analyses revealed a significant reduction (−54%) in repeat hospitalisations in a subset of high-risk patients [43]. This subgroup may represent a particular COPD phenotype that would benefit more from remote monitoring with FOT.

In addition, novel analysis approaches exist [45], which could add value to telemonitoring data by focusing on the day-to-day variability in FOT measurements, known to be increased in asthma and COPD compared with healthy controls [46]. These analyses are based on the idea that biological systems exhibit natural fluctuations which change with disease states and in response to stimuli [32]. They have already shown promise in predicting future deteriorations in lung function in asthma [47] and may help predict risk of future clinically defined exacerbations in both asthma and COPD.

Disease phenotyping and classification

Asthma and COPD are both highly heterogeneous conditions. In a clinical setting, and in older patients in particular, it can often be challenging to differentiate between these conditions, with prognostic and therapeutic implications [48]. PAREDI *et al.* [49] applied within-breath FOT analyses to differentiate between asthma and COPD in those with more severe airflow obstruction, demonstrating greater magnitude in ΔXrs in COPD compared to asthma. This finding may reflect the occurrence of dynamic expiratory airway narrowing and closure in COPD, but requires confirmation in larger studies.

The advent of machine learning methods may further help with disease diagnosis and/or phenotyping [50, 51]. AMARAL *et al.* [52] applied four different machine learning algorithms to FOT measurements from health and COPD, and improved the diagnostic accuracy of using FOT alone in categorising COPD severity. Whether the powerful combination of FOT with such automated, data-driven approaches could aid prediction of disease trajectories and acute exacerbations remains to be seen.

Multiple breath nitrogen washout

The MBNW test allows measurement of ventilation heterogeneity [53], *i.e.* unevenness of ventilation distribution within the lungs. It provides information about the efficiency of gas mixing within the lungs, possible mechanisms behind abnormal ventilation distribution and the relative location of underlying pathological processes. The test involves measurement of the concentration of an inert tracer gas (*i.e.* nitrogen) in the expired breath, which is progressively washed out by inhalation of 100% oxygen over a series of tidal breaths. If ventilation heterogeneity is increased (*i.e.* abnormal), there is a delay in clearance of the tracer gas, therefore more breaths will be required to "washout" the nitrogen.

The anatomical and physiological basis of the MBNW test is centred around the principles of gas transport and mixing [54]. Compartmentalisation of ventilation distribution [53, 55–57] allows indices to be derived which reflect ventilation heterogeneity or specific ventilation (ventilation per unit lung volume) within the small airways [58]. Uneven ventilation or differences in specific ventilation in lung units larger than the acini (*i.e.* the more proximal conducting airways), where gas transport occurs by convection, is termed convection–dependent inhomogeneity (CDI, also known as S_{cond}). In the more distal acinar airways where gas transport occurs by diffusion, it is termed diffusion-convection–dependent inhomogeneity (DCDI, or S_{acin}) [57, 58]. Relative contributions to gas mixing from interactions between the convection- and diffusion-dependent airways occur in an intermediate zone and form the "diffusion–convection front" [54]. This quasi-stationary diffusion-convection front determines where CDI and DCDI mechanisms operate and is thought to arise around the acinar entrance in healthy adult lungs [59]. While the terms S_{cond} and S_{acin} reflect putative locations in the conductive and acinar airways, it is worth noting that these indices are primarily functional rather than anatomical measures.

These indices are calculated from analyses of the MBNW expirogram, *i.e.* the plot of nitrogen concentration *versus* expired breath volume for each breath, specifically that portion of the expirogram (also termed

"phase III") where the expired breath no longer comes from the anatomical dead space and is dominated by alveolar gas alone [53]. A global measure of ventilation heterogeneity, the lung clearance index (LCI), can also be derived from the MBNW test, which describes overall gas mixing efficiency in the lungs.

Relationship with symptoms and disease status

Ventilation heterogeneity can be abnormal in both asthma [60–62] and COPD [63]. Abnormal S_{cond} and S_{acin} have been associated with poor asthma control [64]. Both improve with treatment and are also associated with improvement in symptom control [65]. During asthma exacerbations, S_{cond} and S_{acin} can become more abnormal; however, only S_{acin} is correlated with FEV1 during exacerbations and stable periods [61]. Thus, the acinar airways play a significant role in airflow obstruction in asthma. MBNW indices are also associated with different airway inflammatory profiles in asthma [66]; S_{cond} with airway eosinophilia and S_{acin} with airway neutrophilia. These associations may have implications on future treatment modalities such as the new biologicals.

Abnormalities measured by MBNW seem to be more pronounced in COPD [67], particularly in S_{acin} compared to S_{cond} [62, 67]. In COPD, relationships between S_{acin}, S_{cond} and different lung function indices have been linked to "acinar lung-zone" and "conductive lung-zone" factors, respectively [63]. Acinar lung-zone factors include lung diffusion capacity; this is consistent with abnormal S_{acin} and reduced diffusion capacity often seen in COPD, specifically emphysema due to alveolar destruction [68]. A recent modelling study has also demonstrated how depletion of terminal bronchioles leads to an increase in S_{acin} in COPD, more so when diffusion capacity is low [69]. Conversely, the conductive lung-zone factors include specific airway conductance and forced expiratory flows [63]. This suggests that in COPD, S_{acin} and S_{cond} reflect alterations of different lung compartments; in contrast to asthma, where an abnormal S_{acin} may be a sensitive marker of structural alveolar changes, an abnormal S_{acin} in COPD may involve changes in the proximal acinar airways rather than in the alveoli themselves [62].

Abnormalities in both S_{acin} and S_{cond} have also been demonstrated in smokers with normal spirometry, with a majority of the abnormalities seen in S_{acin} [70]. Furthermore, abnormal S_{acin}, but not S_{cond}, is associated with smoking history and the number of pack-years. These findings point to MBNW as a potential marker of "early" COPD and would support the concept of smoking-related changes beginning in the small airways. This is consistent with studies showing reduced airway count [71] in smokers with normal spirometry, and loss of patent terminal bronchioles occurring even in mild COPD [72], before the onset of emphysematous destruction and beyond with increasing disease severity [73]. Curiously, in smokers who have yet to develop COPD, symptoms of chronic bronchitis were associated with an abnormal S_{cond} but not S_{acin} [70], suggesting that perhaps structural changes may occur before symptoms manifest.

In smokers with COPD, both S_{acin} and S_{cond} increase with increasing pack-year smoking history [68]. Following smoking cessation, there is an initial improvement in both S_{acin} and S_{cond} after 1 week of cessation [74]. However, only S_{cond} shows a persistent improvement after 12 months of smoking cessation with no change in spirometry, diffusion capacity and airway conductance [74]. This suggests early smoking-related lung damage in the acinar airways may be irreversible.

Relationship with airway hyperresponsiveness

MBNW is also related to other features of airway disease. Airway hyperresponsiveness (AHR) is a hallmark characteristic of asthma, independent of airway inflammation [55]. In healthy subjects, during bronchial provocation testing S_{acin} and S_{cond} worsens [57], *i.e.* small airways affected by bronchial provocation may be proximal to the acinar airways. However, in those individuals who demonstrated AHR, baseline S_{acin} was significantly increased compared to those without AHR. Following bronchoprovocation challenge using methacholine, S_{cond} also related to volume of gas trapping [75]. These responses probably reflect overall decrease in airway calibre and heterogeneous narrowing of parallel airways. The relationships between ventilation heterogeneity with AHR and airway closure in asthma have been further corroborated by imaging studies [76, 77].

These relationships also appear to be age-dependent, providing insight into the possible interaction between asthma and ageing. In young adults with asthma, S_{cond} is a major determinant of AHR. In contrast, in older people AHR is predicted by S_{acin} [78], suggesting the acinar rather than conductive airways contribute to ventilation heterogeneity in older people with asthma. It is worth noting that ventilation heterogeneity increases with age in health [79, 80], with an accelerated increase seen in S_{acin} and LCI after the age of 60 years, *versus* a steady linear increase in S_{cond} [80, 81]. However, S_{acin} and LCI are both associated with loss of lung elastic recoil in elderly asthma independently of ageing [82]. Alterations to recoil pressure may provide a mechanism for altered distribution of ventilation in these patients, as individual airways are varyingly brought closer to the point of airway closure.

Evaluation of bronchodilator/treatment response

MBNW has provided insight on whether abnormalities in ventilation heterogeneity are reversible or respond to treatment, and how this varies between different diseases. In asthma, both S_{cond} and S_{acin} improve following administration of SABA [62]. However, abnormal S_{cond} may fail to normalise after a SABA even in mild disease [83].

In contrast, in COPD, despite high levels of abnormality at baseline, S_{cond} and S_{acin} do not improve following inhalation of a SABA [62]. Similarly, in a study following a 6-week treatment period with tiotropium, ventilation heterogeneity did not improve yet FEV_1 and inspiratory capacity did [84]. These COPD subjects also had a low diffusion capacity [62, 84], which was consistent with emphysema and may explain the reason for the lack of a significant bronchodilator response. In contrast, in smokers with normal spirometry (*i.e.* no established COPD), S_{acin} improved significantly following SABA, and only those with an abnormal baseline S_{cond} demonstrated a significant bronchodilator response [85].

Ventilation heterogeneity is also a known important physiological determinant of response to asthma treatment, with implications for guiding therapy [65, 66, 86]. MBNW indices improve with ICS therapy [55, 65] in association with an improvement in symptoms [65]. Ultrafine ICS improves S_{acin} but not S_{cond} in stable asthma, but only in those whose baseline S_{acin} was abnormal [86]. Furthermore, worse S_{cond} predicts symptomatic improvement to ICS dose up-titration, which may simply reflect opening up of previously closed conducting airways with ICS. However, worse S_{acin} predicts worse symptom control during dose down-titration [65]. These findings are useful as they imply that patients who are well-controlled but have abnormal S_{acin} may not tolerate ICS down-titration.

Current limitations and open questions

The increasing availability of commercial devices for both FOT and MBNW have supported their ongoing transition from a pure research tool to emerging use in clinical respiratory medicine. Despite the information we have gained about airway disease, made possible by these tests, there still exist gaps in knowledge and limitations that need to be overcome for either test to become commonplace in the clinical evaluation of chronic airways disease.

While international recommendations exist for best practice for both tests [53, 87], issues remain regarding standardisation across centres. There are known differences between equipment, software algorithms and protocols that limit comparability and thus clinical utility, for both FOT [88, 89] and MBNW [90–92]. This lack of comparability has also impacted the availability of reliable and/or widely applicable reference values from a healthy population to derive predicted equations. For FOT, these have either only been collected in specific equipment [93], or there is an inability to pool data across multiple centres [94]. Similarly, reference values exist for MBNW only for specific equipment [60], some of which are custom built by specialised labs and, therefore, are not widely available [79, 80].

In terms of clinical applicability, for both tests there is a need for more rigorously defined cut-off values that define a significant bronchodilator response to aid in diagnosis, as well as identification of minimal clinically important differences to serve as a target for interventions.

Further work into structure–function relationships as higher resolution imaging measures and processing methods become available will add to the insights already gained surrounding the small airways. Most FOT and MBNW studies to date have been limited to smaller mechanistic studies; including those detailed, highly sensitive functional measures in future large cohort studies would enable us to correlate small airway dysfunction with a comprehensive range of biomarkers and clinical outcomes, and add a whole new dimension to clinical phenotyping [95]. Furthermore, coupling these functional measures with inflammatory profiling in interventional studies involving new modalities of treatment (*e.g.* thermoplasty and the new biologics in asthma) would help elicit a role for small airway dysfunction as a potential treatable trait, in the personalised management of airways disease [96].

Conclusion

FOT and MBNW are emerging clinical tests that provide novel pulmonary function indices, which have helped us dismantle some of the complex mechanisms underpinning chronic airway diseases. We have demonstrated the knowledge gained and potential clinical utility in the assessment of pulmonary mechanics, response to bronchodilator and other inhaled treatments, the relationship with symptoms and disease status during acute exacerbations and their recovery, and the role in home and clinical monitoring. Overcoming existing limitations, future research and increasing use will further substantiate the role of these tests in clinical evaluation, and their potential in phenotyping and treating chronic airways disease, and personalisation of disease management.

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