The Need For Physiological Phenotyping To Develop New Drugs For Airways Disease

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Abstract

Asthma and COPD make up the majority of obstructive airways diseases (OADs), which affects ~11% of the population. The main drugs used to treat OADs have not changed in the past five decades, with advancements mainly comprising variations on existing treatments. The recent biologics are beneficial to only specific subsets of patients. Part of this may lie in our inability to adequately characterise the tremendous heterogeneity in every aspect of OAD. The field is currently moving towards the concept of personalised medicine, based on a focus on treatable traits that are objective, measurable and modifiable. We propose extending this concept via the use of emerging clinical tools for comprehensive physiological phenotyping. We describe, based on published data, the evidence for the use of functional imaging, gas washout techniques and oscillometry, as well as potential future applications, to more comprehensively assess and predict treatment response in OADs. In this way, we hope to demonstrate how physiological phenotyping tools will improve the way in which drugs are prescribed, but most importantly, will facilitate development of new drugs for OADs.

Keywords

oscillometry; Obstructive Airways Disease; phenotyping; inert gas washout; ventilation imaging

Introduction

Asthma and COPD make up the majority of obstructive airways diseases (OADs) and airflow obstruction is present in around 11% of the population(1) (defined by the older criterion of post-bronchodilator FEV1/FVC ratio of 0.70, prior to the introduction of new criteria(2)). The annual cost of asthma alone to the Australian economy in over 2 million asthmatic sufferers is nearly $AUD30M. The clinical expression of both asthma and chronic obstructive pulmonary disease (COPD) are highly variable and heterogeneous, as well as the responses to treatment. The histopathology of asthma and COPD also differ markedly, although there is overlap in clinical and pathophysiologic features e.g. alveolar enlargement(3) (4), loss of lung elasticity(5, 6), inflammation(7) and bronchodilator responsiveness(8).

Until the recent developments on biological treatments in asthma and COPD, the main drugs used to treat OADs have not changed since the introductions of salbutamol in 1969, the inhaled corticosteroid (ICS) beclomethasone in 1972 (9), and ipratropium in 1974. Better versions have arrived but the 'new treatment paradigms' for OADs are just varying combinations of long acting versions of those three basic drugs, e.g. dual long acting β_2-agonist (LABA) / long acting muscarinic antagonist (LAMA) vs ICS containing formulations in COPD, and regular vs as needed (PRN) ICS in asthma. The clinical trials to test efficacy of these variations required thousands of subjects to be enrolled in each trial. The large numbers are due to the high degree of heterogeneity in the underlying pathophysiologic processes of the study populations. It is highly unlikely that there will be any further 'development' of those 3 drug classes given that there are once-daily preparations of highly potent formulations, of low systemic activity, delivered to the lungs by highly efficient aerosol delivery devices. The problem remains that we (clinicians and researchers) have not

defined airways diseases in sufficient depth, to allow development of new drugs to proceed with any confidence; medications with specific targets may work for some but not others (biologics being a case in point), due to the wide heterogeneity in the disease population.

Physiological Phenotyping and Treatable Traits

OADs are traditionally given disease labels (diagnoses). The Global Initiative for Asthma defines asthma as a heterogeneous disease often associated with chronic airway inflammation in which symptoms and airflow obstruction vary over time(10). The Global Initiative for COPD defines COPD as persistent respiratory symptoms and airflow limitation caused by inhalation of noxious particles/gases(11). It is associated with airway and/or alveolar abnormalities. We note with particular interest that variability in both symptoms and lung function are a key distinguishing feature between asthma and COPD. In practice, diagnosis of OADs are done predominantly by symptoms alone and by response to treatment, both of which perform poorly since neither are sensitive nor specific, and can suffer from poor subjective perception or recall bias. Furthermore, many patients' symptom perception is not in proportion to their underlying disease severity(12). The gold standard measurement of airflow obstruction, spirometry, is infrequently done and abnormal spirometry can occur due to a variety of pathophysiological processes, which also makes it non-specific for OAD diagnosis. Therefore, the definitions by which labels are given are problematic. A common definition of asthma for clinical trials and epidemiological studies is a past doctor diagnosis of asthma and respiratory symptoms in the absence of significant smoking history, with or without bronchodilator reversibility. A common definition of COPD is respiratory symptoms, smoking history and obstructed spirometry, in the absence of any doctor diagnosis of asthma. However, the 'Dutch hypothesis' arose from Orie et al(13, 14) in

which asthma, bronchitis and COPD were considered a continuum of airways disease, rather than being considered as separate entities. Within this paradigm, genetic predisposition (family history and genetic associations), early life exposures (e.g. maternal smoking and infections), airway hyperresponsiveness, allergy, airway narrowing, reversibility in response to treatment, day-to-day variability and inflammatory phenotype, all play a part in the manifestation of disease, regardless of whether it is asthma or COPD. This inherently suggests that OADs should be characterised extensively in a clinical and pathophysiologic sense.

Although this concept is not yet commonplace in clinical practice, there is increasing appreciation in the field for the idea of label-free diagnosis(15), with an emphasis on treatable traits, i.e. those that can be modified by treatment(16), biomarkers and consequently 'precision' or 'tailored' therapy, rather than disease labelling. The ultimate ambition of this approach is the determination of endotypes of OAD, in which specific pathways are identified that control the disease and can be targeted to resolve the clinical manifestations(17). Compare this with other common diseases, such as coronary heart disease, hypertension and diabetes, where despite having different underlying causes and clinical significances in individuals, the focus is instead on treatment on the basis of measurable biomarkers(16). In the same way, we argue that OAD requires a similar approach, rather than just based on disease labels (diagnoses) such as asthma and COPD. While this goal has yet to be realised in respiratory medicine, the discovery of molecular phenotypes and associated inflammatory markers has successfully driven recent drug development such as the new biological treatments(18, 19). A recent example is the realisation that blood eosinophilia identifies an asthma phenotype that may respond to anti-

IL5 targeted treatment. The individual response rate at the outset of such treatment may vary although there is a mean group benefit. Furthermore, the definition of response is debated but often relates to patient reported outcomes rather than an objective marker of the underlying disease being treated.

We propose that physiological phenotyping can take us further, enabling us to better take into account the heterogeneous origins and pathophysiological mechanisms of OADs, and consequently better characterise responses to treatment, in the form of physiologically defined treatable traits. Some of these concepts are already known and already in use in clinical practice to varying extents, e.g. peak flow variability and airway hyperresponsiveness.

Physiological Phenotyping: What Tools are Available?

The tools that are useful for physiological phenotyping take into account the underlying anatomy and physiology of the lung. The lung is an asymmetrically shaped organ, with an elastic alveolar component supplied by asymmetrically bifurcating airways which have a mechanical compliance that is matched to alveolar compliance. This anatomical structure leads to ventilation being somewhat uneven (ventilation heterogeneity) and with increasing age, ventilation reduces and even ceases in the basal portions of the lung (airway closure), while in non-basal zones, ventilation becomes more heterogeneous. Phenotyping tools ideally also allow us to measure the function of the large and small airways. This is important because spirometry is insensitive to small airway function, yet this is the site where early abnormalities are thought to manifest(20).

Functional imaging allows measurement of ventilation heterogeneity. Computed Tomography (CT) is easily accessible and relatively cheap, and its most clinically relevant use is in measuring lung density (emphysema, gas trapping), providing a measure of extent and distribution. Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are imaging techniques that provide measurements of ventilation distribution. They have been used extensively in research and will likely be used routinely in the clinical assessment of OAD in future, but require further research to achieve this.

Lung function techniques that reflect ventilation heterogeneity include inert gas washout techniques, especially the **multiple breath washout (MBW)** technique. Recent standardisation work, across both paediatrics and adult testing(21, 22), has resulted in validated commercial equipment(23, 24), and increased interest in use in clinical care. The technique may utilise an exogenous inert gas (e.g. sulphur hexafluoride (SF6), helium or argon) which is inhaled in low concentration until steady state is reached within the lungs (wash-in). Once the inspired inert gas is removed, the subject then breathes room air to 'wash out' the gas from the lungs and the pattern of the inert gas concentration change during each breath, as the inert gas is progressively washed out of the lungs by normal breathing, provides information on the severity of ventilation heterogeneity (25). An alternative method is to utilise the nitrogen that is resident in the lungs (nitrogen washout test or resident gas technique). A nitrogen (N_2) inert gas washout test does not require an initial wash-in phase as the gas of interest is already resident within the lungs. During washout 100% oxygen washes N_2 out of the lungs. Since ventilation distribution is determined predominantly at the small airway level, MBW reflect heterogeneity of function

in the small airway compartment. Advances in technology will provide potentially more clinically useful parameters from this technique(26).

The **forced oscillation technique (FOT)**, also known as **oscillometry**, is another method, which measures the mechanical properties of the respiratory system (lungs and upper and lower airways), based on the response to oscillatory pressure or flow stimuli, usually applied at the mouth and during quiet, tidal breathing. The response of the respiratory system is measured by the input impedance, i.e. the ratio between pressure and airflow oscillations at the mouth. This in turn can be partitioned into the mechanical parameters resistance (the flow-dependent component of impedance, which primarily reflects airway calibre) and reactance (the volume-dependent component, which primarily reflects elasticity of the respiratory system). Thus, both oscillatory resistance and reactance have a physiologic basis that suggests that they should be physiologically informative in OAD. Oscillations of multiple frequencies can be delivered simultaneously, with typical frequencies used being 5, 11 and 19 Hz. This is important because different parts of the lung respond to different frequencies – while resistance and reactance at 5 Hz reflect the mechanical properties of the airway tree, the influence of the small airways and peripheral lung diminish with increasing frequency. The frequency dependence of resistance between 5 to 19 Hz has been shown to reflect heterogeneity in the distribution of airway narrowing and/or closure across the airway tree(27-29). Furthermore, it is possible to track changes in resistance and reactance within a breathing cycle, which can be useful to non-invasively detect expiratory flow limitation during breathing(30).

Armed with these tools, physiological phenotypes may not only help us provide better insight into the causal mechanisms of disease, they may also help us assess interventions, e.g. bronchodilator responsiveness measured by FOT and MBW measurements of ventilation heterogeneity could be helpful in identifying patients that respond to bronchodilator or inhaled corticosteroid treatment, or provide more comprehensive markers of response to both existing and new treatments for OAD. Monitoring of disease activity i.e. progression of airflow obstruction, changes in day-to-day variability of airway calibre (that characterises asthma), risk of exacerbations or attacks, early detection of those at risk of disease progression (e.g. rate of loss of FEV1) are just some examples of how physiologic phenotyping, when combined with cellular and genetic markers of disease, can provide the necessary information to advance the understanding and management of OADs.

Current Evidence for Clinical Utility

Here we describe, based on published data, the evidence for the use of functional imaging, MBW and FOT to better assess and predict treatment response in OADs. In this way, we hope to demonstrate how physiological phenotyping tools will improve the way in which drugs are prescribed, but most importantly, will facilitate development of new drugs for OADs.

Paediatric Utility

Cystic Fibrosis

MBW is of particular interest in paediatrics due to its high feasibility as a tidal breathing technique: >80% feasibility reported in infancy and preschool age ranges and >90% above

that age range(31). The OAD where MBW is closest to integration into clinical care is Cystic Fibrosis (CF): greater sensitivity to detect early OAD vs spirometry has been shown across all ages(31), with progression over time(32), and exciting ability to detect the beneficial effects of intervention(33, 34). These beneficial effects of intervention can be detected in far smaller numbers than required for spirometry(33, 35), and its main outcome Lung Clearance Index (LCI) has been formally endorsed as a primary outcome for research studies(36). This has led to the first successful implementation of LCI as a primary outcome measure in large pharmaceutical sponsored multicentre international studies(37) using a structured approach to training, certification and quality control of MBW data(38).

Asthma and wheeze

MBW utility in paediatric asthma is less well defined but emerging(39). Histological changes in early asthma have been demonstrated in endobronchial biopsies in recurrent wheezers during the preschool years (e.g. higher reticular basement membrane thickness and mucosal eosinophilia), and were not only associated with higher ventilation inhomogeneity, but also later early school age recognised markers of asthma (exhaled nitric oxide levels)(40). LCI is increased in school aged asthmatic subjects, compared to healthy controls(41), is related to AHR(42) and is higher in those with poor asthma control(43). Increased ventilation inhomogeneity is still detectable in well controlled asthmatics after SABA administration(44, 45). Advanced analysis of the change in phase III slope throughout MBW suggests a pattern of abnormality in the conducting airways rather than acinar airway abnormality in paediatric asthma(42-45).

The utility of oscillometry in paediatric asthma has also been of long standing interest due to its high feasibility as a tidal breathing test in young children(46). Diagnostic utility of conventional FOT methodologies (i.e. mean values of resistance and reactance over a recording period) in children with asthma appear limited(47, 48). FOT parameters objectively measure bronchodilator response(49, 50) and airways hyperresponsiveness(51, 52). However, within-breath differences in FOT parameters appear to hold additional utility to conventional mean measurements across the monitoring period. Czovek and colleagues examined utility in preschool subjects with acute and recurrent wheeze(53). The change between end-inspiratory and end-expiratory resistance detected airway obstruction with high sensitivity and specificity (92% and 89%, respectively) in the acute wheeze setting, and was able to distinguish children with recurrent wheeze from healthy children with high sensitivity.

Adult Utility

It should be noted that the role of spirometry as a diagnostic test of airway function for OADs in adults is, in itself, bona fide physiological phenotyping. The accuracy and ability to perform spirometry repeatedly meant the test could be used as an important endpoint in multicentre clinical trials to document efficacy of therapeutic targets. Nevertheless, a monolithic view of airway function that can only be assessed by spirometry, has resulted in a respiratory community that has struggled to grapple with the complexity of airway physiology and the heterogeneous nature of OADs.

COPD

This can be appreciated in the approach to COPD where the condition is defined by abnormal spirometry. Yet, clinicians have long appreciated the importance of emphysema observed in some patients that have normal spirometry and another group of patients that seem to have 'early' lung disease or 'at risk' of developing COPD. Here, guidelines have variably introduced (and removed) new categories to define these patient groups such as "Stage 0" in the 2001 GOLD publication that was subsequently removed(54, 55).

Large observational cohort studies such as Spiromics and COPDGene have contributed to renewed interest in understanding 'early' COPD, especially in smokers who have preserved FEV1/FVC ratio who may progress towards obstruction. Significant effort has been made to identify molecular signatures to identify these patients but along the way this has led to greater appreciation of abnormalities in imaging and lung function that can also be assessed. Previous work from our group in such 'smokers with normal spirometry' found abnormalities were frequently detected in peripheral airway function whether measured with MBW or oscillometry(56). Interestingly, most patients displayed an abnormality in one but not both peripheral lung function modalities highlighting, yet again, the importance of a multifaceted approach to physiologically phenotyping patients using a variety of tests.

Oscillometry is now an established clinical lung function test with commercial devices increasingly available and the recent publication of a standards document to guide its implementation into a clinical laboratory(57). Just as is the case in paediatrics, it has the appeal of being a relatively effort independent test and, hence, is perfectly suited for monitoring patients with very severe disease or the very old. In a pilot study of people with

COPD, Milne et al(58) found a correlation between baseline oscillometry and the subsequent improvement in gas trapping following the inhalation of a long acting beta-agonist. Indeed, subsequent work confirmed that oscillometry in COPD measures those areas of lung that are participating in ventilation (and hence likely to respond to an inhaled medication) (59). Thus, oscillometry may serve as a useful predictor of specific therapeutic interventions. In contrast, current COPD guidelines are heavily focussed on symptoms, and evaluation of a long acting bronchodilator in an individual patient involves switching or adding another therapeutic class if the symptomatic response is deemed less than optimum.

Asthma

The importance of small airways disease in asthma is now established. Here, therapeutics have sought to optimise delivery to the periphery of the lung with mixed success (60). The importance of having the correct tools to assess such intervention is once again highlighted. For example, the presence of a bronchodilator response measured with oscillometry identifies more patients with poorly controlled asthma compared to spirometry(61). Meanwhile, MBW indices improve with treatment, both in mild-to-moderate(62) as well as severe uncontrolled asthma(63). In severe eosinophilic asthma, we recently reported on the early improvement in MBW indices after the commencement of anti-IL5 treatment(64). Importantly, improvement in these indices correlates with symptom improvements and may be a predictor of a more sustained symptomatic response. In mild-to-moderate asthma, MBW indices predicted symptomatic response to ICS titration, with greater apparent sensitivity than exhaled nitric oxide (FeNO), whereas FEV1 did not(65). In severe uncontrolled asthma, both MBW and oscillometry predicted improvements with high dose ICS, again where FEV1 did not(63). Both MBW and oscilllometry have been studied

extensively in asthma but often in smaller single centre studies. The recent publication of the multinational ATLANTIS study is the first to bridge this gap reporting on the role of such tests in assessing the different phenotypes in asthma(66).

In terms of imaging, MRI-based ventilation defect measures relate to asthma symptoms and quality of life, independently to oscillometry(67). More importantly, they are normalised by biologic treatment in asthma(68).

Other diseases and co-morbidities

In addition to applications in smokers, COPD and asthma, MBW and oscillometry have also been shown to be a sensitive measure of small airway function in bronchiolitis obliterans in haemopoietic stem cell recipients(69), and airway dysfunction in obesity(70). Similarly, ventilation imaging has also provided important insights into the respiratory effects of obesity(71), as well as in detection of early lung disease in cystic fibrosis(72).

Physiological phenotyping: some pitfalls

If these novel physiological tools are now available, and if the body of recent clinical studies suggest that they have consistent and strong clinical associations, then why has there been little or slow uptake into respiratory medicine practice? Why have we not moved forward from conventional spirometry?

Structure-function relationships in pathology

A potential reason may be the lack of strong or consistent structure-function correlations with histopathological measures. For example, reticular basement membrane thickness

does not correlate with ventilation heterogeneity measured by inert gas washout in paediatric patients with asthma or severe wheeze(40, 73). In contrast, increased ventilation heterogeneity in patients with CF correlated with reticular basement membrane thickness and HRCT scores of abnormal lung structure(73, 74). There is circumstantial evidence that oscillometry is sensitive to airway remodelling in asthma, since the relationship between lung volume and respiratory system conductance (reciprocal of resistance) does not normalise following bronchodilator administration(75). In terms of inflammation, ventilation heterogeneity in diffusion-dependent airways (i.e. acinar airways) correlated with sputum neutrophils whereas heterogeneity in convection-dependent airways (i.e. conducting airways) correlated with sputum eosinophils(76).

The mixed evidence is perhaps not surprising since these tests of lung mechanics and ventilation heterogeneity by their nature measure the summative process of many pathological abnormalities, rather than individual cellular interactions. ASM contraction, airway thickening due to inflammation, as well as structural remodelling of the ASM, sub-epithelial layer, reticular basement membrane or epithelial layer, can all contribute to an overall increase in airway resistance. Similarly, changes in alveolar size, loss of alveolar septa or changes in surfactant function would all contribute in varying extents to reduced lung compliance. All of these in turn would contribute to changes in ventilation distribution. Given this complexity, it is difficult to directly and specifically infer the pathology underlying some of these physiologic measures.

On the other hand, functional imaging may disentangle the individual contributions of different pathological processes. Recent development of a complex image registration

technique called Parametric Response Mapping (PRM) allows comparison of lung density on CT between functional residual capacity and total lung capacity in order to distinguish small airways disease from emphysema(77). Importantly, a post-mortem study recently provided much needed pathological verification of PRM, reporting that PRM small airway function corresponded to abnormal terminal bronchial pathology, while PRM emphysema corresponded to alveolar enlargement(78). Ventilation measures from MRI also show similar promise; extent of non-ventilated lung volume correlates with eosinophilic inflammation in sputum and mucus plugs and, may also reflect airway tone(79). Finally, the recent development and validation of optical coherence technology (OCT), which allows quantification of airway wall layers, may provide a sensitive and comparatively non-invasive method to measure multiple lung sites for each individual(80, 81). A combination of OCT and ventilation imaging may be able to further link specific structural changes with physiological phenotypes of OAD and thereby promote localised and pathology-guided intervention.

Moving beyond spirometry?

Despite its own lack of validation in structure-function studies, spirometry has been and will likely remain a cornerstone of respiratory measurement. It has the advantage of being simpler in principle to understand and explain, even though it difficult to perform in some. In contrast, the tests described in this paper are complex in underlying principles and require good knowledge of underlying basic pulmonary physiology and skill in teaching by experts. Whilst the feasibility to train operators across a large number of sites within international research studies with techniques such as these has been demonstrated(82),

and provides insight into what infrastructure may be required for widespread clinical implementation(38), this has not been done to date. This and the lack of guideline recommendations on how to utilise these tests to improve clinical outcomes are the final hurdles before widespread clinical implementation. Future studies assessing and predicting response to treatment, outcome risks and monitoring, and especially determining magnitude of clinically meaningful changes remain areas of urgently needed research. Also, the most appropriate test choice will likely differ according to clinical scenario. For example, inert gas washout may be sensitive to detect change in subjects with CF or bronchiolitis obliterans syndrome, whereas oscillometry may offer greater insight in asthma or COPD.

Emerging Applications

Lung volume dependence

There is growing evidence that physiological measurements that encompass the entire lung volume range may provide clinically meaningful insight into OAD. As described above, imaging methods such as PRM examine changes in lung density over excursions in lung volume to provide insight into small airways disease and emphysema. While PRM has predominantly been measured in COPD, recent evidence that it correlates with asthma control and quality of life suggests it also has clinical utility in asthma (83). Similarly, extending MBW through multiple inspiratory capacity manoeuvres after inert gas concentrations fall below 2% allows calculation of the volume of trapped gas at functional residual capacity(84). Similarly, the non-linear relationship between lung volume and reactance is thought to indicate the volume at which airway closure begins since it correlates with predicted closing capacity in people without lung disease(85). The reactance

measured at the onset of airway closure is an independent predictor of asthma control(86), suggesting that it reflects important clinical information not detected by traditional lung function. Since airway closure and gas trapping are well-recognised markers of severe disease, the measurement of early airway closure and gas trapping provides attractive measures for phenotyping OADs.

Home monitoring and day-to-day variability

The simplicity and ease of oscillometry lends itself to frequent/daily monitoring particularly in the home where unsupervised spirometry or peak flow measurements remain challenging. Technological advances now allows measurements to be sent over (wireless) internet networks increasing its usefulness in telemedicine. Feasibility has been demonstrated in both children under parental supervision(87), adults with asthma(88) and elderly people with COPD(89). A recent large trial suggested an improvement in re-hospitalisation rates with home monitoring using oscillometry compared to usual care in COPD patients with a previous exacerbation(90).

Day-to-day variability appears to offer exciting insight into the variable airflow obstruction that characterises asthma. In children, day-to-day variability in resistance or reactance is increased in those with poor asthma control, and missed by peak flow monitoring(91). Home telemonitoring over longer term (months) reveal patterns of increased day-to-day variability prior to an exacerbation in both asthma(87) as well as COPD(92), suggesting utility in detecting onset of exacerbation.

Furthermore, there is promise in the use of advanced analysis techniques to better capture this day-to-day variability in lung function. Specific patterns in lung function over time have been shown to occur naturally and altered as a result of pathology, as well as in response to stimuli or treatment(93). Day-to-day patterns in peak expiratory flow are different between health and asthma(94), and are altered and predict response to treatment in asthma(95, 96) (97). These patterns also relate to asthma control(98), and could be used to predict future risk of exacerbations(99). Combining these approaches with oscillometry has the potential to further increase sensitivity in predicting exacerbations(100).

As these new methodologies mature, their application to lung function variability could open a new era of research in OAD. First, having an objective marker for detecting exacerbation onset, perhaps earlier than symptoms, may provide novel targets for pharmacological developments, since it is likely that the initial immune response during an exacerbation is significantly different to when symptoms are present. Second, the ability to predict exacerbations in a more timely manner (e.g. days or weeks versus the current best predictor of a previous exacerbation in the past 12 months) may provide the opportunity to develop medications with differing timing/dynamics of action, perhaps instigating a change in the way we currently treat exacerbations.

Complex system approaches

While these physiological tools offer superior objectivity and sensitivity to symptoms and conventional lung function, separately they still represent only specific aspects of a larger, more complex picture. The lung in health and disease comprises an essentially complex

system, which may not be captured by single, simple biomarkers. A complex system has multiple components all interacting with one another, and exhibits nonlinearities in structure and function, often resulting in deterministic patterns in measureable markers over time(93, 101). Thus, truly comprehensive disease phenotyping should take these complex behaviours into account, and include physiological as well as genetic, molecular and cellular measures, in addition to patient-based measures such as obesity, adherence, symptom perception, etc (Figure 1). Meanwhile, physiological treatable traits themselves could be visualised as the numerous spokes on a hypothetical wheel (Figure 2). Physiological phenotypes of airways disease could then be described based on the different extents of abnormality along the different spokes, including different variability over time (indicated by the dotted profile). Treatment targeting each physiological trait (or clusters/networks of traits) then aims to reduce these abnormalities to a physiological profile that is more similar to health. In this way physiological phenotyping would contribute to a label-free, treatable traits, approach to the management of OADs.

Conclusions

Patient-reported outcomes are important diagnosis tools and endpoints in chronic disease such as OADs, and some may argue that research into drug development should focus entirely on symptoms as the endpoint of interest. However, they are by nature subjective, and the physiological processes that contribute to symptoms can be varied. A purely symptom-based approach would be detrimental to future therapeutic developments and eventually patient care will suffer. We are now already moving towards the concept of personalised medicine, based on a focus on treatable traits that are objective, measurable and modifiable. We propose extending this concept via the use of emerging clinical tools for

measuring lung structure and function, to identify physiological phenotypes and their ability to assess and predict response to treatment. Characterising the physiological characteristics of OAD is clinically useful and will facilitate drug development for OAD, and enable us to account for the tremendous heterogeneity seen in OADs. Furthermore, advances can only be achieved if the complexity of the disease (and patient) is assessed across a number of platforms including lung function, imaging, biomarkers and genetic information where available. This comprehensive approach will enable us to better tailor interventions to the patients that will benefit the most from specific therapeutics.

Conflict of Interest

D.G. Chapman reports no relevant conflict of interest.
G.G. King reports a collaborative research agreement and IP agreement with Restech, a commercial company producing oscillometry devices. He also reports grants and personal fees for lectures from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Menarini, MundiPharma and Cyclomedica, grants from NH&MRC, Philanthropic Societies, Sydney University, outside the submitted work.
P.D. Robinson reports research collaborative agreements with manufacturers of oscillometry equipment (Thorasys Ltd), but does not have any financial relationships with that company. His institution, The Children's Hospital at Westmead, have received renumeration for services provided for Multiple Breath Washout training and quality control for pharmaceutical-sponsored and investigator led research studies.
C.S. Farah reports no relevant conflict of interests. He has received personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Sanofi Genzyme outside the submitted work.
C. Thamrin has a patent WO 2006130922 A1 issued which is broadly relevant to the work, and has intellectual property arrangements with Thorasys Medical Systems and Restech srl, both commercial produces of oscillometry devices, relating to research collaborations, but does not have any financial relationships with either company.

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FIGURES

Figure 1. Comprehensive phenotyping of airways disease should take into account physiological as well as genetic, molecular and cellular measures, in addition to patient-based measures such as obesity, adherence, symptom perception, etc.

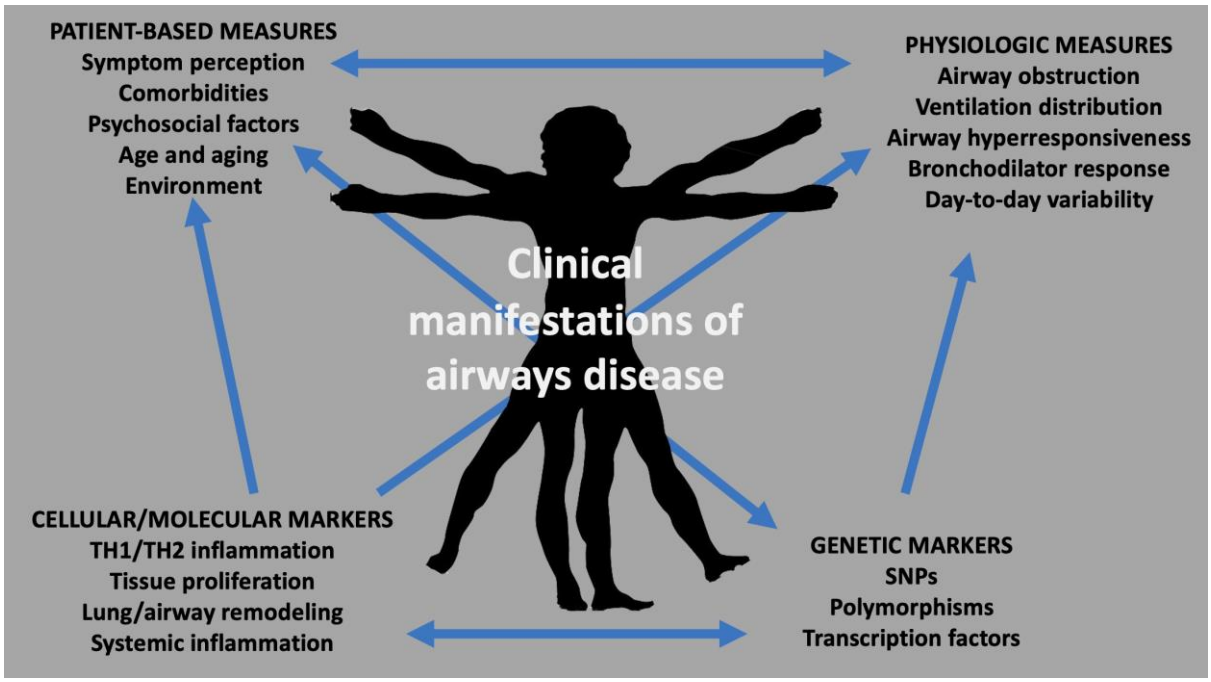

Figure 2. Possible physiological treatable traits. Different airways disease phenotypes can manifest as different profiles, with different extents of abnormality along the different spokes, including different variability over time (indicated by the dotted profile).