Unmet needs for the assessment of small airways dysfunction in asthma: introduction to the ATLANTIS study

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Filling the knowledge gap of small airways dysfunction across all asthma severities: the ATLANTIS study http://ow.ly/LnuUL

Background

An estimated 300 million people suffer from asthma worldwide, which is a major public health problem [1]. Asthma is a chronic inflammatory lung disease that affects the entire bronchial tree. The small airways, *i.e.* <2 mm diameter, can be affected by inflammation and remodelling, resulting in changes occurring in the smooth muscle cells and the surrounding tissue. These changes all contribute to dysfunction of the small airways, which may contribute to the clinical expression of asthma [2]. However, their contribution to asthma control and exacerbations has been minimally investigated and the majority of studies performed have only occurred in cross-sectional, small-sized patient groups with a narrow spectrum of severity.

Small airways function can be assessed with invasive and non-invasive techniques, including physiological and radiographic testing, in addition to direct and indirect assessments of inflammation. These tests are usually only available in specialised chest clinics, requiring the use of trained staff with good quality standards [3]. Unfortunately, there is no gold standard tool, or an easy-to-apply measure, available in which to assess small airways dysfunction (SAD). Thus, there is an unmet need to identify SAD easily and correctly across all severities of asthma, and to assess its role in the control of the disease.

Approaching the small airways by pulmonary function tests

The pulmonary function tests used to assess small airways pathology can be subdivided in tests measuring flow, airway resistance, inhomogeneity of ventilation distribution and hyperinflation or air trapping.

Flow measures commonly used in small airways studies are forced expiratory flow at 50% ($FEF_{50\%}$) and at 25–75% ($FEF_{25-75\%}$) of forced vital capacity (FVC) [4]. Airway resistance can be measured with impulse oscillometry system (IOS) and small airways obstruction is associated with an increase in resistance, predominantly at lower frequencies [5]. SAD, as reflected by a higher difference between resistance at 5 Hz

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and resistance at 20 Hz (R_5–R_{20}), using IOS, is associated with symptoms of wheezing, dyspnoea and chest tightness [5]. Both R_5–R_{20} and reactance at 5 Hz, but not FEV_1, increased at the time symptoms developed during a methacholine challenge, suggesting that an increase in small airways resistance is coupled with symptom development. Also, increased small airways reactance is associated with more severe respiratory symptoms [6].

Measurement of lung volumes may contribute in the function assessment of the small airways. Increased functional residual capacity or thoracic gas volume (TGV), total lung capacity and residual volume (RV) greater than 120% predicted were associated with SAD [7]. Peripheral airways resistance, as determined by wedged bronchoscope technique, also correlated with residual volume measured at 16:00 h and 04:00 h [8]. A reduction of RV produced by montelukast treatment was accompanied by improvement in wheezing and shortness of breath [9]. A higher TGV correlates with more eosinophilic distal lung inflammation in mild-to-moderate asthmatics not adequately treated [10].

Inhomogeneity of peripheral ventilation distribution can be assessed by the multiple-breath nitrogen washout (MBNW) test after inhaling 100% oxygen. The MBNW test has an advantage over IOS, as the washout phase-3 slope analysis can be linked to mathematical models that describe uneven ventilation in both small conducting airways and airways at the entrance to the pulmonary acinus. MBNW test metrics are reproducible in asthma [11]. They correlate with measures of small airways inflammation [12], hyperresponsiveness [13] and, of importance, with clinical improvement [14] and better asthma control [15] following small particle corticosteroid treatment, but not with baseline asthma patient-related outcome measures [11, 15]. To date very few studies specifically addressed the relationship of small airways dysfunction with hyperresponsiveness, a hallmark of asthma. However, available evidence suggests there is an association; however, this has not been studied across all severities of asthma or associated directly with control of asthma and airway inflammation [13]. There is a clear need to evaluate all these measures of SAD in a large asthma population with the full spectrum of severity, since data with evidence-based information for clinical practice are now lacking.

Approaching the small airways by transbronchial biopsies

Direct evaluation of inflammation *via* lung biopsy remains the gold standard to assess the inflammatory profile and to compare it with physiological tests of SAD. Unfortunately, transbronchial biopsy (TBBX), an effective method to assess small airways inflammation in living patients with asthma, is an invasive procedure. It carries a low risk of pneumothorax, ~1–3% [16]. The specimens obtained by TBBX contain both alveolar and small airways tissue, and the amount of each to quantify inflammation is limited as the total volume of recovered tissue is small. Despite these barriers, several studies have documented increased inflammation in the distal lung compartment, which includes the small airways and alveolar tissue [17]. Lung samples from surgery in asthmatics show significant inflammation with eosinophils and mast cells both in large and small airways [18].

Approaching small airways inflammation indirectly

Indirect measurements of inflammation, as used in clinical practice, include fractional exhaled nitric oxide (F_{ENO}), induced sputum and serum biomarkers.

F_{ENO} measurements are easy to perform and can even be repeated in patients with severe airflow obstruction. Many patients with asthma have high levels of F_{ENO} and high levels of inducible nitric oxide synthase enzyme expression in airway epithelial cells [19].

Sputum eosinophil counts have been tested as a biomarker for the response to anti-inflammatory treatments. The frequency of exacerbations in severe patients can be reduced when the inhaled corticosteroid (ICS) dose is adjusted to keep sputum eosinophil counts within the "normal" range [20]. It has never been explored whether currently known and/or additional biomarkers under assessment have specific relationships or target pathobiological mechanisms related to SAD, as assessed by the different available tools (lung function, imaging, inflammation, clinical questionnaires); again, another gap in our knowledge of SAD.

Approaching the small airways by computed tomography

Indirect changes caused by the small airways on the lung parenchyma can be detected by computed tomography (CT), as SAD results in reduced ventilation of parts of the lung, which in turn induces a reflex reduction in perfusion, highlighted as areas of decreased attenuation on CT images [21]. Heterogeneity of lung attenuation in asthma can be noticeably accentuated in expiratory scans compared to inspiratory CT scans, due to regional differences in small airways closure or the rate of emptying. Although asymptomatic individuals without lung function abnormalities also demonstrate low attenuation regions on CT scans [22], asthmatic patients have significantly more air trapping that correlates with lung function abnormalities [23, 24]. Air trapping correlates with asthma severity [25], airway hyperresponsiveness,

disease duration [23] and airflow limitation [23, 24], and may be used to evaluate the response to inhaled corticosteroid therapy [26].

The state-of-the-art imaging approach to assess SAD in a multicentre study could be inspiratory and expiratory CT-derived densitometry carefully standardised for extra-thoracic air, and blood and regression equations calculated from the scanning of densitometry standards embedded within lung phantoms [27].

Approaching the small airways by questionnaires

Patient Reported Outcomes (PROs), such as questionnaires, have gained a prominent place to better quantify asthma symptoms longitudinally and to monitor asthma control, *e.g.* asthma control questionnaire (ACQ) and asthma control test (ACT) [28]. The Asthma Quality of Life Questionnaire (AQLQ) measures functional problems, *e.g.* physical, emotional, social and occupational [29]. The European quality of life five dimension (EuroQol-5D) questionnaire provides a simple, generic measure of health for clinical and economic appraisal [30]. Finally, the bronchial hyperresponsiveness questionnaire (BHQ) aims to indirectly assess hyperresponsiveness in hyperresponsiveness that is associated with SAD [13, 31]. Whether these questionnaires can predict or correlate with SAD is not known. We are still lacking a questionnaire that specifically addresses small airways function that can be used by general practitioners or pulmonary specialists. This might be of interest if patients can perceive situations (*e.g.* exercise), signs (*e.g.* tightness around the chest) and symptoms (wheezing with cat exposure) derived from the small airways [32].

The ATLANTIS study

To answer the unmet need to better assess the contribution of SAD across all asthma severities and determine the best (combination of) tests to identify SAD, a multinational consortium has developed the ATLANTIS study (AssessmenT of smalL Airways involvemeNT In aSthma). The ATLANTIS study for the first time determines how small airways abnormalities drive the clinical expression of asthma, both in cross-sectional and longitudinal manner, and ascertains the prospective value of the best available tools to assess SAD in asthma and associates this with the control of asthma and exacerbation frequency over time. Moreover, this study allows further development and validation of a questionnaire specifically assessing SAD, the Small Airways Dysfunction Tool (SADT) [32], a questionnaire based on relevant differences in signs and respiratory symptoms between asthma patients with and without SAD. This is important to clinical practice, since this short SADT can easily be applied to asthma patients and allows the impact of SAD to be assessed in daily practice. Therefore, the ATLANTIS study will characterise a large group of 900 subjects divided into 800 asthmatic patients (including smokers) and 100 healthy controls. Recruitment will be balanced, at the extent possible, in order to achieve at least >150 patients, each, for steps 1–4 and >50 patients for step 5, as indicated in the international guidelines [1] on the basis of their previous therapy. Patients with stable asthma on any previous regular asthma treatment ("rescue" β2-agonists alone included) at a stable dose, for a minimum of 8 weeks prior to baseline visit, will be included. Healthy controls will be recruited on the basis of absence of respiratory symptoms, airway obstruction and hyperresponsiveness. The participants will be followed for 1 year with 6-month clinical follow-ups and 3-month telephone follow-ups (table 1). Treatment will be according to standard clinical care, without any pharmacological intervention defined by the protocol.

The study will assess which (combination of) biomarkers, physiological testing and imaging markers best measures the presence and extent of SAD in asthma. To this aim we will use structural equation modelling, a method to study the relationships among "latent variables" (constructs) that are indicated by multiple measures [33]. These constructs cannot be observed directly, but can be measured by more than one variable indirectly. We will thus assess SAD through all baseline measurements based upon criteria defined as consistent with small airways disease given the literature available for each test. The final result of the model building process will be an index defining to what extent SAD is present in each individual patient. With this index, its usefulness for prediction of asthma control and occurrence of exacerbations is evaluated in both cross-sectional and longitudinal analyses.

Of importance, the study will have additional value by obtaining normal reference values of lung function, CT and questionnaire variables where they are scarce (SADT questionnaire, MBNW, IOS, and CT measurements). In addition, transbronchial biopsies will be performed in a subset of asthmatics across the severity stages and results will be associated with clinical measures. As a rich source for further asthma phenotyping, material of epithelial brushes and blood (cells) will be stored for future studies.

Thus, ATLANTIS will fill in the gaps of our knowledge on SAD in asthma and:

1) Determine the role of small airways abnormalities in the clinical manifestations of asthma.

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TABLE 1 Study assessments

	First visit	In follow-up visits	In follow-up telephone contacts
Demographics	√		
Spirometry (reversibility)	√	√	
Lung volumes (body box)	√	√	
MBNW test	√	√	
Methacholine challenge test	√		
Asthma exacerbations	√	√	√
Blood, total and differential, cell count	√		
Phadiatop test	√		
Questionnaires			
Asthma Control Test	√	√	√
Asthma Control Questionnaire 6	√	√	√
Bronchial Hyperresponsiveness Questionnaire	√	√	√
Mini Asthma Quality of Life Questionnaire	√	√	√
Standardised measure of health status	√	√	√
Small Airways Dysfunction Tool	√	√	√
Morisky Medication Adherence Scale	√	√	√
Optional assessments			
Sputum induction[#]	√		
IOS[¶]	√	√	
F_{eNO}[¶]	√	√	
Bronchoscopy with TBBX and EBBX[+]	√		
Nasal brushing[#]	√	√	
Computed tomography scan[§]	√		
Blood sample collection for future analyses	√	√	

MBNW: multiple-breath nitrogen-washout; IOS: impulse oscillometry system; F_{eNO}: exhaled nitric oxide fraction; TBBX: transbronchial biopsies; EBBX: endobronchial biopsies. [#]: European Union, USA, and Canada only; [¶]: in sites with equipment available; [+]: two centres in USA only; [§]: selected sites, total target 530 asthmatic patients and 50 healthy subjects.

2) Evaluate which (combination of) clinical methods best assesses the abnormalities of small airways and large airways dysfunction in asthma and best relates to asthma severity, control and future risk of exacerbations, both cross-sectional and longitudinal.
3) Further develop and validate the small airways dysfunction tool (SADT).

Additional aims are to define:
1) The physiological and radiographical characteristics that correlate with small airways function in asthma *versus* healthy controls.
2) Which direct and indirect measures of inflammation best discriminate between the large and small airways' compartments.
3) If questionnaires such as ACQ-6 and ACT assess small airways function

The protocol can be found at www.clinicaltrials.gov (NCT02123667).

The ATLANTIS study started in 2014 and the first results are expected in 2016. We believe that the powerful data gathered through such a unique study will not only improve our understanding of small airways pathobiology in asthma now, but also provide a database and sample repository to answer additional questions that will undoubtedly be raised in the future. We eagerly await the results to optimise future patient care of asthma.

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