If your patient with asthma wheezes when sitting or lying quietly, lung function testing may reveal small airway disease

Peter B. Noble [1] and Graham M. Donovan [2]

[1]School of Human Sciences, The University of Western Australia, Crawley, Australia. [2]Department of Mathematics, The University of Auckland, Auckland, New Zealand.

Corresponding author: Peter B. Noble (peter.noble@uwa.edu.au)

Shareable abstract (@ERSpublications)
Diagnostic protocols for the assessment of small airway disease have been advanced to optimise the clinical management of patients with asthma https://bit.ly/3lpECHO

Cite this article as: Noble PB, Donovan GM. If your patient with asthma wheezes when sitting or lying quietly, lung function testing may reveal small airway disease. *Eur Respir J* 2023; 61: 2202307 [DOI: 10.1183/13993003.02307-2022].

Received: 1 Dec 2022
Accepted: 6 Feb 2023

The paradigm of "small airway disease" (SAD) continues to be advanced with considerable enthusiasm by clinicians and scientists alike [1, 2], having full knowledge that the binary classification of airways as "small" or "large" is somewhat arbitrary [3, 4]. Nonetheless, important questions that remain unanswered are: 1) how does SAD manifest; 2) how do we detect SAD, ideally in a cost-effective manner that can be adopted in primary care; and finally 3) once a patient has been classified as having SAD, what can we do about it? The second of these questions is amply addressed in the present issue of the *European Respiratory Journal* by Kocks *et al.* [5].

Before discussing the original findings of Kocks *et al.* [5], it is important to acknowledge the context of earlier contributions by the collaborative team striving to find better and easier ways to examine SAD in asthma. In 2014, the initial groundwork for a convenient SAD Toolkit (survey) was laid where investigators identified 63 questions that were sensitive to SAD as defined by combined oscillometry and spirometry [6]. In 2019, the ATLANTIS study ("the Assessment of Small Airways Involvement in Asthma") developed a clinical score of SAD based on the aforementioned physiological techniques, adding also body plethysmography and multiple-breath nitrogen washout [7]. Finally, to the present study: after presumably acknowledging that a 63-item questionnaire may not be practical for routine and efficient use, Kocks *et al.* [5] adopted structured statistical modelling to extract questions that were most sensitive to the above clinical SAD score. The result is a simple diagnostic model that can be customised based on available expertise and resources to the benefit of the patient and healthcare provider.

Kocks *et al.* [5] were firstly able to demonstrate that a positive response to the question "I sometimes wheeze when I am sitting or lying quietly" in combination with basic patient characteristics (age, age of disease onset and body mass index) provided "acceptable" diagnostic discrimination of SAD, quantified by area under the receiver operating curve [8]. As to be expected, when the criterion was refined to include spirometry and subsequently oscillometry, diagnostic utility increased substantially, making it clear that when such testing is available, the "Gold model" provides the greatest sensitivity to SAD and is accordingly recommended. The added prognostic power provided by physiological measures is intuitive when considering that patients with SAD are at times asymptomatic [9]. However, when, for whatever reason (limited time, resources or patient cooperation) such physiological measurements cannot be performed, a simple questionnaire-based approach provides early indication of small airway involvement, impacting treatment strategies that may include referral and potentially further lung function assessment. Study findings will therefore be very impactful if the diagnostic model can be successfully implemented into various medical facilities.

An interesting question is why a virtual single questionnaire response is at all associated with SAD. Sitting or lying down essentially describes a resting patient who should be relatively safe from at least some

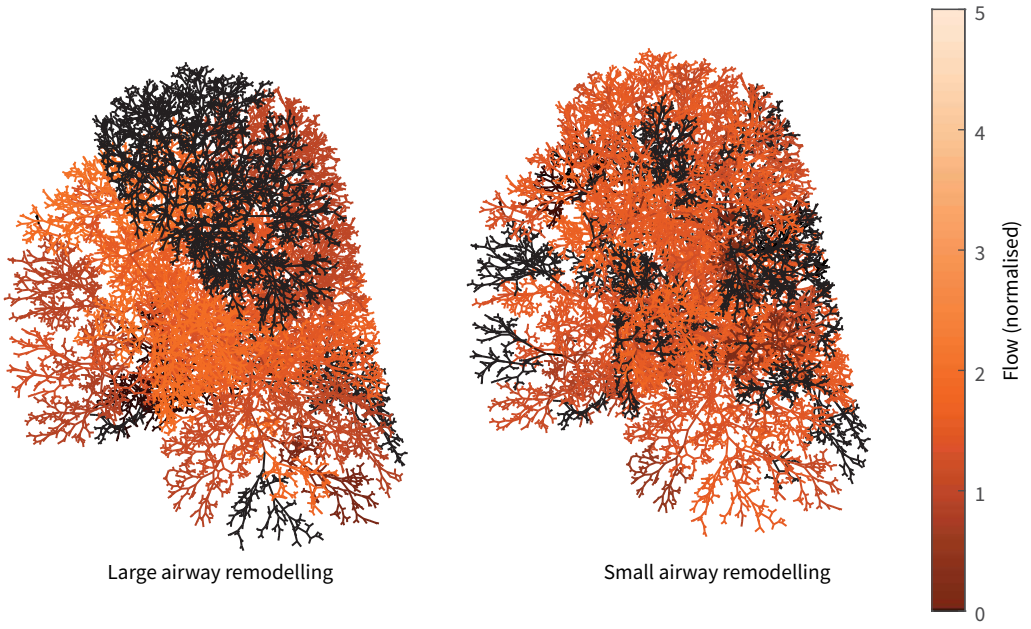

FIGURE 1 Mathematical simulation of ventilation distribution (dark to light reflecting low to high flow) during bronchoconstriction in a unilateral human lung. Two scenarios are considered; remodelling is localised to proximal (left panel, "large airway remodelling") or distal lung regions (right panel, "small airway remodelling"). Both scenarios produce flow limitation in the lung periphery, which is particularly apparent by the black shading. The take-home message is that prioritised treatment of small airways, based on this ventilation profile, could on occasions bypass the site of pathology, *i.e.* when remodelling is predominant in large proximal airways.

common environmental triggers for disease exacerbation, for instance exercise, amongst other stimuli. Wheeze under such low stress conditions implies a more severe disease with persistent symptoms that appears characteristic of patients with greater small airway involvement [7]. In fact, "wheeze at rest" was the intended meaning of the question, only worded a little differently because direct translation would cause confusion in certain countries (particularly in Asia). Some patients, however, may be drawn to the "lying down" element of the question, opening the door for alternative explanations behind the association with SAD. It is possible that respiratory symptoms when lying down reflect postural changes in lung ventilation [10], perhaps to regions that are more affected by disease processes, or through increased interregional heterogeneity [11]. There is also some historical evidence that a shift to supine position is itself a stimulus for bronchoconstriction [12]. Such considerations certainly point to the hidden complexity of constructing useful questionnaires across different languages, but also in this scenario, potentially leading to the serendipitous unveiling of underlying pathophysiology.

We return now to the other unanswered questions regarding how SAD manifests, which goes hand in hand with the treatment approaches used to remedy the abnormal physiology. Remodelling of the airway wall is apparent throughout the bronchial tree in both proximal and distal locations, with pronounced heterogeneity within and between patients [13]. It seems logical to conclude that SAD can be explained by a phenotype where remodelling is limited to the small airways, although this is expected to represent only a low proportion of patients, if you consider specifically airway smooth muscle thickness [13, 14]. Of course, the airways are functionally interdependent where pressure–flow characteristics in one region impact another, and are further modified by lung volume dependent parenchymal loads [15, 16]. A simple mathematical simulation using an established model of human lung function [17, 18] demonstrates that peripheral dysfunction is apparent when remodelling is localised to distal locations, as expected, but also when remodelling is localised to proximal airways that feed into downstream regions of the lung (figure 1). The point of these data is to show that detection of functionally abnormal small airways may not always be due to structural changes developed at the same anatomical level.

Decoupling of structure and function is a clear complication when considering the appropriate therapeutic intervention. Enhancing delivery of pharmaceutical particles to the lung periphery is feasible [19, 20], but

not necessarily the right solution if the disease process manifests more proximally. Regardless, understanding where the functional deficit lies will be informative; ruling out SAD alone provides good physician confidence to alternatively target proximal airways [21, 22].

In closing, the present study of Kocks *et al.* [5] brings an emphasis on the smaller airways to the clinic, and in particular a pragmatic perspective for clinical environments lacking spirometry or oscillometry capabilities. In our view, which is primarily one of basic science, this is most welcome. We would also emphasise, however, that the smaller airways deserve further attention not just in a clinical or translational context but also in terms of the mechanistic origins of SAD in asthma. The ATLANTIS study [7] made ground-breaking use of the techniques currently at our disposal, yet even with a complete set of modern diagnostics available in a research setting (spirometry, oscillometry, plethysmography and multiple-breath washout testing), characterisation will remain very much indirect until further technological advancements are made. While the purpose of this communication is to highlight the commendable achievements of Kocks *et al.* [5] with respect to identifying SAD in patients with asthma, at the same time it is appropriate to remind ourselves that the broader quest to truly understand small airway pathophysiology is not fully resolved.

Conflict of interest: None declared.

References

1 van den Bosch WB, James AL, Tiddens HAWM. Structure and function of small airways in asthma patients revisited. *Eur Respir Rev* 2021; 30: 200186.
2 O'Sullivan CF, Nilsen K, Borg B, *et al.* Small airways dysfunction is associated with increased exacerbations in patients with asthma. *J Appl Physiol (1985)* 2022; 133: 629–636.
3 Donovan GM, Noble PB. Small airways *vs* large airways in asthma: time for a new perspective. *J Appl Physiol (1985)* 2021; 131: 1839–1841.
4 Commentaries on Viewpoint: Small airways *vs*. large airways in asthma: time for a new perspective. *J Appl Physiol (1985)* 2021; 131: 1842–1848.
5 Kocks J, van der Molen T, Voorham J, *et al.* Development of a tool to detect small airways dysfunction in asthma clinical practice. *Eur Respir J* 2023; 61: 2200558.
6 Schiphof-Godart L, van der Wiel E, Ten Hacken NH, *et al.* Development of a tool to recognize small airways dysfunction in asthma (SADT). *Health Qual Life Outcomes* 2014; 12: 155.
7 Postma DS, Brightling C, Baldi S, *et al.* Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. *Lancet Respir Med* 2019; 7: 402–416.
8 Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. *J Thorac Oncol* 2010; 5: 1315–1316.
9 Pisi R, Aiello M, Frizzelli A, *et al.* Detection of small airway dysfunction in asymptomatic smokers with preserved spirometry: the value of the impulse oscillometry system. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 2585–2590.
10 Harris RS, Winkler T, Musch G, *et al.* The prone position results in smaller ventilation defects during bronchoconstriction in asthma. *J Appl Physiol (1985)* 2009; 107: 266–274.
11 Gronkvist M, Bergsten E, Gustafsson PM. Effects of body posture and tidal volume on inter- and intraregional ventilation distribution in healthy men. *J Appl Physiol (1985)* 2002; 92: 634–642.
12 Larsson K, Bevegard S, Mossberg B. Posture-induced airflow limitation in asthma: relationship to plasma catecholamines and an inhaled anticholinergic agent. *Eur Respir J* 1988; 1: 458–463.
13 James AL, Donovan GM, Green FHY, *et al.* Heterogeneity of airway smooth muscle remodelling in asthma. *Am J Respir Crit Care Med* 2023; 207: 452–460.
14 Elliot JG, Jones RL, Abramson MJ, *et al.* Distribution of airway smooth muscle remodelling in asthma: relation to airway inflammation. *Respirology* 2015; 20: 66–72.
15 Lambert RK, Pare PD. Lung parenchymal shear modulus, airway wall remodeling, and bronchial hyperresponsiveness. *J Appl Physiol (1985)* 1997; 83: 140–147.
16 Hughes JM, Jones HA, Wilson AG, *et al.* Stability of intrapulmonary bronchial dimensions during expiratory flow in excised lungs. *J Appl Physiol* 1974; 37: 684–694.
17 Donovan GM, Elliot JG, Green FHY, *et al.* Unraveling a clinical paradox: why does bronchial thermoplasty work in asthma? *Am J Respir Cell Mol Biol* 2018; 59: 355–362.
18 Donovan GM, Langton D, Noble PB. Phenotype- and patient-specific modelling in asthma: bronchial thermoplasty and uncertainty quantification. *J Theor Biol* 2020; 501: 110337.
19 De Backer W, Devolder A, Poli G, *et al.* Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients. *J Aerosol Med Pulm Drug Deliv* 2010; 23: 137–148.

20 Peterson JB, Prisk GK, Darquenne C. Aerosol deposition in the human lung periphery is increased by reduced-density gas breathing. *J Aerosol Med Pulm Drug Deliv* 2008; 21: 159–168.
21 Donovan GM, Elliot JG, Boser SR, *et al.* Patient-specific targeted bronchial thermoplasty: predictions of improved outcomes with structure-guided treatment. *J Appl Physiol (1985)* 2019; 126: 599–606.
22 Hall CS, Quirk JD, Goss CW, *et al.* Single-session bronchial thermoplasty guided by (129)Xe magnetic resonance imaging: a pilot randomized controlled clinical trial. *Am J Respir Crit Care Med* 2020; 202: 524–534.