Unravelling the Small Airways: Structure-Function-Treatment Relationships in Asthma and COPD

Omar S. Usmani

National Heart and Lung Institute, Imperial College London and Royal Brompton Hospital, London, UK

The small airways are currently a hot topic in pulmonary medicine, receiving renewed interest and attention regarding their role and involvement in asthma and chronic obstructive pulmonary disease (COPD). Historically, this relatively inaccessible region of the lungs has been termed the ‘quiet zone’, and understanding its contribution to the clinical presentation of disease has been challenging not only because the small airways are difficult to assess in clinical practice but also because it has been technically demanding to successfully deliver inhaled therapy to this region.

The pioneers who began to ‘unravel’ the significance of this region were Green [1], whose calculations were applied to the lung anatomical findings of Weibel [2] and, together with the techniques developed to assess small airway resistance by Macklem and Mead [3], led to the seminal article of Hogg et al. [4] that established the small airways as the major site of airflow limitation in obstructive airway disease. These observations subsequently inspired researchers from many respiratory disciplines to contribute and advance our understanding of the small airways, investigating the relations of anatomical structural abnormalities to the pathology of the underlying airways and identifying physiology and radiological correlates.

The current Thematic Review Series in Respiration is dedicated to the ‘structure-function-treatment’ relationships of the small airways, with particular focus on the obstructive lung diseases of asthma and COPD. The series includes contributions from leading international experts in the field who communicate an engaging and unfolding story, taking us back to the basic sciences we learnt in medical school and through a journey revisiting and integrating respiratory anatomy, pathology, immunology, physiology and pharmacology.

In the first article of the series in this issue of Respiration, Hamid [5] introduces us to the pathophysiology of the small airways in asthma and sets the foundation for the relevance of the anatomy and pathology of small airway disease in the clinical presentation of these patients. We are reminded that the inflammatory changes and airway remodelling observed in asthma are present throughout the pulmonary tree and that asthma is a disease of small, as well as, of large airways [5, 6]. Our second contribution, from Saetta and colleagues [7, 8], discusses the pathophysiological features of COPD, conveying the importance of morphometric abnormalities and their relationships with the physiological manifestations seen in COPD patients. The article highlights the immunopathological pathways through which cigarette smoke can dam-
age the small airways and how the pathological alterations parallel derangement of pulmonary function in smokers with COPD [7,8].

Juxtaposed, these two articles contrast the different histological, immunological and biological features between asthma and COPD, yet together they reinforce the contribution of small airway pathology to both of these obstructive airway diseases.

Our next set of articles further develop the series’ theme, focussing on the assessment and function of the small airways. In the third article, Verbanck [9, 10] provides a systematic overview of the physiological techniques that have been applied in a clinical context to study the small airways and their contribution to obstructive lung disease. We are informed that many of the newer physiological tools have actually been utilised for many years and have been ‘rediscovered’ in their application to small airway assessment [9,10]. The article describes that most of these tools remain indirect or surrogate markers requiring further validation and that complementing these tools with imaging modalities into an integrated functional imaging approach may yield the true potential of physiologic small airway tests. This assertion nicely introduces our fourth contribution to the series by King [11,12], who reviews the current advances in medical imaging technologies as well as the emerging modalities that are being applied in the measurement of structure and function with respect to the small airways. The article comprehensively examines the imaging techniques that have been used to provide regional anatomical information about the small airways.

The fifth and final article in this series evaluates the approaches undertaken to treat the small airway region of the lungs and the clinical implications of targeting inhaled therapy to the periphery in patients with asthma and COPD [13,14]. The recent advances in medical aerosol technologies and inhaler design are discussed with respect to improving drug delivery to the pulmonary tree and small airways. Dotted throughout the series are Novel Insights from Clinical Practice, which showcase the role of small airways in our day-to-day clinical practice in the form of peer-reviewed clinical case reports.

Collectively, this series will provide an up-to-date, state-of-the-art review in this topical arena. It will become apparent, as each of the authors states, that there is research that needs to be done to answer whether we are using the right biological markers to assess regional airway physiology and anatomy. There are many challenges that need addressing; the newer techniques need standardisation for their methodology and validation; population data is needed for the small airway measures [15]; we need to understand how the small airway measures relate to a meaningful clinical difference and to patient-centred clinical outcomes such as symptoms, quality of life and exacerbations, and we need large clinical studies to test whether small airway-directed therapy does indeed provide added value and clinical benefit. To researchers in the field it is also tantalizing to investigate whether there may be a ‘small airways phenotype’ and, indeed, if small airway measures can predict the clinical course of a disease.

These are exciting times and, with reinvigoration of the interest in the small airways, there may be a realisation now that the small airways may not quite be the quiet zone we once thought they were.

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References

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