



CLINICAL RELEVANCE OF

SMALL AIRWAY DISEASE

The bronchial tree continuously divides down to the 23rd generation (division). One consequence of this division is that the mucosal surface area of the airways is relatively larger in the distal lung than in the proximal lung. This may be important when dealing with an airway disease.

After the 8th division the airways are smaller than 2mm. This zone of the lung that contains these small airways has also been called the silent zone of the lung and this is probably due to the fact that it is difficult to access the small airways and disease that develops there in the small airways can go undetected until late in the disease. Disease in this zone often is advanced before diagnosis and examples of disease that also affect small airways are asthma and COPD (chronic obstructive pulmonary disease), both of which are associated with airway inflammation of a different nature. Using the techniques of peripheral-wedged catheters and wedged bronchoscopy it was demonstrated that there is a large increase in airway resistance in this distal small airway part of the lung in patients who have airflow obstruction such as asthma and chronic obstructive pulmonary disease (COPD).

Diagnosis of small airway dysfunction

There is a preserved (normal) FEV1 of higher than 80% of predicted, but there is evidence of an impaired (lower than 60% predicted) forced expiratory flow between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅). The main drawback of using the Forced Expiratory rate at 25-75% is that it is less reproducible than FEV1 because it is a volume dependent measurement. When this combination is present, one can suspect the presence of small airways disease but it should be confirmed with another test.

Other tests for small airways disease include: Impulse oscillometry, which is effort-independent, done during quiet breathing and needs minimal patient co-operation. The airway resistance measured at 5Hz (R5) represents both large and small airways and the resistance at 20Hz (R20) represents airway resistance in larger airways only and therefore R5

minus R20 is the resistance in the peripheral airways and this value is abnormal defined as higher than 0.03kPa/L.s.

Another test that is indicative of small airways abnormality is evidence of air trapping such as residual volume (especially the ratio of residual volume to total lung volume) using whole-body plethysmography and abnormal closing volumes using a single breath nitrogen-washout. Measurement derived from the slope three of the single-breath

Drugs and devices delivering extra-fine particles

- 1 Solution-based hydrofluoroalkane (HFA)-propelled pMDI's delivering at least three inhaled steroids: Beclomethasone dipropionate (BDP), Ciclesonide and flunisolide
- 2 Long acting beta agonists (LABA): Formoterol. Extra-fine Formoterol is not available in SA yet.
- 3 Novel device such as a soft mist inhaler with Tiotropium (a long-acting Muscarine antagonist)
- 4 Multidose DPI (Nexthaler) delivering extra-fine particle ICS/LABA combination (Beclomethasone +Formoterol). Not available in SA yet.
- 5 Multidose pMDI delivering extra-fine particle ICS/LABA combination: BDP/ Formoterol. Not available in SA yet.



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PULMONOLOGY

washout can also be used to calculate regional ventilation. CT and MRI of the lungs are also possible tools when evaluating the effects of small airways disease.

Lipworth *et al* use the following pragmatic lung function values to diagnose small airways disease: FEV1 higher than 80% predicted, lower than 60% for FEF 25-75%, higher than 150% for R5 and higher than 0.10kPa/L.s for R5-R20.¹

Small airways asthma phenotype

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. This definition is from the 2017 GINA guidelines on the management of asthma and can be accessed at www.ginasthma.org

Asthma affects 5-18% of people globally with varying prevalence in different countries. The heterogeneous nature of asthma has led to the concept of asthma subtypes based on demographic, clinical and/or pathophysiological characteristics. Much more research is needed to understand the clinical utility of phenotypes.

In the management of asthma it is frequently found by doctors that patients seem to be difficult to reach satisfactory control of their disease.

Current advice with such patients includes: check adherence to therapy which can be poor due to many reasons, check that the diagnosis is correct and the symptoms are not due to another clinical condition (eg cardiac failure, lung fibrosis etc.), and manage co-morbidities and triggers for asthma. One such overlooked condition can be uncontrolled disease of the small

Key aspects of extra-fine particle aerosols



airways in asthma. The idea of uncontrolled small airways disease in asthma is probably not new but was neglected in the past.

Pathophysiologic studies demonstrated that airway inflammation in asthma is present in all airways and in the small airways and this region is the main contributor to airflow limitation.

Patients with the small airways phenotype can be clinically suspected as those patients that are presenting with not-optimally controlled asthma but who have relatively healthy lung function values such as FEV1 \geq 80% predicted together with the other abnormal lung function parameters as described above. Clinically they can be identified as asthmatic patients

with asthma questionnaire $>$ 1.5, persistent daytime and night-time symptoms, the need to use a reliever regularly or a requirement for oral corticosteroids during a viral infection.

There are quite a number of studies linking small airways dysfunction to asthma control and some of these studies involve children with poor asthma control as well.

The question to ask is how small airways disease in asthma with typical abnormal lung function could be managed?

The treatment of asthma has certainly greatly improved with the combination of inhaled corticosteroids and long-acting beta agonists. The GINA guidelines recommend

starting with low-dose inhaled corticosteroids (ICS) and with persistent symptoms escalating up to a combination of moderate/high dose ICS plus Long-acting beta-agonist (LABA). Yet, data suggest that with our current drug treatment approach asthma control remains poor across all disease severity. Could addressing specifically the small airways improve asthma control?

The first issue is that of particle size of the inhaled drugs could be important and particles smaller than five micrometres are thought to reach in the lung past the carina in the trachea and reach bronchial division three to seven. Most inhaled therapies do not reach the small airways and these aerosols deposit \pm 20% of the dose in the lungs with most of the drug being deposited in the oropharynx. Only inhaled particles that are smaller than two micrometres are able to penetrate to reach the small airways (also called extra-fine particles).

Conclusions

- 1 There is pathophysiological evidence for small airways dysfunction
- 2 There is evidence for a small-airway phenotype
- 3 We should consider treating the small airways when reviewing the therapy of asthma and COPD and in this regard recognise the role that extra-fine particle inhaled drugs can play in possibly improving the treatment and treatment response
- 4 Real-life studies suggest that extra-fine particle therapy has advantages over large-particle drugs that are relevant to daily practice
- 5 Large well-conducted studies are needed to establish the precise role of extra-fine particle vs large-particle inhaled drugs.

References are available on request. [SE](#)

The CPD questions have to be completed online. To complete the questionnaire, go to <https://www.medicalacademic.co.za/courses/clinical-relevance-small-airway-disease/>