Small airways treatment and asthma: When, how and how long?

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Asthma is a chronic inflammatory airway disorder. This inflammation has been shown to extend throughout the airway tree, involving both central and peripheral airways (1-2). The peripheral airways are those with a diameter < 2 mm. They account for approximately 98% of the airway volume but contribute less than 10% to standard measures of lung function. As such the involvement of the small airways are often overlooked and demonstrating the impact of therapy at this site has proved challenging. Direct measures of airways resistance identify that there is increased airways resistance in asthma and that this is greatest in those with more severe and long standing disease (3). Impulse oscillometry (IOS), which computes the reflective behaviour of emitted sound waves of varying amplitude, is an effort independent method of evaluating total airway resistance (R5), large airways resistance (R20) and small airways resistance (R5-R20). R5-R20 is increased in asthma and correlates with measures of disease control, dyspnea and health status (4). Measurements of R5-R20 in the Wessex Severe Asthma Cohort study, focusing on severe asthma with comparator mild and moderate asthma groups as well as healthy controls, identified disease related increases that correlated with disease severity (5). Administration of nebulized salbutamol (2.5mgs) was associated with similar and statistically comparable reductions in small airways resistance in all asthmatic groups. This identifies that beta-agonists, at high dose, beneficially impact on small airway function in asthma.

It is appreciated that for inhaled therapy to reach the small airways that the mass median aerodynamic diameter (MMAD) of the inhaled particles needs to be in the 1-5 um range, with greatest deposition being in the 1-2 micron range (6,7). Inhalers with a MMAD between 1.0-1.5 µm have been termed ultrafine particle inhalers. The impact of ultrafine particle steroid inhalers with or without a long acting beta-agonist has been assessed on measures of small airway function. These have been shown that steroid therapy alone can also improve small airways resistance, with a reduction in R5-R20 (8). Improvements have been reported in forced vital capacity (FVC), which may be reduced if there is an increase in peripheral airway resistance causing gas trapping. Improvement in peripheral resistance allows lung deflation, improves breathlessness and is associated with an increase in FVC (9). Therapy with ultrafine, as opposed to standard inhaled therapy, has been reported to improve disease control (10). It has been difficult to directly prove that these benefits are related to a reduction in peripheral airway inflammation as sampling the peripheral airway tissue can only be undertaken by transbronchial biopsy which carries inherent risks, so no placebo controlled trials have been undertaken with this endpoint. However, indirect measures support an effect on peripheral airway inflammation. It has been proposed that a two compartment model of pulmonary NO

production can be used to calculate the bronchial (JNO) and alveolar contribution (Calv) to exhaled NO concentration (11, 12). Calv has been related to bronchoalveolar lavage eosinophil counts and eosinophil cationic protein levels in asthma (13, 14), supporting its value as a surrogate measure of distal airway inflammation. Ciclesonide, an ultrafine steroid, has been reported to reduce Calv (15) and in support of this, a study of ultrafine beclometasone (QVAR), in comparison with standard beclometasone, found that only the ultrafine steroid particle delivery reduced Calv, while both formulations improved levels of JNO (16).

Thus in conclusion, small airways disease evident in asthma and relates to disease severity. Bronchodilators improve small airways resistance. Ultrafine small particle steroid inhalers are better than standard inhalers at penetrating small airways and improve lung function, disease control and in reducing alveolar NO. There is no data available on long term outcome.

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