Unlocking the quiet zone: the small airway asthma phenotype

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The small airways in the distal lung have been called the quiet zone because they are difficult to assess and treat in patients with asthma who have disproportionate impairment of small airway function. Evidence is accumulating to support a distinct clinical phenotype for patients with asthma who have impaired small airway function. The small airway asthma phenotype, which is prevalent in patients at all steps of management guidelines, seems to be associated with poor disease control. Alternatively, small airway dysfunction might be a sensitive indicator of early disease rather than a phenotype. Conventional coarse-particle inhalers, which emit particles larger than 2 μm, might not address persistent small airway dysfunction in patients with asthma. To target the entire lung with extra-fine particle formulations (smaller than 2 μm) of inhaled corticosteroids alone or in combination with long-acting β-agonists might result in improved long-term asthma control along with a commensurate improvement in small airway function. Prospective randomised controlled trials with extra-fine-particle inhaled drugs are now needed for patients with the small airway asthma phenotype.

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Introduction

Asthma management guidelines advocate a step-wise approach, with inhaled corticosteroids as first-line preventive treatment and second-line drugs as add-on therapy, most commonly a long-acting β-agonist. Such treatment is usually adjusted in accordance with symptoms, reliever use, and pulmonary function.

The bronchial tree continually divides down to the twenty-third generation, such that the mucosal surface area is relatively greater in the distal lung than it is in the proximal lung, particularly after the eighth generation, at which point airways are smaller than 2 mm in diameter. The acinar compartment of the lung contains the airway divisions after the sixteenth generation, comprising the terminal and respiratory bronchioles, alveolar ducts, and sacs. This area of the lung has been termed the quiet zone because it is difficult to assess and its contribution to overall airway resistance is relatively small. Peripheral-wedged catheter and subsequent wedged bronchoscopy show a large increase in airway resistance in this distal part of the lung in patients who have airflow obstruction.[1–3] Hence, it could be postulated that inhaled therapies comprising coarse particles larger than 2 μm do not reach the small airways and therefore are unable to treat an important component of the asthmatic disease process (figure).

In this Personal View, we discuss the outcome measures available for assessment of small airway function and how they relate to asthma control; we then consider the available treatment options to address the putative unmet need of patients with the small airway asthma phenotype. We have not attempted a systematic review as described elsewhere,[4] but rather, we will highlight the key areas of clinical relevance for general and specialist physicians who treat patients with asthma. Pathological evidence of an underlying inflammatory process of the small airways is not in the scope of our Personal View and has been reviewed elsewhere.[5]

The small airway asthma phenotype

Patients with the small airway asthma phenotype are individuals in whom disease is not optimally controlled but who have relatively healthy values for conventional measures of pulmonary function, such as forced expiratory volume in 1 s (FEV_1), despite a disproportionate amount of small airway dysfunction (panel). Such patients can be identified by an asthma control questionnaire score higher than 1·5, persistent daytime and night-time symptoms, regular use of reliever therapy in response to bronchoconstrictor stimuli, or a requirement for oral corticosteroids during a viral respiratory infection. In a primary or secondary care clinic setting in which spirometry is used, patients with small airway asthma phenotype typically have a preserved FEV_1 of higher than 80% predicted but have evidence of an impaired forced

Key messages

- The small airways in the distal lung have been called the quiet zone because they are difficult to assess and treat in patients with asthma
- The small airway asthma phenotype is characterised by patients with suboptimum disease control who also have a disproportionate amount of small airway dysfunction
- Diagnosis of persistent small airway dysfunction might require measurements of flow, resistance, air trapping, or ventilation heterogeneity, as well as imaging
- Conventional coarse-particle inhalers that emit particles larger than 2 μm might not be able to treat persistent small airway dysfunction
- Prospective randomised controlled trials with extra-fine inhaled therapies smaller than 2 μm are now needed in patients with asthma with an enriched small airway phenotype to unlock the quiet zone and improve long-term outcomes

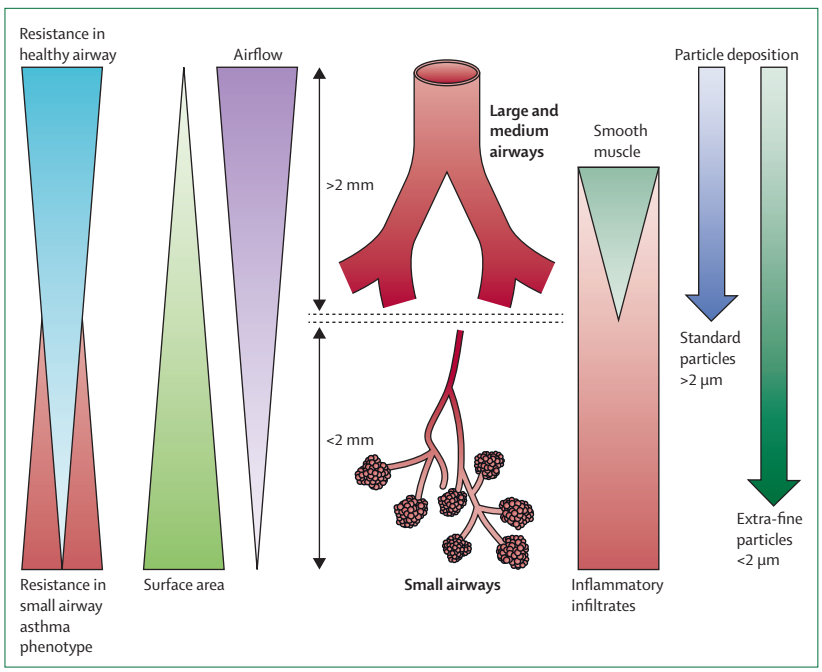

***Figure*: Small airway asthma phenotype**
In people with healthy airways, resistance, airflow velocity, and the presence of smooth muscle in the bronchial walls all decrease from large (>2 mm diameter) through to small (<2 mm diameter) airways with an increase in cross-sectional surface area. In asthma, mucosal inflammatory infiltration occurs throughout the bronchial tree, but with disproportionately increased peripheral resistance in people with the small airway phenotype. Standard inhaled particle sizes (>2 µm) only reach proximal large and medium diameter airways, whereas extra-fine inhaled particles (<2 µm) reach the most distal small airways thus potentially unlocking the so-called "quiet zone" in asthma.

***Panel:* Clinical pattern recognition of the small airway asthma phenotype**

Suboptimum asthma control
- Asthma control questionnaire score higher than 1·5
- Daytime and night-time symptoms
- Regular use of relievers in response to bronchoconstrictor stimuli
- Oral corticosteroid use with viral exacerbations
- Failure to respond to conventional coarse-particle inhaled corticosteroids and long-acting β-agonists

Small airways dysfunction
Normal FEV_1 in conjunction with any of:
- Reduced FEF_{25-75}
- Abnormal airway resistance (R5–R20, R_{aw}) or reactance area (AX)
- Evidence of air trapping (closing volume, residual volume)
- Abnormal ventilation heterogeneity (S_{acin} and S_{cond})

FEV_1=forced expiratory volume in 1 s. FEF_{25-75}=forced mid-expiratory flow between 25% and 75% of forced vital capacity. R5–R20=peripheral airways resistance as difference between measurements at 5 Hz and 20 Hz. R_{aw}=plethysmographic airway resistance. S_{acin}=acinar (diffusion) dependent ventilation heterogeneity. S_{cond}=conductive (convection) ventilation heterogeneity.

expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) of lower than 60% predicted. The main drawback for use of FEF_{25-75} is that it tends be less reproducible than FEV_1 because it is a volume-dependent measurement. Another possible interpretation is that FEF_{25-75} might simply show heterogeneity of airflow, even in moderately sized airways, and (as with other tests of pulmonary function) it is changed by the presence of more severe obstruction at any level of the bronchial tree.

Diagnosis of small airway dysfunction

Table 1 summarises the different tests available for assessment of small airways in asthma. Other authors have comprehensively reviewed the physiology of small airway measurements.[6] When feasible, the presence of an abnormal FEF_{25-75} should be supported by other pulmonary function tests of the small airways to confirm a diagnosis of small airway dysfunction. One such test is impulse oscillometry, which is an effort-independent test that is done during normal quiet tidal breathing, needs minimum patient cooperation, and is considered to be more physiological than the effort-dependent spirometry.[7,8] The resistance at 5 Hz (R5) represents that of the large and small airways, whereas the resistance at 20 Hz (R20) represents resistance in the larger airways only; hence the difference between the two values (R5–R20) is the resistance in the peripheral small airways. The reactance area (AX) is the area under the curve between 5 Hz and the resonant frequency (Fres), which is the point where the reactance curve crosses zero. Reactance (X) is a measure of lung capacitance or stiffness, which is also frequency dependent. A limitation of available impulse oscillometry systems is that they do not allow assessment at frequencies lower than 5 Hz.[9]

Anderson and colleagues[10] studied the prevalence of small airway dysfunction in 368 patients with community managed persistent asthma who were receiving treatment as defined by British Thoracic Society (BTS) treatment steps two to four. An abnormal value for peripheral airways resistance (defined as R5–R20 higher than 0·03 kPa/L.s) was noted in 65% of patients on step two BTS treatment, 64% of patients on step three treatment, and 70% of patients on BTS step four treatment, despite 100% of patients at step three and 78% of patients at step four taking long-acting β-agonists.

Boudewijn and colleagues[11] carried out a cross-sectional study of patients with mild asthma (symptomatic and asymptomatic) who had a similar level of methacholine hyper-responsiveness. Symptomatic patients had worse small airway function—as determined by R5–R20 and reactance at 5 Hz, both before and after the challenge—than had patients who were asymptomatic; both groups had similar values for R20 and had healthy FEV_1 values (a mean FEV1 of 102% predicted). Tgavalekos and colleagues[12] used PET to assess the link between regional lung ventilation and

	Outcome	Measures
Spirometry	Dynamic volumes and flow	FEF_{25-75}, ratio of forced vital capacity to relaxed vital capacity*
Single-breath and multiple-breath nitrogen washout	Air trapping and ventilation heterogeneity	Functional residual capacity, ratio of closing volume to vital capacity, ratio of residual volume to total lung capacity, S_{acin}, S_{cond}
Impulse oscillometry	Airway obstruction and capacitance	R5–R20, reactance area under curve, reactance at 5 Hz, resonant frequency
Whole-body plethysmography	Airway obstruction and air trapping	R_{aw}, ratio of residual volume to total lung capacity
Oesophageal balloon	Small airway closure	Closing volume and dynamic compliance
Exhaled-breath nitric oxide	Airway inflammation	Alveolar and bronchial nitric oxide fractions
Imaging	Air trapping and regional distribution	High-resolution CT, gamma scintigraphy, PET, hyperpolarised ^{3}He MRI
Bronchoscopy	Airway resistance and inflammation	Wedged airway resistance, transbronchial biopsy, bronchoalveolar lavage
Late-phase induced sputum sample investigation	Airway inflammation	Cell and cytokine profile

FEF_{25-75}=forced mid-expiratory flow between 25% and 75% of forced vital capacity. S_{acin}=acinar (diffusion) dependent ventilation heterogeneity. S_{cond}=conductive (convection) dependent ventilation heterogeneity. R5–R20=peripheral airways resistance as difference between measurements at 5 Hz and 20 Hz. R_{aw}=total airway resistance. *Forced vital capacity can be reduced in severe asthma due to air trapping, whereby the relaxed vital capacity will exceed the forced vital capacity.

Table 1: **Assessment of small airways**

airway conductance, before and after methacholine-induced bronchoconstriction, in individuals with asthma. They reported an inverse relation between the reduction in airway conductance and the amount of lung involved in ventilation defects.

The single-breath nitrogen washout test can be used to assess early closure of the small airways and the regional distribution of ventilation. S_{acin} and S_{cond} are measurements derived from the phase 3 slope of the nitrogen washout test and represent, respectively, the heterogeneity of the acinar and conductive compartments of the lung.[6] Downie and colleagues[13] noted that ventilation heterogeneity was an important independent determinant of the severity of methacholine-induced airway hyper-responsiveness, which is one of the hallmarks of the asthma disease process.

Whole-body plethysmography in a constant-volume body box enables the measurement of both total airway resistance and air trapping (with use of the ratio of residual volume to total lung capacity). It is considered to be the gold standard for static lung volumes and resistance, although many patients, especially children, do not like to be enclosed in the body box.

Thus, a pattern of results can be described for patients who fulfil the criteria for the small airway asthma phenotype (panel). Ultimately, because of expediency, the use of additional pulmonary function tests will depend on local availability and expertise. Our practice is to routinely use spirometry and impulse oscillometry to assess patients attending outpatient clinics, and then to use plethysmography and nitrogen washout for patients in whom diagnosis of small airways dysfunction might be less certain. When the FEV_1 is higher than 80%, we use pragmatic cutoff values to diagnose the small airway asthma phenotype: lower than 60% for FEF_{25-75}, higher than 150% for R5, and higher than 0·10 kPa/L.s for R5–R20.

Small airways dysfunction and asthma control

Table 2 shows some key studies[14–25] linking small airways function to asthma control. Gonem and colleagues[26] used impulse oscillometry to measure small airway function in a cross-sectional assessment of 74 adults with asthma (31 of whom were severely asthmatic) who had a mean asthma control questionnaire score of 1·82, indicating poor control (asthma control questionnaire score higher than 1·5). The researchers observed that abnormal values for R20 (reflecting larger airways), but not R5–R20 nor AX (showing smaller airways), was unexpectedly associated with asthma severity, control, and exacerbations.

Shi and coworkers[14] assessed 57 children with controlled asthma and 44 children with uncontrolled asthma. They reported abnormal values for FEV_1 (<80% predicted) in 5% of children in both groups, whereas they noted abnormal values for FEF_{25-75} (<65% predicted) in 64% of children with uncontrolled asthma and 4% of children with controlled asthma. FEV_1 to forced vital capacity ratios ($FEV_1$to FVC ratio <0·80) were abnormal in 61% of children with uncontrolled asthma and 21% of children with controlled asthma. Significant differences were shown between controlled and uncontrolled groups for both FEF_{25-75} and FEV_1 to FVC ratio, but not for FEV_1. Abnormal values for peripheral resistance on impulse oscillometry (R5–R20 >0·15 kPa/L.s]) and reactance area (AX >0·93 kPa/L) were highly predictive of disease control, with 83% and 85% of uncontrolled children being correctly classified with use of R5–R20 and reactance area, respectively. In a prospective follow-up study,[15] the same group reported that reactance area (>0·70 kPa/L) was better than R5–R20 (>0·10 kPa/L.s) for predicting subsequent loss of control. Reactance area correctly classified 91% of patients, whereas R5–R20 correctly classified 83% of patients.

	Test	Measurements	Comments
Thompson and colleagues,[18] Farah and colleagues,[19,20] and Sonnappa and colleagues[21]	Nitrogen washout	Ventilation heterogeneity	Increased S_{cond} and S_{acin} associated with symptoms, exacerbations, inhaled corticosteroid response
Shi and colleagues[14,15] and in 't Veen and colleagues[22]	Impulse oscillometry	Resistance and reactance	Increased R5–R20 and area under the reactance curve associated with poorer control
Shi and colleagues,[14,15] Rao and colleagues,[16] and Manoharan and colleagues*	Spirometry	Dynamic flow and volumes	Reduced FEF_{25-75} and FEV_1 to forced vital capacity ratio associated with poorer control
Bourdin and colleagues[17] and Mahut and colleagues[23]	Plethysmography	Air trapping	Increased residual volume to total lung capacity ratio associated with exacerbations
Mahut and colleagues[24] and Puckett and colleagues[25]	Exhaled nitric oxide	Inflammation	Increased alveolar nitric oxide related to symptoms and exacerbations

S_{cond}=convection dependent ventilation heterogeneity. S_{acin}=acinar (diffusion) dependent ventilation heterogeneity. R5–R20=peripheral airways resistance as difference between measurements at 5 Hz and 20 Hz. FEF_{25-75}=forced mid-expiratory flow between 25% and 75% of forced vital capacity. FEV_1=forced expiratory volume in 1 s. *Unpublished data.

Table 2: **Key studies that have linked small airway function to asthma control**

Rao and colleagues[16] used linkage data for electronic prescriptions for 1 year before and 1 year after index spirometry measurements to compare matched groups of children with asthma. 37 children had a healthy FEV_1 (>80% predicted) and abnormal FEV_1/FVC ratio (<0·85) and abnormal $FEF_{25–75}$ (<60% predicted); 35 children with asthma had normal values for these measures. The investigators reported significantly increased odds ratios (OR) for loss of control in children with abnormal values, with disease activity defined by oral corticosteroid use (OR 2·8; 95% CI 1·07–8·78), controller use (6·0; 1·3–55·0), and asthma exacerbations (6·3; 18·6–33·42).

In a health informatics study from Scotland, prescribing data for oral corticosteroids and short-acting β-agonists over 2 years was linked to adults with asthma who had a recorded index measurement for spirometry and impulse oscillometry (Manoharan A, unpublished). 302 (68%) of 442 patients had a preserved FEV_1 higher than 80% predicted (mean 97%). Median inhaled corticosteroid dose was 800 µg, with 42% of patients taking long-acting β-agonists. The presence of persistent small airway dysfunction, defined as $FEF_{25–75}$ lower than 70%, was associated with significantly increased ORs for prescription of oral corticosteroids (OR 1·67; 95% CI 1·04–2·68) and of short-acting β-agonists (OR 2·00; 95% CI 1·27–3·16). Dysfunction, when defined as R5–R20 higher than 0·07 kPa/L.s, had an OR for prescription of oral corticosteroids of 1·99 (95% CI 1·23–3·19) and an OR for prescription of short-acting β-agonists of 1·83 (95% CI 1·16–2·89). In patients who had abnormal values for both $FEF_{25–75}$ and R5–R20; ORs were 2·77 (95% CI 1·48–5·18) for oral corticosteroid and 3.07 (95% CI 1·66–5·67) for short-acting β-agonist use. Taken together, these studies provide evidence for a putative small airway asthma phenotype in patients with a healthy FEV_1 with persistent small airway dysfunction that results in poorer control.

Bourdin and colleagues,[17] using single-breath nitrogen washout, showed that ventilation heterogeneity and plethysmographic residual volume to total lung capacity ratio were correlated with asthma control score and to exacerbation frequency. Verbanck and colleagues[27] reported abnormal values for S_{cond} in individuals with stable asthma, which were not correlated to bronchial nitric oxide flux measured in the same compartment. By contrast, S_{acin} was abnormal in patients taking moderate to high doses of inhaled corticosteroids and was correlated to corrected alveolar nitric oxide, in turn, suggesting a potential role for targeted inhaled corticosteroids to treat asthma in the acinar compartment. Thompson and coworkers[18] investigated people with unstable acute asthma and reported that S_{acin}, but not S_{cond}, was correlated with FEV_1 and symptom scores. Farah and coworkers[19,20] reported that S_{acin} and S_{cond} were both worse in patients with poorly controlled asthma, and were also predictive of symptomatic response during dose titration with inhaled corticosteroid therapy. Sonnappa and coworkers[21] reported that S_{cond}, but not S_{acin}, was higher in wheezy children aged 4–6 years compared with healthy controls, but did not correlate with presence of reticular basement membrane thickness or mucosal eosinophilia.

Measurement of static lung volumes using single-breath nitrogen washout has shown differences in the ratio of closing volume to vital capacity and the ratio of closing capacity (ie, closing volume plus residual volume) to total lung capacity in patients with controlled asthma compared with patients with poorly controlled asthma who have frequent exacerbations.[22] Mahut and colleagues[23] reported that the plethysmographic residual volume to total lung capacity ratio was higher in children with asthma who have severe exacerbations.

Measurement of nitric oxide in exhaled breath at multiple flow rates allows for the assessment of alveolar fractions from the slope and bronchial fractions from the intercept; alveolar fractions require correction for axial back diffusion from the conducting compartments to the acinar compartments.[28] Earlier studies that

measured uncorrected alveolar nitric oxide concentrations reported increased concentrations that were related to symptoms and control and to airway remodelling in children with asthma.[24,29,30] Another study of children with asthma showed that children with raised concentrations of corrected alveolar nitric oxide had worse scores on the asthma control test and more frequent exacerbations.[25] Gelb and colleagues[31] noted that corrected alveolar nitric oxide concentrations were not raised during asthma exacerbations in adults. The conductive, rather than the acinar, component is mostly the cause of high exhaled nitric oxide concentrations when measured at a single-flow rate of 50 mL/s (ie, fractional exhaled nitric oxide).

Management of small airway disease

Consideration of airway size in asthma treatment

The first relevant issue to address is the effect that extra-fine particles could have on the distal lung in terms of outcome measures of small airway function. Particles smaller than 5 μm are thought to be able to reach the lungs past the carina in the trachea and be deposited on stages three to seven on an in-vitro Andersen cascade impactor (comprising a series of collection plates whereby aerosol particles of varying sizes deposit by inertial impaction on different stages to assess in-vitro particle distribution). Only particles smaller than 2 μm will be able to penetrate the small airways; these are termed extra-fine particles and they are deposited on impactor stages five, six, and seven. However, the exact representation of in-vivo regional lung deposition by in-vitro fine-particle distribution is not clear. Furthermore, there is a normal distribution curve of particle size around the mass median aerodynamic diameter, such that there will inevitably be a small number of extra-fine particles that will reach the small airways, even with a coarse-particle formulation.

Inhaled corticosteroids

Yamaguchi and colleagues[32] compared an extra-fine-particle formulation of beclometasone dipropionate (200 μg, twice a day; mass median aerodynamic diameter of 1·1 μm) with coarse-particle formulations of beclometasone dipropionate (400 μg, twice a day; mass median aerodynamic diameter of 3·5 μm) over 12 weeks in patients with mild persistent asthma. They noted significant improvements in R5–R20 and reactance. R5–R20 reduced by 50% in patients given extra-fine particle beclometasone dipropionate but not in those given coarse-particle beclometasone dipropionate. In a dose-ranging study, Busse and colleagues[33] compared 100 μg, 400 μg, and 800 μg doses of extra-fine-particle or coarse-particle beclometasone dipropionate over a period of 6 weeks. Parallel slope analysis over all three doses showed relative dose potency ratios of 2·6 times for change in FEV_1 and 3·2 times for change in $FEF_{25–75}$, showing a leftward shift in the dose-response curve.[33]

Manoharan and colleagues[34] gave coarse-particle fluticasone (50 μg, twice a day) to corticosteroid-free individuals with mild-to-moderate persistent asthma, assessing effect with the asthma control questionnaire. Spirometry (FEV_1 and $FEF_{25–75}$) and impulse oscillometry (R5 and R5–R20) measurements were correlated significantly with the asthma control questionnaire score before and after treatment with inhaled fluticasone. When classified according to responders who had a change of at least 0·5 units on the asthma control questionnaire score (the minimum important difference), significant improvements were observed in FEV_1, R5, and $FEF_{25–75}$ after treatment. Verbanck and colleagues[35] did an open-label study in people with asthma, switching their treatment from coarse-particle budesonide dry-powder inhaler (full dose) to extra-fine-particle hydrofluoroalkane (HFA) beclometasone dipropionate (at half dose) for 12 weeks. Results showed improvements in S_{acin} and residual volume in 16 of 30 patients who had impaired acinar function at baseline, although no follow-up observation of asthma control was done to assess whether this change was clinically relevant.

Goldin and colleagues[36] gave extra-fine-particle and coarse-particle formulations of beclometasone dipropionate (400 μg, twice a day) over 4 weeks to 19 patients with mild persistent asthma. High-resolution CT was done after a standardised methacholine challenge to assess peripheral air trapping induced by bronchoconstriction, assessed by the degree of relative lung attenuation (ie, a higher amount of trapped air due to peripheral bronchoconstriction would show as a lower amount of lung attenuation with a greater degree of radiolucency). After 4 weeks of treatment, significantly less air was trapped after methacholine challenge in patients using the extra-fine-particle formulation than in those using the course-particle formulation, in keeping with enhanced peripheral deposition of extra-fine formulation. In another high-resolution CT study, investigators used the difference between inspiratory and expiratory lung attenuation to determine air trapping in 25 patients with uncontrolled mild to moderate asthma who were treated with either extra-fine-particle beclometasone dipropionate (200 μg, twice a day) or coarse-particle fluticasone dry powder inhaler (250 μg, twice a day) for 3 months.[37] Both inhaled corticosteroids formulations were associated with significant, but similar, reductions in lung attenuation. However, unlike in Goldin and colleagues' study,[36] CT scans were not done after methacholine challenge (therefore distal air trapping would be less likely). Furthermore, although both treatments led to better scores on the asthma control questionnaire, dynamic and static lung volumes did not significantly increase with either treatment.[37]

Leach and colleagues[38] studied the relative lung distribution of extra-fine-particle HFA beclometasone dipropionate and coarse-particle HFA fluticasone-salmeterol using technetium-labelled aerosol in 7 patients with asthma. The in-vitro particles that were 0·7 μm (extra-fine) had a 58% total lung deposition, compared with 16% for particles of 2·7 μm (coarse). 3D single-photon-emission CT showed that the central–peripheral ratio for regional deposition was 1·6 for HFA beclometasone dipropionate and 4·9 for HFA fluticasone-salmeterol and that the coarse-particle formulation had a greater variability in distribution.

Nicolini and colleagues[39] compared extra-fine-particle beclometasone dipropionate (100 μg, twice a day) with coarse-particle beclometasone dipropionate (250 μg, twice a day) in 14 individuals with asthma. Extra-fine-particle beclometasone dipropionate significantly reduced both bronchial and uncorrected alveolar fractions of exhaled nitric oxide, whereas the coarse-particle formulation reduced only bronchial nitric oxide concentrations. In a different study of 78 patients with mild asthma who had a healthy FEV_1 (mean FEV_1 of 100%), the corrected alveolar fraction was 40% higher in patients with uncontrolled disease than in patients with controlled disease.[40,41] In the same study,[40] a subgroup of 55 corticosteroid-naive patients was given 100 μg, twice a day, of open-label extra-fine-particle beclometasone dipropionate. The reduction in asthma control score correlated significantly to the alveolar, but not bronchial, fraction of exhaled nitric oxide after 3 months. In a study of children with asthma,[42] researchers compared extra-fine-particle beclometasone dipropionate (100 μg, twice a day) with coarse-particle fluticasone dry powder inhaler (100 μg, twice a day); neither drug significantly decreased the primary outcome of uncorrected alveolar nitric oxide, presumably because patients' baseline levels were already suppressed as a result of them already receiving inhaled corticosteroids at a mean fluticasone dose of 312 μg per day. Berry and colleagues[43] reported significant falls in uncorrected alveolar nitric oxide after 1 week of oral corticosteroids, but no change in response to an increased dose of coarse-particle inhaled beclometasone dipropionate in patients with refractory asthma.

Williamson and colleagues[44] assessed extra-fine-particle beclometasone dipropionate (200 μg, twice a day), fluticasone dry powder inhaler (250 μg, twice a day), or oral prednisolone (25 mg, once a day) as add-on therapy in patients with severe asthma (mean FEV_1 of 58% predicted) who were already receiving inhaled fluticasone-salmeterol dry powder inhaler (500 μg fluticasone and 50 μg salmeterol, twice a day). Corrected and uncorrected alveolar nitric oxide concentrations were not significantly reduced by either inhaled or oral corticosteroids. Extra-fine-particle beclometasone dipropionate and oral prednisolone both significantly reduced bronchial nitric oxide flux and exhaled nitric oxide measured at 50 mL/s, whereas only oral prednisolone was associated with significant reductions in systemic markers (including plasma eosinophilic cationic protein, E-selectin, intracellular adhesion molecule 1, and cortisol).[44] Small airway function (measured with use of impulse oscillometry and plethysmography), asthma control and quality of life were not significantly improved by either inhaled or oral corticosteroids, presumably because of insufficient further room for improvement due to airway remodelling; an effect that was also evident by patients' high mean residual volume (193% predicted) and R5 (184% predicted).[44]

In a similar study,[45] extra-fine-particle beclometasone dipropionate (400 μg per day) or coarse-particle fluticasone (330 μg per day) was given as add-on treatment to usual therapy for 3 months in 30 patients with refractory asthma. Although airway inflammation was not measured, significantly greater improvements in closing volume and the ratio of closing volume to vital capacity (as determined by single-breath nitrogen washout) and in $FEF_{25–75}$ were obtained with extra-fine-particle beclometasone dipropionate compared with coarse-particle fluticasone. Extra-fine-particle beclometasone dipropionate was associated with significantly reduced residual volume.[45]

Transbronchial biopsy samples taken from patients with mild to moderate asthma before and after 6 weeks of inhalation of extra-fine-particle flunisolide showed significant reductions in interleukin 5 and eotaxin concentrations and the number of eosinophils in central and peripheral airways.[46] Expression of smooth muscle α-actin was also reduced, which correlated with improvements in $FEF_{25–75}$.[47] In a study that used different particle sizes of AMP for a bronchial challenge, extra-fine-particle ciclesonide attenuated airway hyper-responsiveness to small-particle AMP and coarse-particle fluticasone attenuated airway hyper-responsiveness to large-particle AMP, inferring their relative sites of anti-inflammatory activity in small and large airways.[48]

Real life studies with inhaled corticosteroids

A series of observational real-life health informatics studies have been done in matched cohorts to investigate whether treatment of inflammation with extra-fine-particle beclometasone dipropionate might result in better outcomes for long-term asthma control than would coarse-particle corticosteroids (beclometasone dipropionate or fluticasone).[49–52] In all these studies, a pragmatic composite definition for loss of asthma control comprised an acute prescription for oral corticosteroid, any recorded episode of asthma-related hospital attendance, or any consultation resulting in antibiotic treatment for respiratory infection. Two of these studies[49,50] used a UK general

practice research database to assess asthma control over 12 months before and after an initial index prescription of extra-fine-particle or coarse-particle beclometasone dipropionate. Barnes and colleagues[49] reported an OR of 1·15 (95% CI 1·02–1·28; 11 528 patients) for achievement of asthma control with the extra-fine-particle formulation versus the course-particle formulation; Price and colleagues[50] reported an OR of 1·12 (95% CI 1·02–1·23; 11 289 patients) in favour of the extra-fine-particle formulation. Extra-fine beclometasone dipropionate in these studies was prescribed at about half the nominal dose of coarse-particle beclometasone dipropionate. Price and colleagues[50] also identified a cohort of 19 065 matched patients who were switched from coarse-particle to fine-particle beclometasone dipropionate formulations, and reported an OR for achievement of control of 1·10 (95% CI 1·01–1·19).

In two other similar studies, extra-fine-particle beclometasone dipropionate was compared with coarse-particle fluticasone. Using a US database of 10 312 patients with asthma, Colice and colleagues[51] reported an OR for control of 1·19 (1·08–1·31). Price and colleagues,[52] using a UK database of 2638 patients with asthma, reported an OR of 1·30 (1·02–1·65) for disease control with extra-fine-particle beclometasone dipropionate. In the study by Colice and colleagues,[51] median doses (320 µg *vs* 440 µg) and respiratory related health-care costs (mean annual saving of US$390 per patient) were both significantly lower for extra-fine-particle beclometasone dipropionate than were those with coarse-particle fluticasone.

Taken together, these real-world data present compelling evidence for the hypothesis that formulations of extra-fine-particle inhaled corticosteroids result in better long-term asthma control at a lower effective maintenance dose. However, it is not clear whether such improvements were due to increased total intrapulmonary deposition or to improved regional distribution of the drug.

Inhaled long-acting β-agonists

Extra-fine-particle formulations have been developed for long-acting β-agonist inhalers and combined long-acting β-agonists and inhaled corticosteroid inhalers, namely formoterol and beclometasone-formoterol. These drugs have a particle size of about 1·5 µm, and beclometasone-formoterol is also available as either a solution or dry powder formulation. The density of β2 adrenoceptors is higher in the distal airways than in the proximal airways;[53] density of glucocorticoid receptors is similar in both types of airways.[54] However, most studies done for regulatory requirements have used FEV_1 or peak expiratory flow rather than small airways outcomes.

A single-dose comparison of extra-fine-particle solution versus coarse-particle dry powder formoterol showed no differences in impulse oscillometry outcomes for resistance at 5 Hz, resonant frequency, reactance at 5 Hz, or in $FEF_{25–75}$, although these patients were not chosen for having small airways obstruction as such.[55] A comparison of extra-fine-particle beclometasone-formoterol and coarse-particle fluticasone-salmeterol noted significant improvements in methacholine hyper-responsiveness only with the extra-fine-particle formulation.[56] Extra-fine-particle beclometasone-formoterol has also been shown to significantly reduce closing volume.[57] Vos and coworkers[58] assessed 24 people with stable asthma who were switched from coarse-particle inhalers to extra-fine-particle beclometasone–formoterol formulations. Functional high-resolution CT at 6 months showed significant improvements in image-based measures for small airways resistance and volume, whereas volume correlated with improvements in an asthma control test. After switching patients from coarse-particle combination therapy to extra-fine-particle beclometasone-formoterol treatment, Popov and coworkers[59] noted that those patients who had the largest improvement in FVC also had significant decreases in inflammatory markers such as exhaled breath temperature, blood eosinophils, and high sensitivity C-reactive protein, perhaps inferring of an effect through reduced air trapping.

Findings from other long-term studies of extra-fine-particle beclometasone-formoterol have supported better asthma control and quality of life scores with these treatments compared with coarse-particle inhaled corticosteroids and long-acting β-agonists at equipotent doses.[60–62] Outcomes of a health informatics study of 1528 patients with asthma showed that those who were switched from coarse-particle fluticasone-salmeterol to extra-fine-particle beclometasone-formoterol had significantly better overall asthma control (OR 1·56, 95% CI 1·14–2·14), in association with lower inhaled corticosteroid dose exposure and reduced annual health-care costs of £93·6 per patient.[63]

Further research

Clinicians should know the best tests to identify the small airway asthma phenotype and how this phenotype relates to control and response to targeted treatment. It is likely that no one pulmonary function test will be sufficient and the highest predictive value will probably be achieved by use of a few different tests, which, for example, measure indices of flow, resistance, air trapping, or ventilation heterogeneity. Large-scale prospective follow-up studies are needed to clarify which small airway pulmonary function tests are predictive of control through inclusion of patients with asthma of different severities across the range of treatment steps. This analysis might then lead to an enriched cohort of patients with asthma who have predetermined inclusion criteria for enrolment in a

Search strategy and selection criteria

We searched PubMed, Medline (EBSCO), Scirus, Scopus, and Google Scholar for papers published from Jan 1, 1967, to March 31, 2014, using cross-search for the following keywords: "small airways", "asthma", "inhaled corticosteroid", "long acting β-agonist" , "hydrofluoroalkane 134a", "extra-fine particle", "impulse oscillometry", "spirometry", "nitrogen washout", "exhaled nitric oxide", "plethysmography", "air trapping", "transbronchial biopsy", and "airway hyper-responsiveness". We did the search between November, 2013, and March, 2014. We chose cited articles on the basis of their relevance to small airways and their adequacy of description for patient selection, study design, and data analysis. We only chose articles published in English. We cited review articles only when we considered further in-depth discussion to be beyond the scope of our Personal View. We resolved discrepancies in selection through open discussion between all authors.

prospective randomised controlled trial for the long-term effects of extra-fine-particle inhaled corticosteroid or combination inhaled corticosteroid and long-acting β-agonist. This cohort of patients might include, for example, adults with poorly controlled asthma who have FEV_1 higher than 80%, along with at least two of the following criteria: $FEF_{25–75}$ lower than 60%, R5 higher than 150%, or R5–R20 higher than 0·1 kPa/L.s. In such a trial, the asthma control questionnaire could be chosen as a pragmatic primary endpoint to assess the proportion of patients who either improve in disease control (ie, a change in score of >0·5) or end the trial well controlled (ie, asthma control questionnaire score <0·75). We estimate that about 20–30% of patients taking inhaled corticosteroids or a combination inhaled corticosteroids and long-acting β-agonist might be eligible for such a trial. Other studies could perhaps focus on inclusion criteria in patients with abnormal values on plethysmography and nitrogen washout.

Conclusion

In asthma, a clinically distinct phenotype exists in some patients who have a disproportionate degree of persistent small airway dysfunction, which seems to be associated with poor disease control. An alternative interpretation is that abnormalities of small airway function might merely be sensitive indicators of early disease across a range of phenotypes in asthma. Measurements derived from spirometry, impulse oscillometry, plethysmography, nitrogen washout, and imaging tell us about different, yet complimentary, aspects of small airway function; hence, no single outcome should be considered in isolation as the gold standard. Treatment strategies, such as extra-fine-particle formulations of inhaled corticosteroids and combination inhaled corticosteroids and long-acting β-agonists, might be able to unlock the small airways compartment. In everyday clinical practice, available guidelines are unclear with regards to when such treatments should be used rather than conventional coarse-particle inhalers.

Contributors

All authors contributed to the writing and editing of this Personal View.

Declaration of interests

BL has received payment for speaker bureaus and unrestricted research grant support from Teva (who make extra-fine-particle hydrofluoroalkane [HFA] beclometasone and coarse-particle formulations of fluticasone-salmeterol and budesonide-formoterol); payment for educational talks, advisory boards, consultancy, unrestricted research grant support, and attendance at the European Respiratory Society from Chiesi (extra-fine-particle HFA and dry powder formulations of beclometasone-fomoterol); grant support from Nycomed (who make extra-fine-particle HFA ciclesonide); payments for consulting from Cipla and Sandoz (who make inhaled steroid long-acting β-agonist combination inhalers); payments for advisory boards and attendance at the British Thoracic Society and European Respiratory Society from Boehringer Ingelheim (who make tiotropium); and payments for research grant support from Almirall (who make aclidinium). AM has received support to attend the European Respiratory Society from Teva and Chiesi. WA has received support to attend the European Respiratory Society from Chiesi.

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