

Alveolar nitric oxide concentration, small airways inflammation, and targeted asthma therapy: Are we there yet?

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In recent years there has been increasing focus on inflammation in the small airways as a significant contributor to the severity of asthma.¹ The increased interest, at least in part, is a result of the development of extrafine aerosol particle formulations of inhaled corticosteroids (ICSs) and oral therapies that may better target the small airways.^{1,2} However, the development of newer noninvasive methods of assessing the inflammation found in small airways has been a significant contributor.³⁻⁵ Alveolar nitric oxide concentration ($C_{A}NO$) is one of those measures of small airways inflammation that has spawned numerous studies of the effect of various therapies targeting small airways.^{4,6-8} The results of these trials have been mixed, showing both improved $C_{A}NO$ and no difference in $C_{A}NO$ with targeted therapy compared with nontargeted therapy. In this issue of the Journal, Van Muylem et al⁹ provide a possible reason for these disparate results but also keep open the more important question about targeted therapy: Does it matter?

The measurement of $C_{A}NO$ is not direct but a derived value using a 2-compartment mathematical model after measuring the fraction of exhaled nitric oxide (NO) at different expiratory flows.¹⁰ However, the model was based on normal physiology, and when the model met the pathophysiology of asthma, including air trapping and patchy heterogeneous ventilation, its use provided large variability in $C_{A}NO$ values. Indeed, the group that developed the initial model has recently shown that a multicompartiment model taking into account the heterogeneity is more accurate in assessing $C_{A}NO$ in children with mild asthma.¹¹ One of the primary issues producing variability in asthma, more precisely described in the article by Van Muylem et al,⁹ is the role of “back-diffusion” as a contributor to $C_{A}NO$. Simply put, in the standard model, back-diffusion of NO into the small airways and alveoli can be prevented by airway closure, thus increasing fraction of exhaled NO and decreasing $C_{A}NO$. Therefore, they posit that both an increase in $C_{A}NO$, from reducing obstruction (air trapping) increasing back-diffusion, and a

decrease in $C_{A}NO$, from reducing airway inflammation and NO production, can result from improved inflammation in the small airways depending on the contribution of either physiologic abnormality. Hidden in these results is the fact the authors used the budesonide Turbohaler (AstraZeneca AB, Sodertalje, Sweden) as the ICS to improve both the overall fraction of exhaled NO and $C_{A}NO$ in their patients. This device does not produce extrafine particles, and the mode of inhalation (deep forceful) favors central deposition, thus raising the question of the necessity for “targeted therapy.” In fact, there is currently no conclusive evidence that targeted therapy improves measures of small airways dysfunction, much less other significant clinical outcomes, over standard inhaled therapy with ICSs or ICSs in combination with long-acting inhaled β_2 -agonists.

Inflammation of the small airways has been a constant finding in autopsy specimens and endobronchial and transbronchial biopsy specimens.^{1,2} Although using measures of small airway function from invasive wedged bronchoscope measures of intra-airway pressure, closing volumes, air trapping with nitrogen washout, or low-frequency forced oscillometry can demonstrate increased resistance in small airways, these changes do not translate to abnormalities in standard lung function tests, spirometry, and specific airway conductance and resistance.¹ Therefore, unless there are specific measures of small airways dysfunction in studies comparing targeted therapy with standard therapy, any difference will likely be missed. High-resolution computed tomography that can detect regional air trapping is another promising measure of small airway dysfunction.¹² Although initial studies using these various techniques have provided suggestive evidence that targeted therapy may improve small airways disease, they were inconclusive because of design flaws (open-label preliminary before-and-after trials, lack of appropriate controls, and lack of rigorous attention to dosing). For example, an initial report comparing extrafine hydrofluoroalkane-propelled beclomethasone dipropionate (HFA-BDP) with chlorofluorocarbon-propelled beclomethasone dipropionate (CFC-BDP) with high-resolution computed tomography found greater reduction in air trapping and methacholine-induced air trapping with the HFA-BDP.¹² However, they used equivalent microgram doses of each beclomethasone dipropionate preparation, and radiolabel delivery studies have shown that HFA-BDP delivers 50% to 60% of the dose to the lung, whereas CFC-BDP delivers 4% to 10%.¹ Was this difference caused by small airways targeting or just a 5-fold greater dose of ICS? A more recent trial comparing HFA-BDP with fluticasone propionate by the Diskus (GlaxoSmithKline, Research Triangle Park, NC) dry-powder inhaler in relatively equipotent ICS doses based on potency and delivery as well as comparative clinical trials failed to demonstrate a significant difference in air trapping by high-resolution computed tomography after 3 months of therapy.³

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Small airways dysfunction has been shown to have significant clinical consequences. It is predominant in nocturnal asthma, one of the most sensitive indicators of asthma severity.² Small airways inflammation is associated with an increased risk of future exacerbations and increased bronchial hyperresponsiveness and severe asthma.^{1,2} Unfortunately, few to no studies have assessed the value of targeted therapy on these outcomes. In fact, most comparative studies between targeted and standard therapies have been performed in patients with relatively mild asthma to separate out the effects on small and large airways.³⁻⁸ However, this is problematic in that many of these patients may not have significant small airways dysfunction. In a study of air trapping by high-resolution computed tomography, only 25 of 58 patients with guidelines-defined mild to moderate asthma had abnormal air trapping.³ In another study of 30 adults with asthma receiving ICS/long-acting inhaled β_2 -agonists at baseline, only 20% had abnormal C_{ANNO} values.⁴ A small trial assessing impulse oscillometry compared HFA-BDP 400 mg/d (N = 26) to CFC-BDP 800 mg/d (N = 12) for 12 weeks.⁵ They reported improvement in small airways resistance in only the HFA-BDP group that was significantly better than CFC-BDP, and there was no significant improvement in the sensitivity to methacholine in the CFC-BDP group. However, the median change in methacholine sensitivity was the same for both groups, with the small number of patients in the CFC-BDP group and greater variability likely accounting for the apparent lack of statistical significance ($P = .08$). Other studies have failed to demonstrate a significant difference in improvement in methacholine responsiveness between extrafine particle ICSs and standard ICSs when given in relatively equipotent doses.¹³

It has been argued that systemic administration of anti-inflammatories is more likely to reduce small airways inflammation, and that has a high degree of face validity.¹ In small trials, the addition of prednisone to patients receiving ICSs even in high doses demonstrated improvement in C_{ANNO} , suggesting that the systemic activity had a greater effect on small airways.^{8,14} Whether just the added anti-inflammatory activity of the prednisone versus the targeting of small airways was the primary cause of the improvement is unknown, but these results are highly suggestive of a peripheral action. However, this improvement has not been seen with the addition of oral montelukast to ICS therapy.^{4,6} Whether this is lack of a peripheral effect of montelukast or just a reflection of its relatively poor anti-inflammatory effect relative to ICSs is unknown.

In conclusion, small airways inflammation plays a significant role in the pathogenesis of asthma but may have more clinically

significant importance in certain phenotypes such as nocturnal asthma and severe asthma. We need to be cognizant of its presence, particularly in patients resistant to therapy. The measurement of C_{ANNO} for assessing small airways inflammation is attractive because it is noninvasive and easy; however, we still do not have an accurate grasp on the meaning of changes resulting from therapy, but we are getting there. Finally, in studies of targeted versus standard therapies, we need rigorous clinical trials in which we can clearly assess differences in clinically meaningful outcomes as well as which airways are affected.

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