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Exhaled nitric oxide (NO) in wheezy infants: a marker of inflammation determined by airways acidification and *S*-nitrosothiol degradation?

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In this issue of the *Journal* Debley et al report that in infants and toddlers with frequent early wheeze, single breath exhaled nitric oxide (NO) concentrations correlate with the magnitude of bronchodilator responsiveness and decline in $FEV_{0.5}$ over the subsequent six months [1]. Furthermore exhaled NO was superior to either lung function variable in predicting later exacerbations of wheezing requiring systemic corticosteroid treatment. These findings are in accord with the results of a recent clinical study conducted by the NIH/NHLBI CARE Network wherein elevated exhaled NO in pre-school children with moderate to severe intermittent wheezing was associated with an increased risk of respiratory tract illness in the subsequent year and with aeroallergen sensitization [2]. Likewise exhaled NO is higher in non-wheezing atopic infants [3], high in three to four year olds with recurrent wheeze and a positive stringent predictive index for asthma [4], increases during exacerbations of infants [5], and decreases in response to treatment with inhaled fluticasone [6] and montelukast [7–8]. Thus expired NO has promise as a useful marker of asthma activity in pre-school children, a population in whom it is difficult to non-invasively assess airways inflammation.

What is the source of exhaled NO in the lung and can we confidently link its biochemistry to airways inflammation? Clinical studies in children with asthma suggest that exhaled NO is primarily a biomarker for atopy. Exhaled NO correlates positively with the magnitude of blood eosinophilia, serum IgE, number of positive skin prick tests to aeroallergens, airway hyperresponsiveness, and disease severity [9–10]. However, there is a wide gap between the aforementioned clinical correlations and NO biochemical pathways in the human airway. The traditional view holds that NO is primarily formed in the respiratory epithelium through Th2 inflammatory cytokine-induced stimulation of inducible nitric oxide synthase (iNOS). However most cytokines that upregulate iNOS are Th1 cytokines. Moreover, exhaled NO correlates most robustly with eosinophil counts in the lung, but eosinophils are not the principal cells in the airway that express iNOS. Furthermore, despite significant airways inflammation, exhaled NO levels are not elevated in many adults with severe asthma compared to mild to moderate asthma [11]. As perplexing, exhaled NO levels in emergency department treated patients with acute exacerbations do not correlate with standard measures of asthma severity [12].

Analysis of NO biochemical pathways in the lung may shed light on this dilemma and the interpretation of exhaled NO values in patients. Arginine is the primary nitrogen donor which forms NO and its reaction products in the lung. In adults with severe asthma but not healthy controls, arginine bioavailability highly correlates with the degree of airflow obstruction but not inflammation [13]. Once formed, NO is highly reactive and in the presence of molecular oxygen at normal pH forms nitrite/nitrous acid (pKa 3.6), an important reservoir of nitrogen species which can be measured in exhaled breath condensate or airway surface liquid in μM concentrations. Indeed when volunteers with asthma inhale airway buffer solutions, expired NO levels acutely fall as more nitrite is formed when airway pH increases [14]. Another vital NO reaction in the lungs involves loss of an electron to form the nitrosonium ion (NO^+), a strong oxidizing agent which can then react with cysteine residues of proteins to form *S*-nitrosothiols. One of these is *S*-nitrosoglutathione (GSNO), a protective anti-inflammatory and bronchodilator compound endogenous to the airway surfaces which is depleted in children with severe asthma [15]. The catabolism of GSNO in the airways is regulated by several enzymes, including an alcohol dehydrogenase also known as GSNO reductase, known to be up-regulated in mild asthma [16], and carbonyl reductase [17]. One product downstream of GSNO degradation is NO; thus regulation of GSNO degradation may be a critical determinant of exhaled NO levels in humans. Indeed therapeutic inhalation of GSNO increases exhaled NO in humans as GSNO is broken down [18]. Thus challenge testing with arginine, buffer, GSNO and other determinants of NO metabolism may identify candidate sub-populations who might respond to treatment with the aforementioned interventions.

Thus before exhaled NO concentrations in wheezing infants can be directly linked to specific inflammatory mechanisms or pathways, the biochemistry of NO reactions in the lung must be considered. Exhaled NO may be high with acute acidification and enhanced catabolism of GSNO, but low when important nitrogen reservoirs like GSNO are depleted or there is impaired degradation of endogenous GSNO. The association of these biochemical events with inflammatory mechanisms is highly preliminary and deserving of further study so as to improve the application of exhaled NO values to the care of children with asthma.

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