In moderate-to-severe asthma patients monitoring exhaled nitric oxide during exacerbation is not a good predictor of spirometric response to oral corticosteroid

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Background: The importance of monitoring exhaled nitric oxide (NO) in asthma remains controversial.

Objective: To measure exhaled NO, postnebulized albuterol/ipratropium spirometry, and Asthma Control Test (ACT) during asthma exacerbation requiring 8- to 10-day tapering oral corticosteroid in nonsmoking patients with moderate-to-severe asthma on moderate-dose inhaled corticosteroid and long-acting β_2-agonist but not maintenance oral corticosteroid.

Methods: After measuring the fraction of exhaled NO (FENO [ppb]) at 50, 100, 150, and 200 mL/s, the total FENO at 50 mL/s (ppb), large central airway NO flux (J'_{awNO} [nL/s]), and peripheral small airway/alveolar NO concentration (C_{ANO} [ppb]) were calculated and corrected for NO axial back-diffusion. Outpatient exacerbation required the patient with asthma to be afebrile with normal chest x-ray and white blood cell count.

Results: Group 1 included 17 patients (6 men) with asthma, age 52 ± 12 years, studied at baseline, during 18 exacerbations with *abnormal* FENO at 50 mL/s, J'_{awNO}, and/or C_{ANO}, and post 8- to 10-day tapering 40 mg prednisone (recovery). Baseline: IgE, 332 ± 243 Kμ; total blood eosinophils, 304 ± 266 cells/μL; body mass index, 28 ± 6; ACT, 16 to 19; and FEV_1, 2.5 ± 0.7 L (86% ± 20% predicted); exacerbation: FEV_1, 1.7 ± 0.4 L (60% ± 17%) ($P < .001$); recovery: FEV_1, 2.5 ± 0.7 L (85% ± 13%) ($P < .001$). Group 2 included 11 (7 men) similarly treated patients with asthma, age 49 ± 14 years, studied at baseline, during 15 exacerbations with *normal* FENO at 50 mL/s, J'_{awNO}, and C_{ANO}. Baseline: IgE, 307 ± 133 Kμ; total blood eosinophils, 296 ± 149 cells/μL; body mass index, 28 ± 6; ACT, 16 to 19; and FEV_1, 2.7 ± 0.9 L (71% ± 12% predicted); exacerbation: FEV_1, 1.7 ± 0.6 L (54% ± 19%) ($P < .006$); recovery: FEV_1, 2.7 ± 0.9 L (70% ± 14%) ($P = .002$). On comparing group 1 versus group 2, there was no significant difference for baseline IgE, eosinophils, body mass index, and ACT and similar significant (≤.006) decrease from baseline in FEV_1 (L) during exacerbation and similar increase (≤.006) at recovery.

Conclusions: Increased versus normal exhaled NO during outpatient exacerbation in patients with moderate-to-severe asthma on inhaled corticosteroid and long-acting β_2-agonist but not maintenance oral corticosteroid does not preclude a robust clinical and spirometric response to tapering oral prednisone. (J Allergy Clin Immunol 2012;129:1491-8.)

Key words: *Asthma, exhaled nitric oxide, asthma mechanisms*

Measurement of fraction of exhaled nitric oxide (FENO [ppb]) at 50 mL/s is a relatively simple, reproducible, and noninvasive biomarker test for monitoring the arginine-nitric oxide synthase pathway that signals airway inflammation.[1] Increased FENO at 50 mL/s in asthma has been thought to reflect predominantly eosinophilic-mediated inflammation in central airways, although the supporting data are only modest.[1-5] Increased FENO has also been reported to identify an increased response to inhaled corticosteroid (ICS) in ICS-naive adult patients with asthma but not to reduce exacerbations.[3] The currently accepted method of measuring FENO at a single constant expiratory flow rate, usually 50 mL/s, is incapable of separating whether the source of increased NO production is located in the large central airways versus peripheral small airways/alveolar or both.[6] Therefore, several investigators have developed newer techniques to discriminate NO gas exchange between large central airways and peripheral smaller airways/alveolar compartments.[7-12]

By using a 2-compartment model developed by Tsoukias and George,[11] central airway NO flux and peripheral airway/alveolar concentration can be estimated by measuring FENO at multiple expiratory flows and plotting NO output versus expiratory flow. The slope of the linear regression line between NO output and flow reflects peripheral small airway/alveolar NO concentration (C_{ANO} [ppb]), whereas the Y intercept reflects large central airway NO flux (J'_{awNO} [nL/s]).[11] Gelb et al[13,14] and others[8,12,15-21] using this model[11] have previously reported NO gas exchange in central as well as in peripheral airway/alveolar sites in patients with mild[8,12,15,18-21] and moderate-to-severe[8,13,14,16,17,20] clinically stable asthma. However, 2 groups independently[12,22] have also demonstrated, both experimentally and theoretically, axial back-diffusion (against the direction of exhalation) of NO from proximal to peripheral airway/alveoli. Furthermore, axial back-diffusion may contaminate peripheral airway/alveolar levels, leading to an underestimation of central airway NO flux and an overestimation of peripheral airway/alveolar NO levels. None of the above asthma studies[8-11,13-21] corrected for NO axial back-diffusion.[12,22]

Gelb et al[23] recently reported outpatient studies in acute asthma using the 2-compartment NO model[11] with correction for axial

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Abbreviations used
ACT: Asthma Control Test
C_{ANO}: Peripheral small airway/alveolar nitric oxide concentration
CT: Computed tomography
FENO: Fraction of exhaled nitric oxide
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
J'_{awNO}: Large central airway nitric oxide flux
LABA: Long-acting β_2-agonist
MDI: Metered-dose inhaler
NO: Nitric oxide

back-diffusion of NO.[22] In 13 of the 15 evaluated adults with asthma, there was increased NO flux in predominantly central airway sites in patients with clinically stable, moderate-to-severe asthma at baseline with abnormal spirometry despite moderate-dose ICS and long-acting β_2-agonist (LABA).[23] NO production in central airway sites was further increased in the same 13 of the 15 patients during exacerbation prior to the initiation of oral corticosteroid with robust clinical and spirometric response following an 8-day tapering course. The absence of increased C_{ANO} was in contrast to our previous observations of increased C_{ANO} in patients with clinically stable asthma[13,14] even after correction for axial NO back-diffusion.[22] This suggests that peripheral airway/alveolar NO concentration (C_{ANO}) in adults with acute asthma may be normal. Moreover, in 2 sentinel cases, we noted similar robust clinical and spirometric improvement during exacerbation in which both central and peripheral airway/alveolar NO concentration was normal at baseline as well as during exacerbation when compared with that in the 13 patients with asthma with predominantly increased central airway NO flux.[23]

The current prospective outpatient study used the 2-compartment model after correcting for NO axial back-diffusion.[11,22] We planned to study clinically stable, nonsmoking, asthma patients with moderate-to-severe expiratory airflow limitation despite treatment with moderate-dose ICS and LABA but no oral corticosteroid maintenance. Asthma patients were to be evaluated at baseline and subsequently during exacerbation and following recovery. Our goal was to evaluate the clinical and spirometric response in a larger group of patients with asthma who maintained normal NO gas exchange during exacerbation and compare their recovery response to that of patients with asthma with increased NO gas exchange during exacerbation. We hypothesized that while the difference in NO gas exchange during exacerbation may potentially reflect the source (eg, eosinophilic vs neutrophilic inflammation[1]), it would not preclude a subsequent robust clinical and spirometric response to treatment with add-on oral corticosteroid during exacerbation in patients with moderate-to-severe asthma. This hypothesis has not been investigated previously.

METHODS

Patient selection

We recruited adult patients followed in our referral clinic with moderate-to-severe persistent asthma who were on maintenance combination moderate-dose ICS/LABA for at least 2 years. This included either fluticasone propionate 250 μg/salmeterol 50 μg twice daily (Advair 250/50; GlaxoSmithKline, Research Triangle Park, NC) or budesonide 160 μg/formoterol 4.5 μg 2 inhalations twice daily (Symbicort 160/4.5; AstraZeneca, Wilmington, Del). Smoking history was less than 5 pack-years, and currently all were nonsmokers for at least 5 years. All patients with asthma were clinically stable for at least 8 weeks and were monitored in our tertiary referral outpatient clinic for 2 or more years. Their asthma symptoms and spirometry were optimal when compared with clinical and spirometric results obtained over the previous 2 or more years. When needed for acute relief, medical therapy included short-acting inhaled β_2-agonist (albuterol sulfate metered-dose inhaler [MDI] or solution) and inhaled antimuscarinic agent ipratropium bromide (Atrovent MDI or solution; Boehringer-Ingelheim Pharmaceuticals, Inc, Ridgefield, Conn). All patients with asthma were off oral corticosteroids, antibiotics, and leukotriene-modifying agents for at least 8 weeks before entry into the study. Serum eosinophil and IgE levels were measured only at baseline. Asthma Control Test (ACT) at baseline was used to characterize clinical status.[24] All patients with asthma had demonstrated bronchodilator reversibility within the past 2 years defined as an increase of 200 mL or more in FEV_1 and 12% or more 15 minutes following the intake of 180 μg albuterol via an MDI with a tube spacer. The definition of moderate-to-severe asthma was consistent with clinical and spirometric National Asthma Education and Prevention Program guidelines.[25] This study was approved by both Lakewood Regional Medical Center Institutional Review Board and Western Institutional Review Board, Olympia, Wash, and registered as NCT#00576069 and NCT#01225913. These data have not been previously published.

Normal controls

Normal values for FENO were obtained from 40 normal subjects (20 men), age 57 ± 9 years (similar age as of patients with asthma who were studied), who were asymptomatic, healthy lifelong nonsmokers with no history of lung disease and not on any medications.[26] No provocative bronchoconstrictor challenge tests were obtained. All asthmatic subjects and normal subjects studied had given informed consent for participation.

Measurement of exhaled nitric oxide gas exchange

All subjects abstained from food and coffee for 2 hours and alcohol for 12 hours prior to studies. Exhaled nitric oxide was measured in triplicate prior to spirometry at 4 separate constant expiratory flow rates (50, 100, 150, and 200 mL/s), and the mean of 3 values obtained within 10% of each other was reported by using a Sievers NOA 280 chemiluminescence analyzer with varying expiratory airflow resistors (GE Analytical Instruments, Inc, Boulder, Colo) as previously described.[13,14,23] Furthermore, to avoid nasal NO contamination, a mouth pressure of more than 5 cmH_2O was used, as previously recommended.[13,14,23] The technique of Tsoukias and George[11] was used to calculate J'_{awNO} (nL/s) (y intercept) and steady-state C_{ANO} (ppb) (slope) by using a linear regression line for each subject with a minimum of 3 expiratory flow rate data points and an r^2 of 0.9 or more. Correction was made for the potential underestimation of large airway NO flux due to axial back-diffusion of NO by using the method of Condorelli et al[22] by multiplying J'_{awNO} by a factor of 1.7. Furthermore, to adjust for possible spurious overestimation of values for peripheral lung C_{ANO}, the initial uncorrected J'_{awNO} (nL/s) was divided by a correction factor of 0.53 and subtracted from the initial uncorrected C_{ANO}.[22] This could yield negative or near-zero values for peripheral lung C_{ANO}.[22] This correction factor was determined in normal subjects and patients with mild asthma by using flow rates ranging from 50 to 250 mL/s.[22] Increased J'_{awNO} (nL/s) and/or C_{ANO} was defined as values more than 1.64 SD from age-matched controls.[25] Investigators responsible for measuring FENO gas exchange and lung function (C.F.T., R.M., and D.H.S.) were blinded to the therapeutic intervention. Spirometry and NO gas exchange were measured at the initiation of the study when the patients with asthma were clinically stable at baseline, and subsequently prior to the initiation of oral corticosteroid during exacerbation, and then during recovery immediately after treatment with an 8-day course of tapering oral corticosteroid.

Lung computed tomography studies

Our goal was to include only those patients with asthma who were without clinically occult significant lung computed tomography (CT) scored

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