FRACTIONAL EXHALED NITRIC OXIDE MEASUREMENTS IN RHINITIS AND ASTHMA IN CHILDREN

MIRAGLIA DEL GIUDICE M[1], MARSEGLIA GL[2], LEONARDI S[3], TOSCA MA[4], MARSEGLIA A[2], PERRONE L[1], CIPRANDI G[5].

[1]*Department of Pediatrics "F. Fede", Second University of Naples, Italy*
[2] *Department of Pediatrics, University of Pavia - Foundation IRCCS Policlinico San Matteo, Pavia, Italy*
[3]*Department of Pediatrics, University of Catania, Italy*
[4] *Department of Pediatric Pulmonology, Ospedale Gaslini, Genoa, Italy*
[5]*Department of Internal Medicine, IRCCS Azienda Ospedaliera Universitaria San Martino, Genoa, Italy*

Exaled nitric oxide (FeNO) is considered a good noninvasive marker to assess airway inflammation in asthma and allergic rhinitis. In asthma, exhaled NO is very useful to verify adherence to therapy, and to predict upcoming asthma exacerbations. It has been also proposed that adjusting anti-inflammatory drugs guided by the monitoring of exhaled NO, could improve overall asthma control. Other studies showed increased FeNO levels in subjects with allergic rhinitis.

United airway disease (UAD) hypothesis suggests that asthma and rhinitis are both different clinical manifestation of the same inflammatory process (1). There is increasing evidence that suggests a major involvement of airway epithelial cells in the pathogenesis of both asthma and allergic rhinitis and this hypothesis have been confirmed by means of epidemiological observations, functional and immunological evidence (2).

Exhaled nitric oxide is thought to be a sensitive marker of ongoing eosinophilic airway inflammation (3), and fractional exhaled nitric oxide (FeNO) is particularly attractive for use in children, because it can be measured by using noninvasive and standardized methods and can provide real-time results (4).

EXHALED NITRIC OXIDE AND ASTHMA

Asthma is due to chronic inflammation of the airways involving various cells, mainly eosinophils, mast cells, T lymphocytes, and their mediators (5). This chronic inflammation damages airway tissue thereby leading to progressive loss of respiratory function, to bronchial hyperresponsiveness (BHR), and to airflow obstruction that result in the typical asthma symptoms, such as wheezing, cough and dyspnea (6,7).

The main noninvasive methods for the evaluation of airways inflammation are induced sputum and measurement of fractional exhaled nitric oxide (FeNO). The former is time-consuming, needs a skillful operator, and the results depend on the patient's age and degree of cooperation (8). Differently, the measurement of FeNO is simple, well tolerated and reproducible (9, 10). FeNO levels are considered a good noninvasive marker to assess airway inflammation (11). In fact, they increase during asthma exacerbations (12, 13), decrease after inhaled steroid therapy (14, 15), and are higher in atopic asthmatic children than in nonatopic asthmatic children (16-19). Furthermore, FeNO is well correlated with eosinophils in bronchoalveolar lavage fluid (20), in sputum (21), and in blood (22).

In asthma, exhaled NO is very useful to verify adherence to therapy (23), and to predict upcoming asthma exacerbations(24). It is also proposed that adjusting anti-inflammatory medications guided by the monitoring of exhaled NO, could improve overall asthma control (23).

Atopy seems to be a significant factor associated with a raised exhaled NO independently from asthma (25). FeNO was most significantly associated with the presence of allergic sensitization (26) and specific allergen exposure

Key Words: asthma, allergic rhinitis, fractional exhaled nitric oxide and children

Corresponding Author:
Michele Miraglia Del Giudice MD
Dipartimento di Pediatria "F.Fede" - Seconda Università di Napoli- Naples, Italy
michele.miraglia@unina2.it

0394-6320 (2011)

increased FeNO levels in sensitized, but not in un-sensitized, children (27). In our experience, FeNO was elevated only in children with asthma and atopic dermatitis who also demonstrated allergic sensitization (28). The increasing in FENO levels observed in allergic disease is most likely driven by an up-regulation of inducible nitric oxide synthase by cytokines released during airway inflammation (29). Although Buchvald et al.(30) reported no association between FeNO and atopy as measured by RAST testing in children 2 to 5 years old. Recently, Jackson et al. (25) reported significantly differences in FeNO in atopic versus non-atopic children. A greater elevation of FeNO in older atopic children has been demonstrated in the Buchvald's study (31) suggesting that FeNO values progressively increase with age during childhood.

There is no general consensus about correlations between FeNO and respiratory function and between FeNO and bronchial hyperresponsiveness (BHR) (32-35) . The correlations reported thus far can probably be attributed to differences in the subjects investigated. In fact, population homogeneity, different measurement techniques, disease duration (36), time of suspension of inhaled steroid therapy, atopic status (19), sensitization and exposure to allergens (27) may influence the results of FeNO, respiratory function and BHR. Asthmatic children with normal respiratory function could be affected by airway inflammation (37). Horvath and Barnes found high FeNO levels in symptom-free atopic subjects, and concluded that FeNO could be correlated with an early, not clinically apparent state of airway inflammation (38). Similar results were found in a teenage population (39), and it was suggested that persistence of subclinical airway inflammation could be a continuous risk of the clinical reappearance of asthma.

EXALED NITRIC OXIDE MEASUREMENT

FeNO can be measured by using chemiluminescence analyzer (chemiluminescence technology) or electrochemical method. The detection limit of the instrument must be from 1 to 5 parts per billion (ppb) volume, as required by guidelines (40), with a resolution of 1 ppb. The analyzer should be calibrate daily, using a certified NO mixture. The single-breath online measurement method represents the preferred method to record FeNO in children who can cooperate. Children have to inhale to total lung capacity from NO-free air and to exhale a single breath (without nose clip) through a mouthpiece at a mouth pressure of >5 cm H_2O, corresponding to an expiratory flow of 50 mL/s. Mouth pressure was displayed on a computer screen as a prompt for the children to maintain a steady flow. Nitric oxide is measured at the plateau and the measurement has to be rejected if a stable flow is not maintained for at least 6 s of exhalation. Audiovisual aids can facilitate expiratory flow control.

In preschool children, who often have difficulty in maintaining flow rate or pressure within the required limits the offline method with constant flow rate, this tool is the best choice. The child blows air through a mouthpiece into a Mylar or Tedlar balloon, while nasal contamination is prevented by closing the velum by exhaling against at least 5 cmH_2O mouth pressure (41)

EXHALED NITRIC OXIDE AND RHINITIS

Nasal NO concentrations are higher than in the lower respiratory tract (42) probably because nasal NO may have physiologic roles, such as preserving sinus sterility (43) and modulating ciliary motility (44). In fact, children with primary ciliary dyskinesia and cystic fibrosis have extremely low nasal NO (45) and nasal NO measure may become a useful clinical test (40). Nasal NO concentration has been proposed as a marker of nasal inflammation in allergic rhinitis, but results are controversial (40,47-49)

The measurement of nasal NO output requires generation of airflow through the nasal cavity. Flow through the nasal cavities is generally achieved by insufflating air via one naris while the velum is closed, so that air circulates from one naris to the other around the posterior nasal septum (40).

On the other hand, other studies showed increased FeNO levels in subjects with allergic rhinitis (50,35). In a recent study, in non-asthmatic children, only the atopic children with rhinitis had an elevated FeNO, asthmatic children who were not atopic and who did not suffer from rhinitis had a lower FeNO whereas asthmatics with atopy but without rhinitis had a twofold increase in eNO level (51)

CONCLUSION

In conclusion, FENO seems to be a good tool for measuring and monitoring the extent of airway inflammation in asthmatic subjects. Indeed, FENO is closely correlated with other parameters of airway inflammation (21), inhaled steroids quickly reduce FENO levels (14,15), and modification of FENO levels seems to be related to changes in anti-inflammatory therapy (23,24). Further studies are needed to understand better the clinical implications of FeNO measurement in children with allergic rhinitis.

REFERENCES

1. Profita M, Montuschi P, Bonanno A et al Novel perspectives in the detection of oral and nasal oxidative

stress and inflammation in pediatric united airway diseases. Int J Immunopathol Pharmacol. 2010; 23:1211-9.
2. Marseglia GL, Caimmi S, Marseglia A, Poddighe D, Leone M, Caimmi D, Ciprandi G, Castellazzi AM. Rhinosinusitis and asthma.Int J Immunopathol Pharmacol. 2010; 23:29-31.
3. Payne DN, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. Am J Respir Crit Care Med 2001; 164:1376-81.
4. Jackson JD, Virnig CM, Gangnon RE et al. Fractional exhaled nitric oxide measurements are most closely associated with allergic sensitization in school-age children J Allergy Clin Immunol 2009; 124:949-53
5. Kay AB Asthma and inflammation J Allergy Clin Immunol 1991 ;87:893-907.
6. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma. Bethesda MD, May 1997.
7. Global Strategy for Asthma Management and Prevention – updated April 2002 (Scientific information and recommendations for asthma programs. NIH Publication No. 02-3659).
8. Pin I, Gibson PJ, Kolendowicz R, Girgis Gabardo A, Denburg JA, Hargreave FE, Dolovich J. Use of induced sputum cell counts to investigate airway inflammation in asthma. Thorax 1992; 47:25-29.
9. Barnes PJ, Liew FY. Nitric oxide and asthmatic inflammation. Immunol Today 1995; 16:128-130.
10. Barnes PJ, Kharinotov SA. Exhaled nitric oxide: a new lung function test. Thorax 1996; 51:233-237.
11. Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. Am J Respir Crit Care Med 2001; 163:1693-1722.
12. Lanz MJ, Leung DY, White CW. Comparison of exhaled nitric oxide to spirometry during emergency treatment of asthma exacerbations with glucocorticoids in children. Ann Allergy Asthma Immunol 1999; 82:161-164.
13. Baraldi E, Dario C, Ongaro R, Scollo M, Azzolin NM, Panza N, Paganini N, Zacchello F. Exhaled nitric oxide concentration during treatment of wheezing exacerbation in infants and young children. Am J Respir Crit Care Med 1999; 159:1284-1288.
14. Lanz MJ, Leung DY, White CW. Comparison of exhaled nitric oxide to spirometry during emergency treatment of asthma exacerbations with glucocorticoids in children. Ann Allergy Asthma Immunol 1999; 82:161-164.
15. Kharinotov SA, Yates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med 1996; 153: 454-457.
16. Amin K, Lúdvíksdóttir D, Janson C, Nettelbladt O, Björnsson E, Roomans G M, Boman G, Sevéus L, Venge P. Inflammation and structural changes in the airways of patients with atopic and non atopic asthma. Am J Respir Crit Care Med 2000; 162:2295-2301.
17. Frank TL, Adisesh A, Pickering AC, Morrison JFJ, Wright T, Francis H, Fletcher A, Frank PI, Hannaford P. Relationship between exhaled nitric oxide and childhood asthma Am J Respir Crit Care Med 1998; 158:1032-1036.
18. Silvestri M, Sabatini F, Spallarossa D, Fregonese L, Battistini E, Biraghi MG, Rossi GA. Exhaled nitric oxide levels in non-allergic and allergic mono or polysensitised children with asthma. Thorax 2001; 56:857-862.
19. Gratziou C, Lignos M, Dassiou M, Roussos C. influence of atopy on exhaled nitric oxide in patients with stable asthma and rhinitis. Eur Respir J 1999; 14:897-901.
20. Warke TJ, Fitch PS, Brown V, taylor R, Lyons JDM, Ennis M, Shields MD. Exhaled nitric oxide with airway eosinophils in childhood asthma. Thorax 2002; 57:383-387.
21. Jatakonon A, Lim S, Kharitonov SA, Ghung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils and methacholine responsiveness in patients with mild asthma. Thorax 1998; 53:91-95.
22. Silvestri M, Spallarossa D, Frangova Yourukova V, Battistini E, Fregonese B, Rossi GA. Orally exhaled nitric oxide levels are related to the degree of blood eosinophilia in atopic children with mild-intermittent asthma. Eur Respir J 1999; 13:321-326.
23. Beck-Ripp J, Griese M, Arenz S, Koring C, Pasqualoni B, Bufler P. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. Eur Respir J 2002; 19: 1015–1019
24. Harkins MS, Fiato KL, Iwamoto GK. Exhaled nitric oxide predicts asthma exacerbation. J Asthma 2004; 41:471–476
25. Jackson JD, Virnig CM, Gangnon RE et al. Fractional exhaled nitric oxide measurements are most closely associated with allergic sensitization in school-age children J Allergy Clin Immunol 2009; 124:949-53
26. van Asch CJ, Balemans WA, Rovers MM, Schilder AG, van der Ent CK. Atopic disease and exhaled nitric oxide in an unselected population of young adults. Ann Allergy Asthma Immunol 2008; 100:59-65..
27. Sordillo JE, Webb T, Kwan D. Allergen exposure modifies the relation of sensitization to fraction of exhaled nitric oxide levels in children at risk for allergy and asthma. J Allergy Clin Immunol 2011; 127:1165-72.
28. Miraglia del Giudice M, Capasso M, Maiello N, Capristo C, Piacentini GL, Brunese FP, Capristo AF. Exhaled nitric

oxide and atopy in children. J Allergy Clin Immunol. 2003; 111:193.

29. Hamid Q, Springall DR, Riveros-Moreno V, Chanez P, Howarth P, Redington A, et al. Induction of nitric oxide synthase in asthma. Lancet 1993; 342:1510-3
30. Buchvald F, Bisgaard H. FeNO measured at fixed exhalation flow rate during controller tidal breathing in children from the age of 2 yr. Am J Respir Crit Care Med 2001; 163:699-704
31. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MW, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005; 115:1130-6
32. Dupont LJ, Rochette F, Demedts MG, Verleden GM. Exhaled nitric oxide correlates with airway hyperresponsiveness in steroid-naive patients with mild asthma. Am J Respir Crit Care Med 1998; 157:894-898.
33. Piacentini GL, Bodini A, Costella S, Suzuki Y, Zerman L, Peterson C.G.B., Boner AL. Exhaled nitric oxide, serum ECP and airway responsiveness in mild asthmatic children. Eur Respir J 2000; 15:839-843.
34. Silvestri M, Spallarossa D, Battistini E, Brusasco V, Rossi GA. Dissociation between exhaled nitric oxide and hyperresponsiveness in children with mild intermittent asthma Thorax 2000; 55:484-488.
35. Ciprandi G, Tosca MA, Capasso M. Exhaled nitric oxide in children with allergic rhinitis and/or asthma: a relationship with bronchial hyperreactivity. J Asthma. 2010; 47:1142-7.
36. Tsujino I, Nishimura M, Kamachi A, Makita H, Munakata M, Miyamoto K, Kawakami Y. Exhaled nitric oxide – is it really a good marker of airway inflammation in bronchial asthma? Respiration 2000; 67:645-651
37. Miraglia del Giudice M, Brunese FP, Piacentini GL, Pedullà M, Capristo C, Decimo F, Capristo AF Fractional exhaled nitric oxide (FENO), lung function and airway hyperresponsiveness in naïve atopic asthmatic children. J Asthma. 2004; 41:759-65
38. Horvath I, Barnes PJ. Exhaled monoxides in asymptomatic atopic subjects. Clin Exp Allergy 1999; 29:1276-1280
39. Van den Toorn LM, Prins JB, Overbeek SE, Hoogsteden HC, de Jongste JC. Adolescents in clinical remission of atopic asthma have elevated exhaled nitric oxide levels and bronchial hyperresponsiveness Am J Respir Crit Care Med 2000; 162:953-957.
40. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, Am J Respir Crit Care Med 2005; 171:912–930
41. Jobsis Q, Schellekens SL, Kroesbergen A, Hop WC, de Jongste JC. Sampling of exhaled nitric oxide in children: end-expiratory plateau, balloon and tidal breathing methods compared. Eur Respir J 1999; 13:1406–1410
42. Kimberly B, Nejadnik B, Giraud GD, Holden WE. Nasal contribution to exhaled nitric oxide at rest and during breathholding in humans. Am J Respir Crit Care Med 1996;153:829–836
43. Xia Y, Zweier JL. Superoxide and peroxynitrite generation from inducible nitric oxide synthase in macrophages. Proc Natl Acad Sci USA 1997; 94:6954–6958.
44. Jain B, Rubinstein I, Robbins RA, Leise KL, Sisson JH. Modulation of airway epithelial cell ciliary beat frequency by nitric oxide. Biochem Biophys Res Commun 1993; 191:83–88.
45. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, Pavord ID, Ratjen F, Silkoff PE, Taylor DR, Zamel N. Chest. 2010; 138:682-92.
46. Wodehouse T, Kharitonov SA, Mackay IS, Barnes PJ, Wilson R, Cole PJ. Nasal nitric oxide measurements for the screening of primary ciliary dyskinesia. Eur Respir J 2003; 21:43–47
47. Martin U, Bryden K, Devoy M, Howarth P. Increased levels of exhaled nitric oxide during nasal and oral breathing in subjects with seasonal rhinitis. J Allergy Clin Immunol 1996; 97:768–772.
48. Arnal JF, Didier A, Rami J, M'Rini C, Charlet JP, Serrano E, Besombes JP. Nasal nitric oxide is increased in allergic rhinitis. Clin Exp Allergy 1997; 27:358–362.
49. Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. Subjective and objective markers of treatment response in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2000; 85:111–114.
50. Cardinale F, de Benedictis FM, Muggeo V, Giordano P, Loffredo MS, Iacoviello G, et al. Exhaled nitric oxide, total serum IgE and allergic sensitization in childhood asthma and allergic rhinitis. Pediatr Allergy Immunol 2005; 16:236-42.
51. Jouaville L. F. , Annesi-Maesanoz I., Nguyen L. T. ,. Bocage A. S ,. Bedu M and Caillaud D. Interrelationships among asthma, atopy, rhinitis and exhaled nitric oxide in a population-based sample of children. Clin Exp Allergy 2003; 33:1506–1511