

CHEST[®]

Official publication of the American College of Chest Physicians



Exhaled Nitric Oxide in Asthma: From Diagnosis, to Monitoring, to Screening: Are We There Yet?

Natalia M. Grob and Raed A. Dweik

Chest 2008;133:837-839
DOI 10.1378/chest.07-2743

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournal.org>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2007 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder (<http://www.chestjournal.org/misc/reprints.shtml>). ISSN: 0012-3692.

A M E R I C A N C O L L E G E O F
 C H E S T
P H Y S I C I A N S[®]

promising, a few words of caution are warranted. First, the number of patients with chest wall invasion in this cohort was small (26 patients), and larger studies are needed to duplicate these findings. Second, the operators in the study were experienced interventional pulmonologists who perform hundreds of thoracic and endoscopic ultrasound per year. It remains to be seen whether less experienced operators, either radiologists or pulmonologists, can replicate these findings. Third, ultrasound may not be a suitable modality in all cases either due to patient factors (morbid obesity or chest wall deformities) or lesion factors (lesions situated behind ribs or high in the apex).

So can any pulmonologist perform ultrasound to detect chest wall invasion by lung tumor? The answer is probably not. Training of pulmonologists in ultrasound has been a complex and controversial issue.⁷ At this time, no clear competency metrics exist for ultrasound, and proficiency is based on number of procedures. Training for practicing pulmonologists is limited to attending specialized courses and institutional proctoring by skilled sonographers. Pulmonary trainees may have a better opportunity to learn ultrasound skills by virtue of an expanding number of dedicated interventional pulmonologists and intensivists who have embraced and become proficient in ultrasound. To incorporate the skill of using ultrasound for detection of chest wall abnormalities in daily practice, pulmonologists must first acquire cognitive and manual proficiency in basic and advanced thoracic ultrasound to enable them to go to the “next step.”

Although no studies have been performed to assess the effect of multidisciplinary care on the survival of lung cancer patients, it has gradually become the standard of care. The gathering of minds of thoracic surgeons, medical oncologists, radiation oncologists, and pulmonologists undoubtedly provide thoughtful diagnostic and therapeutic planning that leaves no stone unturned. Adding a simple inexpensive noninvasive test such as ultrasound to the office in a multidisciplinary lung cancer program is yet another step on the road to optimal patient-focused care.

*Momen M. Wahidi, MD, FCCP
Durham, NC*

Dr. Wahidi is Director, Interventional Pulmonology, and Assistant Professor of Medicine, Duke University Medical Center. The author has no conflict of interest to disclose.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Momen M. Wahidi, MD, FCCP, Director, Interventional Pulmonology, Duke University Medical Center, Box 3683, Durham, NC 27710; e-mail: momen.wahidi@duke.edu
DOI: 10.1378/chest.07-2770

REFERENCES

- 1 Beckh S, Bolcskei PL, Lessnau KD. Real-time chest ultrasonography: a comprehensive review for the pulmonologist. *Chest* 2002; 122:1759–1773
- 2 Bandi V, Lunn W, Eberhardt R, et al. Ultrasound vs. computed tomography in detecting chest wall invasion by tumor: a perspective study. *Chest* 2008; 133:881–886
- 3 Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997; 111:1710–1717
- 4 Doddoli C, D'Journo B, Pimpec-Barthes F, et al. Lung cancer invading the chest wall: a plea for en-bloc resection but the need for new treatment strategies. *Ann Thorac Surg* 2005; 80:2032–2040
- 5 Voltolini L, Rapicetta C, Luzzi L, et al. Lung cancer with chest wall involvement: predictive factors of long-term survival after surgical resection. *Lung Cancer* 2006; 52:359–364
- 6 Birnholz J. Chest wall and lung surface viewing with ultrasound. *Chest* 1988; 94:1275–1276
- 7 Feller-Kopman D. Ultrasound-guided internal jugular access: a proposed standardized approach and implications for training and practice. *Chest* 2007; 132:302–309

Exhaled Nitric Oxide in Asthma From Diagnosis, to Monitoring, to Screening: Are We There Yet?

Nitric oxide (NO) has long been known as an atmospheric pollutant present in vehicle exhaust emissions and cigarette smoke, but the discovery that it is a biological mediator lead to many breakthroughs in our understanding of human physiology and disease. NO is endogenously synthesized by one of three NO synthases that convert L-arginine to L-citrulline and NO in the presence of oxygen and several cofactors. All three NO synthases (type I, II, and III) are widely expressed in various tissues including the lungs.^{1,2}

The advent of chemiluminescence analyzers in the early 1990s allowed the detection of low (parts per billion [ppb]) levels of NO in exhaled breath.³ Patients with asthma were found to have high levels of NO in their exhaled breath⁴ that decreased in response to treatment with corticosteroids.⁵ This quickly prompted the evaluation of exhaled NO as a potential noninvasive method to diagnose asthma and monitor the response to antiinflammatory therapy. Potential advantages for exhaled NO in asthma included its noninvasive nature, ease of repeat measurements, and use in children and patients with severe airflow obstruction for whom other techniques would be difficult or not possible to perform.⁶ Exhaled NO may also be more sensitive than previously available tests in detecting airway inflammation.⁷

Several issues, however, needed to be addressed before exhaled NO could become a useful clinical tool in routine asthma monitoring and management.⁸ First, a better understanding of the role of NO in asthma pathogenesis was needed. Second, the meth-

ods and equipment for measuring NO needed to be standardized. Third, large population studies^{6,8} were needed to determine the normal range of exhaled NO levels and the effect of confounding factors. Last, but not least, interpretative strategies needed to be devised and put in place for the different potential uses and applications. While the answers have not always been straightforward and simple, most of these issues have either already been addressed or are currently under investigation allowing exhaled NO measurement to make the transition from the research to the clinical arena.

Although several studies⁴⁻⁹ suggest a role for NO in asthma pathogenesis, the exact role of NO in asthma and airway reactivity has remained elusive. Whether NO is beneficial through its bronchodilator and antioxidant effects or harmful by inducing inflammation remains unclear.^{6,9} The observation that NO levels are dependent on the expiratory flow rates¹⁰ resulted in the standardization of the measurement and reporting.¹¹ The term *fraction of exhaled NO* (FENO) is currently recommended for reporting exhaled NO levels.¹¹ While the role of NO in the pathophysiology of asthma remains an area of active investigation, the standardization of FENO measurement was followed by several large clinical and population studies demonstrating that FENO levels can be useful in the diagnosis of asthma,⁷ and in monitoring disease activity/airway inflammation and response to therapy.⁵ Kostikas and colleagues,¹² in this issue of *CHEST* (see page 906), take the field a step further by suggesting that FENO measurement can be useful as a screening tool for asthma and by using a newer portable device for this purpose.

Kostikas and colleagues¹² evaluated the utility of FENO measured by a portable device as a screening tool for asthma in young adults during pollen season. Although screening studies^{13,14} have been performed on pediatric populations, this study evaluated an adult population. The authors¹² recommended a cut-off value of FENO > 19 ppb for the diagnosis of asthma, and reported median values with interquartile ranges for the healthy control (10.5 ppb; 7 to 14 ppb) and asthmatic populations (20 ppb; 14 to 31 ppb) in their study. In addition to the use of a novel portable device,¹⁵ a couple of important issues are worth pointing out about this study that help frame the status of the FENO field: the confounding variables affecting FENO, and the normal values and cut points for FENO in the different clinical settings.

Different studies¹²⁻¹⁸ have identified various possible confounders that affect FENO including age, gender, weight, height, diurnal variation, and food intake, among others. Kostikas et al,¹² however, confirm an observation that has been consistent in

the literature: atopic individuals tend to have higher FENO, while smokers tend to have lower FENO.

A more difficult problem to address in the NO field has been the establishment of normal healthy population values for FENO. In a recent large population study,¹⁶ the mean FENO (17.9 ppb) was higher than that found for the smaller sample of healthy control subjects included in the study by Kostikas et al.¹² This discrepancy may be a result of the relatively smaller sample size in the study by Kostikas et al,¹² as well as their inclusion of smokers in the healthy control population. While several studies^{13,16-18} have tried to address this issue of normative values, they were done in different populations, addressed different potential confounders, and reported their results in different ways. Furthermore, "reference values" derived from a "normal" population may not be applicable in patients with asthma. This raises the question whether normal values are at all useful when it comes to the use of FENO in asthma. It is very clear from reviewing the literature that the FENO value by itself is not sufficient; rather, it needs to be taken within the clinical context. Beyond the confounding variables such as atopy and smoking, several issues need to be considered. Was the measurement obtained in someone who has symptoms, or in an asymptomatic individual? Was it performed as a screening, or to aid in the diagnosis? Is the individual known to have asthma? And if so, is he/she receiving therapy? Do they have previous levels, and how does this level compare?

Combined with the fact that there is considerable overlap in FENO values between healthy individuals and asthmatics, defining different cut points for different clinical settings may be more clinically useful than normative values. Once the clinical setting is taken into consideration, certain patterns begin to emerge. FENO levels > 45 to 50 ppb may predict steroid responsiveness,¹⁹ while levels < 35 ppb can suggest optimal asthma control in an asthmatic patient receiving therapy.²⁰ FENO levels > 20 to 25 ppb suggest the presence of asthma in a steroid-naive individual with symptoms, while lower levels are not likely to be associated with airway inflammation.^{7,21,22} The report by Kostikas and colleagues¹² suggests that the 20- to 25-ppb cut point can be used to screen for asthma as well.

Advances in technology and standardization made FENO measurement simple and allowed us to easily perform it in different settings from diagnosis, to monitoring, to screening, and possibly others. In order for this simple yet powerful tool to achieve its potential, however, we need to understand what FENO levels mean in different clinical settings. Inclusion of FENO as an end point in asthma clinical trials would be very helpful in understanding the role

of FENO in monitoring response to therapy. FENO measurement in large population-based studies like the National Health and Nutrition Examination Survey²³ would provide more reliable normative values. Finally, we now need interpretation guidelines to make FENO levels more clinically useful to practitioners. For while some tests are difficult to perform and easy to interpret, others like FENO are easy to perform but may need considerable skill in interpretation.

*Natalia M. Grob
Raed A. Dweik, MD, FCCP
Cleveland, OH*

Ms. Grob is a medical student, School of Medicine, Case Western Reserve University, and Dr. Dweik is Director, Pulmonary Vascular Program, Department of Pulmonary, Allergy and Critical Care Medicine, Cleveland Clinic.

The authors have no conflicts of interest to disclose. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Raed A. Dweik, MD, FCCP, Department of Pulmonary, Allergy and Critical Care Medicine, Cleveland Clinic, 9500 Euclid Ave/A90, Cleveland, OH 44195; e-mail: dweikr@ccf.org

DOI: 10.1378/chest.07-2743

REFERENCES

- 1 Ignarro LJ, Buga GM, Wood KS, et al. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci U S A* 1987; 84:9265–9269
- 2 Dweik RA, Erzurum SC. Regulation of nitric oxide (NO) synthases and gas phase NO by oxygen. In: Marczin N, Kharitonov SA, Yacoub MH, et al, eds. *Disease markers in exhaled breath (Lung Biology in Health and Disease)*. New York, NY: Marcel Dekker, 2003; 235–246
- 3 Gustafsson LE, Leone AM, Persson MG, et al. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. *Biochem Biophys Res Commun* 1991; 181:852–857
- 4 Kharitonov SA, Yates D, Robbins RA, et al. Increased nitric oxide in exhaled air of asthmatic patients. *Lancet* 1994; 343:133–135
- 5 Silkoff PE, McClean P, Spino M, et al. Dose-response relationship and reproducibility of the fall in exhaled nitric oxide after inhaled beclomethasone dipropionate therapy in asthma patients. *Chest* 2001; 119:1322–1328
- 6 Ozkan M, Dweik RA. Nitric oxide and airway reactivity. *Clin Pulm Med* 2001; 8:199–206
- 7 Smith AD, Cowan JO, Filsell S, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med* 2004; 169: 473–478
- 8 Dweik RA. The promise and reality of nitric oxide in the diagnosis and treatment of lung disease. *Cleve Clin J Med* 2001; 68:486,488,490,493
- 9 Dweik RA, Comhair SA, Gaston B, et al. NO chemical events in the human airway during the immediate and late antigen-induced asthmatic response. *Proc Natl Acad Sci U S A* 2001; 98:2622–2627
- 10 Silkoff PE, McClean PA, Slutsky AS, et al. Marked flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide. *Am J Respir Crit Care Med* 1997; 155:260–267
- 11 ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005; 171:912–930
- 12 Kostikas K, Papaioannou AI, Tanou K, et al. Portable exhaled nitric oxide as a screening tool for asthma in young adults during pollen season. *Chest* 2008; 133:906–913
- 13 Buchvald F, Baraldi E, Carraro S, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. *J Allergy Clin Immunol* 2005; 115:1130–1136
- 14 Prasad A, Langford B, Stradling JR, et al. Exhaled nitric oxide as a screening tool for asthma in school children. *Respir Med* 2006; 100:167–173
- 15 Gill M, Graff GR, Adler AJ, et al. Validation study of fractional exhaled nitric oxide measurements using a handheld monitoring device. *J Asthma* 2006; 43:731–734
- 16 Olin AC, Bake B, Toren K. Fraction of exhaled nitric oxide at 50 mL/s: reference values for adult lifelong never-smokers. *Chest* 2007; 131:1852–1856
- 17 Olivieri M, Talamini G, Corradi M, et al. Reference Values for Exhaled Nitric Oxide (REVENO) Study. *Respir Res* 2006; 7:94
- 18 Travers J, Marsh S, Aldington S, et al. Reference ranges for exhaled nitric oxide derived from a random community survey of adults. *Am J Respir Crit Care Med* 2007; 176:238–242
- 19 Smith AD, Cowan JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med* 2005; 172:453–459
- 20 Smith AD, Cowan JO, Brassett KP, et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005; 352:2163–2173
- 21 Berry MA, Shaw DE, Green RH, et al. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005; 35:1175–1179
- 22 Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. *Chest* 2003; 123:751–756
- 23 National Center for Health Statistics. National Health and Nutrition Examination Survey. Available at: <http://www.cdc.gov/nchs/nhanes.htm>. Accessed March 19, 2008

The Hypoxia Altitude Simulation Test

An Increasingly Performed Test for the Evaluation of Patients Prior to Air Travel

More than one billion people throughout the world travel on commercial aircraft each year.^{1–4} The number of airline passengers has been increasing in recent years and include individuals of all ages, from infants to elderly individuals with chronic medical disorders.^{5,6} For most passengers, commercial air travel causes no significant health risk.^{1–3,5,7–9} However, some passengers with cardiopulmonary disease may have significant hypoxemia during flight.^{10–20}

At the present time, US federal regulations require that all aircraft cabins be pressurized to ≥ 565 mm Hg at maximum altitude. This is equivalent to a

Exhaled Nitric Oxide in Asthma: From Diagnosis, to Monitoring, to Screening: Are We There Yet?

Natalia M. Grob and Raed A. Dweik

Chest 2008;133;837-839

DOI 10.1378/chest.07-2743

This information is current as of April 8, 2008

Updated Information & Services	Updated information and services, including high-resolution figures, can be found at: http://chestjournal.org/cgi/content/full/133/4/837
References	This article cites 21 articles, 12 of which you can access for free at: http://chestjournal.org/cgi/content/full/133/4/837#BIBL
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://chestjournal.org/misc/reprints.shtml
Reprints	Information about ordering reprints can be found online: http://chestjournal.org/misc/reprints.shtml
Email alerting service	Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]