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

Natalia M. Grob and Raed A. Dweik

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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.

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References

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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 breath 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 studies\(^4\)–\(^9\) 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 rates\(^10\) 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 colleagues\(^12\) 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 authors\(^12\) 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 studies\(^12\)–\(^18\) 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-naïve individual with symptoms, while lower levels are not likely to be associated with airway inflammation.\(^7,21,22\) The report by Kostikas and colleagues\(^12\) 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 Survey 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.

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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. 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. For most passengers, commercial air travel causes no significant health risk. However, some passengers with cardiopulmonary disease may have significant hypoxemia during flight.

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
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