

Utility and limitations of objective measures of asthma

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by airway inflammation, airway hyperresponsiveness, and variable airways obstruction.¹ National estimates show that approximately 22 million people currently have asthma in the United States.² In 2007, the American Lung Association estimated that the annual economic cost of asthma in the United States was \$19.7 billion.³ From 1980 to 1996, the number of work and school days missed increased by more than 50% to 14 million days each.⁴ These increases correspond to increased prevalence because the days missed per person have not changed significantly.

The diagnosis of asthma is generally based on a combination of symptoms and demonstration of reversible airflow obstruction on pulmonary function testing or spirometry. Spirometry is used for diagnosis and monitoring of asthma control. Reversibility in adults is defined as an increase in forced expiratory volume in 1 second (FEV₁) of 200 mL or more and 12% or more from the baseline measurement after bronchodilation. Bronchoprovocation testing is often used to help with the diagnosis when, despite symptoms suggestive of asthma, spirometry results are normal or inconclusive and reversibility is not demonstrated. However, bronchoprovocation can also help in monitoring response to therapy and overall asthma control. In addition, bronchoprovocation can also aid in the evaluation of occupational asthma. Agents

used for bronchoprovocation can act directly on the airways, such as methacholine and histamine, or indirectly, such as adenosine monophosphate, hypertonic saline, and exercise. More recently, fractional exhaled nitric oxide (FeNO) has been used as a marker of airway inflammation. FeNO has been studied as a tool to not only help in the diagnosis but also follow disease control.

Overall, evidence is conflicting on whether objective measures of asthma correlate well with one another. We review 4 commonly used objective measures of asthma: spirometry, methacholine challenge, hypertonic saline challenge, and FeNO (Table 1).

SPIROMETRY

Spirometry is a physiologic test that measures volumes of air that a person inhales or exhales as a function of time. Variables of interest in asthma are the forced vital capacity (FVC), FEV₁, and the ratio of FEV₁ to FVC (FEV₁/FVC). Worldwide guidelines, including the National Asthma Education and Prevention Program Expert Panel Guidelines in 2007, consider spirometry an essential objective measure to diagnose and monitor asthma, and many consider the FEV₁ measure the criterion standard measurement for asthma.¹ The advantages are that it is well validated, noninvasive, reproducible, relatively easy to perform, and relatively inexpensive. Physicians must rely on spirometry for asthma diagnosis and monitoring because history and physical examination often cannot reliably diagnose asthma or evaluate control. The guidelines also integrate FEV₁ and FEV₁/FVC into the classification of asthma severity; thus, spirometry plays a key role in guiding treatment options.¹

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Disclosures: Authors have nothing to disclose.

Received for publication February 4, 2009; Received in revised form March 10, 2009; Accepted for publication March 19, 2009.

Table 1. Characteristics of Individual Tests

Test	Characteristics
Spirometry	Measures airflow obstruction and assesses disease severity and control
Methacholine (direct) challenge	Assesses level of airway responsiveness and if result is negative helps exclude asthma
Hypertonic saline (indirect)	Assesses level of airway responsiveness, more helpful for atopic asthma or exercise-induced symptoms, and responds more than direct challenges to treatment
Fractional exhaled nitric oxide	Measures airway inflammation and follows individual patient's level of control and therapy response

BRONCHOPROVOCATION TESTS: DIRECT AND INDIRECT

Bronchoprovocation can be induced by agents that act directly or indirectly on the airway smooth muscle. Of the direct-acting agents, methacholine is the most widely used, whereas hypertonic saline and exercise are 2 of the more commonly used indirect challenges in the United States. Methacholine, a direct airway-narrowing stimulus, causes airflow limitation by causing airway smooth muscle contraction via stimulation of muscarinic M3 receptors. Methacholine also acts on mucous glands and on airway microvasculature without involving intermediate pathways. By contrast, hypertonic saline induces airflow limitation by acting on cells other than smooth muscle cells (eg, inflammatory cells, epithelial cells, and nerves), which on stimulation release mediators that provoke secondary smooth muscle contraction. Other indirect challenges include mannitol and adenosine monophosphate. These agents are not approved by the Food and Drug Administration. Adenosine works by directly stimulating adenosine receptors and by causing mast cell degranulation. Mannitol may become a good practical option for the physician because it is easy to administer and does not require specialized equipment. It is especially useful for the diagnosis of exercise-induced bronchoconstriction.

DIRECT CHALLENGE: METHACHOLINE

Methacholine (Provocholine) available as a dry crystalline powder is dissolved in saline solution containing 0.4% phenol to generate solutions of increasing concentration. Solutions are administered as aerosols, and patients inhale increasing concentrations of methacholine until a decrease of 20% in FEV₁ has been achieved or the maximum concentration of methacholine has been inhaled. The 2 most commonly used dosing protocols are the 2-minute tidal breathing method and the 5-breath dosimeter method. The bronchial response to the inhaled methacholine is expressed as the concentration of methacholine that results in a 20% decline in FEV₁ (PC₂₀). The maximum dose of methacholine used may vary from 16 to 25 mg/mL. A PC₂₀ of 8 to 16 mg/mL is the usual cutoff used to identify patients with asthma from those without asthma. PC₂₀ values above 8 mg/mL are associated with lower sensitivity and specificity.

The methacholine challenge test has been shown to be highly sensitive (85% to 91%) and specific (90%) for the diagnosis of asthma.^{5,6} The negative predictive value of a methacholine challenge test is higher than its positive predictive value, thus making it more useful in excluding a diagnosis of asthma than in establishing one.⁷ This is because airway hyperresponsiveness can be seen in various other disorders, including allergic rhinitis, congestive heart failure, cystic fibrosis, bronchitis, and chronic obstructive pulmonary disease.

INDIRECT CHALLENGE: HYPERTONIC SALINE

The standard hypertonic saline challenge protocol used is the one outlined by the International Study of Asthma and Al-

lergies in Childhood.⁸ Baseline FEV₁ is first established by spirometry. The patient then breathes at tidal volume while hypertonic saline (4.5%) is nebulized at 1.5 mL/min. The exposure time increases from 30 seconds to 1, 2, 4, and then 8 minutes. After each exposure, FEV₁ is recorded. If FEV₁ decreases by 15% or more after inhalation of a provocative dose of 23 g of hypertonic saline or more (PD₁₅, ≤23 g of hypertonic saline) then the test result is considered positive and the test stopped.^{9,10} The provocation time causing a 15% decrease in FEV₁ (PT₁₅) has also been used as an indicator of airway hyperresponsiveness.¹¹

Hypertonic saline is a sensitive (62%) and specific (83%) test for asthma diagnosis. Interestingly, a pediatric study showed sensitivity (83%) to be higher in those who have current atopic asthma, although specificity (60%) is lower in this group.⁹ Another study in 1,107 children found that a continuous measure such as the dose-response slope better addresses the continuous relationship between asthma symptoms and airway hyperresponsiveness than a threshold measure such as PD₁₅.¹⁰

FRACTIONAL EXHALED NITRIC OXIDE

Nitric oxide (NO) is an endogenous regulatory molecule whose synthesis is mediated by nitric oxide synthase (NOS).¹² NOS exists in constitutive and inducible forms. Inducible NOS in the epithelial cells of the bronchial wall is the key source of NO present in the airways of patients with asthma. Most FeNO is derived from the lower airways.¹³ FeNO is measured in exhaled air and is expressed in parts per billion.¹⁴ It is a reliable marker of airway eosinophilic inflammation.¹⁵ There are 2 main ways of measuring NO, online and offline. The online method involves the continuous sampling of exhaled air by the NO analyzer, whereas in the offline method, exhaled air is collected in a reservoir and subsequently analyzed for NO. Expiratory flow rate, respiratory tract infections, certain drugs, caffeine, alcohol, smoking, and other factors can affect FeNO values.¹⁶ Contamination by nasal NO can falsely increase measured levels. In healthy adults exhaled NO concentrations are between 10 and 35 ppb at standardized flow rates of 50 mL/s.¹⁷

CORRELATIONS BETWEEN MEASURES OF CONTROL

Bronchoprovocation and Spirometry

Bronchoprovocation is typically not performed when FEV₁ values are below 70% of the normal predicted value because of patient safety concerns. Thus, few data exist for correlations between lower FEV₁ values and bronchoprovocation results. Furthermore, patients can have a high degree of airway hyperresponsiveness with normal spirometry values.

Methacholine and Hypertonic Saline

Interestingly, the different bronchoprovocation tests may not correlate well with each other. This may be explained in part by the inherent differences in direct and indirect bronchoprovocation challenges. A study of 29 asthmatic patients with

exercise-induced asthma showed no significant correlation between hypertonic saline and methacholine challenges. This may be attributed to the fact that the study used a 20% decrease in FEV₁ as the diagnostic criteria for hypertonic saline as opposed to the usual 15%.¹⁸ A significant correlation was found between hypertonic saline PD₂₀ and exercise-induced asthma symptom scores, whereas such a correlation was not seen with methacholine. Indirect airway challenges, such as hypertonic saline, probably reflect the mechanism of exercise-induced asthma better than a direct challenge.

Although widely used, direct airway challenge models, such as methacholine and histamine challenges, have their limitations.¹⁹ It has been shown that inhaled corticosteroids, the current criterion standard anti-inflammatory treatment for asthma, reduce responsiveness to methacholine only to a small degree.²⁰ On the other hand, airway responsiveness to hypertonic saline challenge correlates better with serum markers of inflammation than airway responsiveness to methacholine,²¹ and it is also more responsive to therapeutic interventions than methacholine.²⁰

FeNO and Bronchoprovocation Tests

Jatakanon et al²² showed a significant correlation between FeNO and methacholine responsiveness in 35 steroid-naïve atopic patients with mild to moderate asthma. This finding may indicate that FeNO or the mechanisms that cause its increase may contribute to airway hyperresponsiveness in asthma, but other studies produced conflicting results. Dupont et al²³ compared this relationship in steroid-naïve vs steroid-treated adults with mild asthma and also found a significant correlation between FeNO and histamine challenge in steroid-naïve adults but not in steroid-treated adults. In this study, there was a mix of atopic and nonatopic asthmatic patients, but no difference was noted between the 2 groups. Two large pediatric studies confirmed the correlation between FeNO and methacholine. Covar et al²⁴ found a significant correlation of FeNO with methacholine challenge testing in the large cohort of 118 children with mild to moderate asthma who participated in the Childhood Asthma Management Program (CAMP) study. Another large multicenter trial of 144 children with mild to moderate asthma also showed a significant correlation between FeNO and methacholine. The participants in this study had discontinued steroid treatment for more than 1 month.²⁵

Contrary to these findings, a study of 32 steroid-naïve atopic children with mild intermittent asthma evaluated the relationship between FeNO and airway hyperresponsiveness. This study showed no correlation between FeNO and PC₂₀ or FEV₁ values.²⁶ In another study of 10 steroid-naïve adult asthmatic patients, baseline levels of FeNO and PC₂₀ did not correlate.²⁷ This lack of correlation has been noted in other results of tests of pediatric and adult asthmatic patients.^{28,29}

These conflicting studies indicate that FeNO levels may not be accurate predictors of the degree of airway hyperresponsiveness. However, both FeNO and the degree of airway

hyperresponsiveness have been shown to correlate with airway inflammation as measured in a variety of ways.^{15,20,25}

FeNO and Spirometry

A consensus report on FeNO found it to be useful for the diagnosis and management of asthma, as well as for monitoring response to therapy.¹⁷ Comparing FeNO and FEV₁ with regard to asthma symptoms, Spergel et al³⁰ studied 30 patients during a 6-month period and showed good correlation between spirometry and clinical symptoms. Since FEV₁ measures airflow obstruction and obstruction manifests as cough, chest tightness, and wheezing, this is expected. Interestingly, there was better correlation between FeNO and symptoms than between FEV₁ and symptoms. This is not as easily explained because FeNO measures airway inflammation and it is not clear how patients may perceive inflammation. Another study of 50 patients with asthma symptoms showed the use of FeNO to be more sensitive than spirometry in diagnosing asthma (77% vs 22%).³¹

A pediatric study by de Meer et al³² also showed that FeNO had a higher positive predictive value (83%) than FEV₁ (33%) for the presence of airway hyperresponsiveness in symptomatic children. However, the authors used a fairly high cutoff value of 43 ppb for FeNO. Negative predictive values of FeNO (90%) and FEV₁ (80%) were comparable. More recently, a pediatric study of 26 children with stable asthma noted that FeNO values better reflected the anti-inflammatory effects of inhaled corticosteroids in asthma compared with sputum inflammatory markers and pulmonary function testing.³³

These studies establish FeNO as a useful test in asthma diagnosis and management. However, as with FeNO and bronchoprovocation, studies have shown conflicting results on whether FeNO and spirometry measurements correlate with each other.

A pediatric study in 37 steroid-naïve patients with mild intermittent atopic asthma measured FeNO, FEV₁, and methacholine PC₂₀ at a single point in time. A significant correlation was found between FeNO and FEV₁. Interestingly, the study described a distinct pattern of allergen sensitivity (almost all patients were sensitized to house dust mite).³⁴ This result was reproduced in another pediatric study in 32 steroid-treated patients with mild to moderate persistent asthma, which showed good correlation between FeNO and both prebronchodilator and postbronchodilator FEV₁.³⁵

However, several large studies have shown a lack of correlation between FeNO and spirometry measurements. The aforementioned study involving the 118 children who participated in the CAMP study showed no correlation between FeNO and FEV₁ before or after bronchodilation.²³ Strunk et al,²⁵ in a large multicenter trial of 144 children with mild-moderate asthma, also saw no correlation between FeNO and FEV₁. The participants in this study had discontinued steroid treatment for more than 1 month. A smaller more recent study of 26 stable asthmatic patients with mild, moderate, and severe disease treated for 3 months with inhaled corticoste-

roids according to their disease severity examined several parameters, including FeNO and FEV₁, measured 3 times during the study period at intervals of 6 weeks. FeNO and FEV₁ did not correlate on any of the 3 evaluation visits.³² Likewise, a negative correlation has been noted in several other studies.^{22,28,35}

Bellamkonda et al³⁶ evaluated 18 patients with asthma with each of these diagnostic modalities. The results showed that these measures did not correlate well with each other.

IMPLICATIONS FOR CLINICAL PRACTICE

Spirometry is critical to both the diagnosis and evaluation of asthma control. Methacholine challenge testing is important in assessing airway hyperresponsiveness and is useful for diagnosis in patients with symptoms suggestive of asthma who have normal spirometry results. A negative result helps exclude asthma. A positive result should be interpreted in light of pretest probability and with caution because methacholine test results can be positive in many other disease states. Hypertonic saline is a sensitive and specific test to diagnose exercise-induced asthma and to evaluate change in airway hyperresponsiveness secondary to medications. FeNO is a reliable marker of airway eosinophilia. It is also effective in assessing response to treatment with corticosteroids. It cannot reliably be used as the only objective test to diagnose asthma, although it can certainly complement other objective data. Furthermore, recent studies have questioned the utility of FeNO for monitoring the control of asthma as well for guiding treatment strategies.^{37,38} Noninvasive investigative modalities that may play an important role in the future include sputum eosinophil measurements and the analysis of

inflammatory mediators in exhaled breath condensate. Currently, these are valuable research tools.

CONCLUSION

A clinical history suggestive of asthma combined with consistent physical examination and spirometry findings are necessary to make an accurate evaluation of asthma. However, there are occasions when these criteria do not align well with each other. In such instances, the physician looks for other objective tests that can help either establish or exclude asthma and evaluate severity and control. Several studies in the recent past that have compared these tools have produced conflicting results. This is not entirely surprising when one considers that these tools measure different aspects of the same disease. A single biomarker of inflammation is not sufficient to reflect the complex inflammatory and noninflammatory mechanisms that contribute to bronchial hyperactivity (Fig 1). Further studies may reveal distinct uses for the various objective tests in asthma care. The optimal diagnosis and management of asthma require the educated use of available objective tests in conjunction with clinical data.

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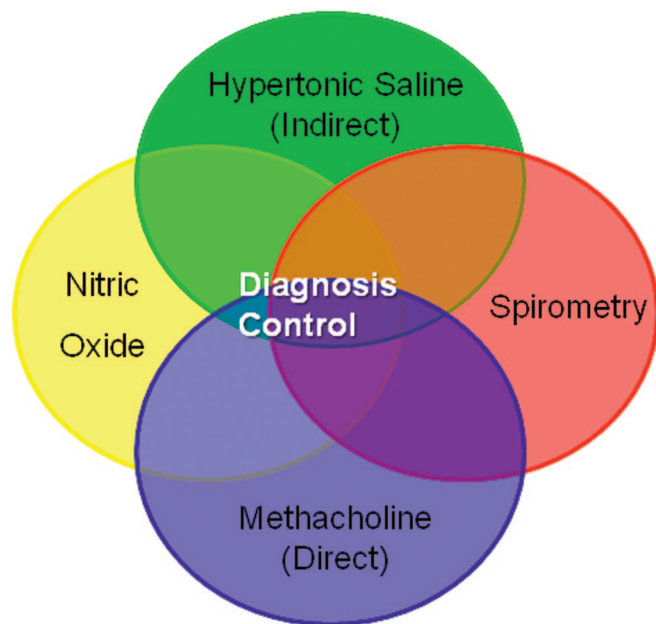


Figure 1. Association among common testing modalities.

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