

A Positive Methacholine Challenge Test in the Absence of Symptoms

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Introduction

A 20-year-old white female nonsmoker presented to the pulmonary function laboratory for a methacholine challenge test. The patient denied wheezing, dyspnea, cough, or chest tightness. In fact, she competes in collegiate basketball and softball without respiratory complaints. She stated that her primary care physician wanted to “screen her for asthma,” because her father is asthmatic. Her medical history was remarkable only for allergic rhinitis. She denied recent or active chest infections. Table 1 shows her baseline spirometry values. She had a substantial bronchospastic response to methacholine inhalation; the provocation concentration (PC₂₀) that caused a 20% decline in forced expiratory volume in the first second (FEV₁) was 3.95 mg/mL.

Questions

Question 1: How should these data be interpreted?

Answer: Asymptomatic airway hyperresponsiveness

Question 2: Are patients with asymptomatic airway hyperresponsiveness just asthmatics with a poor perception of bronchoconstriction?

Answer: No

Question 3: Is asymptomatic airway hyperresponsiveness associated with the development of symptomatic asthma?

Answer: Yes

Question 4: Is the presence of atopy (in this case allergic rhinitis) in patients with asymptomatic airway hyperresponsiveness associated with the development of symptomatic asthma?

Answer: Yes

Question 5: Once it is established that a patient has asymptomatic airway hyperresponsiveness (often described categorically as a “positive methacholine challenge test”), does the PC₂₀ affect the probability of asthma?

Answer: Yes

Discussion

Asymptomatic airway hyperresponsiveness is usually a feature of epidemiologic studies^{1–3} rather than a conundrum of clinical practice, because asymptomatic patients usually do not undergo bronchoprovocation studies. Brand et al¹ challenged 412 middle-age patients with inhaled histamine and found that 80% of those with airway hyperresponsiveness were asymptomatic. Brand et al theorized that patients with asymptomatic airway hyperresponsiveness had episodes of airway obstruction but were poor perceivers of changes in bronchial tone. This theory was subsequently challenged by Salome et al,² who found that, during histamine challenge, the same percentage of patients with asymptomatic airway hyperresponsiveness develop symptoms as do asthmatics. In addition, there was no difference between those groups' median Borg dyspnea scores during histamine challenge. Another important finding of that study was that 68% of the patients with asymptomatic airway hyperresponsiveness who experienced symptoms during histamine challenge reported that they had experienced these symptoms previously. Obviously, this puts into question how many patients with purported asymptomatic airway hyperresponsiveness are truly asymptomatic. Gibson et al⁴ conducted methacholine challenge tests on 12 children with a diagnosis of asymptomatic airway hyperresponsiveness, and found that all of them experienced symptoms during the test, and 2 of them reported that they had felt these symptoms previously. Interestingly, the mean diurnal peak expiratory flow variation was similar between symptomatic asthmatic control subjects and the children with asymptomatic airway hyperresponsiveness. Finally, Laprise and Boulet⁵ found that normals and subjects with asymptomatic airway hyperresponsiveness actually had a better perception of methacholine-induced bronchoconstriction than did asthmatics.

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Table 1. Baseline Spirometry Results

Test	Predicted	Measured	Percent of Predicted
FVC (L)	3.69	3.52	95
FEV ₁ (L)	3.22	3.21	100
FEV ₁ /FVC (%)	87.7	91.1	104
FEF _{max} (L/s)	6.73	6.86	102
T _{tot} (s)	NA	3.0*	NA

*Patient had difficulty exhaling for more than 3 seconds, but a plateau was observed on the volume/time tracing.

FVC = forced vital capacity

FEV₁ = forced expiratory volume in the first second

FEV₁/FVC = ratio of FEV₁ to FVC

FEF_{max} = maximum forced expiratory flow

T_{tot} = total expiratory time

NA = not applicable

Another important question is whether some patients with asymptomatic airway hyperresponsiveness have latent asthma that has yet to clinically emerge. Some studies have shown pathophysiologic similarities between asthmatics and subjects with asymptomatic airway hyperresponsiveness. Laprise et al⁶ found a similar pattern of bronchial epithelial desquamation among asthmatics and subjects with asymptomatic airway hyperresponsiveness. Though to a lesser degree than the asthmatics, subjects with asymptomatic airway hyperresponsiveness had patchy subepithelial fibrosis and an increased number of T lymphocytes and eosinophils in bronchial biopsy specimens than did normal subjects. Airway remodeling with subepithelial fibrosis correlates well with asymptomatic airway hyperresponsiveness in asthmatics.⁷ However, it is important to point out that evidence of airway inflammation does not always accompany asymptomatic airway hyperresponsiveness.^{8,9} In addition to patterns of inflammation, Japanese researchers found a β_2 adrenergic receptor polymorphism that was common to asthmatics and subjects with asymptomatic airway hyperresponsiveness.¹⁰

Though pathophysiologic similarities clearly exist, the clinical question remains: are patients with asymptomatic airway hyperresponsiveness at greater risk of developing symptomatic asthma?

Several studies have shown a relationship between asymptomatic airway hyperresponsiveness and the subsequent development of clinical asthma. Hopp et al¹¹ examined the data from 13 subjects before and after the diagnosis of asthma, who were asymptomatic during their initial examination as participants in an epidemiologic study. Methacholine challenge test showed asymptomatic airway hyperresponsiveness in 10 of the 13 subjects preceding the development of clinical asthma. Laprise and Boulet⁵ studied 30 patients with asymptomatic airway hyperresponsiveness over 3 years and found that, as a group, their PC20 fell significantly, compared to normal and asthmatic

controls. In addition, 14% of the asymptomatic subjects developed symptomatic asthma over the 3-year study period, all of whom were atopic. Laprise and colleagues followed this investigation with a study to assess signs of inflammation in patients with asymptomatic airway hyperresponsiveness.⁶ In that study, 4 of 10 patients with asymptomatic airway hyperresponsiveness developed asthma over the 2-year study period. Patients who developed asthma had a higher mean atopic index (5 on a scale of 0–6) than those who did not develop asthma (mean atopic index 1.3, $p = 0.02$).

Though allergic rhinitis can be a source of a false-positive methacholine challenge test,¹² Braman et al¹³ found that 19% of patients with allergic rhinitis and asymptomatic airway hyperresponsiveness went on to develop asthma. The association between allergic rhinitis and asthma is strong.

In a population study, Linneberg et al¹⁴ found that 100% of subjects with pollen-triggered allergic asthma also had pollen triggered allergic rhinitis. Similarly, all subjects with allergic asthma and sensitivity to animals and mites also had rhinitis exacerbated by these allergens.

In a 23-year follow-up study of freshman students at Brown University, Greisner and colleagues¹⁵ found that 86% of asthmatic subjects also had allergic rhinitis. In most subjects allergic rhinitis emerged either before or at the same time as asthma. In addition, the link between allergic rhinitis and airway smooth muscle is strengthened by evidence that seasonal increase in rhinitis symptoms is associated with lower PC20.¹⁶ Moreover, there is some evidence that treatments aimed at allergic rhinitis may reduce^{17,18} or even prevent¹⁹ the development of bronchial reactivity and asthma.

Not all investigators have found an association between atopy and the development of asthma in patients with asymptomatic airway hyperresponsiveness. In a 2-year study of Chinese children, Zhong et al²⁰ found that 20% of patients with asymptomatic airway hyperresponsiveness developed asthma; however, there was no difference in the atopic index between these patients and matched controls. Moreover, not all studies have found an association between asymptomatic airway hyperresponsiveness and the development of symptomatic asthma. In a study spanning 27 years, de Gooijer et al²¹ found no relation between childhood asymptomatic airway hyperresponsiveness and adult asthma; in fact, asymptomatic airway hyperresponsiveness actually decreased after the initial evaluation. Boulet²² has articulated a theory of how asymptomatic airway hyperresponsiveness may develop and progress to symptomatic asthma. Genetic predisposition, atopy, and bronchial insults (eg, infections, exposure to injurious substances) may trigger airway inflammation and remodeling (eg, subepithelial fibrosis), leading to airway hyperresponsiveness that may initially be asymptomatic. If the inflam-

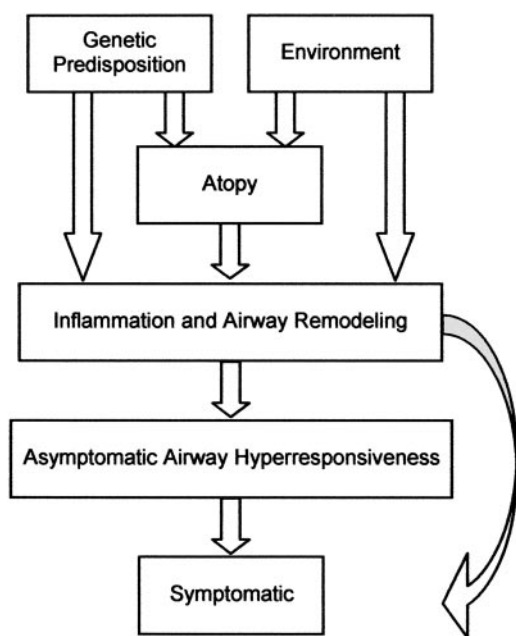


Fig. 1. A theoretical pathway depicting how genetics, atopy, and environmental exposures may trigger airway inflammation and remodeling, which may progress to asymptomatic airway hyperresponsiveness and symptomatic asthma. (Adapted from Reference 22, with permission.)

matory state persists and becomes amplified, symptomatic asthma may emerge (Fig. 1).

The interpretation of a methacholine challenge test and its utility for determining whether the patient has asthma is not as straightforward as we might think. The test result is often categorized as “positive” or “negative,” based on a single PC₂₀ threshold (eg, < 8 mg/mL); however, when Bayes’s theorem is applied to the methacholine challenge test, we find that the post-test probability of asthma for a given PC₂₀ is dependent on the pre-test probability (a priori) of asthma.¹² Though not intended to calculate probabilities in patients, Figure 2 depicts how the pre-test probability of asthma and the PC₂₀ affect the post-test probability of asthma. For example, the patient in this case has 2 significant risk factors for asthma: allergic rhinitis and familial history of asthma. If we assign this patient a 30% pre-test probability of asthma, a PC₂₀ of 8 mg/mL would yield a post-test probability of about 30%, whereas a PC₂₀ of 4 mg/mL would yield a post-test probability of about 70%. This theory was found to apply in the work by Zhong et al,²⁰ which showed that the probability of patients with asymptomatic airway hyperresponsiveness developing asthma was greater if their PC₂₀ was lower.

Asymptomatic airway hyperresponsiveness is common in epidemiologic studies and may occasionally be encountered in clinical practice. Boulet²² theorized that it might be possible to prevent asthma by identifying and treating asymptomatic airway hyperresponsiveness in high-risk (eg,

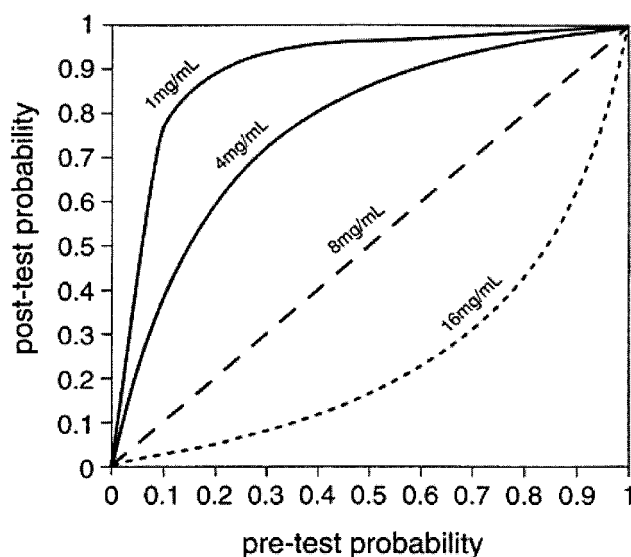


Fig. 2. The relationship of post-test probability of asthma to pre-test probability of asthma, with 4 different PC₂₀ (provocation concentration that causes a 20% decline in forced expiratory volume in the first second) values. These curves are only intended to illustrate basic principles of interpretation and should not be used to calculate probabilities with patients. (From Reference 12, with permission.)

atopic, familial asthma) asymptomatic patients. The patient described in this case was a healthy asymptomatic collegiate athlete—hardly the type of subject that would create much suspicion of underlying asthma. However, she arrived at the pulmonary function laboratory with 2 risk factors (allergic rhinitis and family history of asthma) and left with a third (airway hyperresponsiveness). It is certainly conceivable that this patient had underlying bronchial inflammation that had yet to be expressed as symptomatic asthma. Asymptomatic airway hyperresponsiveness appears to be a risk factor for the development of asthma; however, screening patients with bronchoprovocation studies to try to predict future asthma cannot be recommended at this time, because the predictive values of such testing is low.^{23,24}

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