

Is methacholine challenge sufficient to rule out bronchial hyperresponsiveness in patients with suspected asthma?

Bronchial provocation challenges may be useful for establishing a definitive diagnosis of asthma in individuals with compatible symptoms and normal pulmonary function test results.¹ The methacholine challenge is the most commonly performed test. Because of the high sensitivity and negative predictive value of the methacholine challenge, a negative result practically excludes current asthma with reasonable certainty.² However, recent data show that challenges with indirect stimuli (eg, adenosine) associate better with airway inflammation³ and may be ideal for confirming bronchial hyperresponsiveness due to their high specificity.

Airway inflammation may be easily and rapidly assessed by measuring the fraction of exhaled nitric oxide (FeNO) using the standardized procedure,⁴ and although there is some discrepancy among studies, its upper normal limit is between 25 and 30 ppb.⁴ The updated version (2009 edition) of the Spanish Guideline on the Management of Asthma acknowledges the importance of FeNO as an inflammation marker and recommends considering the diagnosis of asthma in steroid-naïve patients with suggestive symptoms and FeNO values of 30 ppb or higher.⁵

The aim of this study was to establish to what extent performing an additional inhalation challenge with adenosine is necessary in patients with suspected asthma who had a negative methacholine challenge result in function of their airway inflammation status assessed by FeNO.

Thirty patients (13 males; mean age, 37.3 years; age range, 13–69 years) were consecutively recruited among those reporting persistent asthma-like symptoms (shortness of breath, wheezing, cough, and chest tightness). Inclusion criteria were normal spirometric parameters, negative bronchodilator test result (after inhalation of a metered-dose inhaler of 400 µg of salbutamol), and negative methacholine challenge result (provocative concentration inducing a 20% decrease in forced expiratory volume in 1 second [PC₂₀] of >16 mg/mL).⁶ Exclusion criteria were those previously described for bronchial challenge tests.^{6,7} Written informed consent was obtained before the challenges. Asthma medication was withdrawn before the challenges, as described elsewhere.^{6,7}

In all study participants, FeNO (NIOX MINO; Aerocrine; Solna, Sweden) was measured, thus dividing them into 2 groups: group 1 (FeNO ≥30 ppb; 23 patients) and group 2 (FeNO <30 ppb; 7 patients). They also completed the validated Spanish version⁸ of the Asthma Control Test (ACT). Demographics and clinical information regarding smoking habit, body mass index, personal history of rhinitis, presence of atopy (defined as one or more positive skin prick test results with common aeroallergens), and current treatment were recorded for both groups.

One week after the methacholine challenge, adenosine challenge was performed in all patients.⁷ The adenosine challenge result was regarded as positive when the PC₂₀ was 400 mg/mL or less.⁷ Both methacholine and adenosine were performed using the dosimeter method.⁶ Comparisons between the groups were performed using the nonparametric Mann-Whitney test. Categorical variables were compared using the χ^2 test. $P < .05$ was considered significant. All tests were performed using SPSS statistical software,

Table 1

Comparison of Variables Between the 2 Groups^a

Variable	Group 1, No. (%) (n = 23)	Group 2, No. (%) (n = 7)
Smoking		
Yes	2 (8.7)	1 (14.3)
No	21 (91.3)	6 (85.7)
Atopy		
Yes	17 (73.9)	5 (71.4)
No	6 (26.1)	2 (28.6)
Rhinitis		
Yes	16 (69.5)	3 (42.8)
No	7 (30.5)	4 (57.1)
Positive adenosine challenge result	6 (26)	0

^aThe mean (range) Asthma Control Test scores were 21 (15–24) and 23.71 (22–25) in group 1 and group 2, respectively ($P = .01$).

version 11.0 (SPSS Inc, Chicago, Illinois).

All the patients from group 2 had a negative adenosine challenge result (PC₂₀ >400 mg/mL), whereas in group 1, 6 of 23 patients (26%) exhibited a positive result (geometric mean PC₂₀, 35.56 mg/mL; range, 7.5–294.8 mg/mL). Four of these 6 patients were atopic and also had rhinitis.

No statistically significant differences were found between the 2 groups for the following variables: age, sex, smoking, body mass index, concomitant rhinitis, presence of atopy, and current treatment (Table 1). The only significant difference was the ACT score, which was lower in group 1.

In our study, asthma was eventually confirmed by a positive adenosine challenge result in 20% of all the suspected cases and in 26% of the patients with FeNO values of 30 ppb or higher and lower ACT scores. The FeNO of the 6 patients diagnosed as having asthma by means of adenosine challenge was increased when compared with the rest (mean, 87.5 ppb [range, 32–191 ppb] vs 62.5 ppb [range, 16–298 ppb]), as expected in patients who respond to indirect stimuli.

Because we used the dosimeter method, the deep inhalations may have induced a decrease in the sensitivity of the methacholine challenge.² Even though the issue of deep inhalations and indirect challenges has not been properly studied, indirect challenges are considered to be less affected by deep inhalations than the direct ones,² and this could be an alternative explanation of why a small number of patients with negative methacholine challenge results but with present airway inflammation had a positive adenosine test result.

The fact that no differences were found in the clinical characteristics of the patients in the 2 groups could be due to the sample size; nevertheless, our study confirms that, when diagnosing asthma in clinical practice, methacholine and adenosine are complementary but not interchangeable.

In conclusion, in patients with asthma-like symptoms who have a negative methacholine challenge results but FeNO levels of 30 ppb or higher, we recommend performing an adenosine challenge before definitely ruling out asthma.

Acknowledgments

Dr Calderon and Dr Guillén contributed equally to this work. We thank Elia Perez, PhD (Department of Biostatistics in Medicine, Hospital Universitario La Paz) for statistical assistance.

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