
Complementary roles of capsaicin cough sensitivity test and induced sputum test to methacholine bronchial provocation test in predicting response to inhaled corticosteroids in patients with chronic nonproductive cough

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Background: The capsaicin cough sensitivity test (CCST), methacholine bronchial provocation test (MBPT), and induced sputum test (IST) are widely used in the clinical evaluation of chronic nonproductive cough. However, little is known about their roles in predicting response to inhaled corticosteroids (ICSs) in patients with chronic nonproductive cough.

Objective: To test the hypothesis that the CCST and IST play complementary roles to the MBPT for predicting the response to ICS treatment in patients with chronic nonproductive cough.

Methods: A total of 43 patients with chronic nonproductive cough who showed isolated capsaicin cough hypersensitivity (CCST group) and 55 patients with chronic nonproductive cough who had methacholine airway hyperresponsiveness (MBPT group) were enrolled. These patients underwent the IST followed by treatment with ICSs for 4 weeks. Measurement of symptom improvement was recorded by the visual analog scale.

Results: The response rates to ICS treatment in the CCST and MBPT groups were similar (74.5% vs 86.0%; $P = .21$). Only the neutrophil count in the IST group was significantly different in responders and nonresponders after the ICS treatments ($P = .005$ for the CCST group and $P = .006$ for the MBPT group). Interestingly, the absence of sputum neutrophilia used as a criterion for subgroup analysis increased response rates in the patients with either methacholine airway hyperresponsiveness or capsaicin cough hypersensitivity.

Conclusions: In the present study, we demonstrate that CCST and IST play complementary roles to MBPT. By combining the results of these tests, we are able to identify more patients with chronic nonproductive cough and treat patients more successfully with ICSs by improving the response rate to ICS treatment.

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INTRODUCTION

Recent advances in the understanding of the pathophysiology of human cough have revealed that airway inflammation is a common underlying feature of all the main causes of cough.^{1,2} In accordance with these findings, inhaled corticosteroids (ICSs), which are potent anti-inflammatory agents, are often

used empirically in clinical practice when patients first present with a chronic nonproductive cough.

For recognition, clinical evaluation, and treatment of chronic nonproductive cough, the capsaicin cough sensitivity test (CCST), methacholine bronchial provocation test (MBPT), and induced sputum test (IST) are widely used. However, methacholine airway hyperresponsiveness (AHR) is known to reflect airway inflammation insufficiently.³ Furthermore, it has been reported that the presence of AHR in children with recurrent cough is not related to response to ICS treatment.⁴ On the other hand, the IST has been extensively studied and validated as a measure of airway inflammation.^{5,6} Observation of inflammatory cells in induced sputum is a useful measure for predicting the response to ICS treatment in a variety of pathologic conditions.^{7–9} However, the IST requires adequate sputum and time for processing and specific concerns for the safety of the procedure.¹⁰ These factors are significant barriers to the implementation of this test in clinical practice.

Enhanced cough sensitivity in response to inhaled capsaicin has been demonstrated in numerous conditions that cause

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chronic nonproductive cough.^{11–13} The cough reflex at sensory (afferent) levels is known to be enhanced by inflammation through a variety of mechanisms. These mechanisms include increase of tussive mediators such as histamine or prostanoids,^{14,15} increase of neuropeptides such as substance P or calcitonin gene-related peptide,^{16,17} and reduced pH or chloride levels.^{18,19} These findings collectively suggest that the CCST may reflect airway inflammation, which is a common underlying feature of all the main causes of cough^{1,2} as discussed earlier, and thus have a role in predicting the response to ICS treatment in patients with chronic nonproductive cough. Importantly, a recent investigation revealed that airway hyperreactivity and cough sensitivity in cough variant asthma were not always related and its different expression could be modulated by different inflammatory mechanism.²⁰ This observation also implies the complementary role of CCST in chronic cough management. In the present study, we tested the hypothesis that the CCST and IST play complementary roles to MBPT for predicting the response to ICS treatment in patients with chronic nonproductive cough.

METHODS

Study Participants

Participants for this study were recruited from patients referred to Seoul National University Hospital with nonproductive cough persisting for more than 3 weeks as their sole respiratory symptom. They had normal chest radiography and pulmonary function test results and no signs or symptoms associated with postnasal drip, sinusitis, or gastroesophageal reflux. Patients with a history of pulmonary disease, current smoking, systemic disease, or upper respiratory tract infection within the preceding 8 weeks or those taking angiotensin-converting enzyme inhibitors were excluded. No patient produced audible wheezing or rhonchi on chest auscultation, even at forced expiration. No patient had ever taken systemic or inhaled bronchodilators, corticosteroids, cromoglycate, or other antiallergic agents. This study was approved by the institutional review board at the Seoul National University Hospital, and informed consent was obtained from all patients.

Study Design

At the first visit, each patient underwent a standard clinical evaluation that consisted of physical examinations, completion of a medical questionnaire about demographic factors, duration of cough, frequency of cough, and laboratory tests, including skin prick test to 55 common inhalant allergens (Allergopharma, Hamburg, Germany), chest radiography, and spirometry. If signs or symptoms associated with sinusitis or gastroesophageal reflux were observed, paranasal sinus radiography, 24-hour esophageal pH monitoring, or a trial of treatment with a proton pump inhibitor was performed, and patients with abnormal findings or responders to treatment were excluded. At the second visit, all of the patients underwent MBPT 1 hour after CSST on the same day, and on the

following day, sputum induction was performed to evaluate the sputum cell count. A previous report showed that MBPT and CCST (and even sputum induction) could be performed on the same day without significant interaction.²¹ Then, treatment with ICSs (250 µg of fluticasone twice daily as Flixotide discus; GlaxoSmithKline, Bredtfred, England) for 4 weeks was initiated.

Measurements

Cough severity was rated on a 100-mm horizontal visual analog scale (VAS), with 0 representing no cough and 100 the worst cough ever. Cough frequency was graded as I (1 episode per week), II (2 to 3 episodes per week), III (daily episodes but duration of cough was less than 1 hour per day), IV (daily episodes and duration of cough was more than 1 hour per day), and V (all day long without cessation). Grades IV and V were classified as frequent cough. A positive skin test response was defined when the mean diameter of the wheal formed by an allergen was greater or equal to that of the wheal formed by histamine. Atopy was defined to be present if a patient exhibited a positive skin test response to any 1 or more of the 55 aeroallergens. AHR was measured by a modified method based on that of Chai et al.²² In brief, concentrations of 0.5, 1, 2, 4, 8, and 16 mg/mL of methacholine were prepared by dilution with buffered saline. A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, MD) was used to deliver aerosols generated by a nebulizer (DeVilbiss, Carlsbad, CA). Patients inhaled 5 inspiratory capacity breaths of increasing methacholine concentrations until either a decrease of 20% or more in forced expiratory volume in 1 second (FEV₁) was obtained or 16 mg/mL of methacholine was reached. Results were expressed as the provocative concentration of methacholine causing a 20% decrease in FEV₁ from the baseline value (PC₂₀), and methacholine AHR was defined as a PC₂₀ that was lower than 16 mg/mL. Cough sensitivity was evaluated by the CCST using a modified version of the methods described by Fujimura et al.,²³ which was proved to measure cough sensitivity effectively by many investigators, although methods for the CCST have not been standardized.^{13,20,24} Patients inhaled, at just below their functional residual capacity, doubling concentrations of capsaicin (2.5 to 500 µM). The process proceeded in a sequential order at 1-minute intervals via a nebulizer attached to a breath-activated dosimeter delivering 8 µL. The number of coughs in response to each concentration was counted and recorded. The challenge was stopped when the concentration elicited 5 coughs or the highest dose of capsaicin was reached. Cough sensitivity was expressed as the lowest concentration of capsaicin that provoked 5 consecutive coughs (C5), and capsaicin cough hypersensitivity was defined as a C5 lower than 16 µM. In a previous study, we proved that this value was an optimal cutoff for cough hypersensitivity in Korean adults.²⁵ Sputum induction was performed as follows. After measurement of basal FEV₁, all study participants were pretreated with 200 µg of albuterol (Ventolin, GlaxoSmithKline, Bredtfred, En-

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