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Capsaicin cough threshold test in diagnostics

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KEYWORDS
Capsaicin;
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Single-breath method;
Threshold test

Summary
Background: Among patients with chronic unexplained cough, there is a recognized subgroup with respiratory symptoms induced by environmental irritants like chemicals and odours. The diagnosis of sensory hyperreactivity (SHR) has been suggested for this group of patients and can be made using a tidal breathing capsaicin inhalation test. The aim of the present study was to evaluate the ability of a single-breath, dose-response capsaicin threshold test to discriminate such patients from control subjects.
Methods: A total of 46 patients with chronic cough and SHR who had previously shown a positive reaction in accordance with limits set for a tidal breathing capsaicin test were tested once with a single-breath, dose-response capsaicin cough threshold test, assessing capsaicin concentrations to evoke 2 (C2), 5 (C5) or 10 (C10) coughs. Twenty-nine subjectively healthy control subjects were also included and tested with the threshold method.
Results: Patients had significantly lower C2, C5 and C10 in comparison to controls. From the results among patients and controls, sensitivity and specificity were calculated, and a receiver operating characteristic curve was constructed, showing excellent ability for C5 and C10 to discriminate patients from control subjects.
Conclusions: For patients with SHR and chronic cough, capsaicin cough sensitivity was once again confirmed to be increased, in this case, using the single-breath dose-response method. Limits set for cough reactions regarded as more sensitive than normal can be useful in diagnostics and further research. C5 seems to be the best measure to use in research and differential diagnostics.

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Background

Inhaled capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) has long been used to induce cough in a safe and dose-dependent manner, and the degree of induced cough reflects the reactivity of sensory C-fibres in the respiratory mucosa [1—4]. In cough research the use of capsaicin has been important, and has good short- and long-term reproducibility [5—12]. The most commonly used method to assess capsaicin cough sensitivity is the single-breath dose-response method: Doubling doses are given at 1-min intervals to assess the cough thresholds, stating the concentration of capsaicin causing 2 (C2), 5 (C5), or 10 or more (C10) coughs during the 1-min period between each dose. This single-breath method is recommended in the European Respiratory Societies (ERS) guidelines [13], and some studies suggest that C5 is the clinically superior value [6].

It has been suggested that patients with upper and lower airway symptoms induced by odours and chemicals, such as flower scents, perfume, cleaning agents, car exhaust fumes and tobacco smoke, suffer from airway sensory hyperreactivity (SHR) [5]. Common symptoms are cough, hoarseness, difficulty in getting air, rhinorrhoea, and eye irritation. Most of these patients could also be diagnosed with chronic cough, having coughing that persists for more than 8 weeks [4,11]. The symptoms may be misinterpreted as asthma and/or allergy, except that the clinical picture shows no bronchial obstruction or IgE-mediated reactions. Such patients are often diagnosed as having idiopathic or unexplained chronic cough, and might also be included in the newly established *cough hypersensitivity syndrome* [14—18]. In a recent report there was a high degree of agreement among opinion leaders as to the concept that cough hypersensitivity underlies the aetiology of chronic cough in the majority of patients [19].

Stimulation of the unmyelinated C-fibres of the trigeminal and vagal nerves is likely involved in chemical-induced airway symptoms [20,21]. In line with the hypothesis of SHR, these patients react to inhaled capsaicin with more coughing and other symptoms than healthy individuals and asthmatic patients, and the reactions can be blocked by preinhalation of a local anaesthetic [5,22]. The suggested diagnosis of SHR can, together with pronounced airway symptoms from scents and chemicals, be assessed using a standardized capsaicin inhalation test to identify patients and to differentiate between healthy subjects, patients with asthma and those with SHR [23,24]. In this test, incremental concentrations of capsaicin are inhaled to induce coughing using a tidal breathing method, and limits for the number of coughs in a normal reaction are set. This capsaicin inhalation test has shown good reproducibility using a simple device for tidal breathing (Pari Boy or Maxin MA3), and no influence on lung function has been found [5,23,24]. However, for research purposes, and in clinics with access to more sophisticated nebulizer systems, the single-breath method may have advantages, giving more specified data on delivered aerosol and being in accordance with ERS guidelines. In this study we aimed to evaluate the extent to which capsaicin inhalation testing in conjunction with the single-breath dose-response method can distinguish patients with chronic cough and SHR from healthy control subjects.

Methods

Patient group

The study group included 46 non-smoking patients, 41 women and 5 men, 21—74 years of age (mean 56 years). They were referred to an asthma and allergy outpatient clinic because of cough and airway symptoms suggestive of asthma or allergy. The patients were screened using a questionnaire on airway symptoms and on symptoms in response to environmental irritants, and all had a history of at least two years of coughing and pronounced upper and/or lower airway symptoms induced by irritants like chemicals and scents. They had within the previous five years had positive reactions to a capsaicin inhalation test administered with the tidal breathing method according to the method described by Johansson et al. [23], and were diagnosed as having SHR as an explanation for their airway symptoms. All patients had negative skin-prick test results when tested with a standard panel of 10 allergens in sources common to Sweden and had also undergone a methacholine test within the previous five years. The methacholine test was performed in accordance with international guidelines [25] and was negative for all patients, indicating the absence of bronchial asthma.

The patients were asked to take no medication for at least 4 h, and no long-acting β2-agonists for at least 72 h, prior to the inhalation tests.

Control group

The control group consisted of 29 non-smoking, subjectively healthy individuals, 25 women and 4 men, 27—66 years of age (mean 52 years). They were also screened using questions on airway symptoms and on symptoms in response to chemicals and scents. None had a history of asthma, allergies or airway symptoms in response to environmental irritants, and none was taking any medication for the airways.

Study design

Each participant visited the clinic once and was tested with a single-breath capsaicin provocation. The cough thresholds of the study participants were registered manually during the provocations. Cough was defined as the characteristic sound that follows a forced expiratory effort against a closed glottis and distinguished from other sounds such as clearing the throat [13,26], by a discretionary decision of the investigator upon observation of the subjects. The total time for each provocation was about 15 min.

Provocations were not carried out on subjects who had experienced respiratory infections in the past month.

The participants could not be using angiotensin-converting enzyme inhibitors or any medication for gastro-oesophageal reflux. Pregnancy and breastfeeding were exclusion criteria.