

ENVIRONMENTAL DETERMINANTS

Sensitivity to Environmental Irritants and Capsaicin Cough Reaction in Patients with a Positive Methacholine Provocation Test before and after Treatment with Inhaled Corticosteroids

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Background. Increasing evidence points to a potential role for members of the transient receptor potential family of cation channels on several features of asthmatic disease. The cough sensitivity to inhaled capsaicin is known to reflect the reactivity of these airway sensory nerves. **Objective.** The aim was to study, among patients having a positive methacholine provocation and diagnosed with asthma, capsaicin cough sensitivity, sensitivity to methacholine, and levels of exhaled nitric oxide before and after treatment with inhaled steroids, and further, to measure the self-reported impact from environmental irritants. **Methods.** Eighteen steroid-naïve patients with a positive methacholine test underwent capsaicin inhalation provocation on two occasions, before and after regular use of inhaled steroids over at least 3 months. Comparisons were made to 21 healthy controls. Sensitivity to methacholine and levels of exhaled nitric oxide were measured before and after the treatment. The participants also answered a validated questionnaire regarding environmental irritants. **Results.** The patients displayed higher capsaicin cough sensitivity than the controls before the treatment period, but not afterward. Before treatment, capsaicin cough answer correlated significantly with levels of exhaled nitric oxide, but not with methacholine sensitivity. After treatment with inhaled corticosteroids, the capsaicin cough sensitivity and the inflammatory parameters were normalized. In comparison to the control group, the patients reported more affective reactions to and behavioral disruptions induced by environmental irritants. **Conclusions.** In steroid-naïve patients with a positive methacholine test, there is a link between that part of the airway inflammation that is reflected by exhaled nitric oxide and that followed by an augmented reactivity of capsaicin-sensitive sensory nerves. This association disappears after steroid treatment.

Keywords asthma, capsaicin, environmental irritants, hyperresponsiveness, sensory hyperreactivity

INTRODUCTION

Bronchial asthma as a disease is characterized by an underlying inflammation that in recent decades has been the main target for pharmacological treatment and the focus of intensive research activity (1, 2). However, the link between the inflammatory cascade of asthma, causing bronchial hyperreactivity, and the axon reflex of bronchoconstriction remains unclear (3). Increasing evidence points to a potential role for members of the transient receptor potential (TRP) family of cation channels on several features of asthmatic disease (3–5).

The TRP channel receptor vanilloid subunit 1 (TRPV1) is activated not only by capsaicin, the pungent ingredient in chili, but also by different noxious stimuli, as well as heat, lipids, and protons (6, 7). It is regarded as an integrator of the thermosensitive members of group I of the TRP family (7, 8). An increased expression of TRPV1 is found in several conditions characterized by general hypersensitivity, such as thermal hyperalgesia, esophagitis, and chronic cough (9–12). There is a growing body of evidence that sensory nerves may mediate many of

the symptoms in asthma patients and that, in the future, TRP antagonists may be useful in the treatment of asthma (4, 13). With respect to the role of capsaicin as an indicator of TRP sensitivity, studies of capsaicin cough sensitivity and the influence of anti-inflammatory treatment on the capsaicin-induced cough may contribute to our knowledge of this aspect of the asthma pathophysiology.

It is a common clinical experience that patients with asthma complain of airway symptoms provoked by environmental irritants like chemicals and scents, although few studies can confirm such connections (14). Some studies have found increased capsaicin cough sensitivity in asthma patients (15,16), whereas other studies have failed to detect this phenomenon (17–20). In most studies of capsaicin-induced cough in asthma patients, the patients were being, or had recently been, treated with inhaled corticosteroids (ICS). In cough-variant asthma, a few studies report that treatment with a leukotriene receptor antagonist or ICS proved to decrease capsaicin cough sensitivity (21,22). No relation has been found between capsaicin cough sensitivity and sensitivity to histamine or methacholine (16,17,19,23).

The Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SHR) was developed to quantify self-reported affective reactions to and behavioral disruptions by odorous/pungent substances (24). The 11 items of the CSS-SHR were found to generate

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approximately normal distributions, have good test–retest reliability, have good internal consistency and predictive and concurrent validity, and be unidimensional. The metric properties were satisfying despite the few items. In a random general population of adults, the prevalence of such problems, defined as a CSS-SHR score ≥ 43 , has been determined to be 19% with an increased risk for female gender (odds ratio = 2.3) (25).

The main aim of this study was to clarify whether capsaicin cough sensitivity in steroid-naïve patients with a positive methacholine provocation differs from that in healthy subjects and to measure any possible influence of ICS on the capsaicin cough response. Another aim was to relate capsaicin sensitivity to methacholine sensitivity and to fraction of nitric oxide in the exhaled air (FE_{NO}) before and after treatment with ICS. The final aim was to measure the affective and behavioral consequences by environmental irritants in patients with a new diagnosis of asthma.

METHODS

Study Participants

This prospective study included 18 consecutively chosen patients, 9 women and 9 men, aged between 18 and 60 years, with a median age of 35 years (95% confidence interval [CI]: 25–44).

The patients were recruited from January 2007 to March 2009. Because of lower respiratory symptoms, they had been referred from primary healthcare or hospital clinics to an allergy and asthma outpatient clinic at the Sahlgrenska University Hospital in Gothenburg, Sweden. During this period, approximately 400 patients per year were referred to the clinic due to lower airway symptoms. Only steroid-naïve patients with a positive methacholine provocation were consecutively invited to take part in the study.

Additional inclusion criteria were that the patients had to be non-smokers and otherwise healthy, and the exclusion criterion was treatment during the past year with steroids (oral, nasal, injection, or inhalation steroids), leukotriene antagonist, angiotensin-converting enzyme inhibitors, or tricyclic antidepressants. The patients were all prescribed ICS on a regular basis by the doctor they had first met at the allergy and asthma clinic. The doctors in the clinic were informed in advance of the study and its purpose, and they were asked to invite steroid-naïve patients with a positive methacholine provocation test to participate. The physicians were not influenced in the choice of prescribed ICS. Three of the patients also had symptoms of rhinitis and two were prescribed nasal steroids as well. None had a history of pronounced cough or wheezing, but described more diffuse symptoms of “heavy breathing” and “difficulty getting air,” especially in relation to exercise and airway infections. All patients were given the diagnosis of asthma, but no further classifications in this regard were done and no testing of induced sputum was performed. None of the patients had a history of gastroesophageal or laryngopharyngeal reflux disease. Provocations were not carried out in subjects who had experienced respiratory infections during the previous month. No tests were performed during the pollen season. Pregnant women and breastfeeding mothers were excluded. Demographic data, data on cough symptoms, skin-prick test (SPT), lung function, methacholine tests, levels of FE_{NO}, and chosen ICS are given in Table 1.

The control group consisted of 21 subjectively healthy non-smoking subjects (12 women and 9 men) aged between 25 and 54 years, with a median age of 41 years (95% CI: 30–49). They were screened using questions on airway symptoms and symptoms in response to chemicals and scents. None of the controls had a history of allergy or symptoms in response to chemicals, scents, cold air,

TABLE 1.—Demographic baseline data and data on cough symptoms, skin-prick test, lung function, and chosen ICS in 18 patients with diagnosed asthma and a positive methacholine test.

Subject number	Sex	Age (years)	Cough symptoms	SPT	PD20	FEV ₁ (% predicted)	FE _{NO}	Treatment with ICS
1	F	27	Monthly	+ ^{a,b}	0.22	106	mv	Budesonide 400 µg × 1
2	F	44	Never	–	0.07	100	<5	Budesonide 200 µg × 2
3	F	22	Daily	+ ^{a,b}	0.07	109	83	Budesonide 200 µg × 2
4	M	19	Never	+ ^{a,b,c}	0.05	98	41	Fluticasone 250 µg × 2
5	F	47	Daily	–	0.22	105	40	Budesonide 400 µg × 1
6	M	33	Monthly	+ ^a	0.7	85	18	Budesonide 200 µg × 2
7	M	24	Weekly	+ ^a	0.6	80	mv	Budesonide 400 µg × 2
8	M	25	Monthly	+ ^{a,b}	1.22	109	31	Budesonide 200 µg × 1
9	F	60	Weekly	–	0.15	96	mv	Fluticasone 100 µg × 2
10	M	50	Monthly	–	1.01	95	79	Budesonide 400 µg × 1
11	M	28	Never	+ ^{a,b}	0.2	107	49	Budesonide 200 µg × 1
12	F	45	Weekly	+ ^{a,c}	0.15	113	14	Beclomethasone 200 µg × 2
13	F	18	Never	+ ^b	0.03	102	115	Budesonide 400 µg × 1
14	F	25	Monthly	+ ^{a,b}	0.22	88	11	Budesonide 200 µg 2 × 2
15	M	38	Weekly	+ ^{a,b,c}	0.1	108	21	Budesonide 400 µg × 2
16	M	36	Weekly	–	0.09	111	55	Budesonide 200 µg 2 × 2
17	F	44	Never	–	0.19	85	8	Budesonide 400 µg × 2
18	M	37	Never	+ ^b	0.06	102	22	Fluticasone 100 µg 2 × 2

Note: SPT, skin-prick test; mv, missing value.

^aPollen, ^bfurred animals, ^cmite

allergy, or asthma. No further medical examination was performed.

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all patients at the start of the investigation, and the Regional Ethics Review Board of Gothenburg, Sweden, approved the study.

Protocol

After the first appointment with a doctor at the clinic and a following visit, which included an SPT and methacholine provocation, each patient visited the clinic three more times. A capsaicin provocation test was performed before starting use of ICS. After at least 3 months of ICS treatment with a median use time of 3 months (95% CI: 3–5), the methacholine test and the capsaicin test were repeated, with at least 1 week in between.

FE_{NO} was recorded before both capsaicin provocations. All patients filled out the CSS-SHR questionnaire (24) before their first capsaicin provocation and then once more before the second capsaicin provocation.

The control subjects were only tested at one occasion with a capsaicin provocation, and they also filled out the CSS-SHR questionnaire.

SPT

An SPT was routinely performed at the patients' first visit to the clinic, testing 10 of the most common respiratory allergens in Sweden (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Aspergillus fumigatus*, *Cladosporium*, dog, cat, horse, timothy, mugwort, birch).

Methacholine Provocation Test

As a part of asthma investigation, a methacholine provocation test was performed, administered in accordance with international guidelines (26,27). Methacholine was prepared from a stock solution of 128 mg/mL (0.656 mmol/mL). Aqueous provocation solutions of 32, 8, 2, 0.5, and 0.125 mg/mL were prepared from this stock solution by dilution with 0.9% saline. The test was carried out using an air-driven compressor (Pari Boy, type 038, Paul Ritzau Pari-Werk KG, Germany) controlled by a breath-activated dosimeter system (Spira dosimeter, Spira Respiratory Care Centre Ltd., Hameenlinna, Finland). The dosimeter time for each breath was 0.6 sec, the flow to be reached was 0.5 L/sec, and the inhalation volume 1.5 L. To prevent incorrect inhalations, the device gave a red light signal if the inspiratory flow rate was too high. A nose clip was used. The patients inhaled two or four breaths every 5 min, receiving doubling doses of methacholine until a provocation concentration causing a 20% fall in forced expiratory volume in 1 second (FEV₁) was reached. FEV₁ was recorded 30 and 90 sec after each provocation step. PD20 (the methacholine dose causing a 20% fall in FEV₁) was calculated by the following formula:

$$PD20 = \frac{\text{antilog} [\log C1 + (\log C2 - \log C1) (20 - R1)]}{(R2 - R1)}$$

Where

C1 = the second highest given dose;

C2 = the highest given dose;

R1 = % reduction of FEV₁ after C1;

R2 = % reduction of FEV₁ after C2.

When PD20 was reached from <2.6/mg methacholine, the test was classed as positive. The limit for a positive test was based on a large series of methacholine provocations in comparison to an earlier used method (28).

Measurement of Exhaled NO

Levels of FE_{NO} were measured in accordance with ATS/ERS recommendations (29) with NIOX MINO (Article no. 03-1000, Aerocrine AB, Stockholm, Sweden). FE_{NO} was measured during a slow single exhalation against an oral pressure of 5 cmH₂O at an exhalation flow rate of 47.5–52.5 mL/sec. The mean concentration in parts per billion (ppb) during the plateau phase was registered.

Capsaicin Provocation

Three concentrations of capsaicin (0.4, 2.0, and 10.0 µmol/L) were prepared from a stock solution of capsaicin (1 mmol/L in ethanol [99.5%]; Sigma-Aldrich Sweden AB, Stockholm, Sweden) in accordance with a previous study (30). Capsaicin was nebulized (Pari Boy 36, type 37.0130; Paul Ritzau Pari-Werk GmbH, Starnberg, Germany) and inhaled through a mouthpiece (Pari Inhalierboy, No. 36.75) by tidal volume breathing; nose clip was not used. The patients inhaled each concentration for 6 min, followed by 4 min rest. Thus, there was an interval of 10 min between each concentration. The number of coughs was counted during the inhalation and the rest period (30). Out of consideration for the patients, provocation was stopped if one concentration of capsaicin provoked more than 50 coughs. FEV₁ was measured before and after each provocation. In accordance with dose–response relationships seen in several earlier studies using the same capsaicin provocation model (18, 19, 31, 32), the missing data for those patients whose provocations were halted due to excess coughing were filled in by doubling the number of coughs evoked by 2.0 µmol/L capsaicin to represent the cough response to 10.0 µmol/L capsaicin.

Cough registration was performed manually during the capsaicin provocations, by the same investigator in all cases. Cough was defined as the characteristic sound that follows a forced expiratory effort against a closed glottis and is distinguished from other sounds such as clearing the throat (33, 34).

CSS-SHR

The CSS-SHR questionnaire was developed to quantify self-reported affective reactions and behavioral disruptions due to odorous/pungent substances (24). Selected from among a larger number of items about odor intolerance, the CSS-SHR consists of 11 statements/questions (Table 2) that are particularly sensitive for discriminating patients with sensory hyperreactivity (SHR) from controls. The unweighted sum of all 11 items makes up the individual's total CSS-SHR score (ranging from 0 to 54 points; a high score indicating severe odor intolerance and ≥ 43 points is regarded as a cut-off value).

Statistical Analysis

The Mann–Whitney *U*-test was used for non-paired data and the Wilcoxon signed-rank test was used for paired data. Correlations were tested with linear regression. Data are presented as medians with 95% CIs. Results were considered significant if $p < .05$. All data were analyzed using version 13.0 of the SPSS software package (SPSS, Inc., Chicago, IL, USA).

RESULTS

SPT

Patients with a positive SPT ($n = 12$) did not differ from those with a negative SPT ($n = 6$) in any respect.

Methacholine Provocations

Median FEV₁ before the first methacholine provocation was 102% of predicted value (95% CI: 95–108). Before the second methacholine provocation, after the treatment period with ICS, the corresponding FEV₁ value was 103%

(95% CI: 97–107) of predicted value (*ns*). Median dose of mg methacholine causing a 20% fall in FEV₁ (PD₂₀) was 0.17 (95% CI: 0.07–0.22) before the start of the study and 0.7 (95% CI: 0.32–1.18) after at least 3 months of using ICS ($p < .01$). Five of the patients did not reach PD₂₀ after the treatment period.

FE_{NO}

FE_{NO} was measured in 15 of the patients. Median FE_{NO} was 31 ppb (95% CI: 14–55) before the start of the study and 20 ppb (95% CI: 15–26) after at least 3 months of using ICS ($p < .01$).

Capsaicin Provocations

Both the patients and the control group had a dose-response cough reaction to the capsaicin provocations.

Among the patients, median FEV₁ was 101% of predicted value (95% CI: 97–109) before the first capsaicin provocation and 100% of predicted value (95% CI: 94–107) after the provocation (*ns*). After the treatment period with ICS, the corresponding FEV₁ value was 104% (95% CI: 97–109) before the capsaicin provocation and 104% (95% CI: 97–109) after the provocation (*ns*).

On the first provocation occasion, 2 of the 18 patients did not inhale the highest concentration of 10.0 $\mu\text{mol/L}$ capsaicin, in one case due to excessive coughing (more than 50 coughs) and in the other due to a feeling of irritation in the airways. After ICS treatment, one of the patients who did not fulfill the first capsaicin provocation also stopped the test before completion at this second opportunity, after inhaling 2.0 $\mu\text{mol/L}$ capsaicin. The results of the provocations with the three concentrations of capsaicin (0.4, 2.0, and 10.0 $\mu\text{mol/L}$), expressed as number of coughs, are presented in Figure 1.

TABLE 2.—Items on the Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SHR).

A.	I would not mind living on a street with odorous/pungent car exhausts if the apartment I had was nice. ^a
B.	I am more aware of odorous/pungent substances than I used to be. ^{a,b}
C.	At movies, other persons' perfume and after shave disturb me. ^{a,b}
D.	I am easily alerted by odorous/pungent substances. ^{a,b}
E.	I get used to most odorous/pungent substances without much difficulty. ^a
F.	How much would it matter to you if an apartment you were interested in renting was located close to a factory that emits odorous/pungent substances? ^{b,c}
G.	In public places, I do not mind some smell of cigarette smoke. ^a
H.	There are often times when I want a complete odor-free environment. ^{a,b}
I.	I find it hard to relax in a place that evokes odor/pungent sensations. ^{b,d}
J.	I would not mind living in an apartment that has a weak smell. ^a
K.	I am sensitive to odorous/pungent substances. ^{a,b}

^aScale: Agree strongly (0), agree (1), agree mildly (2), disagree mildly (3), disagree (4), disagree strongly (5). The numbers in parenthesis refer to the score given for that response.

^bItem scored in opposite direction before responses are summed.

^cScale: It would completely deter me (0), or it would be very important (1), important (2), slightly important (3), or not important at all (4).

^dScale: Always (0), very often (1), often (2), occasionally (3), seldom (4), never (5).

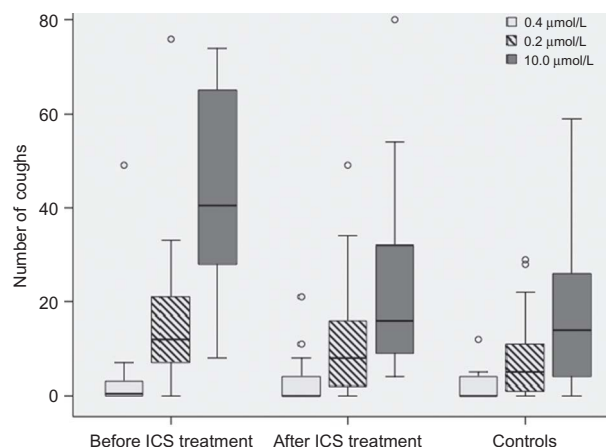


FIGURE 1.—Box plot presentation of cough response after inhalation of 0.4, 2.0, and 10.0 $\mu\text{mol/L}$ capsaicin in 18 patients with bronchial asthma before and after treatment with ICS and in 21 control subjects. Five horizontal lines on each box graph (from bottom to top) represent 10th, 25th, 50th (median), 75th, and 90th percentiles. Circles plotted above 90th percentiles are individual maximum data points.

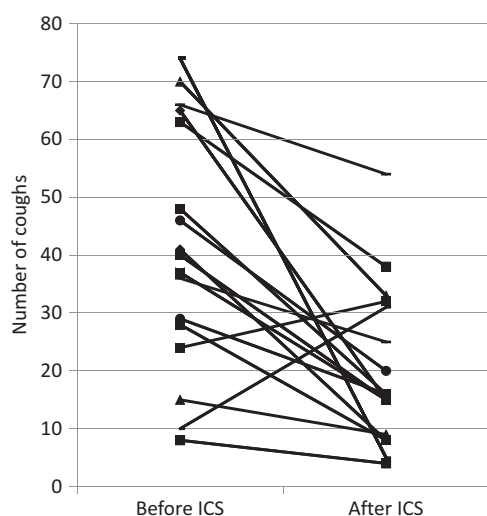


FIGURE 2.—Individual results of coughing on 10.0 $\mu\text{mol/L}$ capsaicin in 17 patients before and after treatment with ICS. In two patients, the values at this concentration are filled in by doubling the number of coughs evoked by 2.0 $\mu\text{mol/L}$ capsaicin to represent the cough response to 10.0 $\mu\text{mol/L}$ capsaicin. The results of one outlier (coughing more than 150 times) are not shown.

The patient group coughed significantly more than the control group before treatment with ICS on the two highest concentrations of capsaicin, 2.0 $\mu\text{mol/L}$ ($p < .05$) and 10.0 $\mu\text{mol/L}$ ($p < .005$). After the treatment period, there were no significant differences between the patients and the control subjects (Figure 1).

All but two patients coughed less after the ICS treatment when the total outcome of coughing was counted, illustrated by the individual cough outcome on 10.0 $\mu\text{mol/L}$ capsaicin in Figure 2. On the concentration of 0.4 $\mu\text{mol/L}$ capsaicin, the patients' median numbers of coughs were 1 (95% CI: 0–3) before ICS treatment and 0 (95% CI: 0–4) after the treatment period (*ns*). The corresponding values for the concentration of 2.0 $\mu\text{mol/L}$ capsaicin were 12 (95% CI: 7–21) and 8 (95% CI: 2–16), respectively (*ns*), whereas those for 10.0 $\mu\text{mol/L}$ capsaicin were 41 (95% CI: 28–65) and 16 (95% CI: 9–33), respectively ($p < .001$) (Figure 1).

The median number of coughs in the control group was 0 (95% CI: 0–4) for the concentration of 0.4 $\mu\text{mol/L}$ capsaicin, 5 (95% CI: 1–11) for 2.0 $\mu\text{mol/L}$ capsaicin, and 14 (95% CI: 4–26) for 10.0 $\mu\text{mol/L}$ capsaicin (Figure 1).

CSS-SHR

The patients' median CSS-SHR score was 34 (95% CI: 27–41) on the first occasion and 35 (95% CI: 30–43) on the second occasion, after ICS treatment (*ns*). Among the controls, the median score was 25 (95% CI: 20–27); this differed significantly from the results of the patients ($p < .001$).

Correlations

Among the patients, before treatment with ICS, the number of coughs on 0.4 $\mu\text{mol/L}$ capsaicin correlated significantly with FE_{NO} ($p < .01$, $r = 0.63$). The corresponding

values for the concentration of 2.0 $\mu\text{mol/L}$ capsaicin were $p < .01$, $r = 0.63$, and those for 10 $\mu\text{mol/L}$ capsaicin were $p < .05$, $r = 0.5$. No such correlations were found after the ICS treatment period. In addition, no correlation was found between capsaicin cough sensitivity and PD₂₀ or the CSS-SHR score. FE_{NO} and PD₂₀ did not correlate significantly, either before or after the ICS treatment period.

DISCUSSION

This study demonstrated that steroid-naïve patients with a positive methacholine test had increased cough sensitivity to inhaled capsaicin before treatment with ICS and that the cough response was normalized after at least 3 months of ICS treatment. The augmented capsaicin sensitivity at the start of the study was associated with increased levels of FE_{NO} , but not with sensitivity to methacholine. In comparison to a healthy control group, the patients reported higher social and emotional influence from environmental irritants.

The patients in this study all had 80% or more of predicted $\text{FEV}_{1\text{L}}$, indicating a good lung function. This probably explains why none had used ICS because, in Sweden, most asthma patients are treated with ICS long before they go to an asthma clinic. Also the long time period needed to recruit the patients illustrates the difficulty of finding steroid-naïve patients.

We hypothesize that the mechanisms of cough from different environmental (non-allergen) irritants depend on an “upregulation” of the TRP receptors and that this “upregulation” among the study patients was caused by the asthmatic inflammation. The finding of a relationship between an ongoing airway inflammation, illustrated by increased levels of FE_{NO} in combination with positive methacholine tests, and augmented sensitivity to capsaicin is in concordance with earlier studies demonstrating that capsaicin cough sensitivity in allergic, asthmatic patients was increased during the pollen season (35, 36). Also, other studies indicate a change in neural responsiveness in connection with allergic inflammation, especially in the nose (37). Despite these earlier results, it has remained unclear how, and to what extent, neurogenic mediators play a role in bronchial airway hyperreactivity and in inflammation of the lower airways (3–5, 38). The current results are in accordance with other findings showing no correlation between methacholine sensitivity and capsaicin sensitivity (16, 17, 19) and with reports that, in asthma, augmented coughing from mannitol and hypertonic saline may occur independently of bronchoconstriction, suggesting a sensorineural dysfunction (39, 40). To further confirm a hypothesis of increased expression of TRPV1 in asthma inflammation, bronchial biopsies before and after ICS treatment would be crucial.

Di Franco et al. (20) found that asthmatic patients showed a significant improvement in cough sensitivity to citric acid, but not to capsaicin, after treatment with ICS; however, earlier treatment was withdrawn for only

4 weeks before the start of the study, and the baseline capsaicin cough sensitivity did not differ from that in the healthy control subjects. Doherty et al. (16) reported no relationship between capsaicin responsiveness and treatment with ICS, but the outcome of *new* ICS treatment was not studied. In an earlier report, well-controlled asthma patients treated with ICS did not show increased cough sensitivity when tested with the same tidal breathing, capsaicin provocation model as used in the current study (18). Others have found that augmented capsaicin cough sensitivity also occurs in asthmatic patients treated with ICS on a regular basis; however, the provocation model used was the “single-breath” technique, in which increasing concentrations of capsaicin are inhaled until the individual coughs a specific number of times (5 times: C5, 10 times: C10) (15, 16). This technique may be a more sensitive method than the tidal breathing method with fixed concentrations of capsaicin used in the present study and may provide some explanation of the different results. However, to assess capsaicin cough thresholds in normal subjects, Nejla et al. (41) evaluated the repeatability of and the agreement between the dosimeter method and the tidal breathing method and found good repeatability for both methods and also good agreement between them. Ternesten-Hasseus et al. (42) also found that both methods showed good repeatability and also similar ability to distinguish patients with airway sensitivity to environmental irritants from healthy control subjects. It would, however, be of interest to analyze the capsaicin cough outcome before and after ICS treatment in a corresponding group of asthma patients provoked with the “single-breath” method.

Airway sensitivity to inhaled irritants in asthma has been described earlier and can be assessed by an airway reactivity score (43). It has been proposed that patients with pronounced airway sensitivity to environmental irritants like odorous chemicals and scents, but without asthma or allergy, and who have increased cough sensitivity to inhaled capsaicin, have a condition known as SHR (18, 44, 45). As they have for the point scores of the CSS-SHR questionnaire, limits for the diagnosis of SHR have been set for the number of coughs in response to a standardized capsaicin inhalation test with the same provocation model used in the current study. Based on these tools, the prevalence of SHR was estimated at 6.3% in an adult Swedish population (24, 45, 46). The limit values for a positive capsaicin inhalation test for SHR were then determined to be 10, 35, and 55 coughs at 0.4, 2.0, and 10.0 $\mu\text{mol/L}$ capsaicin, respectively, and a proposed diagnostic cut-off score for the CSS-SHR questionnaire was set at ≥ 43 points. According to these confines, before treatment with ICS, the asthma patients in the present study coughed less compared to patients with SHR and also scored lower on the CSS-SHR questionnaire. In 103 subjects randomly chosen in a population-based study, the CSS-SHR score correlated with the capsaicin cough sensitivity, indicating that symptoms described by the patients are mirrored by the capsaicin cough sensitivity (45). The present number of patients was not large enough to make proper comparisons with the population-based results of

the CSS-SHR and capsaicin cough sensitivity, and the cough outcome from capsaicin did not correlate to the CSS-SHR score in this small group of patients. Still, both the capsaicin sensitivity and the CSS-SHR score were significantly higher than in the control group. Steroid-naïve asthma patients seem to have a milder variant of a syndrome resembling SHR, where at least the increased cough sensitivity can be normalized by ICS treatment. There are, however, no indications that patients with SHR and without any bronchial obstruction will benefit from ICS; the symptoms, the increased CSS-SHR score, and the augmented cough sensitivity to capsaicin remained over a 5-year period, regardless of medical treatment (30). In the present study, the CSS-SHR score did not change significantly after ICS treatment, and this would be of interest to follow up in a longer perspective. Asthma and SHR do have similarities, despite also having fundamental differences, and this encourages further studies.

The lack or weakness of correlation between FE_{NO} and sensitivity to methacholine in some asthmatic groups is not a new finding (47, 48). Both parameters, when heightened, indicate an asthmatic airway inflammation, but it is likely that they have different pathways. The role of FE_{NO} as a valuable tool in the diagnosis and management of asthma seems to increase with better and cheaper analytical methods, though this topic has been controversial (49, 50). To our knowledge, a correlation between increased levels of FE_{NO} and capsaicin cough sensitivity has not been shown earlier. However, the present study was a small one, and larger numbers of asthma patients need to be studied to confirm the results.

In conclusion, the part of airway inflammation that is reflected by FE_{NO} seems to have a link to an increased reactivity of the TRPV1 receptors in the respiratory system. This association disappears after treatment with ICS which improves augmented cough sensitivity to capsaicin and decreases sensitivity to methacholine and levels of FE_{NO} .

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DECLARATION OF INTEREST

The authors report no conflicts of interests. The authors alone are responsible for the content and writing of this paper.

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