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To cite this article: Ewa-Lena Johansson, Per Gustafsson, Eva Millqvist & Ewa Ternesten-Hasséus (2019): Small and large airways' reactions to inhaled capsaicin in patients with chronic idiopathic cough, or asthma and in healthy control subjects, Experimental Lung Research, DOI: [10.1080/01902148.2019.1611971](https://doi.org/10.1080/01902148.2019.1611971)

To link to this article: <https://doi.org/10.1080/01902148.2019.1611971>



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Published online: 15 May 2019.



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ORIGINAL ARTICLE



Small and large airways' reactions to inhaled capsaicin in patients with chronic idiopathic cough, or asthma and in healthy control subjects

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ABSTRACT

Aims: Cough is a common medical problem, and when it persists for more than 8 weeks it is arbitrarily defined as chronic. While spirometry assesses the large airways, impulse oscillometry system (IOS) measures peripheral airway function. The present study investigated whether provocation with inhaled capsaicin affects the large and small airways in patients with chronic idiopathic cough (CIC) or asthma and in healthy controls. **Materials and methods:** Twenty-one patients with CIC, 18 patients with asthma, and 22 healthy controls were subjected to a provocation with capsaicin, and lung function was assessed by IOS and spirometry. **Results:** At baseline, before the capsaicin provocation, the CIC group had significantly increased airway resistance compared to the controls. After capsaicin provocation, the CIC group exhibited a significant increase in total airway resistance. The asthma group showed a small but significant reduction in spirometry, increased airway resistance, and reactance after capsaicin provocation. Capsaicin inhalation affected neither the spirometry nor the IOS of the healthy controls. **Conclusions:** The present study demonstrates that inhaled capsaicin induces changes in lung function, both in patients with CIC and in patients with asthma, when IOS, which measures changes also in the peripheral airways, is used. IOS appears to be a more sensitive tool than spirometry for the detection of airway impairment in airway provocation studies. In patients with CIC, higher peripheral resistance at baseline may have clinical significance.

ARTICLE HISTORY

Received 5 November 2018
Accepted 21 April 2019

KEYWORDS

Asthma; Capsaicin; Cough; Lung function; Impulse oscillometry system

Introduction

Cough is a common medical problem, and when it persists for more than 8 weeks it is arbitrarily defined as chronic.¹ When all evident medical causes are excluded, the explanation to the chronic coughing may include gastroesophageal reflux disease (GERD), and post-nasal drip syndrome, though these hypotheses are often disputed.² In the absence of any underlying causes for the cough, certain patients, most of them women, can be designated as suffering from chronic idiopathic cough (CIC).^{3,4} CIC prevalence has been reported as being 6%–20% in the adult population.⁵ CIC is essentially a “hidden” disease, in that it receives little attention from the medical community. While it is not dangerous or

life-threatening, it causes distress to both patients and physicians. CIC has a substantial impact on the quality of life, often also affecting the family of the patient.^{6–8} One clinical characteristic in CIC is the cough reflex that is readily evoked by exposure to environmental stimuli (e.g., noxious substances, chemicals, and perfumed products), as well as to cold air and temperature changes. This sensitivity is mirrored by an exaggerated cough provoked by capsaicin inhalation.⁴ Transient receptor potential (TRP) ion channels sense numerous stimuli in the environment, and the first identified TRP was transient receptor vanilloid 1 (TRPV1), also called the ‘capsaicin receptor’.⁹ TRPV1 is involved in the pathophysiology of CIC, as biopsies of lung tissues from

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patients show increased expression of TRPV1 channels.^{10,11} The current consensus is that refractory chronic cough is a neuropathic condition related to the TRPs.^{12,13}

The diagnostic assessment of pulmonary function using spirometry has long been the “Gold standard”, although the parameter of forced expiratory volume in one second (FEV₁), which is often used to assess lung function, mainly provides information on the condition of the large airways.¹⁴ In contrast, impulse oscillometry (IOS) monitors both the large and peripheral airways using sound waves to evaluate resistance.¹⁵ The IOS method was described already in the 1950’s.¹⁶ Recently, computerized devices for conducting IOS have simplified the technique and interpretation of the results. IOS measurements are easy to perform and require minimal co-operation from the subject.^{15,17} Recent studies have shown that IOS sensitively discriminates small airway diseases in cases of asthma,^{18–20} chronic obstructive lung disease²¹ and bronchiectasis.²²

The effects on FEV₁ and IOS of different osmotic stimuli (hypertonic saline, mannitol, and eucapnic voluntary hyperventilation) have been evaluated in patients with CIC and in patients with mild asthma, as well as in healthy controls. The CIC group demonstrated no significant changes in spirometry values following osmotic provocation, as compared to the healthy controls. After exposure to hypertonic saline, patients with CIC demonstrated increased IOS values and the change differed significantly compared to the control group. The asthma group reacted to all three osmotic provocations with both spirometric and oscillometric changes, albeit with some variations.²³

The way in which inhaled capsaicin influences spirometry has been evaluated in patients with CIC^{4,24} and in patients with asthma,^{24–26} as well as in healthy controls without any signs of airway obstruction.^{24–27} However, the effects of capsaicin inhalation on the small peripheral airways, as measured with IOS, have not been reported previously. Based on the above-described study,²³ the aim of the present investigation was to “narrow” the findings by analyzing using the differences between the CIC, asthma, and healthy control groups regarding airway reactions to inhaled capsaicin, with special focus on the small

peripheral airways. The finding of peripheral airway reactions to hypertonic saline in the CIC group prompted the study of the effect of inhaled capsaicin.

Materials and methods

Study design

Each participant visited the clinic on one occasion. All the participants received oral and written information about the study, and signed a letter of consent before any study-related activity was conducted. The participants filled in a questionnaire concerning demographic data and reported airway symptoms (yes/no), as well as the Swedish version of the Hull Airway Reflux Questionnaire (HARQ-S).⁷ Cough sensitivity was assessed by a capsaicin inhalation cough test using the threshold method.^{27,28} Before and immediately after each concentration of capsaicin was administered, lung function testing was performed using calibrated instruments for IOS^{15,17} and flow-volume spirometry.¹⁴ The total time for each provocation test was about 20 min.

Airway provocation testing was not performed on subjects who had experienced a respiratory infection in the past month. The exclusion criteria for the study were: use of angiotensin-converting enzyme inhibitor, β -blockers or corticosteroids; medication for or symptoms of GERD; inadequate ability to read, write or understand the Swedish language; and smoking during the last 5 years. For women, pregnancy and breast-feeding were also exclusion criteria. The participants were asked to abstain from using short-acting β_2 -agonist medication for at least 6 hours prior to the test.

The study was performed in accordance with the ethical standards laid out in the 1967 Declaration of Helsinki and subsequent amendments and was approved by the Regional Ethical Review Board of Gothenburg, Sweden (no. 630-13).

Participants

Twenty-one patients with CIC, 18 steroid-naïve patients with mild asthma, and 22 healthy controls from an earlier study that included 26 patients with CIC, 18 patients with asthma, and

22 healthy controls were included in the present study.²³ Following, five patients, earlier classified as having CIC were excluded in the present analyses due to a “limit reaction” on the methacholine provocation test,²⁹ that raised the question whether they also could be classified as having mild asthma. Because the inclusion criteria for the present study were more stringent, the number of patients with CIC was reduced, while the numbers of patients in the asthma group and control group remained the same.

CIC Group

All the patients (n=21; two males) with CIC were nonsmokers who experienced daily coughing for at least 2 months with no evident medical explanation, and who had received from their physician a diagnosis of CIC, excluding asthma and other respiratory diseases as a cause for the coughing. Within the past 5 years, all the patients with CIC had shown a positive result in the capsaicin inhalation test,^{27,30} shown a negative reaction in the methacholine provocation test,²⁹ and shown no signs of asthma.³¹ None of the patients with CIC used any medication for the airways.

Asthma group

The asthma group (n=18) comprised nonsmoking female patients. They were steroid-naïve, and had within the last 3 months shown a positive result in the methacholine provocation test, and had a reversibility after β_2 -agonist inhalation of $\geq 12\%$ increase in FEV₁.^{29,32} They had been referred to the clinic due to lower airway symptoms and were given a physician's diagnosis of mild asthma according to international guidelines.³¹ Thirteen of the asthma patients used a short-acting β_2 -agonist but no other medications for the airways.

Control group

The control group (n=22) comprised nonsmoking females who self-reported as being healthy, not having airway symptoms or symptoms of GERD, and not using any medications for the airways or for GERD. No further physical examination was performed.

HARQ-S questionnaire

The HARQ questionnaire was developed to identify coughers. The questionnaire consists of 14 items, with total score range of 0–70. An upper normal total score limit of 13 points is regarded as normal.³³ A Swedish version of the questionnaire (HARQ-S) has been developed.⁷ It has been validated, showing good psychometric properties, internal consistency, and test-retest repeatability.³⁴

Impulse oscillometry (IOS)

Airway resistance testing was conducted in duplicate before and immediately after each concentration of capsaicin applied for airway provocation, using the MasterScreen Impulse Oscillometry System and ver. 4.67 software (Viasys Healthcare GmbH, Hoechberg, Germany). To avoid any disturbance caused by the physical effort of performing spirometry, IOS was performed before spirometry. Sequences that displayed artifacts related to swallowing or glottic closure were excluded from the analysis.^{15,17} The participant was in a seated position, and instructed to adopt relaxed tidal breathing *via* a mouthpiece and a microbe filter (MicroGard II, bacterial/viral filter; Care Fusion, Hoechberg, Germany), with his/her head in a neutral position and using a nose-clip. The palms of the hands were used to support the cheeks. The oscillometric pressure impulses were superimposed on tidal breathing, with a pulse sequence of five per second and a frequency spectrum in the range of 5–35 Hz.¹⁵

The resistance at 5 Hz (R5) represents the total airway resistance, and that at 20 Hz (R20) represents the resistance of the large airways. Thus, the difference between R5 and R20 (R5-R20) reflects the resistance of the small airways. The airway reactance area (AX), which reflects respiratory compliance, is a good index of peripheral airway function. The airway resistance, measured in kPa/L/s over 60 s of normal breathing, was recorded for R5 and R20, respectively, and the AX was calculated in kPa/L.^{15,17} The values obtained for R5, R20, R5-R20, and AX were considered relevant for the present study, and the lower of two measurements was recorded.

Spirometry

Before and after each concentration of inhaled capsaicin, and immediately after the IOS procedure, FEV₁ testing was performed twice using the MasterScope spirometer and ver. 4.67 software (Viasys Healthcare GmbH, Hoechberg, Germany). In a seated position and using a nose-clip, each participant was encouraged to perform the forced breath test to the best of their ability, and the higher of the two values, with less than 5% variation, was recorded.¹⁴

Capsaicin provocation

A stock solution of capsaicin (M2028; Sigma-Aldrich Sweden AB, Stockholm) [1 mmol/L in ethanol (99.5%)] was prepared, and then dissolved in 0.9% saline to provide a stock solution of 500 µmol/L capsaicin. Serial dilutions were prepared from the stock solution using saline diluent to produce a doubling-concentration series that ranged from 0.49 µmol/L to 500 µmol/L.^{27,28} The provocation solutions were prepared regularly and stored in a freezer for a maximum of 3 months.³⁵

Capsaicin solutions were administered to the subjects according to international guidelines,³⁶ using a compressed air-driven side-stream nebulizer (MedicAid Pro; Medicaid Ltd., Pagham, West Sussex, UK), which was controlled by an Airway Aerosol Provocation System with the APS ver. 5.02 software (Viasys Healthcare GmbH, Hoechberg, Germany). The participant inhaled, without a nose-clip, three single, vital capacity breaths before the solution was inhaled during the fourth breath. After one dose of saline, doubling concentrations of capsaicin were administered, starting at 0.49 µmol/L and ending at 500 µmol/L, to determine the concentration that induced the participant to cough two or five times, referred to as C2 and C5, respectively. A value of 1000 µmol/L capsaicin was assigned if the cough threshold value was >500 µmol/L.^{27,28}

Statistical analysis

No sample size calculation was performed due to the unknown effects of the primary variable for the participating groups. The results of the FEV₁ tests are given as a percentage (%) of the

predicted value for each individual according to gender, age, and body length. All other results are reported as absolute values. For categorical variables, numbers (n) and (%) are presented, and for continuous variables, the mean and standard deviation (SD) values are presented. A subgroup analysis evaluated the 19 females (excluding two males) in the CIC group in comparison to the asthma- and the control group, both comprising only women.

All tests were two-tailed, and the results were considered statistically significant for $p < 0.05$.

All the data were analyzed using the SPSS ver. 22 (SPSS Inc., Chicago, IL, USA), and SAS® ver. 9.4 (SAS Institute Inc., Cary, NC, USA) software packages.

Results

All the participants underwent IOS, spirometry, and capsaicin provocation testing according to the study protocol.

Baseline results

At baseline (Table 1), there were no differences in age between the patients with CIC and the control group. On average, the patients with CIC were significantly older than the patients with asthma ($p < 0.001$), and the patients with asthma were significantly younger than the subjects in the control group ($p < 0.01$). Regarding previous smoking habits, the three groups did not differ. There were no differences in the duration of reported symptoms between the two patient groups. Significantly fewer patients with asthma reported symptoms of cough and hoarseness, as compared to the CIC group ($p < 0.05$) (Table 2). Otherwise, there were no differences in reported symptoms between the two patient groups. For the HARQ-S score, the patients with CIC and patients with asthma had significantly higher scores than the control group ($p < 0.001$) but the patient groups did not differ in between.

At baseline, before the inhaled capsaicin provocation, the patients with CIC had significantly higher R5-R20 values than the control group ($p < 0.05$). Besides, the participants did not

Table 1. Demographic and baseline characteristics of the patients and healthy controls.

Variables	CIC (n = 21)	Asthma (n = 18)	Controls (n = 22)	CIC vs. Asthma <i>p</i> -value	CIC vs. Controls <i>p</i> -value	Asthma vs. Controls <i>p</i> -value
Age, in years	55.9 (10.3)	33.6 (12.6)	48.9 (13.5)	<0.001	0.06	<0.01
Female	19 (94.5%)	18 (100%)	22 (100%)	0.54	0.45	1.00
Never smoked	12 (57.1%)	13 (72.2%)	13 (59.1%)			
Former smoker	9 (42.9%)	5 (27.8%)	9 (40.9%)	0.51	1.00	0.60
HARQ-S(score)	27.2 (12.1)	20.2 (10.7) <i>n</i> = 16	2.3 (2.8)	0.051	<0.001	<0.001
R5 (kPa/L/s)	0.45 (0.13)	0.46 (0.14)	0.41 (0.08)	1.00	0.23	0.35
R20 (kPa/L/s)	0.35 (0.11)	0.40 (0.13)	0.34 (0.07)	0.28	0.96	0.33
R5-R20 (kPa/L/s)	0.099 (0.06)	0.068 (0.05)	0.062 (0.04)	0.09	<0.05	0.8
AX (kPa/L)	0.42 (0.35)	0.33 (0.23)	0.26 (0.20)	0.44	0.06	0.19
FEV ₁ % pred	104.2 (13.5)	103.4 (13.7)	106.1 (12.4)	0.81	0.49	0.71

Categorical variables, are presented as n (%), and continuous variables are presented as mean (SD). For pairwise comparisons of the groups, the Mantel-Haenszel Chi Square test was used for categorical variables, and the Mann-Whitney *U*-test was used for continuous variables. Statistically significant *p*-values are highlighted in gray. Ax, reactance area; FEV₁% pred, forced expiratory volume in one second, percent predicted; HARQ-S, the Swedish version of the Hull Airway Reflux Questionnaire; kPa, kilopascal; L, liter; n, number of subjects; R5, airway resistance level at 5 Hz; R20, airway resistance level at 20 Hz; s, second; SD, standard deviation.

Table 2. Patient-reported symptoms.

Reported symptom	CIC (n = 21)	Asthma (n = 18)	<i>p</i> -value
Symptom duration (years)	12.8 (9.3)	7.5 (7.4)	0.07
Cough (n)	21	13	< 0.05
Chest pressure (n)	7	2	0.14
Difficulty getting air (n)	7	9	0.34
Heavy breathing (n)	14	9	0.34
Phlegm (n)	11	14	0.18
Hoarseness (n)	14	4	< 0.05
Throat irritation (n)	16	9	0.11
Rhinitis (n)	12	12	0.74

Categorical variables are presented as n, and continuous variables are presented as mean and (SD). For pairwise comparisons between groups, Fisher's Exact test was used for dichotomous variables, and the Mann-Whitney *U*-test was used for continuous variables. Statistically significant *p*-values are highlighted in gray. n, number of subjects; SD, standard deviation.

differ with respect to the FEV₁% predicted, R5, R20, R5-R20, and AX absolute values (Table 1).

When excluding the two men in the CIC group the number of smokers and duration of year with symptoms did not change. The female CIC group was significantly older [mean age 56.2 (10.8)] than the asthma group ($p < 0.05$). Significantly more female patients with CIC ($p < 0.05$) reported symptoms of cough, hoarseness, and throat irritation compared to the asthma group. At baseline before the capsaicin inhalation, the 19 females in the CIC group had significantly higher R5-R20 values [mean value 0.10 (0.06)] than both the asthma group and the control group ($p < 0.05$ respectively), and a significantly higher AX absolute value [mean value 0.44 (0.36)] than the control subjects ($p < 0.05$).

Effects of capsaicin provocation on IOS

After capsaicin inhalation, there were no differences between the participating groups for any IOS

parameters but compared to baseline, the patients with CIC showed significantly higher R5 ($p < 0.05$) and the asthma group significantly increased values of R5-R20 ($p < 0.05$) and AX ($p < 0.05$). There were no differences in any of the IOS parameters among the healthy controls (Table 3).

Analysis of only the female CIC participants showed no differences between the groups for any IOS parameter from the capsaicin provocation. Compared to baseline the females in the CIC group had significantly higher values for R5 ($p < 0.01$) and R20 ($p < 0.05$) after the capsaicin provocation [mean differences 0.052 (0.06) and 0.035 (0.06) respectively].

Effects of capsaicin provocation on spirometry

After capsaicin inhalation, there were no differences between the participating groups in terms of FEV₁% predicted values. The asthma group showed a small but significant reduction ($p < 0.05$) in the FEV₁% predicted value after capsaicin inhalation. No other spirometric differences were found in any of the groups after capsaicin provocation (Table 3), nor yet when the two male CIC were excluded.

Effects of capsaicin provocation on cough sensitivity

The cough thresholds following capsaicin provocation are shown in Table 3. All the participants coughed in a dose-dependent manner, in terms of showing an exacerbated coughing reaction with increasing concentrations of administered

Table 3. Results of capsaicin provocation tests for the patients and healthy controls.

Variables	CIC (n = 21)	p-value within group	Asthma (n = 18)	p-value within group	Controls (n = 22)	p-value within group	CIC vs. Asthma p-value	CIC vs. Controls p-value	Asthma vs. Controls p-value
R5 (kPa/L/s) (change from baseline to max increase)	0.039 (0.07)	<0.05	0.01 (0.10)	0.22	0.02 (0.05)	0.10	0.39	0.26	0.80
R20 (kPa/L/s) (change from baseline to max increase)	0.024 (0.06)	0.14	−0.01 (0.09)	0.86	0.01 (0.06)	0.25	0.28	0.50	0.75
R5-R20 (kPa/L/s) (change from baseline to max increase)	0.015 (0.049)	0.29	0.02 (0.04)	<0.05	0.003 (0.03)	0.27	0.63	0.53	0.47
AX (kPa/L) (change from baseline to max increase)	0.135 (0.33)	0.23	0.10 (0.26)	<0.05	0.01 (0.09)	0.91	0.36	0.27	0.08
FEV₁ % pred (change from baseline to max reduction)	−0.41 (3.34)	0.84	−1.87 (2.74)	<0.05	−0.09 (3.20)	0.91	0.053	0.95	0.08
Capsaicin cough thresholds									
C2 (μmol/L)	2.39 (3.27)		11.3 (28.6)		31.5 (105.0)		<0.05	<0.0001	0.07
C5 (μmol/L)	2.95 (3.21)		304.4 (448.2)		412.3 (466.2)		<0.01	<0.0001	0.09

Continuous variables are presented as mean (SD) and n. For comparisons within groups, the Wilcoxon Signed-Rank test was used, and for comparisons between groups, the Mann-Whitney U-test was used. Statistically significant p-values are highlighted in gray. Ax, reactance area; C2 and C5, the concentrations (μM) of capsaicin that elicited 2 and 5 coughs, respectively; FEV₁ % pred, forced expiratory volume in one second, percent predicted; kPa, kilopascal; L, liter; n, number of subjects; R5, resistance level at 5 Hz; R20, resistance level at 20 Hz; SD, standard deviation; s, second; μmol, micromol.

capsaicin. The cough thresholds for C2 and C5 were, as expected, significantly lower in the patients with CIC than in the asthmatics and healthy controls, although they did not differ between the patients with asthma and the control group. In the CIC group, excluding the two male participants did not change the outcome of the capsaicin cough thresholds.

Discussion

In the present study, we have analyzed how capsaicin provocation affects the lung function in patients with CIC, patients with mild asthma, and a in group of healthy controls. In general, we did not find any major influence of capsaicin on airway reactivity in any group. A small but scarcely clinically significant decrease in FEV₁ and increase in R5-R20 were recorded in the asthma group, which also showed a small but significant increase in airway reactance. At baseline, the patients with CIC had significantly higher R5-R20 values than the controls, and after the capsaicin provocation increased airway resistance at 5 Hz, reflecting a change in total airway resistance. Comparing the airway reactivity parameters between the groups, there were no significant differences for any pulmonary function. As expected, patients with CIC had a significantly lower capsaicin cough threshold (given that a positive capsaicin test was an inclusion criterion) than the patients with asthma and the healthy controls.^{27,30} The CIC group included two men and inhaled capsaicin is known to provoke more cough in women than in men.³⁷ However, when excluding the two male participants, the overall results were not influenced, maybe due to the small number of men.

This is the first report in the English language to reveal the effects of capsaicin provocation on lung function, as determined by both IOS and spirometry. In 2005, a short report in Chinese described a lack of change in lung functions after capsaicin provocation, as evaluated with both IOS and spirometry in patients with asthma and in healthy volunteers.³⁸ Most of the studies conducted to date have failed to identify any effect on lung function, as measured using FEV₁, of capsaicin provocation.^{24–27,39} Even if FEV₁ is the

Gold standard for lung function assessments, there is growing interest in the involvement of the small airways in various airway diseases, and assessment of the peripheral airways is now available using IOS.^{15,17,19–21}

In the current study, the patients with CIC showed significantly higher R5-R20 values than the controls at baseline. Furthermore, the patients with CIC had a small increase in total airway resistance after capsaicin provocation, indicating airway narrowing. To the best of our knowledge, this has not been reported previously. The patients with asthma exhibited a small but significant obstruction in both the large and peripheral airways after capsaicin provocation. While the extent to which this low-level airway obstruction is clinically significant can be discussed, this finding is in agreement with Fuller et al., who reported a small but very transient and significant increase in airway resistance in both asthmatics and healthy controls after capsaicin provocation.⁴⁰ Nevertheless, previous studies with capsaicin inhalation provocation have shown conflicting results for patients with asthma.^{25,40,41} There appears to be some influence on sensory nerve reaction in asthma, although the underlying mechanism is unknown.

The major finding of the present study is that at baseline, patients with CIC have significantly higher airway resistance. In an earlier study with essentially the same groups of participants as in the present study, no such differences were noted²³ but in the current study patients with a limit reaction on methacholine provocation, earlier classified as having CIC, were excluded. This decreased the number of CIC patients from 26 to 21, which we interpret as the reason for the discrepant results. In the earlier study, the patients with asthma reacted in predictable ways, with impaired IOS and spirometric values upon osmotic stimulation, although there were individual differences that may influence the future choice of inhalation medication. Interestingly, the CIC patients did not show any changes in IOS or FEV₁ following the dry air and mannitol provocations, whereas hypertonic saline, which is known as a noxious stimulus, increased both reactance and resistance peripherally, as compared to the control group.²³

Furthermore, the present results show that patients with CIC and with asthma have significantly higher total scores on the HARQ-S compared to the healthy controls. This indicates that both patient groups had troublesome cough. However, the findings that the asthmatics did not have decreased capsaicin cough threshold, as compared to the healthy controls, or to earlier given normal limit values,²⁷ are somewhat puzzling. Previously, Dicipinigitis has suggested that asthmatics who have symptoms of cough represent a sub-group of patients with a hyper-sensitive cough receptor and increased capsaicin sensitivity; asthmatics who lack symptoms of cough exhibit no such hypersensitivity, and they do not differ from healthy control subjects in terms of capsaicin sensitivity.⁴² However, Hilton et al. have proposed that the standard end-point for C2 and C5 is insufficiently sensitive to distinguish the capsaicin responses between patients with different types of airway disease and healthy individuals.⁴³ A non-linear fix-modelling procedure has been suggested that is better at discriminating patients with chronic cough and patients with asthma from healthy controls. Thus, the maximum cough response to any capsaicin concentration ($E_{\max}$) and the capsaicin dose that induces half-maximal response (E_{50}) have been calculated.²⁶ Yet, it is difficult to compare the results from different studies, partly due to the differences in patients' demographics and the different methods used for capsaicin challenge. Further studies using different models for evaluating capsaicin cough sensitivity are required.

Some limitations of the present study are the small sample size and the selection of patients from only one out-patient allergy specialist clinic. Furthermore, the study comprised mainly female patients (two males in the CIC group), which may restrict the generalisability of the results. An additional limitation could be the differences in age between the two patient groups, and between the asthmatics and healthy controls, but the patients with CIC and the controls did not differ in age. To confirm the present results, larger studies without any differences in age and that include more male participants, patients from different clinical settings are required. Moreover, to further explore the effect of smoking on

peripheral resistance, larger studies are required, including information on both the number of former smokers and a history of pack-year.

Conclusions

Following inhalation of capsaicin, patients with CIC showed a minor change in total airway resistance, and the asthma patients minor influences on both the large airways and small airways, which had not been studied previously. Control subjects showed no changes in lung function after capsaicin provocation, either in spirometry or IOS tests. In addition, patients with CIC had at baseline, increased peripheral resistance. While this may be an indication of small airway disease, it needs to be confirmed in studies with a higher number of patients. The current findings indicate that IOS is a more sensitive tool than spirometry for the detection of airway impairment in patients with different airway diseases and in provocation studies. The findings may also provide an explanation for the often-reported dyspnea in patients with CIC who have normal spirometry values.

Acknowledgment

We are grateful to Margareta Brandt Gertmo for performing the capsaicin inhalation tests, and to Marianne Wallgren for her help with preparing the capsaicin.

Declaration of interest

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

Abbreviations

AX	Area under the reactance curve
CIC	Chronic idiopathic cough
C2	Capsaicin concentration required to evoke two coughs
C5	Capsaicin concentration required to evoke five coughs
FEV ₁	Forced expiratory volume in one second
GERD	Gastro-oesophageal reflux disease
IOS	Impulse oscillometry
kPa/L	KiloPascal per liter
R5	Value for airway resistance at 5 Hz
R20	Value for airway resistance at 20 Hz
TRP	Transient receptor potential

TRPV1 Transient receptor potential vanilloid subtype 1 (channel)
 μmol/L Mikromol per liter

Funding

The Healthcare Committee, Region Västra Götaland (Hälsö och sjukvårdsstyrelsen) (no. 478141, 561541, 611771, and 651751), the Swedish Cancer and Allergy Fund (no. 14836), and the Swedish Heart-Lung Foundation.

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