

Review



Utility of Cough Provocation Tests in Chronic Cough and Respiratory Diseases: A Comprehensive Review and Introduction of New Reference Ranges for the Capsaicin Test

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ABSTRACT

Cough provocation tests (CPTs) are an objective measurement of the sensitivity of the cough reflex arc. However, they are not established in clinical practice because a large variability of response in healthy subjects limits their diagnostic value. There is a paucity of studies that have investigated CPT reference ranges in healthy subjects. This systematic review describes the variability of the responses to CPTs in healthy subjects and factors that influence it. A new analysis of 134 healthy subjects was conducted to create reference ranges for single-breath capsaicin CPT by calculating the interquartile ranges for the provocative concentration of capsaicin to induce 2 and 5 coughs. Female subjects had a more sensitive cough reflex than male counterparts. The ability of CPTs to distinguish various respiratory diseases from healthy subjects was also reviewed. Cough sensitivity was consistently heightened in the following groups: unselected patients with chronic, refractory, or recurrent cough, unexplained chronic cough, gastro-esophageal reflux-associated cough, cough-variant asthma, lower airway symptoms induced by chemical irritants, and fibrotic interstitial lung diseases. In the following groups, hypersensitivity of the cough reflex was present in those individuals whose symptom profile was predominated by cough: asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and sarcoidosis. In the following conditions, patients usually cough in order to expectorate mucus from their airways, not because of a hypersensitive cough reflex arc: productive cough, asthma, upper airway cough syndrome, COPD, bronchiectasis, cystic fibrosis, and chronic respiratory infections. CPTs have the potential to identify patients with chronic respiratory symptoms due to cough reflex hypersensitivity, thereby providing a targeted approach for therapy.

Keywords: Cough; reflex; hypersensitivity, capsaicin; citric acid; mannitol; saline solution, hypertonic solutions; reference values

INTRODUCTION

Most longstanding lower airway respiratory symptoms are probably associated with 1 or more of the following 3 pathophysiological phenomena: the increased tendency of the airway smooth muscle to constrict in response to environmental stimuli (airway hyperresponsiveness), the hypersensitivity of the cough reflex arc, and the increased mucus production.¹⁷ These 3 phenomena are probably independent, involving different mechanisms. Several studies have consistently shown that airway hyperresponsiveness does not correlate with cough reflex hypersensitivity.^{1,8-22} Furthermore, patients with cough due to increased mucus production usually do not show hypersensitivity of the cough reflex arc.^{1,3} None of the 3 phenomena are specific for a single disorder and their relative importance probably varies among patients. Understanding the relative contribution of these phenomena in an individual patient would aid in targeting therapies of longstanding lower airway respiratory symptoms.^{4,20,23}

The tests to measure airway responsiveness, like the methacholine test, have been widely utilized in clinical patient management for decades. On the contrary, the tests to measure the sensitivity of the cough reflex arc, the cough provocation tests (CPTs), have not been established in clinical work. There are some obvious reasons for the unpopularity of the CPTs.²⁴⁻²⁶ First, numerous provocative agents with different mechanisms of action have been utilized. While it may be advantageous to utilize a tussive agent specific for a mechanism of action, the optimal tussive agent is not known in many situations. The cough response to capsaicin, citric acid, and tartaric acid involves the stimulation of the transient receptor potential vanilloid-1 (TRPV1) though the action of the acidic agents also involves other receptor types.²⁷⁻²⁹ The CPTs with hypertonic aerosols involve provocations with hypertonic saline, hypertonic histamine, mannitol, and hyperpnoea. These agents provoke cough without stimulating the TRPV1.²⁶ In addition, water mist and adenosine have been utilized. Secondly, there are many methods to administer provocative agents, but they have not been standardized. Thirdly, the diluents of the provocative agents need to be prepared in specialized pharmacies and the reagents may be expensive and not universally available. Finally, a nebulizer is usually needed and this introduces several problems related to calibration, cleaning, and maintenance of the device. However, many of these shortcomings also apply to the tests that measure airway hyperresponsiveness, which have not hindered their widespread clinical use.

The most common reason for the limited clinical use of CPTs is that the responsiveness to these tests varies widely among healthy subjects, and therefore they cannot distinguish disease from normal healthy state.^{21,24,30,31} In the present article, we first review the evidence for the variability of the sensitivity to CPTs in healthy subjects. Then, we present a new analysis of previously presented material and suggest reference ranges for the single-breath capsaicin CPT. Finally, we review the ability of CPTs to distinguish healthy subjects from patients with various respiratory disorders. The present article does not cover studies investigating a reduced or hyposensitive cough reflex nor studies investigating the therapeutic use of the capsaicin challenge.

LITERATURE REVIEW FOR CPTs

A PubMed search was carried out with the following search terms: cough (with and without Medical Subject Headings definition) AND capsaicin/citric acid/tartaric acid/hypertonic saline/mannitol/hyperpnea/fog/water/adenosine/ATP. Utilizing the filters 'English' and 'humans,' the searches gave 1,143 articles published after the year 1980 up to February 19, 2021. The publications, in which CPTs were applied to a large number of healthy subjects or which included a comparison between healthy subjects and patients with respiratory diseases, were reviewed in detail.

From the publications including a large number of healthy subjects, the authors assessed the variability of the responses, the normality of the distribution of the responses, and the factors affecting the variability. In addition, the authors performed a re-analysis of a large group of healthy subjects previously presented by Prudon *et al.*,³⁰ in order to create reference ranges for the single-breath capsaicin CPT.

From the group comparison studies, the authors investigated whether there were statistically significantly different responses to CPTs ($P < 0.05$) between the healthy subjects and the patients. In addition, the following diagnostic performance indices were searched: the area under the receiver operating characteristic curve (aROC), the sensitivity, and the specificity. Whenever possible, the sensitivity and the specificity were calculated utilizing the cutoff value to give the largest Youden index (the sum of sensitivity and specificity). The level of distinction between groups was classified according to the aROC value of 0.7–0.8 indicating an acceptable, 0.8–0.9 an excellent, and more than 0.9 an outstanding distinction.³²

COUGH REFLEX SENSITIVITY IN HEALTHY SUBJECTS

Capsaicin is the most commonly utilized agent in CPTs. The capsaicin test is safe and has been performed in children as well as in adults. Some subjects report transient throat irritation.^{4,33–36} There are several studies applying single-breath, dosimetric capsaicin tests in large groups of healthy subjects.^{1,3,18,21,30,35,37} Prudon *et al.*³⁰ investigated 134 healthy subjects in 2005. Among them, the geometric mean for the concentration of capsaicin that caused 2 coughs (C2) was 12.6 $\mu\text{mol/L}$ (log SD, 0.5), and the concentration that caused 5 coughs (C5) was 158.5 $\mu\text{mol/L}$ (log SD, 0.6). Another study involved 103 healthy adults with female predominance.³ After applying the anti-log function on the reported log-transformed values, the interquartile ranges were 1.91–15.8 $\mu\text{mol/L}$ for the C2 and 7.76–251 $\mu\text{mol/L}$ for the C5. Three studies reported neither the SDs nor interquartile ranges, but the means and the 99% or 95% confidence intervals.^{1,21,35} Of them, 2 involved adults with geometric mean C2 values of 11.0 and 32.3 $\mu\text{mol/L}$ and C5 values of 64.6 and 151 $\mu\text{mol/L}$.^{1,21} A study in 100 healthy children reported the geometric mean C2 of 15.1 $\mu\text{mol/L}$ and the geometric mean C5 of 64.2 $\mu\text{mol/L}$.³⁵ In addition, there is one population of 96 healthy adults, presented in 2 publications, which only reported the median C5 value. It was more than the maximal concentration of 500 $\mu\text{mol/L}$, indicating that most subjects did not reach it.^{18,37}

Citric acid test was performed on 160 healthy subjects in order to create reference values to investigate a blunted cough response.³⁸ However, the authors used a 15 seconds' tidal breathing method via a face mask instead of the single-breath dosimetric method, which is the preferred method to investigate a hypersensitive cough reflex arc.²⁴ In another study, tartaric

acid test was applied in 71 healthy subjects, but a tidal breathing method was utilized in that study as well.³⁹ To the best of the authors' knowledge, there are no studies about the cough responses to hypo- or hypertonic aerosols or adenosine in large groups of healthy subjects.

The studies among healthy subjects^{30,38,39} as well as those among patients with respiratory disorders^{7,40-42} showed that females are more sensitive than male counterparts to a wide variety of cough-provoking agents, supporting separate reference ranges for both sexes. The cough sensitivity to capsaicin increases with age among healthy adults,³⁰ whereas a converse relationship has been described in children.³⁵ However, these associations were weak. Therefore, the reference ranges must not take the age into account. Atopy and smoking status do not seem to affect the cough sensitivity to capsaicin in healthy subjects.^{1,18,21,30,37}

Cough reflex sensitivity is a dynamic phenomenon. In healthy subjects, cough sensitivity to capsaicin increases significantly during upper respiratory infections and returns to the baseline levels at 4 weeks after the infection.³ Interestingly, the infections did not enhance airway responsiveness to methacholine. Furthermore, children with recurrent chronic cough but without airway hyperresponsiveness are more sensitive to capsaicin during the cough episode than during the cough-free period.⁴

CAPSAICIN REFERENCE RANGES: NEW ANALYSIS OF THE PREVIOUS PUBLICATION

To the best of the authors' knowledge, a study presented by Prudent *et al.*³⁰ is the largest one applying a single-breath, dosimetric capsaicin test in healthy subjects. The authors presented a very limited report of healthy subject data and we therefore conducted a more in-depth analysis to create reference ranges for capsaicin sensitivity.

There were 134 healthy subjects: 83 women, aged 19–78 years, and 51 men, aged 19–74 years. Exclusion criteria were a diagnosis of respiratory disease or current respiratory symptoms, GER, upper airways symptoms, and current smoking, or a history of smoking >10 pack-years. All healthy subjects had normal spirometric values, with 29% defined as being atopic. The subjects inhaled single vital capacity breaths of capsaicin solution via an air-powered dosimeter (KoKo Digidoser; Pulmonary Data Services Instrumentation Inc., Louisville, CO, USA) at increasing concentrations from 0.49 to 500 $\mu\text{mol/L}$. The inspiratory flow was standardized at 0.5 L/sec with an inspiratory flow regulator valve, and the dosimeter output was set at 10 μL . The number of coughs was counted for 30 seconds after exposure to each dose. C2 and C5 were calculated by the linear interpolation of the log dose-response curves. A value of 500 $\mu\text{mol/L}$ was assigned if interpolated values were >500 $\mu\text{mol/L}$. The repeatability of the results was good.

Even after the logarithmic conversion of C2 and C5, the distribution of the data differed significantly from normal distribution (**Fig. 1**). Therefore, instead of reporting SDs, we calculated the reference ranges as the 25–75 percentiles (the interquartile ranges) (**Table 1**). Female subjects were significantly more responsive to capsaicin than men and therefore, we calculated the reference ranges separately for the sex.

The study by Prudon *et al.*³⁰ also involved 18 patients with unexplained chronic cough and 21 patients with cough-variant asthma (**Figs. 2 and 3**). Utilizing the reference values calculated

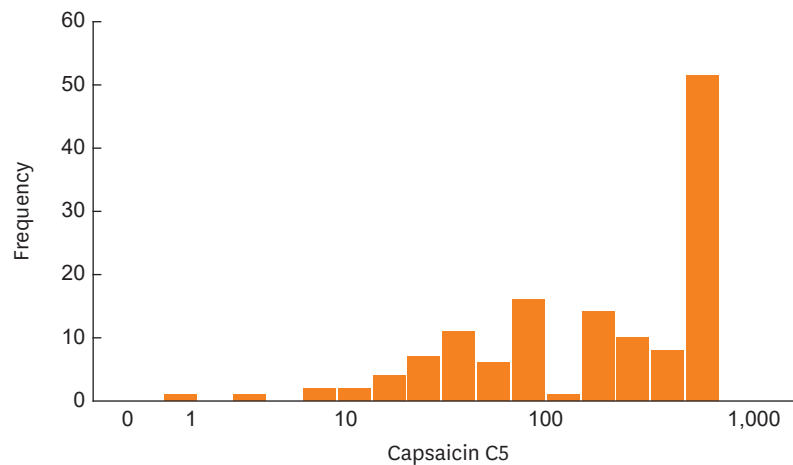


Fig. 1. The distribution of capsaicin concentrations to provoke 5 coughs (C5) among 134 healthy subjects presented by Prudon *et al.*³⁰ Please note the logarithmic scale of the horizontal axis. The distribution of the C5 values differed significantly from the normal distribution even after 10-base logarithmic transformation ($P < 0.001$, one-sample Kolmogorov-Smirnov test). The subjects who did not cough more than 5 times even after the maximum capsaicin concentration were given a value of 500 $\mu\text{mol/L}$.

Table 1. The reference ranges for capsaicin provocative concentration to induce 2 coughs (C2) and 5 coughs (C5)

The variable, sex, unit	25%–75% percentage range (= the interquartile range)
C2, men, $\mu\text{mol/L}$	7.63–35.9
C2, women, $\mu\text{mol/L}$	4.44–18.2
C5, men, $\mu\text{mol/L}$	over 158
C5, women, $\mu\text{mol/L}$	over 37.8

They are calculated from the results of 134 healthy subjects (51 men and 83 women) presented by Prudon *et al.*³⁰ The upper limits could not be calculated for C5, since more than half of the healthy subjects did not cough five times even after the maximal capsaicin concentration of 500 $\mu\text{mol/L}$.

among the healthy subjects, the sensitivity values were 76.5% and 81.0% for discriminating unexplained chronic cough and cough-variant asthma, respectively, from healthy subjects. The specificity for both was 75.3% each. **Table 2** includes the sensitivity and specificity values for the same data when the optimal cutoff values were determined by the Youden index. They

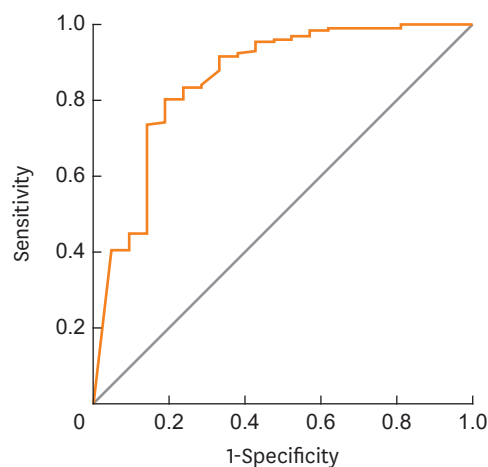


Fig. 2. The receiver operating characteristic (ROC) curve demonstrating the distinction between 21 patients with cough-variant asthma and 134 healthy subjects by the concentration of capsaicin to provoke 5 coughs (C5) in the study by Prudon *et al.*³⁰ The area under the ROC curve is 0.850 indicating an excellent distinction.

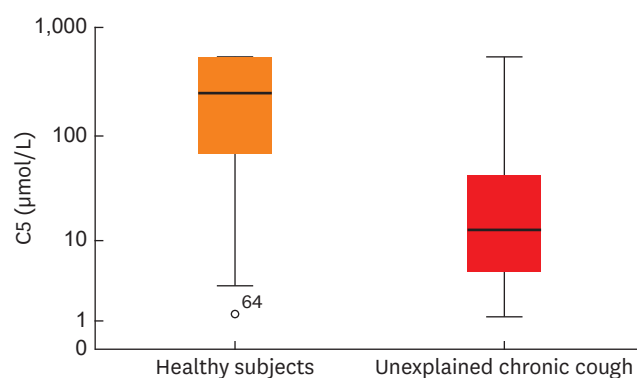


Fig. 3. The concentration of capsaicin to provoke 5 coughs (C5) in 134 healthy subjects and in 18 subjects with unexplained chronic cough, which were presented by Prudon *et al.*³⁰ The lower boundary of the box indicates 25th percentile, a line within the box marks the median, and the higher boundary indicates the 75th percentile. The error bars above and below the boxes indicate the 90th and 10th percentiles. $P < 0.001$ between the groups (Mann-Whitney U test).

showed just slightly better discrimination of these disease groups than those calculated by the new interquartile limits of the healthy subject reference ranges.

COUGH REFLEX SENSITIVITY IN RESPIRATORY DISEASES AND COMPARISON WITH HEALTHY SUBJECTS

Unselected patients with chronic, refractory, and recurrent cough.

CPTs in patients who cough due to a wide range of associated disorders are discussed here. Chronic cough indicates a cough lasting for more than 8 weeks. Refractory cough indicates a cough that persists despite optimal treatment for the presumed background disorder. Recurrent cough indicates cough that tends to recur within a limited period.⁴³ These patient groups have been consistently more sensitive than healthy subjects to a wide variety of cough provoking agents: capsaicin,^{4,20,29,35,40,44-46} citric acid,^{27,29,47} ATP,⁴⁸ mannitol,^{42,47,49} and hypertonic saline.⁷ Some of these studies provide the sensitivity, specificity and aROC values (Table 2), and they suggest that the distinction from healthy subjects ranges from acceptable to outstanding.

Unexplained chronic cough

Unexplained chronic cough indicates a cough that has lasted for more than 8 weeks in which no diagnosable background disorder has been found.⁴³ Compared to healthy subjects, patients with unexplained chronic cough are significantly more hypersensitive to capsaicin,^{1,30,50-54} mannitol,⁵⁵ eucapnic voluntary hyperventilation,⁵⁰ and hypertonic saline.⁵⁰ The studies, from which the diagnostic performance indices were available, have shown an excellent distinction between unexplained chronic cough and healthy subjects (Table 2, Fig. 3).

Gastro-esophageal reflux-associated cough

These patients have been constantly and clearly more sensitive to capsaicin^{1,21,30,52,56} and citric acid⁵⁷ than healthy subjects. The single study providing the diagnostic indices showed an excellent distinction between these patients and healthy subjects by the capsaicin test (Table 2).

Cough Provocation Tests

Table 2. The ability of cough provocation tests to distinguish various groups of patients from healthy subjects

Study (year)	Agent	Cut-off value	Type of patients with cough	Cough patients	Sensitivity	Healthy subjects	Specificity	Youden index	aROC
Singapuri <i>et al.</i> ⁴⁹ (2008)	Mannitol	≤ 550 mg to provoke 5 coughs	Unselected chronic cough	13	62%	16	81%	143	NA
Koskela <i>et al.</i> ⁴² (2018)	Mannitol	≥ 12.0 coughs/100 mg	Unselected chronic cough	17	82%	15	100%	182	0.949
Nurmi <i>et al.</i> ⁴⁷ (2019)	Mannitol	≥ 5.35 coughs/100 mg	Unselected chronic cough	36	92%	25	64%	156	0.847
Nurmi <i>et al.</i> ⁴⁷ (2019)	Citric acid	< 281 mmol/L to provoke 5 coughs	Unselected chronic cough	36	88%	25	67%	155	0.763
Koskela <i>et al.</i> ⁷ (2008)	Hypertonic saline	≤ 2,213 mOsm/kg to provoke 15 coughs	Unselected chronic cough	47	66%	19	84%	150	0.775
O'Connell <i>et al.</i> ⁵¹ (1995)	Capsaicin	< 31.6 μmol/L to provoke 5 coughs	Unexplained chronic cough	16	94%*	8	100%*	194	NA
Prudon <i>et al.</i> ³⁰ (2005)	Capsaicin	< 5.01 μmol/L to provoke 2 coughs	Unexplained chronic cough	18	83%†	134	80%†	163	0.867†
Prudon <i>et al.</i> ³⁰ (2005)	Capsaicin	< 29.2 μmol/L to provoke 5 coughs	Unexplained chronic cough	18	72%†	134	88%†	160	0.853†
Johansson <i>et al.</i> ⁵⁵ (2018)	Mannitol	≥ 69 coughs during the whole test	Unexplained chronic cough	22	95%	21	90%	185	NA
Johansson <i>et al.</i> ⁵⁵ (2018)	Hypertonic saline	≥ 11 coughs during the whole test	Unexplained chronic cough	21	95%	21	95%	190	NA
Johansson <i>et al.</i> ⁵⁵ (2018)	Dry air hyperpnoea	≥ 14 coughs during the whole test	Unexplained chronic cough	23	95%	21	86%	181	NA
Nieto <i>et al.</i> ²¹ (2003)	Capsaicin	< 15 μmol/L to provoke 5 coughs	Gastroesophageal reflux-associated cough	23	98%	86	66%	164	0.880
Koskela <i>et al.</i> ⁶⁵ (2004)	Mannitol	≥ 4.0 coughs/100 mg	Asthma	37	86%	10	90%	186	0.930
Nurmi <i>et al.</i> ⁴⁷ (2019)	Mannitol	≥ 17.2 coughs/100 mg	Asthma	11	91%	25	92%	183	0.956
Johansson <i>et al.</i> ⁵⁵ (2018)	Mannitol	≥ 48 coughs during the whole test	Asthma	16	80%	21	76%	156	NA
Koskela <i>et al.</i> ⁷ (2008)	Hypertonic saline	≤ 1,428 mOsm/kg to provoke 15 coughs	Asthma	26	62%	19	100%	162	0.828
Purokivi <i>et al.</i> ⁶⁶ (2011)	Hypertonic saline	≥ 0.0005 coughs/mOsm/kg	Asthma	36	89%	14	93%	182	0.935
Johansson <i>et al.</i> ⁵⁵ (2018)	Hypertonic saline	≥ 5 coughs during the whole test	Asthma	16	100%	21	81%	181	NA
Koskela <i>et al.</i> ⁶⁷ (2005)	Hypertonic histamine	≥ 12.2 coughs/mg/mL	Asthma	32	62%	15	93%	155	0.830
Purokivi <i>et al.</i> ⁶⁸ (2008)	Hypertonic histamine	≥ 69.2 coughs/mg/mL	Asthma	30	80%	25	96%	176	NA
Purokivi <i>et al.</i> ⁶⁶ (2011)	Dry air hyperpnoea	≥ 0.085 coughs/MVV%	Asthma	36	75%	14	100%	175	0.911
Johansson <i>et al.</i> ⁵⁵ (2018)	Dry air hyperpnoea	≥ 11 coughs during the whole test	Asthma	15	60%	21	81%	141	NA
Prudon <i>et al.</i> ³⁰ (2005)	Capsaicin	< 4.94 μmol/L to provoke 2 coughs	Cough-variant asthma	21	81%†	134	80%†	161	0.838†
Prudon <i>et al.</i> ³⁰ (2005)	Capsaicin	< 42.1 μmol/L to provoke 5 coughs	Cough-variant asthma	21	81%†	134	80%†	161	0.850†
Pullerits <i>et al.</i> ⁷¹ (2014)	Capsaicin	< 15.6 μmol/L to provoke 5 coughs	Chemical sensitive patients	46	96%	29	86%	182	0.972
Ternesten-Hasséus <i>et al.</i> ⁷⁵ (2006)	Capsaicin, tidal breathing	Not defined	Chemical sensitive patients	15	80%‡	15	100%‡	180	0.950
Ternesten-Hasséus <i>et al.</i> ⁷⁵ (2006)	Capsaicin, dosimeter	Not defined	Chemical sensitive patients	15	80%‡	15	87%‡	167	0.900
Doherty <i>et al.</i> ³⁷ (2000)	Capsaicin	< 31.25 μmol/L to provoke 5 coughs	Idiopathic pulmonary fibrosis	15	87%§	96	90%§	177	NA
Hope-Gill <i>et al.</i> ⁸¹ (2003)	Capsaicin	≤ 2 μmol/L to provoke 2 coughs	Idiopathic pulmonary fibrosis	10	70%	10	100%	170	NA

The table includes studies in which the authors had the access to the original data, studies that report the diagnostic performance indices, and studies in which these indices can be reliably estimated utilizing the published tables or the figures. The cutoff values are those giving the largest sum of sensitivity and the specificity (Youden index).

aROC, area under the receiver operating characteristic curve; MVV%, minute ventilation level expressed as percentage of the predicted maximal voluntary ventilation; NA, not available.

*Estimated from the Fig. 1 of the publication, †re-calculated from the original data, ‡estimated from the Fig. 4 of the publication, §estimated from the Fig. 1 of the publication, ||estimated from the Fig. 1B of the publication.

Asthma

In the majority of studies, patients with stable asthma do not differ from healthy subjects with respect to cough sensitivity to capsaicin,^{1,4,5,17,19,29,30,35,45,50,52,53,58-60} citric acid,^{16,19} and tartaric acid.^{12,14} However, there are also some studies demonstrating a statistically significant difference between the two groups utilizing capsaicin^{18,21,61,62} or citric acid.²⁹ A recent study reported a lower capsaicin C2, but not C5, in asthmatic children than in the control subjects.³⁶ The capsaicin sensitivity in asthma may be associated with the subjective cough severity¹⁸ and poor asthma control.⁶³ It is possible that the distinction between healthy and asthmatic subjects is better if maximum cough responses are used instead of threshold values to describe the cough responsiveness.⁶² However, in one study, the capsaicin sensitivity did not differ between the 2 groups even utilizing the maximum responses.⁵³ The conflicting results may be partially explained by the finding that patients with allergic asthma are more sensitive to capsaicin during the pollen season than out of the season.⁶⁴

On the contrary to CPTs with capsaicin and acidic aerosols, the cough responsiveness to hypertonic CPTs has been found to be consistently enhanced in asthma and the distinction from healthy subjects has been from excellent to outstanding (**Table 2, Fig. 4**).^{7,55,65-68} The cough responsiveness to hypertonic saline and dry air hyperpnea are associated with impaired cough-related quality of life in asthma.⁶⁹

Cough-variant asthma

In concordance with a study showing that subjective cough severity is associated with cough responsiveness to capsaicin in classic asthma,¹⁸ the subjects with cough-variant asthma are consistently shown to be more sensitive to capsaicin than healthy subjects.^{1,30,59,70} The material presented by Prudon *et al.*³⁰ shows that the distinction between cough-variant asthma and healthy subjects by the capsaicin test is excellent (**Table 2, Fig. 2**).

Patients with lower airway symptoms induced by chemical irritants

A special subgroup of patients with lower airway symptoms induced by chemical irritants like solvents and perfumes has been shown to be especially hypersensitive to capsaicin demonstrating an outstanding distinction from normal subjects (**Table 2**).^{5,20,71,78} However, the

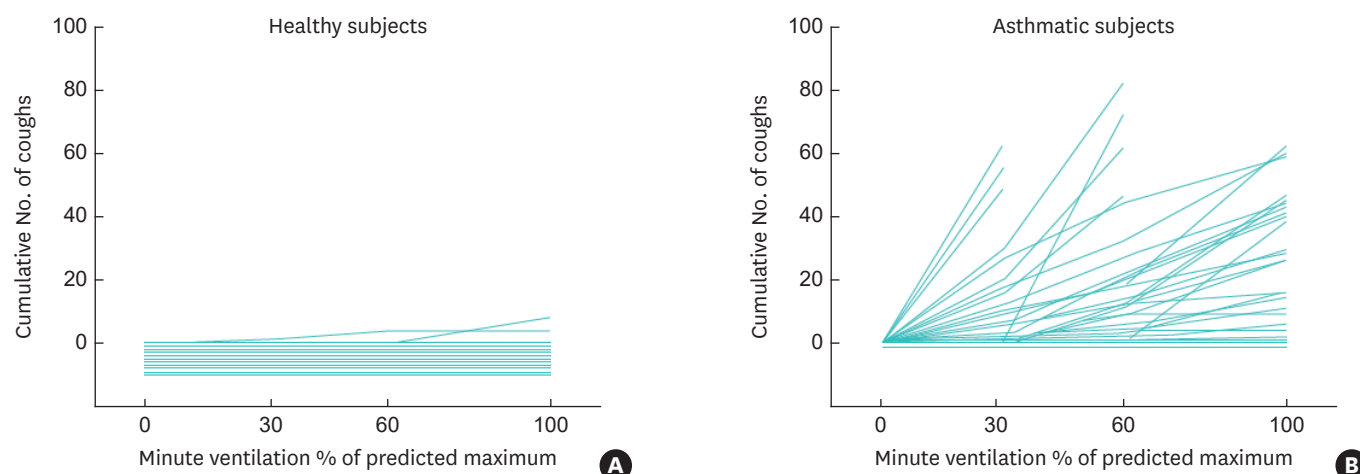


Fig. 4. The cumulative number of coughs in relation to minute ventilation evoked by isocapnic hyperpnea of dry air challenge in 10 healthy (A) and 30 asthmatic (B) subjects. The horizontal lines at or below zero indicate subjects who did not cough at all. Reproduced from reference⁶⁶ with permission.

results of some of these studies must be interpreted with caution as the patients have been selected on the basis of a previous positive capsaicin test result.^{71,74,75}

Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome may cause chronic cough.⁷⁹ According to one study, the patients suffering from this syndrome are more sensitive to capsaicin than healthy subjects and subjects with simple snoring.⁸⁰ More studies are needed to confirm this.

Interstitial lung diseases (ILDs)

A small group of unselected patients with ILD showed similar cough sensitivity to capsaicin when compared to healthy subjects.¹ On the contrary, patients with idiopathic pulmonary fibrosis^{30,37,81} and with systemic sclerosis-associated ILD⁴⁶ have shown to be clearly more sensitive to capsaicin than healthy subjects are (**Table 2**). Of note, patients with systemic sclerosis but without ILD did not differ from healthy subjects in this respect. These results suggest that in ILDs, the heightened cough reflex sensitivity is associated with the degree of lung parenchymal fibrosis.

Sarcoidosis

The studies on patients with sarcoidosis are conflicting. A study by Prudon *et al.*³⁰ included 13 sarcoidosis patients with mild or absent cough; their capsaicin sensitivity did not differ from that of 134 healthy subjects. The largest group of sarcoidosis patients was investigated by Sinha *et al.*²³ They compared 32 patients with pulmonary sarcoidosis and 40 age- and sex-matched healthy controls. The former subjects were significantly more sensitive to capsaicin, although the overlap was large. Among the patients with sarcoidosis, the capsaicin sensitivity was the only factor that was associated with the objectively measured 24-hour cough counts in multivariate analysis that included also lung function parameters, chest radiograph findings, serum angiotensin-converting enzyme level, and smoking status.

Upper airway cough syndrome (UACS) including postnasal drip syndrome and chronic rhinosinusitis-associated cough

The studies on patients with UACS are conflicting. In some studies, these patients have shown a greater sensitivity to capsaicin when compared to healthy subjects.^{52,82,83} However, there are also studies suggesting that these patients' sensitivity to capsaicin is not enhanced^{1,21,58,70} Among the 4 negative studies, 3 included only small groups of UACS patients (n = 11-13), but 1 negative study by Cho *et al.*⁷⁰ included 33 patients, thus decreasing the possibility of the type II statistical error. The authors of that study suggested that chronic cough in postnasal drip associated with sinusitis may be caused by mechanical irritations of cough receptors with normal sensitivity.⁷⁰ Furthermore, the conflicting results may be partially explained by the finding that patients with allergic rhinitis are more sensitive to capsaicin during the pollen season than out of the season.⁸² Among the UACS patients with documented cough hypersensitivity, laryngopharyngeal anesthesia only slightly decreased the responsiveness to inhaled capsaicin, suggesting a major role for lower airway sensory nerves or central sensitizing.⁸³

Chronic obstructive pulmonary disease (COPD)

The studies on patients with COPD are conflicting. In one study, patients with COPD and healthy subjects were challenged to capsaicin and citric acid. The patients with COPD were hypersensitive to capsaicin but not to citric acid.²⁹ In another study, patients with COPD were hypersensitive to citric acid, but not to capsaicin.⁸⁴ One negative study utilizing

capsaicin may have been too small ($n = 8$) to reveal a statistically significant difference.³⁰ A large capsaicin study with 56 COPD patients and 96 healthy subjects demonstrated a clear distinction between the 2 groups. Among the COPD patients, there was a significant association between the subjective cough severity and capsaicin sensitivity.¹⁸

Bronchiectasis and cystic fibrosis

The studies on patients with bronchiectasis are conflicting. In one study involving 7 stable bronchiectasis patients¹ and another involving 5 stable patients,⁵² the cough sensitivity to capsaicin did not differ from that of healthy subjects.^{1,52} However, the former study also included 5 bronchiectasis patients with acute respiratory infection and they were hypersensitive to capsaicin.¹ A study by Prudon *et al.*³⁰ involved 5 patients with bronchiectasis and their capsaicin sensitivity was higher than that of healthy subjects. The largest group was presented by Torrego *et al.*⁸⁵ That study included 22 patients with bronchiectasis and 20 healthy controls matched for age and sex. Patients with bronchiectasis had increased sensitivity to capsaicin compared to controls ($P < 0.03$), but the overlap was large. Capsaicin sensitivity correlated with impaired cough-related quality of life and with the total cough symptom score. Bronchiectasis is often associated with cystic fibrosis. In children with cystic fibrosis, the capsaicin C2 was higher than that in healthy subjects, indicating blunted cough sensitivity, but once these patients started coughing, they coughed multiple times.³⁵

Productive cough

In general, patients with chronic, productive cough do not differ from healthy subjects with respect to capsaicin sensitivity, whereas those with chronic, dry cough do.¹ Interestingly, this seems to apply to acute cough as well. In a prospective study with 103 healthy volunteers, capsaicin sensitivity increased during upper respiratory tract infection only among subjects with dry cough during the infection, but not in those with productive cough during the infection.³ These findings suggest that cough can occur in association with either excess mucus production leading to productive cough or an increase in the sensitivity if the cough reflex arc, leading to non-productive cough.¹

CLINICAL IMPLICATIONS OF CPTs

This review shows that although the responsiveness to CPTs is widely distributed among healthy subjects, these tests can effectively distinguish certain patient groups from healthy subjects. Therefore, they could be useful not only in research, but also in everyday clinical practice. For this purpose, reference ranges are obligatory. This article for the first time presents reference ranges for the single-breath capsaicin CPT.

Usually, the reference ranges are calculated as mean \pm 1.96 SD in a healthy population. However, the C2 and C5 values were not normally distributed even after logarithmic conversion among the healthy population investigated by Prudon *et al.*³⁰ Therefore, we calculated the reference ranges as interquartile ranges. Utilizing the interquartile ranges, the sensitivity and specificity values for unexplained chronic cough and cough-variant asthma were almost as high as those utilizing the optimal cutoff values determined by the Youden index. Thus, a value below these interquartile ranges indicates that cough reflex arc hypersensitivity may explain the patient's respiratory symptoms. The reproducibility of C5 is reported to be superior to that of C2, suggesting that C5 is the preferred end-point when investigating a hypersensitive cough

reflex.⁸⁶ C2 may be suitable to investigate a hyposensitive cough reflex since the upper limit of its reference range could be determined in the present analyses.

Though the healthy subjects' capsaicin C2 and C5 values in other studies^{1,3,18,21,35,37} fit rather well in the interquartile ranges now presented, the present reference ranges can only be applied to results obtained by the exactly the same test protocol and equipment as used by Prudon *et al.*³⁰ Lack of standardization of the CPT protocols is one of the greatest hinders for their use in clinical practice.²⁵ At the moment, the mannitol test is the only CPT, which is standardized.²⁶ Unfortunately, there is no data to calculate reference ranges for the cough responsiveness to mannitol or any other cough provocation agents than capsaicin. Also, the reference ranges for the maximal cough response to capsaicin are lacking.

The present review shows that CPTs can effectively distinguish healthy subjects from unselected patients with chronic, refractory, or recurrent cough, patients with unexplained (idiopathic) chronic cough, gastro-esophageal reflux-associated cough, cough-variant asthma, lower airway symptoms induced by chemical irritants, and fibrotic ILDs. In these disorders, hypersensitivity of the cough reflex arc seems to be a rather uniform phenomenon. In a clinical setting, high cough sensitivity to capsaicin or citric acid in a patient with chronic respiratory symptoms suggests that these disorders should be on the top of the list of possible background disorders.

The review also identified disorders, in which an enhanced sensitivity of the cough reflex arc is not a general feature, but is likely to be present only in those individuals with cough being a predominate feature. These disorders include asthma, COPD, bronchiectasis, and sarcoidosis. In a clinical setting, performing a CPT might be useful in these patients to identify the presence of cough reflex hypersensitivity and potentially alter clinical management. Furthermore, the review also identified disorders in which the timing of the test may be important: in allergic asthma and in allergic rhinitis, cough hypersensitivity may be present during the pollen season, but vanish outside it.^{64,82} The patients with asthma is a special group with hypersensitivity to hyperosmolar aerosols, but in general, normal responses to capsaicin and acidic agents. The possible reasons for this discrepancy have been discussed in detail elsewhere.²⁶ In a clinical setting, high cough sensitivity to hypertonic aerosols may suggest asthma as the most probable cough background disorder.

However, it is important to recognize that not all patients who suffer from chronic cough demonstrate heightened sensitivity of the cough reflex arc. It is probable that many patients with productive cough, asthma, UACS, COPD, bronchiectasis, and cystic fibrosis cough in order to expectorate mucus from their airways, not because of a hypersensitive cough reflex arc.^{1,3,70} This is probably also the case in chronic respiratory infections, although there are no studies utilizing CPTs in them.⁸⁷ In such patients, clinical management should focus on clearing the excessive mucus production. Furthermore, some patients with asthma and cough-variant asthma probably cough due to bronchoconstriction^{88,89} and among them, the clinical management should focus on bronchodilation. However, in some of these patients, cough reflex hypersensitivity may be responsible for their respiratory symptoms. Therefore, performing a CPT in a clinical setting could aid in directing the management of these patients as well. Finally, it should be noted that many of the referred studies included rather small number of patients raising the possibility of the type 2 statistical error.

CONCLUSIONS

Despite the wide variability of the cough sensitivity in healthy subjects, CPTs can distinguish certain chronic cough patients from healthy subjects. This article for the first time presents reference ranges for a dosimetric, single-breath capsaicin test. They are based on the material by Prudon *et al.*³⁰ and can be applied only on results obtained by their protocol. The CPTs should be standardized. Not all patients, who suffer from chronic cough, have an abnormally functioning cough reflex arc. CPTs can help clarify whether an individual patient's chronic respiratory symptoms may be due to cough reflex arc hypersensitivity, thereby helping direct the management of the symptoms. This is especially important now, since new medications are emerging which are capable of reducing the sensitivity of the cough reflex arc.⁹⁰

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