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COUGH HYPERSENSITIVITY AND SUPPRESSION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Take home message:

Cough reflex hypersensitivity and impaired ability to suppress cough are likely important mechanisms in patients with chronic refractory cough. Patients with COPD also have a hypersensitive reflex but in contrast are able to suppress cough effectively.

ABSTRACT

Cough reflex hypersensitivity (CRH) and impaired cough suppression are features of chronic refractory cough (CRC). Little is known about cough suppression and CRH in cough associated with chronic obstructive pulmonary disease (COPD). This study investigated the ability of participants with COPD to suppress cough during a cough challenge test in comparison to participants with CRC and healthy subjects. This study also investigated whether CRH is associated with chronic cough in COPD.

Participants with COPD (n=27), CRC (n=11), and healthy subjects (n=13) underwent capsaicin challenge test with and without attempts to self-suppress cough in a randomised order over 2 visits, 5 days apart. For participants with COPD, the presence of self-reported chronic cough was documented, and objective 24-hour cough frequency was measured.

Amongst participants with COPD, those with chronic cough (n=16) demonstrated heightened cough reflex sensitivity (CRS) compared to those without chronic cough (n=11); geometric mean (SD) capsaicin dose thresholds for 5 coughs (C5) 3.36 (6.88) vs. 44.50 (5.90) $\mu mol \cdot L^{-1}$ respectively ($p=0.003$). Participants with CRC also had heightened CRS compared to healthy participants; geometric mean (SD) C5 3.86 (5.13) vs. 45.89 (3.95) $\mu mol \cdot L^{-1}$ respectively ($p<0.001$). Participants with COPD were able to suppress capsaicin-evoked cough, regardless of the presence or absence of chronic cough; geometric mean (SD) capsaicin dose thresholds for 5 coughs without self-suppression attempts (C5) and with (CS5) were 3.36 (6.88) vs. 12.80 (8.33) $\mu mol \cdot L^{-1}$ ($p<0.001$) and 44.50 (5.90) vs. 183.2 (6.37) $\mu mol \cdot L^{-1}$ ($p=0.006$) respectively. This was also the case for healthy participants (C5 vs. CS5: 45.89 (3.95) vs. 254.40 (3.78) $\mu mol \cdot L^{-1}$, $p=0.033$), but not those with CRC, who were unable to suppress capsaicin-evoked cough (C5 vs. CS5: 3.86 (5.13) vs. 3.34 (5.04) $\mu mol \cdot L^{-1}$, $p=0.922$). C5 and CS5 were associated with objective 24-hour cough frequency in participants with COPD; $\rho=-0.430$, $p=0.036$ and $\rho=-0.420$, $p=0.041$ respectively.

Participants with COPD-chronic cough and CRC both have heightened cough reflex sensitivity but in contrast, only participants with CRC were unable to suppress capsaicin evoked cough. This suggests differing mechanisms of cough between participants with COPD and CRC, and the need for disease specific approaches to its management.

INTRODUCTION

Cough is a common symptom in chronic obstructive pulmonary disease (COPD), and is associated with increased exacerbations and accelerated decline in lung function [1–3]. The mechanism of cough in COPD is poorly understood. In refractory and unexplained chronic cough, cough reflex hypersensitivity (CRH) and impaired cough suppression are thought to be important mechanisms [4–6]. CRH has been reported in patients with COPD but it is not known if this is a general feature of COPD, or is specifically limited to COPD patients with chronic cough [7–9]. A reduction in the activity of central neural cough suppression networks has been observed in functional neuroimaging studies of patients with chronic refractory cough [10]. Cough suppression can be assessed clinically by modifying the capsaicin cough challenge test [11, 12]. Healthy individuals are able to suppress or attenuate capsaicin-evoked coughs [13, 14]. In contrast, patients with chronic refractory cough (CRC) appear unable to do this [11]. Central inhibitory neural pathways may therefore be important in the regulation of cough in health and chronic respiratory diseases. It is not known if the ability to suppress cough is impaired in COPD.

The aim of our study was to investigate the ability of patients with COPD to suppress cough during a capsaicin challenge test compared to patients with chronic refractory cough and healthy subjects. The study also aimed to determine whether cough reflex hypersensitivity in COPD is a general feature or limited to patients with co-existing chronic cough. We also assessed the relationship between threshold capsaicin concentrations and 24-hour objective cough frequency and health status.

METHODS

This prospective observational study was granted research ethics committee approval (East London and The City Research Ethics Committee, 10/H0703/6) and was conducted in accordance with the principles of the Declaration of Helsinki at a single centre (King's College Hospital, London, UK). All participants provided written informed consent for participation in the study.

Participants

Consecutive patients with COPD were recruited prospectively from an out-patient clinic. All had a clinician diagnosis of COPD (≥10-pack year history of smoking and forced expiratory volume in 1 second to forced vital capacity ratio <0.7) [15]. Exclusion criteria were previous capsaicin challenge testing, respiratory tract infection within the preceding 6 weeks, and use of angiotensin converting enzyme (ACE) inhibitor medication. Participants who changed their smoking status, or developed a respiratory tract infection or exacerbation of COPD between recruitment and completion of study were excluded from analysis [16].

Consecutive patients with chronic refractory cough (>8 weeks' duration) were recruited prospectively from a specialist cough clinic. The diagnosis of chronic refractory cough (CRC) was assessed by clinicians following recommendations for the management of chronic cough in adults of the British Thoracic Society [17]. Inclusion criteria were a diagnosis of chronic cough, either unexplained or refractory to treatment of a known potential cause, and a normal chest radiograph. Exclusion criteria were the presence of another chronic respiratory disease, smoking within the past 12 months, angiotensin-converting enzyme inhibitor use within the past 12 months, and upper respiratory tract infection within the past 4 weeks.

Healthy participants were recruited prospectively through local advertisement. Exclusion criteria were identical to those for participants with CRC with the addition of the presence of cough in the past 8 weeks, and a ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1:FVC) <0.7. Healthy and CRC participants were contemporaneously recruited to another study [11].

Protocol

All participants underwent investigations over two visits separated by five days. At visit 1, demographic and anthropometric data were collected. Participants with COPD underwent spirometry, body plethysmography and diffusing capacity measurements, whilst CRC and healthy participants underwent only spirometry. Participants with COPD and CRC completed subjective assessments of cough symptoms, cough severity, cough-specific health status and COPD-specific health status, and were invited to undergo 24-hour objective cough frequency monitoring.

All participants with CRC and healthy participants underwent capsaicin challenge tests with and without self-attempted cough suppression on two separate occasions. Participants with COPD underwent separate capsaicin challenge tests with and without self-attempted cough suppression (CST) at two separate visits in a random order.

Capsaicin challenge test

Cough reflex sensitivity (CRS) was assessed as per the European Respiratory Society (ERS) recommendations [12]. Capsaicin solution (Sigma-Aldrich, St Louis, MO, USA) was delivered as 10-µL single breath inhalations in ascending doubling doses (0.49-1000 $\mu mol \cdot L^{-1}$) at 1-minute intervals with an air-powered digital dosimeter (KoKo Digidoser, nSpire Health Inc, Longmont, CO, USA). To reduce the effect of anticipation, 0.9% saline solution was randomly interspersed [12, 18]. A single characterised nebuliser (Model 646, DeVilbiss Healthcare, Port Washington, NY, USA) with an output of 1.205 $mL \cdot min^{-1}$ was used for all participants. In addition, a valve was utilised to restrict the inspiratory flow to 0.5 $L \cdot s^{-1}$ [12, 19]. A minimum of 3 respiratory cycles were performed prior to the administration of each solution. The inspiratory-expiratory flow-volume signals were inspected in real-time by 2 operators (PC, HF) to ensure a consistent and maximal inspiratory effort (0.5 $L \cdot s^{-1}$) throughout the administration of the nebulised solution. If the participant did not take a full inhalation as observed during the real-time visual display of the flow-volume signal, the test was repeated. The number of coughs induced by each dose

administration was counted for 15 s, with the aid of a digital recorder (ICD-PX333, Sony Corporation, Tokyo, Japan), following each dose inhalation [12, 19]. The challenge test continued until ≥5 coughs were elicited by a single dose administration.

Standard cough challenge test

Participants were instructed, "Please cough if you wish during the test", during a conventional capsaicin challenge test. The capsaicin concentrations required to elicit 2 coughs (C2) and 5 coughs (C5) were calculated by interpolation [20].

Cough suppression test

The ability to suppress cough was assessed by instructing the participants, "Please do not cough during the test", during a capsaicin challenge test [11, 13]. The capsaicin concentrations required to elicit 2 coughs (CS2) and 5 coughs (CS5) were calculated by interpolation [11, 20].

Cough frequency monitoring

Cough frequency was assessed objectively over 24 hours with the validated Leicester Cough Monitor (LCM) [21]. The LCM is an ambulatory system, which comprises a MP3 recorder (ICD-PX333, Sony Corporation, Tokyo, Japan), a lapel free-field microphone (LFH9173, Philips, Amsterdam, Netherlands) and a semi-automated cough detection software. Coughs were detected as single events whether they occurred in isolation or in bouts [21]. Awake cough counts (number of coughs over reported time spent awake) and awake cough frequency (coughs·hr^{-1}) were recorded. The participants recorded and reported their time spent asleep.

Subjective assessments

Identification of chronic cough

Daytime cough symptom severity over the past 8 weeks was self-reported on a Likert scale (range 0-5) [22]. Participants with a daytime score ≥2 were considered to be suffering from chronic cough [23, 24].

Cough severity and cough-specific health status

Cough severity and urge to cough were self-reported on visual analogue scales (VAS) (range 0-100 mm; higher scores indicating more severe cough and more severe urge respectively) [12]. Cough-specific health status was assessed with the Leicester Cough Questionnaire (LCQ), which is a self-administered 19-item questionnaire. The LCQ was developed for chronic cough and has since been validated in COPD (score range 3-21; higher scores indicating better health status) [25, 26]. Individual LCQ item scores range from 1-7; higher scores indicating better health status.

COPD-specific health status

COPD-specific health status was assessed with a validated self-administered 8-item COPD Assessment Test (CAT) (range 0-40; higher scores indicating worse health status) [27]. The presence of sputum was defined as a CAT sputum item 2 score ≥2.

Lung function

Spirometry, body plethysmography and transfer coefficient of the lung for carbon monoxide (Jaeger MS-PFT Analyser Unit with Sentry Suite software version 2.19.96, Vyaire Medical, Mettawa, IL, USA) were measured as per the recommendations of the ERS and the American Thoracic Society guidelines [28].

Statistical analysis

The distribution of data was assessed using the D'Agostino-Pearson test. Parametric data were expressed as mean (standard deviation, SD) whilst non-parametric data were expressed as median (interquartile range, IQR). The capsaicin challenge and cough frequency data were presented as geometric mean (geometric standard deviation, SD). Parametrically distributed data were analysed with paired t-test to compare sample means for paired data. Comparison of non-parametric data was carried out using the Wilcoxon matched-pairs signed rank test for paired data, and Mann-Whitney U-test for unpaired data. Fisher's exact test and Chi-square test were utilised for categorical data. Correlations between variables were assessed with Spearman's rank-order correlation coefficient (ρ) for non-parametric data. P-values <0.05 were considered statistically significant. The threshold concentrations of capsaicin required to induce 2 and 5 coughs were calculated by interpolation of the log dose-response curve [20]. Any interpolated values of >1000 $\mu mol \cdot L^{-1}$ were assigned a value of 1000 $\mu mol \cdot L^{-1}$ [20]. From a previous study, we anticipated 10 or more participants to be a sufficient sample size for making intra-individual comparisons in a cough suppression test and a capsaicin challenge test [11, 19]. We therefore aimed to recruit 20-30 participants with COPD to achieve ≥10 COPD participants with and without chronic cough. All analyses were performed on Prism® Version 8.1.2c (GraphPad Software, San Diego, California, USA) for macOS version 10.14.5.

RESULTS

Participant characteristics

Twenty-seven participants with COPD, 11 participants with CRC and 13 healthy participants were recruited; demographics and clinical characteristics are shown in Table 1. Sixteen participants with COPD self-reported chronic cough whilst 11 participants with COPD reported no chronic cough. There was no

significant difference in age, gender, smoking status, FEV_1 and inhaler regime between participants with and without chronic cough (Table 1). COPD participants with self-reported chronic cough had significantly higher objective cough frequency than participants without self-reported chronic cough; geometric (SD) awake cough frequency 12.4 (2.0) vs. 1.9 (2.6) coughs·hr^{-1} respectively, mean difference (95% CI) 2.71 (1.70-3.72) fold difference ($p<0.001$). Amongst participants with COPD, the prevalence of current smokers was higher in those with chronic cough than in those without chronic cough, but this was not statistically significant ($p=0.093$). There was no difference in symptoms of cough hypersensitivity between COPD patients with cough and patients with CRC: median (IQR) LCQ item 9 scores (odour triggering cough): 3.0 (2.5-6.0) vs. 3.0 (2.0-4.8), $p=0.561$, and LCQ item 18 scores (speech trigger): 4.0 (2.5-5.0) vs. 3.5 (2.0-4.3), $p=0.707$, respectively. Sputum was reported in 63% of patients with COPD with cough compared to 9% in COPD patients without cough.

Standard capsaicin challenge test

Threshold capsaicin concentrations (C2 and C5) were significantly lower in COPD participants with chronic cough than those without (Table 2 and Figure 1). Amongst participants with COPD, the mean difference (95% CI) in C5 between participants with and without chronic cough was 3.72 (1.55-5.90) doubling doses ($p=0.003$). In comparison, the mean difference (95% CI) in C5 between participants with CRC and healthy participants was 3.66 (1.80–5.52) doubling doses ($p<0.001$) (Table 2). There was no significant difference in CRS between COPD participants with chronic cough and participants with CRC ($p=0.981$) (Figure 1).

Cough suppression test

Participants with COPD were able to suppress capsaicin-induced cough regardless of the presence of chronic cough (Table 2, and Figures 2 and 3). Capsaicin concentrations required to induce coughing were

substantially increased in both groups when participants voluntarily attempted to suppress their cough responses. In COPD without chronic cough, geometric mean (SD) C5 vs. CS5 were 44.50 (5.90) vs. 183.2 (6.37) $\mu mol \cdot L^{-1}$ respectively; mean difference (95% CI) 2.04 (0.93-3.15) doubling doses, p=0.006. Amongst COPD participants with chronic cough, corresponding values of C5 vs. CS5 were 3.36 (6.88) vs. 12.80 (8.33) $\mu mol \cdot L^{-1}$, respectively; mean difference (95% CI) 1.93 (0.95-2.90) doubling doses, p<0.001 (Table 2 and Figure 3). Female and male patients with COPD were able to suppress cough (Table E1). CS2 and CS5 were not significantly different between current and ex-smokers in participants with COPD; geometric mean (SD) CS2: 9.30 (5.83) vs. 6.98 (7.61) $\mu mol \cdot L^{-1}$ (p=0.537) and CS5: 24.76 (9.355) vs. 48.58 (12.17) $\mu mol \cdot L^{-1}$ (p=0.569), respectively. Healthy participants were also able to suppress capsaicin-induced cough (geometric mean (SD) C5 vs. CS5 45.89 (3.95) vs. 254.40 (3.78) $\mu mol \cdot L^{-1}$; mean difference (95% CI) 2.77 (1.25–4.28) doubling doses, p=0.033), whilst, in contrast, participants with CRC were not (geometric mean (SD) C5 vs. CS5: 3.86 (5.13) vs. 3.34 (5.01) $\mu mol \cdot L^{-1}$; mean difference (95% CI) -0.21 (-1.37-0.96) doubling doses, p=0.922; Figures 2 and 3). In patients with COPD, there was no association between smoking history (pack years) and CS5 (ρ=0.030, p=0.718) or C5 (ρ=-0.017, p=0.931). There was no significant difference in CS5 or C5 between COPD patients with or without sputum (p=0.713 and p=0.731 respectively).

Objective cough frequency in COPD

Twenty-four participants with COPD underwent 24-hour objective cough monitoring. Awake cough frequency was significantly associated with the capsaicin cough thresholds for 2 and 5 coughs without self-attempted suppression (C2: ρ=-0.411, p=0.046; C5: ρ=-0.430, p=0.036), (Table 3 and Figure 4). In addition, awake cough frequency was significantly associated with the capsaicin cough thresholds for 2 and 5 coughs with self-attempted suppression (CS2: ρ=-0.413, p=0.045; CS5: ρ=-0.420, p=0.041), (Table 3 and Figure 4).

Cough severity and cough-specific health status in COPD

Cough severity and urge to cough VAS scores were significantly higher in participants with chronic cough than those without; median (IQR) VAS scores 55 (34-69) vs. 7 (0-15) mm ($p=0.001$), and 65 (52-84) vs. 13 (0-29) ($p<0.001$), respectively. LCQ health status scores were lower (worse) in participants with chronic cough compared to those without; median (IQR) LCQ total scores 13.3 (8.3-17.3) vs. 20.0 (16.0-20.3) respectively ($p=0.005$). There was no significant association between cough suppression test threshold (CS5) and cough severity VAS, urge to cough VAS or LCQ health status scores (Table E2).

DISCUSSION

We investigated cough reflex sensitivity (CRS) and the ability to suppress capsaicin-evoked cough in patients with COPD with and without chronic cough in comparison to participants with CRC and healthy subjects. Cough reflex sensitivity was heightened in participants with chronic cough (COPD-cough and CRC) compared to those without cough (COPD-no cough and healthy subjects). COPD participants with and without chronic cough, and healthy participants were able to suppress capsaicin-evoked coughs. In contrast, participants with CRC were unable to suppress capsaicin-evoked cough. There were weak associations between cough reflex sensitivity and CS5, and objective cough frequency in patients with COPD.

Our data support the presence of cough reflex hypersensitivity in COPD, specifically associated with the presence of clinically significant cough, of a similar magnitude to participants with chronic refractory cough. As cough reflex hypersensitivity (CRH) was not demonstrated in the absence of chronic cough, CRH may not be a general feature of COPD. Although previous studies have reported cough reflex hypersensitivity in COPD, they did not characterise patients according to the presence or absence of

chronic cough [8, 9, 24, 29, 30]. In our study, 41% of COPD participants did not have a chronic cough. There was an association between cough reflex sensitivity and objectively assessed cough frequency, and this was weak and similar to that reported by Summer *et al* [7]. A wide range of cough reflex sensitivity was observed in patients with COPD, perhaps reflective of multiple mechanisms causing chronic cough in COPD, some of which are possibly also present in chronic refractory cough.

In contrast to patients with chronic refractory cough, patients with COPD could suppress cough, similarly to healthy subjects. In chronic refractory cough, a distinct inability to suppress cough has recently been reported by Cho *et al* [11]. Functional magnetic resonance brain imaging has suggested reduced activity of the central neural networks that regulate suppression of cough, specifically the dorso-medial prefrontal cortex and anterior mid-cingulate cortices [6, 31]. In addition, there were only weak associations between capsaicin concentration thresholds and objective cough frequency in patients with COPD. Our findings suggest important differences between the mechanism of cough in COPD to chronic refractory cough. In COPD, cough reflex hypersensitivity and other yet unknown mechanisms may predominate, whereas in chronic refractory cough an inability to suppress cough is probably also important. The inability of patients with chronic refractory cough to suppress cough may explain why patients with refractory cough have a much higher objectively measured cough frequency, and a greater urge to cough and cough severity compared to patients with chronic cough associated with COPD [32].

A reduction in the efficacy of cough inhibitory neural pathways in chronic refractory cough may have important implications for developing antitussive therapies. There are currently several promising novel therapies in development that target peripheral cough reflex hypersensitivity, such as inhibitors of the P2X3 sensory nerve ion channels that block activation by neurotransmitter ATP [33–35]. Whilst they are highly effective in many patients, up to 30% do not respond, and of those that respond favourably, most continue to cough at significantly elevated cough frequencies [35]. Anti-tussives that activate the

inhibitory neural pathways should be developed since they may benefit a significant number of patients by targeting alternative mechanisms. Indeed, speech therapy and physiotherapy interventions that train patients to suppress their cough have yielded promising results [5, 36]. Our data however suggests that they are likely to benefit specific groups of patients, such as chronic refractory cough and not others, such as COPD. The concept of different phenotypes of chronic cough is supported by the findings of Belvisi *et al* who reported differential responses to a range of tussive agents across several chronic lung disorders [9, 37]. Further support for heterogeneous phenotypes of cough is the finding that a novel nebulised form of Cromolyn (PA101) was effective in chronic cough associated with idiopathic pulmonary fibrosis and not chronic refractory cough [38].

There are some limitations to our study. The sample size for our study was small, particularly for subgroup analysis. The healthy participants were younger than the participants with COPD and CRC. Participants with chronic refractory cough compared to COPD with chronic cough had proportionately more female participants. This however was not statistically significant, and furthermore, our data suggests there was no effect of gender on the ability of COPD participants to suppress cough. We chose capsaicin as the tussive agent, since it is widely used and allows comparison with historic studies. Further studies should evaluate a range of tussive agents that evaluate hypersensitivity of other neural pathways. We were unable to evaluate the effect of smoking status in our COPD patients based on the presence of self-reported cough due to insufficient sample size. There are conflicting findings on the effect of smoking on CRS [7, 39]. In our study, there was no significant difference in the smoking status between the COPD participants with and without cough. Ando *et al* reported that smokers have higher thresholds for suppression during capsaicin inhalation compared to non-smokers in healthy subjects [40]. The impact of smoking on self-attempted cough suppression in COPD is unknown. There was however no significant difference observed in the threshold concentrations with self-attempted suppression between current and ex-smokers in participants with COPD in our study. An effect of

smoking on cough inhibitory pathways cannot be completely discounted and require investigation in future studies.

In conclusion, cough reflex hypersensitivity is associated with the presence of chronic cough in COPD but, in contrast to patients with chronic refractory cough, patients with COPD can effectively suppress capsaicin-evoked cough. Further studies should investigate the optimal tussive target for study of cough in COPD patients, and the factors responsible for cough reflex hypersensitivity in COPD. Further studies should also investigate inhibitory pathways in cough and why some patients can and others can't suppress their cough effectively.

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Table 1. Demographics and clinical characteristics of participants with chronic obstructive pulmonary disease with and without chronic cough, chronic refractory cough and healthy subjects

Table 2. Capsaicin dose thresholds without and with self-attempted cough suppression during tussive challenge tests in participants with chronic refractory cough and healthy subjects

Table 3. Relationships between awake cough frequency and threshold capsaicin concentrations required to elicit 1, 2 and 5 coughs with and without self-attempted suppression in participants with chronic obstructive pulmonary disease

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Figure 1. Threshold capsaicin concentrations required to elicit 5 coughs without (C5) self-attempted cough suppression in participants with chronic obstructive pulmonary disease with and without chronic cough, healthy subjects and participants with chronic refractory cough

Figure 2. Threshold capsaicin concentrations required to elicit 5 coughs with (CS5) self-attempted cough suppression in participants with chronic obstructive pulmonary disease with and without chronic cough, healthy subjects and participants with chronic refractory cough

Figure 3. Threshold capsaicin concentrations required to elicit 5 coughs without (C5) and with (CS5) self-attempted cough suppression in participants with **a.** COPD with chronic cough; **b.** COPD without chronic cough, **c.** chronic refractory cough, and in **d.** healthy subjects

a. COPD with chronic cough

b. COPD without chronic cough

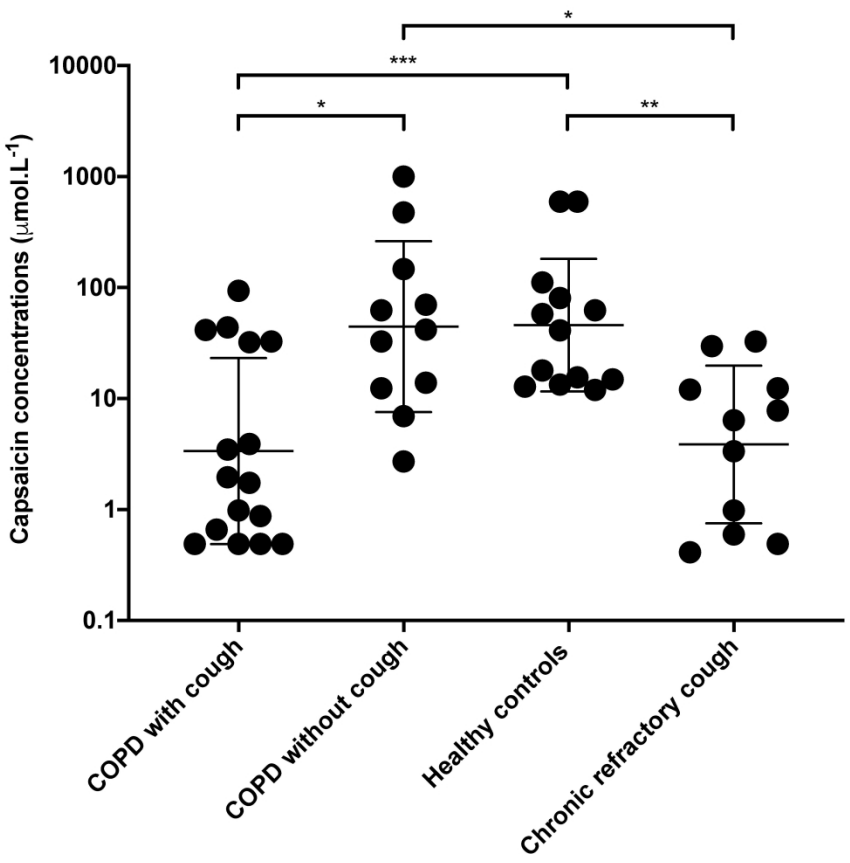
c. Chronic refectory cough

d. Healthy subjects

Figure 4. Association between awake cough frequency and threshold capsaicin concentrations required to elicit 5 coughs **a.** without self-attempted cough suppression (C5), and **b.** with self-attempted suppression (CS5)

a. C5

b. CS5



Data presented as geometric mean (SD).

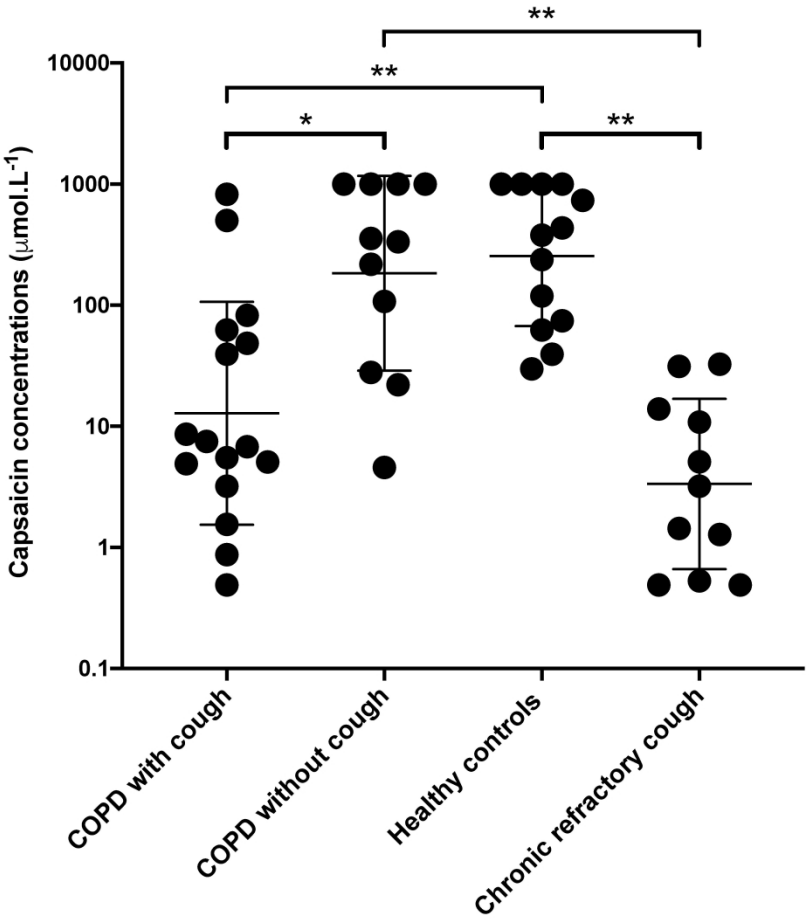
COPD = chronic obstructive pulmonary disease

*p=0.003

**p<0.001

***p=0.002

Participants with COPD and chronic cough vs. participants with CRC (p=0.981)

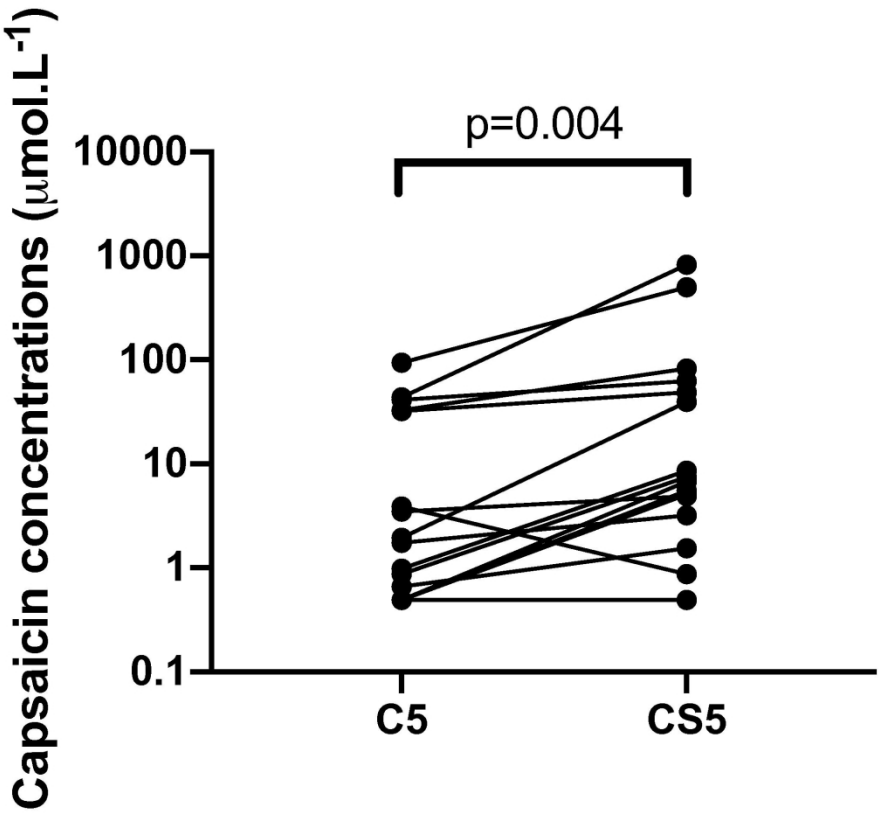


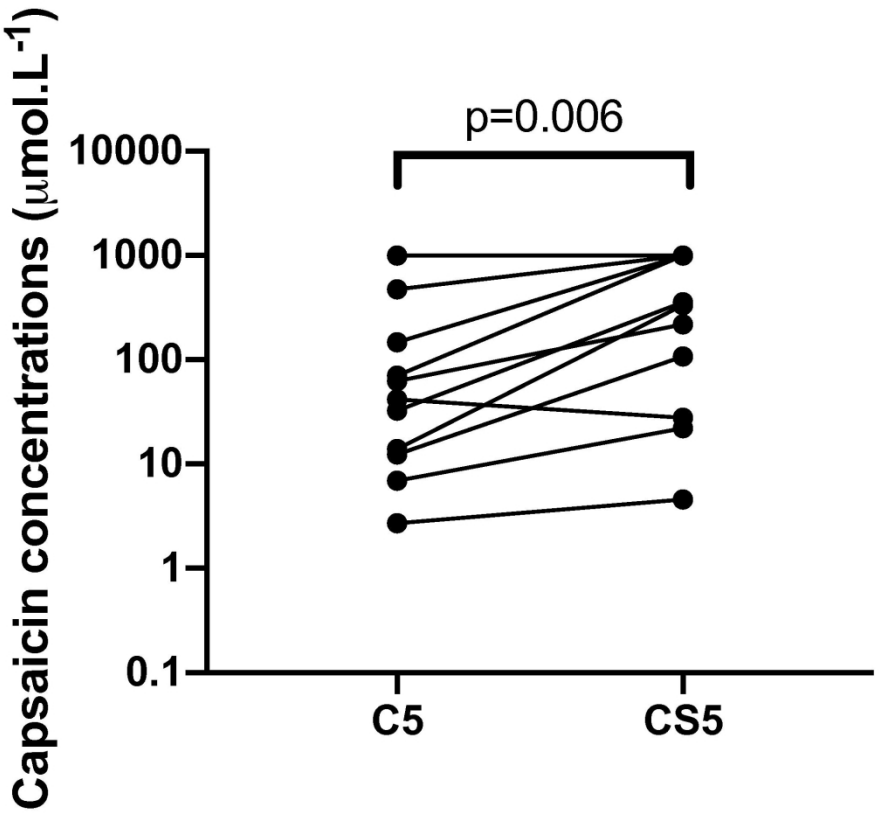
Data presented as geometric mean (SD).

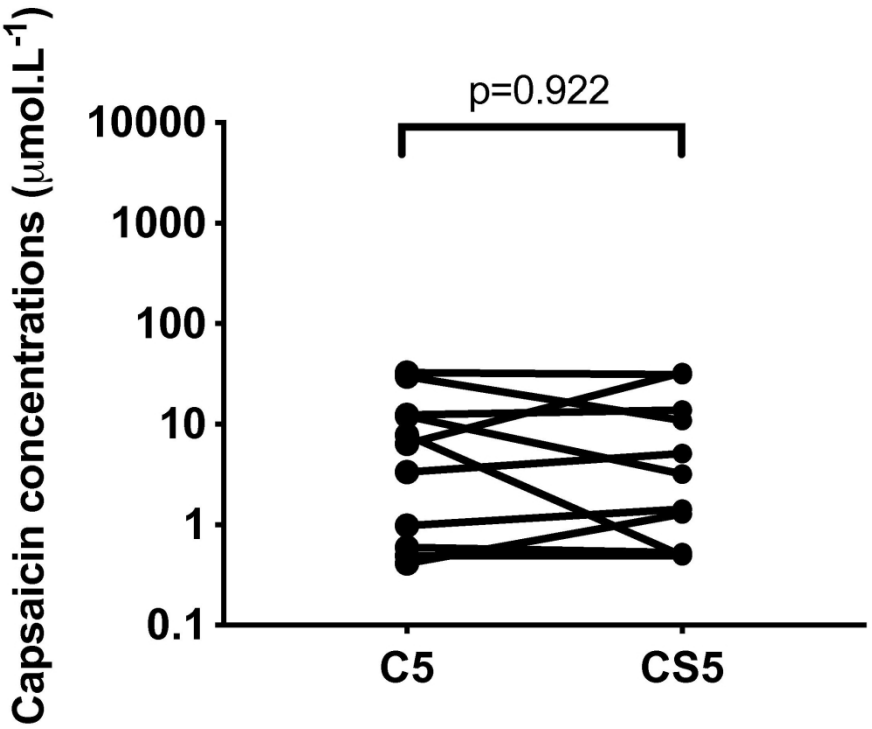
COPD = chronic obstructive pulmonary disease.

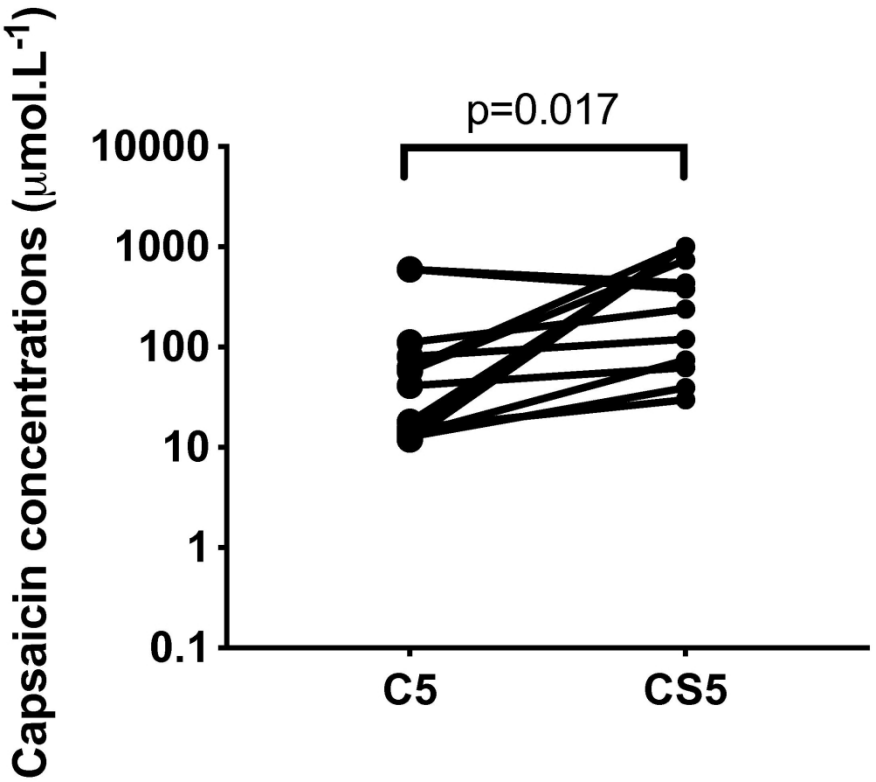
*p=0.005

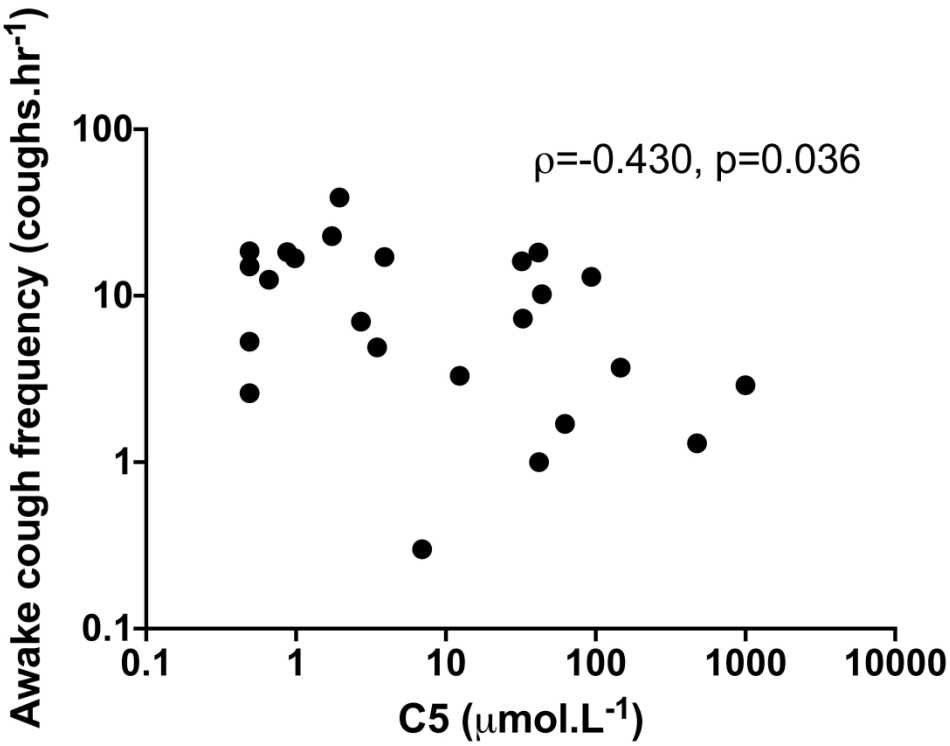
**p<0.001

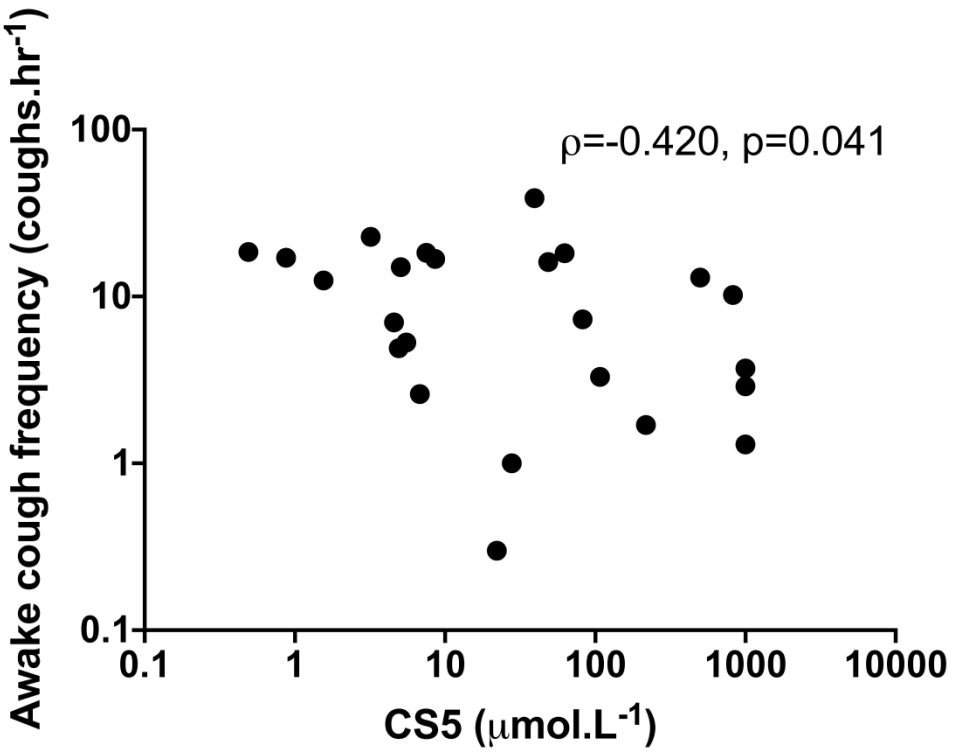

Capsaicin concentrations (μmol.L-1)
p=0.004
10000
1000
100
10
1
0.1
C5
CS5


Capsaicin concentrations (μmol.L-1)
p=0.006
10000
1000
100
10
1
0.1
C5
CS5


Capsaicin concentrations (μmol.L-1)
p=0.922
10000
1000
100
10
1
0.1
C5
CS5


Capsaicin concentrations (μmol.L-1)
p=0.017
10000
1000
100
10
1
0.1
C5
CS5


Awake cough frequency (coughs.hr-1)
100
10
1
0.1
ρ=-0.430, p=0.036
0.1
1
10
100
1000
10000
C5 (μmol.L-1)


Awake cough frequency (coughs.hr-1)
100
10
1
0.1
ρ=-0.420, p=0.041
0.1
1
10
100
1000
10000
CS5 (μmol.L-1)

Online supplement

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Table E1. Capsaicin dose thresholds without and with self-attempted cough suppression during tussive challenge tests (analysis by gender)

Table E2. Relationships of threshold capsaicin concentrations to elicit 1 (CS1), 2 (CS2) and 5 (CS5) coughs with cough severity visual analogue scale scores, urge to cough visual analogue scale scores and Leicester Cough Questionnaire (LCQ) in COPD

Table 1. Demographics and clinical characteristics of participants with chronic obstructive pulmonary disease with and without chronic cough, chronic refractory cough and healthy subjects

	COPD with chronic cough (n=16)	COPD without chronic cough (n=11)	Chronic refractory cough (n=11)	Healthy subjects (n=13)	p value
Age (years)[*]	66.0 (63.3-79.0)	70.0 (67.0-72.0)	64.0 (60.0-69.0)	50.0 (42.5-56.5)	<0.001[**]
Female[†]	8 (50)	5 (45)	7 (63)	8 (62)	0.772[††]
BMI ($kg \cdot m^{-2}$)[*]	30.0 (20.4-34.5)	24.1 (23.2-33.3)	30.5 (26.9-34.4)	23.7 (23.1-28.3)	0.031
Smoking status[†]					<0.001[‡‡]
Ex	8 (50)	9 (82)	2 (18)	5 (38)	
Current	8 (50)	2 (18)	0 (0)	0 (0)	
Never	0 (0)	0 (0)	9 (82)	8 (62)	
MRC dyspnoea scale[‡]	3 (2-4)	2 (1-3)	N/A	N/A	0.013
Spirometry[*]					

FEV_1 % predicted	60.0 (47.0-69.8)	43.0 (33.8-58.0)	100.0 (84.0-113.0)	98.0 (89.5-113.0)	<0.001[§§]
FVC % predicted	89.6 (77.5-102.1)	79.5 (72.0-104.8)	114.0 (87.0-124.0)	102.0 (91.0-120.0)	<0.025[IIII]
Inhaler regime[†]			N/A	N/A	0.941
LAMA	18	11			
LABA	16	9			
ICS	16	8			
CAT[‡]	28 (22-35)	18 (11-30)	N/A	N/A	0.003
24-hr cough monitoring[*]					
Awake cough count (coughs)[§]	169.7 (2.8)[II]	28.3 (2.7)[¶]	408.8 (2.1)[¶]	N/A	<0.001[¶¶]
Awake cough frequency ($coughs \cdot hr^{-1}$)[§]	12.4 (2.0)[II]	1.9 (2.6)[¶]	23.4 (2.1)[¶]		<0.001[¶¶]
Cough severity VAS (mm)[*]	55 (34-69)	7 (0-15)	85.0 (67.0-93.0)	N/A	<0.001[¶¶]
Urge to cough VAS (mm)[*]	65 (52-84)	13 (0-29)	83.0 (78.0-87.0)	N/A	<0.001[¶¶]
LCQ[*]				N/A	

Physical	4.0 (3.0-5.6)	6.5 (5.6-6.6)	3.8 (3.4-5.1)	<0.001[¶¶]
Psychological	4.4 (2.6-6.1)	6.7 (5.6-6.9)	3.7 (2.3-4.9)	<0.001[***]
Social	4.6 (2.8-7.0)	6.8 (5.6-6.8)	3.8 (2.5-5.8)	<0.001[†††]
Total	13.3 (8.3-17.3)	20.0 (16.0-20.3)	11.3 (8.4-13.9)	<0.001[‡‡‡]

Data presented as mean (SD), median (IQR) or absolute value (percentage) unless stated otherwise.

COPD = chronic obstructive pulmonary disease; BMI = body mass index; MRC = Medical Research Council; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LAMA = long-acting muscarinic antagonist; LABA = long-acting $beta_2$-agonist; ICS = inhaled corticosteroid; CAT = COPD Assessment Test; VAS = visual analogue scale; LCQ = Leicester Cough Questionnaire; CRC = chronic refractory cough

[*]Kruskal-Wallis test

[†]Chi-squared test

[‡]Mann-Whitney U-test

[§]Geometric mean (SD)

[||]n=16

[¶]n=8

[**]All p<0.013 except COPD with cough vs. COPD without cough (p=0.198), COPD with cough vs. CRC (p=0.287), COPD without cough vs. CRC (p=0.097).

[††]COPD with cough vs. COPD without cough (p >0.999)

[‡‡]All p<0.004 except COPD with cough vs. COPD without cough (p=0.093) and CRC vs. healthy subjects (p=0.276)

[§§]All p<0.001 except COPD with cough vs. COPD without cough (p=0.087) and CRC vs. healthy subjects (p=0.943)

[||||]All p<0.049 except COPD with cough vs. COPD without cough (p=0.394), COPD with cough vs. CRC (p=0.100), and CRC vs. healthy subjects (p=0.854)

[¶¶]All p<0.04

[***]All p<0.001 except COPD with cough vs. CRC (p=0.298)

[†††]All p<0.001 except COPD with cough vs. CRC (p=0.337)

[‡‡‡]All p<0.005 except COPD with cough vs. CRC (p=0.432)

Table 2. Capsaicin dose thresholds without and with self-attempted cough suppression during tussive challenge tests

	COPD with chronic cough (n=16)	COPD without chronic cough (n=11)	Chronic refractory cough (n=11)	Healthy subjects (n=13)	p values*
Standard capsaicin challenge					
C2 (μmol.L^{-1})	1.53 (4.24)	11.71 (6.55)	1.31 (4.89)	11.44 (2.82)	0.0006*
C5 (μmol.L^{-1})	3.36 (6.88)	44.50 (5.90)	3.86 (5.13)	45.89 (3.95)	0.0003†
With self-attempted cough suppression					
CS2 (μmol.L^{-1})	3.90 (4.16)	21.15 (8.40)	2.19 (4.24)	71.4 (4.26)	<0.0001‡
CS5 (μmol.L^{-1})	12.80 (8.33)	183.2 (6.37)	3.34 (5.04)	254.40 (3.78)	<0.0001§

Data presented as geometric mean (SD)

CS2 and CS5 = capsaicin concentrations to elicit 2 and 5 coughs during self-attempted suppression of coughing respectively; C2 and C5 = capsaicin concentrations to elicit 1, 2 and 5 coughs without self-attempted cough suppression respectively.

*Kruskal-Wallis test

*All p<0.007 except COPD with chronic cough vs. CRC (p=0.827) and COPD without chronic cough vs. healthy subjects (p=0.910)

†All p<0.003 except COPD with chronic cough vs. CRC (p=0.981) and COPD without chronic cough vs. healthy subjects (p=0.955)

[‡]All p<0.034 except COPD with chronic cough vs. CRC (p=0.294) and COPD without chronic cough vs. healthy subjects (p=0.119)

[§]All p<0.004 except COPD with chronic cough vs. CRC (p=0.112) and COPD without chronic cough vs. healthy subjects (p=0.717)

Table 3. Relationships between awake cough frequency and threshold capsaicin concentrations required to elicit 2 and 5 coughs with and without self-attempted suppression in participants with chronic obstructive pulmonary disease

	Awake cough frequency (coughs·hr^{-1})	
	Correlation coefficient	**p value**
With self-attempted cough suppression		
CS2 (μmol·L^{-1})	-0.413	0.045
CS5 (μmol·L^{-1})	-0.420	0.041
Without self-attempted cough suppression		
C2 (μmol·L^{-1})	-0.411	0.046
C5 (μmol·L^{-1})	-0.430	0.036

All correlation coefficients are Spearman's rank-order correlations.

CS2 and CS5 = capsaicin concentrations required to elicit 2 and 5 coughs with self-attempted suppression; C2 and C5 = capsaicin concentrations required to elicit 2 and 5 coughs without self-attempted suppression.

Table E1. Capsaicin dose thresholds without and with self-attempted cough suppression during tussive challenge tests (analysis by gender)

	C5 ($\mu mol \cdot L^{-1}$)	CS5 ($\mu mol \cdot L^{-1}$)	p value
Female			
COPD with chronic cough (n=8)	2.17 (8.5)	15.25 (10.65)	0.008*
Chronic refractory cough (n=7)	3.87 (5.75)	4.48 (4.62)	>0.999*
Male			
COPD with chronic cough (n=8)	5.22 (5.56)	10.75 (7.31)	0.047*
Chronic refractory cough (n=4)	3.86 (5.12)	1.53 (6.75)	0.750*

Data presented as geometric mean (SD)

*Wilcoxon matched-pairs signed rank test

Table E2. Relationships of threshold capsaicin concentrations to elicit 2 (CS2) and 5 (CS5) coughs with cough severity visual analogue scale scores, urge to cough visual analogue scale scores and Leicester Cough Questionnaire (LCQ) in COPD

	CS2		CS5	
	Correlation Coefficient	**p value**	**Correlation Coefficient**	**p value**
Cough severity VAS (mm)	0.112	0.580	-0.218	0.274
Urge to cough VAS (mm)	0.077	0.704	-0.256	0.197
LCQ				
Psych	0.260	0.209	0.281	0.174
Phys	0.210	0.313	0.176	0.401
Social	0.243	0.243	0.283	0.170
Total	0.241	0.246	0.249	0.230

All correlation coefficients are Spearman's rank-order correlations.

CS2 and 5 = capsaicin concentrations required to elicit 2 and 5 coughs with self-attempted suppression; VAS = visual analogue scale; LCQ = Leicester Cough Questionnaire; Psych = psychological; Phys = physical.