Cough hypersensitivity and suppression in COPD

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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. https://bit.ly/38UKzUO

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

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

Amongst patients with COPD, those with chronic cough (n=16) demonstrated heightened cough reflex sensitivity compared to those without chronic cough (n=11): geometric mean±SD capsaicin dose thresholds for five coughs (C5) 3.36±6.88 μmol·L^{-1} *versus* 44.50±5.90 μmol·L^{-1}, respectively (p=0.003). Participants with CRC also had heightened cough reflex sensitivity compared to healthy participants: geometric mean±SD C5 3.86±5.13 μmol·L^{-1} *versus* 45.89±3.95 μmol·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 μmol·L^{-1} *versus* 12.80±8.33 μmol·L^{-1} (p<0.001) and 44.50±5.90 μmol·L^{-1} *versus* 183.2±6.37 μmol·L^{-1} (p=0.006), respectively. This was also the case for healthy participants (C5 *versus* CS5: 45.89±3.95 μmol·L^{-1} *versus* 254.40±3.78 μmol·L^{-1}, p=0.033), but not those with CRC, who were unable to suppress capsaicin-evoked cough (C5 *versus* CS5: 3.86±5.13 μmol·L^{-1} *versus* 3.34±5.04 μmol·L^{-1}, p=0.922). C5 and CS5 were associated with objective 24-h cough frequency in patients with COPD: ρ= −0.430, p=0.036 and ρ= −0.420, p=0.041, respectively.

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

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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 and impaired cough suppression are thought to be important mechanisms [4–6]. Cough reflex hypersensitivity has been reported in patients with COPD but it is not known if this is a general feature of COPD or 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 CRC [10]. Cough suppression can be assessed clinically through modification of 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 (CRC) and healthy subjects. We 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-h 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 outpatient clinic. All had a clinician diagnosis of COPD (⩾10-pack year history of smoking and forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) 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 inhibitor medication. Participants who changed their smoking status or who developed a respiratory tract infection or exacerbation of COPD between recruitment and study completion were excluded from the analysis [16].

Consecutive patients with CRC (>8 weeks' duration) were recruited prospectively from a specialist cough clinic. The diagnosis of CRC was assessed by clinicians following British Thoracic Society recommendations for the management of chronic cough in adults [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 patients with CRC with the addition of the presence of cough in the past 8 weeks, and a ratio of FEV_1 to FVC <0.7. Healthy and CRC participants were contemporaneously recruited to another study [11].

Protocol

All participants underwent investigations over two visits separated by 5 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-h 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 at two separate visits in a random order.

Capsaicin challenge test

Cough reflex sensitivity was assessed as per 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 μmol·L^{-1}) at 1-min 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·min^{-1} was used for all participants. A valve was used to restrict the inspiratory flow to 0.5 L·s^{-1} [12, 19]. A minimum of three respiratory cycles was performed prior to the administration of each solution. The inspiratory and expiratory flow-volume signals were inspected in real-time by two operators (PSPC, HVF) to ensure a consistent and maximal inspiratory effort (0.5 L·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 two coughs (C2) and five 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 two coughs (CS2) and five coughs (CS5) were calculated by interpolation [11, 20].

Cough frequency monitoring

Cough frequency was assessed objectively over 24 h using the previously validated Leicester Cough Monitor (LCM) [21]. The LCM is an ambulatory system that comprises an MP3 recorder (ICD-PX333; Sony Corporation), a lapel free-field microphone (LFH9173; Philips, Amsterdam, the Netherlands) and 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·h^{-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 have 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 to 7; higher scores indicating better health status.

COPD-specific health status

COPD-specific health status was assessed with a validated self-administered eight-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 are expressed as mean±SD and non-parametric data are expressed as median (interquartile range (IQR)). The capsaicin challenge and cough frequency data are presented as geometric mean±geometric SD. Parametrically distributed data were analysed with a 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-squared test were used 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 two and five coughs were calculated by interpolation of the log dose-response curve [20]. Any interpolated values of >1000 μmol·L^{-1} were assigned a value of 1000 μmol·L^{-1} [20]. From a previous study, we anticipated ⩾10 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, CA, USA) for macOS version 10.14.5.

Results

Participant characteristics

In total, 27 participants with COPD, 11 participants with CRC and 13 healthy participants were recruited; demographics and clinical characteristics are shown in table 1. Of those with COPD, 16 self-reported chronic cough and 11 reported no chronic cough. There was no significant difference in age, sex, smoking

TABLE 1 Demographics and clinical characteristics of participants with COPD with and without chronic cough, participants with CRC and healthy subjects

	COPD with chronic cough	COPD without chronic cough	CRC	Healthy subjects	p-value
Subjects n	16	11	11	13	
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·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^{ff}
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$^{\#\#\#}$
Inhaler regime¶			N/A	N/A	0.941
LAMA	18 (100)	11 (100)			
LABA	16 (89)	9 (82)			
ICS	16 (89)	8 (73)			
CAT^{+}	28 (22–35)	18 (11–30)	N/A	N/A	0.003
24-h cough monitoring$^{\#}$					
Awake cough count (coughs)§	169.7±2.8^{f}	28.3±2.7$^{\#\#}$	408.8±2.1$^{\#\#}$	N/A	<0.001¶¶¶
Awake cough frequency coughs·h^{-1}§	12.4±2.0^{f}	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^{fff}

Data presented as mean±SD, median (IQR) or absolute value (%), unless stated otherwise. COPD: chronic obstructive pulmonary disease; BMI: body mass index; MRC: Medical Research Council; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid; CAT: COPD Assessment Test; VAS: visual analogue scale; LCQ: Leicester Cough Questionnaire; CRC: chronic refractory cough; N/A: not applicable. $^{\#}$: Kruskal–Wallis test; ¶: Chi-squared test; $^{+}$: Mann–Whitney U-test; §: geometric mean±SD; ^{f}: n=16; $^{\#\#}$: n=8; ¶¶: all p<0.013 except COPD with cough *versus* COPD without cough (p=0.198), COPD with cough *versus* CRC (p=0.287), COPD without cough *versus* CRC (p=0.097); $^{++}$: COPD with cough *versus* COPD without cough (p>0.999); §§: all p<0.004 except COPD with cough *versus* COPD without cough (p=0.093) and CRC *versus* healthy subjects (p=0.276); ^{ff}: all p<0.001 except COPD with cough *versus* COPD without cough (p=0.087) and CRC *versus* healthy subjects (p=0.943); $^{\#\#\#}$; all p<0.049 except COPD with cough *versus* COPD without cough (p=0.394), COPD with cough *versus* CRC (p=0.100) and CRC *versus* healthy subjects (p=0.854); ¶¶¶: all p<0.04; $^{+++}$: all p<0.001 except COPD with cough *versus* CRC (p=0.298); §§§: all p<0.001 except COPD with cough *versus* CRC (p=0.337); ^{fff}: all p<0.005 except COPD with cough *versus* CRC (p=0.432).

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 mean±SD awake cough frequency 12.4±2.0 coughs·h^{-1} *versus* 1.9±2.6 coughs·h^{-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) *versus* 3.0 (2.0–4.8) (p=0.561); and LCQ item 18 scores (speech trigger): 4.0 (2.5–5.0) *versus* 3.5 (2.0–4.3) (p=0.707), respectively. Sputum was reported in 63% of participants with COPD with cough compared to 9% in COPD participants 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 cough reflex sensitivity 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 *versus* CS5 was 44.50± 5.90μmol·L^{-1} *versus* 183.2±6.37 μmol·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 *versus* CS5 were 3.36±6.88 μmol·L^{-1} *versus* 12.80±8.33 μmol·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 participants with COPD were able to suppress cough (supplementary table E1). CS2 and CS5 were not significantly different between current and ex-smokers in participants with COPD: geometric mean±SD for CS2 was 9.30±5.83 μmol·L^{-1} *versus* 6.98±7.61 μmol·L^{-1} (p=0.537), and for CS5 was 24.76±9.355 μmol·L^{-1} *versus* 48.58±12.17 μmol·L^{-1} (p=0.569), respectively. Healthy participants were also able to suppress capsaicin-induced cough: geometric mean±SD for C5 *versus* CS5 of 45.89±3.95 μmol·L^{-1} *versus* 254.40±3.78 μmol·L^{-1}, mean difference (95% CI) 2.77 (1.25–4.28) doubling doses (p=0.033). In contrast, participants with CRC could not suppress capsaicin-induced cough: geometric mean±SD for C5 *versus* CS5 of 3.86±5.13 μmol·L^{-1} *versus* 3.34±5.01 μmol·L^{-1}, mean difference (95% CI) −0.21 (−1.37–0.96) doubling doses (p=0.922) (figures 2 and 3). In participants with COPD, there was no association between smoking history (pack years) and

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

	COPD with chronic cough	COPD without chronic cough	CRC	Healthy subjects	p-values[#]
Subjects n	16	11	11	13	
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[f]

Data presented as geometric mean±SD, unless stated otherwise. COPD: chronic obstructive pulmonary disease; CRC: chronic refractory cough; C2 and C5: capsaicin concentrations to elicit two and five coughs without self-attempted cough suppression; CS2 and CS5: capsaicin concentration to elicit two and five coughs during self-attempted suppression of coughing. [#]: Kruskal–Wallis test; [¶]: all p<0.007 except COPD with chronic cough *versus* CRC (p=0.827) and COPD without chronic cough *versus* healthy subjects (p=0.910); [+]: all p<0.003 except COPD with chronic cough *versus* CRC (p=0.981) and COPD without chronic cough *versus* healthy subjects (p=0.955); [§]: all p<0.034 except COPD with chronic cough *versus* CRC (p=0.294) and COPD without chronic cough *versus* healthy subjects (p=0.119); [f]: all p<0.004 except COPD with chronic cough *versus* CRC (p=0.112) and COPD without chronic cough *versus* healthy subjects (p=0.717).

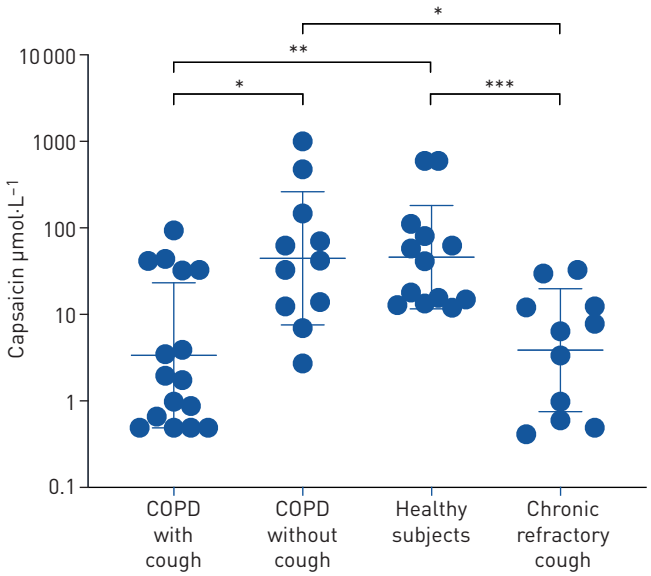

FIGURE 1 Threshold capsaicin concentrations required to elicit five coughs without self-attempted cough suppression in patients with chronic obstructive pulmonary disease (COPD) with and without chronic cough, in healthy subjects and in patients with chronic refractory cough. Data presented as geometric mean±SD. Patients with COPD and chronic cough *versus* patients with chronic refractory cough, p=0.981. *: p=0.003; **: p=0.002; ***: p<0.001.

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 participants with or without sputum (p=0.713 and p=0.731 respectively).

Objective cough frequency in COPD

A total of 24 participants with COPD underwent 24-h objective cough monitoring. Awake cough frequency was significantly associated with the capsaicin cough thresholds for two and five coughs without

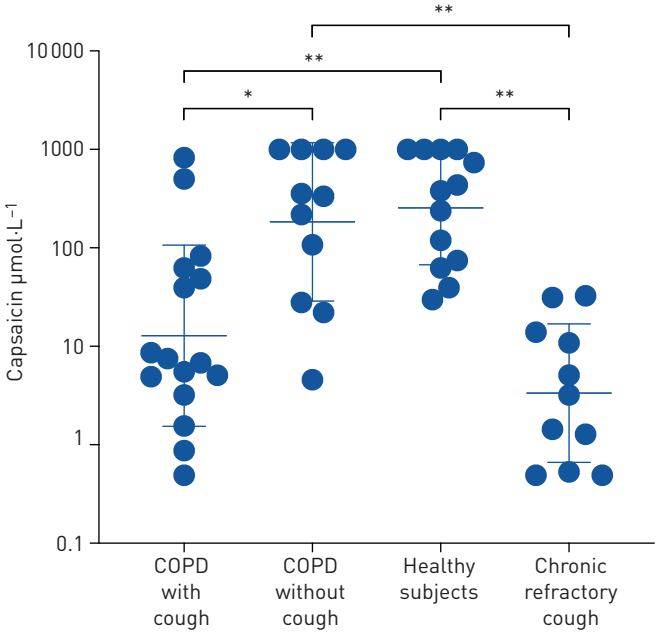

FIGURE 2 Threshold capsaicin concentrations required to elicit five coughs with self-attempted cough suppression in patients with chronic obstructive pulmonary disease (COPD) with and without chronic cough, in healthy subjects and in patients with chronic refractory cough. Data presented as geometric mean±SD. *: p=0.005; **: p<0.001.

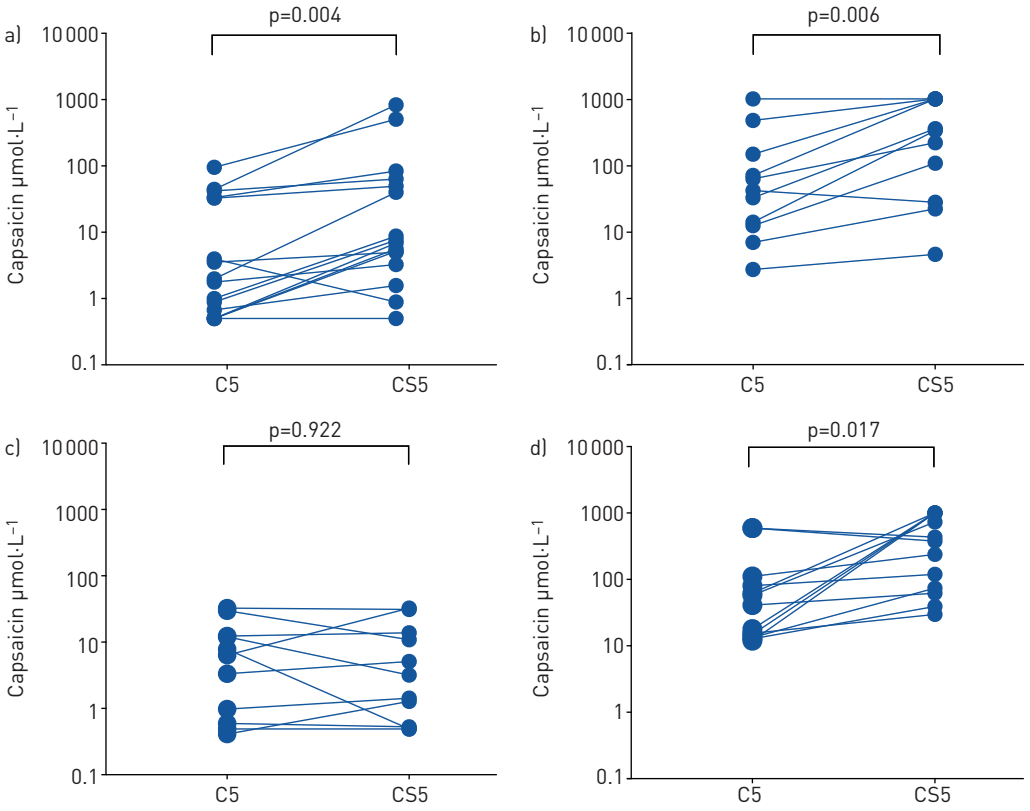

FIGURE 3 Threshold capsaicin concentrations required to elicit five coughs without (C5) and with (CS5) self-attempted cough suppression in patients with a) chronic obstructive pulmonary disease (COPD) with chronic cough; b) COPD without chronic cough; c) chronic refractory cough; and in d) healthy subjects.

self-attempted suppression (C2: ρ= −0.411, p=0.046; C5: ρ= −0.430, p=0.036) (table 3 and figure 4). Awake cough frequency was also significantly associated with the capsaicin cough thresholds for two and five 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 for cough severity 55 mm (34 mm–69 mm) *versus* 7 mm (0 mm–15 mm) (p=0.001), and for urge to cough 65 mm (52 mm–84 mm) *versus* 13 mm (0 mm–29 mm)

TABLE 3 Relationships between awake cough frequency and threshold capsaicin concentrations required to elicit two and five coughs with and without self-attempted suppression in patients with COPD

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

All correlation coefficients are Spearman's rank-order correlations. COPD: chronic obstructve pulmonary disease; CS2 and CS5: capsaicin concentrations required to elicit two and five coughs with self-attempted suppression; C2 and C5: capsaicin concentrations required to elicit two and five coughs without self-attempted suppression.

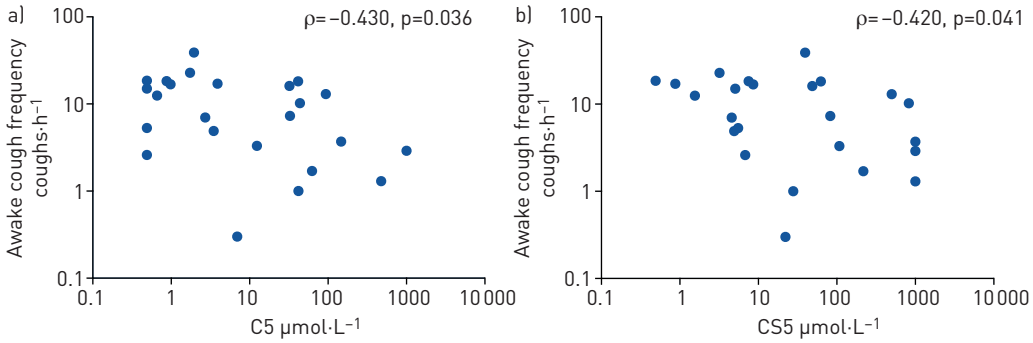

FIGURE 4 Association between awake cough frequency and threshold capsaicin concentrations required to elicit five coughs a) without self-attempted cough suppression (C5) and b) with self-attempted suppression (CS5).

(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) *versus* 20.0 (16.0–20.3) (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 (supplementary table E2).

Discussion

We investigated cough reflex sensitivity and the ability to suppress capsaicin-evoked cough in participants 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 participants 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 that in participants with CRC. Because cough reflex hypersensitivity was not demonstrated in the absence of chronic cough, cough reflex hypersensitivity may not be a general feature of COPD. Although previous studies have reported cough reflex hypersensitivity in COPD, they did not characterise participants 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; this was weak and similar to that reported by Sumner *et al.* [7]. A wide range of cough reflex sensitivity was observed in participants with COPD, perhaps reflective of multiple mechanisms causing chronic cough in COPD, some of which are possibly also present in CRC.

In contrast to participants with CRC, those with COPD could suppress cough, similarly to healthy subjects. In CRC, 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 participants with COPD. Our findings suggest important differences between the mechanisms of cough in COPD and CRC. In COPD, cough reflex hypersensitivity and other yet unknown mechanisms may predominate, whereas in CRC an inability to suppress cough is probably also important. The inability of participants with CRC 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 CRC 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]. Antitussives that activate the inhibitory neural pathways should be developed because 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 those with CRC, and not others, such as those with COPD. The concept of different phenotypes of chronic cough is supported by the findings of Belvisi *et al.* [9], who reported differential responses to a range of tussive agents across several chronic lung disorders [37]. Further support for heterogeneous phenotypes of cough is the finding that a novel nebulised form of cromolyn (PA101) is effective in chronic cough associated with idiopathic pulmonary fibrosis and not CRC [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. There were proportionally more female participants with CRC compared to with COPD with chronic cough. This, however, was not statistically significant; furthermore, our data suggest there was no effect of sex on the ability of COPD participants to suppress cough. We chose capsaicin as the tussive agent because 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 participants based on the presence of self-reported cough owing to insufficient sample size. There are conflicting findings on the effect of smoking on cough reflex sensitivity [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.* [40] reported that smokers have higher thresholds for suppression during capsaicin inhalation compared to non-smoker healthy subjects. 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 requires investigation in future studies.

In conclusion, cough reflex hypersensitivity was associated with the presence of chronic cough in COPD but, in contrast to participants with CRC, participants with COPD could 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 cannot suppress their cough effectively.

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