

Laryngeal Dysfunction in Cough Hypersensitivity Syndrome: A Cross-Sectional Observational Study



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What is already known about this topic? Laryngeal symptoms suggesting laryngeal dysfunction have been demonstrated in patients with cough hypersensitivity syndrome.

What does this article add to our knowledge? Laryngeal dysfunction during phonation breathing and swallowing is common in patients with chronic cough and is similar to other laryngeal conditions.

How does this study impact current management guidelines? Laryngeal function should be considered in patients with cough hypersensitivity syndrome and can be targeted by speech pathology interventions.

BACKGROUND: Chronic refractory cough (CRC), a phenotype of cough hypersensitivity syndrome (CHS), is a disabling problem. Laryngeal dysfunction may be important in CRC and CHS because laryngeal symptoms are common; however, the role of laryngeal dysfunction in CHS has not been systematically examined.

OBJECTIVE: To determine the nature of laryngeal dysfunction in patients with CRC and compare with the related laryngeal conditions of vocal cord dysfunction (VCD) and muscle tension dysphonia (MTD).

METHODS: A cross-sectional analytic design was used. We recruited 69 participants including healthy controls and patients with CRC, VCD, and MTD who were referred for behavioral speech interventions. Participants underwent a comprehensive assessment of laryngeal function during breathing, phonation, and swallowing.

RESULTS: Cough frequency was high in patients with CRC (10.2 coughs/h) and VCD (16.5 coughs/h), but low in healthy controls (1.5 coughs/h) ($P < .001$). Patients with CRC, VCD, and MTD had impaired voice-related quality of life (vs controls,

$P < .05$) and laryngeal hypersensitivity (vs controls, $P < .05$). Most voice assessment measures (3 out of 4) were significantly impaired in the CRC group compared with controls and were similar to the VCD and MTD groups. Paradoxical vocal fold movement during respiration was present in 47% of the patients with CRC at rest and in 67% after odor challenge. Mediolateral laryngeal constriction during phonation was present in 45% of the participants with CRC, 93% of the participants with VCD ($P < .001$ vs CC), and 64% of the participants with MTD.

CONCLUSIONS: Laryngeal dysfunction is common in CRC and CHS and may contribute to CHS mechanisms. Assessment and treatment of laryngeal dysfunction using speech pathology interventions are likely to be beneficial in CHS. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:2087-95)

Key words: Laryngeal hypersensitivity; Chronic cough; Vocal cord dysfunction; Muscle tension dysphonia; Paradoxical vocal fold movement; Cough hypersensitivity syndrome

INTRODUCTION

The current view of chronic cough (CC), based on the anatomic diagnostic protocol,¹ identifies cough as secondary to activation of the peripheral sensory limb of the cough reflex by one of several common diseases, including asthma, rhinosinusitis, and gastroesophageal reflux disease (GERD).² This theory has guided the management of cough, with the implication that treatment directed at the underlying disease will successfully resolve the cough. This approach remains useful, but recently several limitations have been recognized. First, many individuals with these diseases do not develop cough.^{3,4} Second, specific treatment of these diseases in patients with cough is not always effective in resolving cough (termed refractory chronic cough).⁵ Finally, cough can occur in the absence of any of these associated diseases (termed idiopathic chronic cough).⁶ Collectively, these features have been referred to as chronic refractory cough (CRC).

The concept of cough hypersensitivity syndrome (CHS) was developed to address the limitations in the current view of CC.

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Abbreviations used

CAPE-V- Consensus Auditory Perceptual Evaluation of Voice
 CC- Chronic cough
 CHS- Cough hypersensitivity syndrome
 CRC- Chronic refractory cough
 GERD- Gastroesophageal reflux disease
 LHQ- Laryngeal Hypersensitivity Questionnaire
 LMD-Phon- Laryngeal motor dysfunction affecting phonation
 LMD-Resp- Laryngeal motor dysfunction affecting respiration
 MPT- Maximum phonation time
 MTD- Muscle tension dysphonia
 VCD- Vocal cord dysfunction
 VHI- Voice Handicap Index

CHS is characterized by chronic persistent cough that is annoying for the individual and typically triggered by low levels of thermal, mechanical, or chemical stimuli.^{7,8} It is unexplained by associated medical conditions and there is poor response to treatment of associated medical conditions.⁸ This paradigm shift conceptualizes cough primarily as a manifestation of cough hypersensitivity, where heightened cough reflex sensitivity is the defining characteristic of the condition. Associated diseases, such as asthma, GERD, or rhinosinusitis, act as triggers for cough in an already cough-hypersensitive patient.⁹ In CHS, a trigger, either disease or exposure to noxious stimuli, combined with underlying cough sensitivity leads to CC (Figure 1). There is highly increased cough sensitivity, with features of central sensitization of the cough reflex whereby a nontussive stimulus triggers cough.^{10,11} This concept identifies the need to treat both cough hypersensitivity and the underlying disease to achieve successful clinical outcomes. It explains why treatment of a cough-associated disease (eg, GERD) may not be effective in controlling cough,¹² and suggests the need for an additional treatment approach based on treating cough hypersensitivity. It also removes the need for subcategories of cough such as idiopathic or refractory cough.

Although CHS is an attractive concept, the mechanism of CHS is not well understood¹³ and there are additional clinical observations that are not explained by CHS alone. We have identified a role for laryngeal dysfunction in CRC. For the purpose of this article, *laryngeal dysfunction* has been defined as abnormal movement of the vocal folds or supraglottic structures during respiration or phonation.¹¹ The larynx is rich in cough nerve endings, and laryngeal hypersensitivity has been demonstrated in patients with CHS and related laryngeal conditions.¹¹ Many patients with CRC localize symptoms to the larynx.¹⁴ Patients with CRC have also been reported to show laryngeal dysfunction, such as paradoxical vocal fold movement affecting respiration¹⁵ and dysphonia during vocalization.^{11,16,17} Cough is also frequently present in primary laryngeal disorders where there is established laryngeal dysfunction, such as muscle tension dysphonia (MTD) and vocal cord dysfunction (VCD).¹⁸ This suggests that laryngeal dysfunction may be an important element in CHS. However, there is limited objective data that characterize laryngeal dysfunction in patients with CHS, and the role of laryngeal dysfunction as a mechanism of CHS has not been confirmed. Similarly, it is unknown whether the pattern of laryngeal dysfunction in CHS is similar to the pattern in conditions with established laryngeal dysfunction such as MTD and VCD. If laryngeal dysfunction can be demonstrated in patients

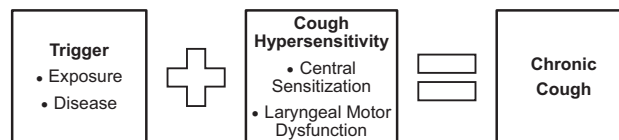


FIGURE 1. Concept of cough hypersensitivity syndrome as described by Song et al⁹ and modified by the current authors where CC is the result of disease or exposure to triggers in an individual with increased hypersensitivity. The components of cough hypersensitivity include central sensitization and laryngeal motor dysfunction.

with CHS, it suggests that laryngeal dysfunction might be a contributing mechanism for cough and that treatment success may depend on the degree to which laryngeal dysfunction is targeted.

The aim of this study was to determine the nature and extent of laryngeal dysfunction in patients with CRC and the related laryngeal conditions of VCD and MTD. We hypothesized that laryngeal dysfunction would be present in patients with CRC and would be similar to other laryngeal conditions. Specific hypotheses were as follows:

1. Laryngeal dysfunction would be present in CRC, VCD, and MTD and would be significantly worse than in healthy controls.
2. There would be no significant difference in the prevalence, pattern, and severity of laryngeal dysfunction between the clinical groups (CRC, MTD, and VCD).

METHODS

Design

The design was a cross-sectional observational study of 4 groups of participants: CRC, VCD, MTD, and healthy controls. Participants in the clinical groups were referred to the Speech Pathology Department at John Hunter Hospital, New South Wales, Australia, between 2014 and 2017 for behavioral management of their symptoms.

Participants

Participants had a primary diagnosis of CRC, VCD, or MTD by a respiratory physician or otolaryngologist. Other conditions causing cough, dyspnea, or dysphonia had been excluded. Exclusion criteria included recent upper respiratory tract infection, lung pathology, abnormal chest radiograph, current or recent smoking, untreated asthma, untreated rhinitis, untreated GERD, significant psychological or cognitive factors that preclude the ability to participate in the assessment, neurological impairment, current angiotensin-converting enzyme inhibitor or neuromodulator use, cough productive of purulent sputum, and current or recent (within the last 12 months) speech pathology intervention. Patients not fitting the criteria were assessed by an adjudication panel to confirm the diagnosis.

CRC was defined as cough that was problematic for the patient and had persisted for at least 8 weeks despite medical treatment based on the anatomic diagnostic protocol.¹ These participants were referred by respiratory physicians for behavioral management of cough.

Participants in the VCD group had a clinical diagnosis of VCD made by an otolaryngologist or respiratory physician, and dyspnea as

a dominant symptom. Patients had clinical symptoms of VCD such as inspiratory dyspnea, noisy breathing, and throat tightness. Asthma and other pulmonary diseases were excluded as a reason for the respiratory symptoms. The diagnosis was confirmed by objective testing, including laryngoscopy, laryngeal computed tomography, hypertonic saline challenge, or flow volume loops.

MTD was diagnosed by otolaryngologists. Patients had a deviation in perceptual voice quality and excessive tension in the intrinsic and/or extrinsic laryngeal muscles^{19,20} in the absence of any structural, neurological, or significant psychological pathology.

Healthy controls were recruited from the Hunter Medical Research Institute volunteer register and by word of mouth. They had no history of voice disorder, CC, asthma, rhinosinusitis, GERD, or symptoms of breathing difficulty, cough, dysphonia, and/or swallowing difficulty.

Measurements

Participants who met the eligibility criteria attended a single assessment visit. A panel of investigations was used to assess laryngeal function (Table I), which measured the domains of voice-related quality of life, laryngeal hypersensitivity, voice, cough, swallowing, and laryngeal motor function.

Voice-related quality of life was measured using the Voice Handicap Index (VHI),²¹ which is a 30-item self-administered questionnaire. It differentiates individuals with voice dysfunction from healthy controls and measures change after treatment. Scores less than 10 are abnormal. The Laryngeal Hypersensitivity Questionnaire (LHQ)²² is a 14-item self-administered questionnaire that measures the patient perception of laryngeal sensation. Scores less than 17.1 are abnormal.

Assessment of voice included several investigations (Table I). Maximum phonation time (MPT) is the maximum amount of time modal phonation can be sustained on one breath. It is an indicator of glottal efficiency and respiratory support.^{24,25} Auditory perceptual voice analysis of connected speech was assessed using the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V),²⁶ a tool that rates the presence and severity of auditory perceptual features of voice. Phonation frequency range, which is the maximum range of frequencies produced by the voice, was measured using the PRAAT acoustic program. Electroglottography was conducted using the laryngograph speech studio. The key measure was the percentage of irregularity of the closed phase of vocal fold vibration.

Cough frequency was measured during 24-hour ambulatory cough monitoring using the Leicester Cough Monitor.²³ Swallowing was tested using the timed swallow test²⁷ to assess the efficiency of swallowing. The speed of swallowing (mL/s) was calculated for each participant.

Participants in the clinical groups underwent functional transnasal laryngoscopy and odor challenge. This procedure was conducted using a flexible endoscope with video chip (Tele Pack X LED [model number TP100], Storz, Tuttlingen, Germany). The nasendoscope was inserted through the nares to sit above the vocal folds after 2 sprays of lidocaine + phenylephrine (Flo, ENT technologies Ltd Pty, Hawthorn East, Australia) to the anterior nares. The larynx was observed during quiet respiration, modal phonation with steady light and stroboscopy, and connected speech. The odor challenge was conducted using the protocol by Forrest et al²⁸ by placing a jar with cotton wool impregnated with perfume ("Papillons and Fleurs" Eau de Parfum) under the nares for 30 seconds and instructing the participant to breathe through

TABLE I. Laryngeal dysfunction measurement panel

Measurement	Domain
VHI ²¹	Voice-related quality of life: normal scores are <10
LHQ ²²	Laryngeal hypersensitivity: normal scores are >17.0
MPT (s)	Voice: normal values are >15.0 s
CAPE-V overall severity	Voice (auditory perceptual analysis): normal values are 0
Phonation frequency range (semitones)	Voice: normal values are >23 semitones
Electroglottography: irregularity of closed phase (%)	Voice: normal values are <11%
Cough frequency (coughs/h): Leicester Cough Monitor ²³	Cough: normal values are <3 coughs/h
Timed swallow test (mL/s)	Swallow: normal values are >10 mL/s
Vocal fold closure during phonation	Laryngeal function: laryngoscopy
LMD-Resp during quiet respiration	
Mediolateral constriction during respiration	
Anterior-posterior constriction during respiration	
LMD-Resp during odor challenge	

their nose. Participants were rated by 2 independent raters as having laryngeal motor dysfunction affecting respiration (LMD-Resp) if they demonstrated moderate-severe paradoxical vocal fold movement during either quiet respiration or odor challenge. Participants were rated as having laryngeal motor dysfunction affecting phonation (LMD-Phon) if they demonstrated abnormal vocal fold closure during phonation, moderate-severe mediolateral constriction of supraglottic structures during phonation, or moderate-severe anterior-posterior constriction during phonation. Laryngoscopic results were scored using standardized scoring systems.^{29,30}

Data analysis

Data were analyzed using descriptive statistics and one-way between-group ANOVA. Planned comparisons were used to determine whether there was a significant difference between the clinical groups and healthy controls (hypothesis 1), and whether there was a difference between the clinical groups (hypothesis 2). Significance was accepted when *P* was less than .05. A Bonferroni correction was made to account for the multiple comparisons, bringing the significance level to *P* = .0167 for both hypotheses 1 and 2. Secondary analysis was conducted on the patients in all clinical groups who had significant cough symptoms (defined as an abnormal Leicester Cough Questionnaire score and abnormal results on ambulatory cough frequency monitoring) to determine dominant patterns of laryngeal motor dysfunction.

The sample size was calculated on the basis of previous studies using the LHQ score. The prespecified difference between patient and control groups was 4.8 with an SD of 3.6. It was estimated that 18 experimental subjects and 18 control subjects were needed to test the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The type I error probability associated with this test of this null hypothesis is 0.01.

TABLE II. Demographic characteristics

Characteristic	Healthy controls (N = 14)	CRC (N = 20)	VCD (N = 20)	MTD (N = 17)
Age (y), mean $\pm$ SD	51 $\pm$ 13	57 $\pm$ 12	59 $\pm$ 17	53 $\pm$ 12
Sex, female (%)	64	81	84	65
BMI, mean $\pm$ SD	26.07 $\pm$ 5.7	31.5 $\pm$ 5.3	30.8 $\pm$ 7.8	30.15 $\pm$ 4.9
FEV ₁ % predicted, mean $\pm$ SD	105 $\pm$ 16.7	85 $\pm$ 12	84 $\pm$ 14	81 $\pm$ 17
FVC% predicted, mean $\pm$ SD	106 $\pm$ 16.2	81 $\pm$ 21	89 $\pm$ 21	84 $\pm$ 17
LCQ score, mean $\pm$ SD	—	13.6 $\pm$ 3.7	13.5 $\pm$ 3.7	19.0 $\pm$ 2.4
Dominant symptom	NA	Cough	Dyspnea	Dysphonia
Duration of symptoms (mo), mean $\pm$ SD	—	54.15 $\pm$ 74.7	63.9 $\pm$ 87.64	89.3 $\pm$ 153.4
Cough severity,* mean $\pm$ SD	1.4 $\pm$ 0.5	3.8 $\pm$ 0.8	3.4 $\pm$ 0.8	2.8 $\pm$ 0.7
Prevalence of abnormal cough	0%	100%	90%	30%
Comorbid diagnoses,† n				
Gastroesophageal reflux	0	11	12	9
Asthma	0	4	10	5
Rhinosinusitis	0	8	11	9
Obstructive sleep apnea	0	1	3	1
Previous treatments for cough, n				
Gastroesophageal reflux medication	NA	15	15	9
Fundoplication	NA	1	0	0
Asthma treatment	NA	11	15	7
Oral corticosteroids	NA	0	2	0
Rhinosinusitis medication	NA	10	10	10
CPAP trial	NA	1	3	1
Antibiotics	NA	5	2	1
Over-the-counter cough medication	NA	3	2	0
Medicated throat lozenges	NA	4	3	0
Withdrawal of ACE inhibitor	NA	2	0	0
Smoking status				
Never smoker	14	14	11	12
Ex-smoker‡	0	6	9	5

ACE, Angiotensin-converting enzyme; BMI, body mass index; CPAP, continuous positive airway pressure; FVC, forced vital capacity; LCQ, Leicester Cough Questionnaire; NA, not applicable.

*Cough severity rated on a 5-point ordinal scale, where 1 = no symptoms and 5 = severe symptoms.

†All comorbid conditions had been treated before assessment.

‡Ex-smokers were at least 6 wk since cessation.

RESULTS

Of the 108 potential participants screened for the clinical groups in this study, 69 met the eligibility criteria. Reasons for exclusion were laryngeal pathology (n = 2), other active respiratory disease (n = 9), purulent sputum (n = 3), pregnancy (n = 1), previous stroke (n = 1), symptoms not significant (n = 6), previous speech pathology intervention (n = 2), inadequate medical diagnosis (n = 4), taking angiotensin-converting enzyme inhibitors (n = 1), currently smoking (n = 2), taking neuromodulators (n = 7), or symptoms acute and not chronic (n = 1). Ten participants who met the eligibility criteria declined participation in the study (did not want laryngoscopy [n = 4]; too many other appointments [n = 3]; no reason provided [n = 3]). Of the 59 who were recruited to the study, 2 failed to attend their assessment visit and were excluded from the study. Demographic details are presented in Table II. Most of the participants in both groups were female and there was no significant difference in age between participant groups ($P = .290$).

Ambulatory cough monitoring

Participants with CRC recorded a mean 24-hour ambulatory cough count of 10.2 coughs/h. Those with VCD also had a high

cough count of 16.5 coughs/h. Cough counts were low in the MTD and healthy groups (Table III; Figure 2). There was a significant difference between all groups ($P = .002$). The number of coughs per hour was significantly greater in the clinical groups combined than in healthy controls ($P < .001$) and there was no significant difference between the clinical groups (Bonferroni-corrected $P > .00167$).

Voice Handicap Index (quality of life)

Results of the laryngeal dysfunction measurements are presented in Table III. Mean VHI scores were outside the normal range for all clinical groups and within the normal range for healthy controls (Table III; Figure 2). VHI scores in the clinical groups combined were significantly worse than those for healthy controls ($P < .001$). Mean scores in the MTD group were significantly higher than those in the CRC group ($P = .011$); however, there was no significant difference between the VCD group and either the CRC group ($P = .868$) or the MTD group ($P = .046$).

Laryngeal Hypersensitivity Questionnaire

Mean LHQ scores were outside the normal range for the clinical groups and within the normal range for healthy controls.

TABLE III. Summary of laryngeal dysfunction measurements

Measurement	Healthy controls, mean $\pm$ SD	CRC, mean $\pm$ SD	VCD, mean $\pm$ SD	MTD, mean $\pm$ SD	<i>P</i> value*	<i>P</i> value†
VHI	4.6 $\pm$ 6.5	23.7 $\pm$ 25.5	27.3 $\pm$ 19.0	45.6 $\pm$ 21.7	<.001‡	.010‡
Laryngeal Hypersensitivity Questionnaire	19.9 $\pm$ 0.8	14.2 $\pm$ 3.5	14.4 $\pm$ 3.2	15.9 $\pm$ 2.5	<.001‡	.221
MPT (s)	19.7 $\pm$ 5.1	12.3 $\pm$ 4.4	12.6 $\pm$ 7.6	12.2 $\pm$ 8.3	.001‡	.981
CAPE-V overall severity	9.8 $\pm$ 13.1	25.4 $\pm$ 22.5	24.6 $\pm$ 16.7	46.1 $\pm$ 24.7	.001‡	.005‡
Phonation frequency range (semitones)	19.5 $\pm$ 5.3	20.1 $\pm$ 7.9	19.1 $\pm$ 6.6	19.6 $\pm$ 8.0	.976	.908
Electroglottography: irregularity of closed phase (%)	11.4 $\pm$ 10.0	51.5 $\pm$ 18.7	50.5 $\pm$ 19.0	51.9 $\pm$ 18.4	<.001‡	.975
Leicester Cough Monitor (coughs/h)	1.5 $\pm$ 1.9	10.2 $\pm$ 9.7	16.5 $\pm$ 18.5	2.4 $\pm$ 3.0	<.001‡	.025
Timed swallow test (mL/s)	29.9 $\pm$ 15.5	19.9 $\pm$ 11.2	16.7 $\pm$ 7.3	20.8 $\pm$ 7.3	.001‡	.360

*Comparison of clinical groups combined vs controls (hypothesis 1).

†Comparison between clinical groups (hypothesis 2).

‡Significant at $P < .0167$ (Bonferroni-corrected value).

The clinical groups combined had higher LHQ scores than healthy controls (Figure 2; $P < .001$) and there was no significant difference between the clinical groups ($P = .221$). There was a significant correlation between cough frequency and LHQ scores ($r_s = -0.488$; $P < .001$).

Voice

We assessed voice using 4 investigations (described in Table I). Participants with CRC were significantly different from controls in 3 of these 4 measures. They were similar to those with VCD in all these 4 measures and to those with MTD in 3 measures.

Mean MPT values were in the abnormal range in the clinical groups but within the normal range for controls. Values in the clinical groups combined were significantly worse than those for healthy controls ($P = .001$). There was no significant difference in MPT between the clinical groups ($P = .981$).

Mean CAPE-V values (Figure 2) were in the moderate range in the MTD group, in the mild-moderate range in the CRC and VCD groups, and in the normal range for healthy controls. Values in the clinical groups combined were significantly worse than those for healthy controls ($P = .001$). There was a significant difference in values between the clinical groups ($P = .005$). Values in the MTD group were significantly worse than those in the CRC ($P = .013$) and VCD ($P = .011$) groups.

There was no significant difference in phonation frequency range values between the clinical groups ($P = .976$) or between the clinical groups and healthy controls ($P > .05$).

Electroglottography results (mean closed quotient irregularity) are presented in Table III. Values in the clinical groups were significantly worse than those for healthy controls. There were no significant differences between the clinical groups.

Laryngoscopy and stroboscopy

Laryngoscopy results are presented in Table IV and shown in Figure 3.

In the CRC group, moderate-severe LMD-Resp was present in 47% of the participants during quiet respiration and 67% after odor challenge. The odor challenge triggered LMD-Resp in all participants with VCD ($P = .011$ vs CRC) and in 45% with MTD ($P < .001$ vs VCD).

LMD-Phon was assessed as laryngeal constriction (either mediolateral or anterior-posterior constriction), or abnormal vocal fold closure. Moderate-severe mediolateral constriction of the false vocal folds during phonation was present in 45% of the

participants in the CRC group, 93% of the participants in the VCD group ($P < .001$ vs CRC), and 64% of the participants in the MTD group. Mediolateral constriction was significantly higher in the VCD group than in the CRC group ($P < .001$); however, there was no difference between the CRC and MTD groups ($P > .05$) or between the VCD and MTD groups ($P > .05$). Most participants in all the groups demonstrated anterior-posterior constriction and there was no significant difference between the groups. The proportion of incomplete or abnormal vocal fold closure during phonation was present in all the groups, but the pattern was variable. The proportion of incomplete or abnormal closure was 75% in the CRC group, which was similar to that in the VCD group ($P = .346$) but significantly higher than that in the MTD group (36%; $P < .001$). A restricted mucosal wave was present in 28% of the participants in the CRC group and in a significantly higher proportion of the participants in the VCD group (54%; $P = .004$).

Timed swallow test

Timed swallow test results were in the normal range for all the groups but were highest in healthy controls, followed by the MTD group, the CRC group, and finally the VCD group. Timed swallow test results in the clinical groups combined were significantly worse than for healthy controls ($P = .001$). There was no difference in values between the clinical groups (Table III).

Characterization of participants with abnormal cough results

On the basis of normal cutoff scores for the Leicester Cough Questionnaire³¹ (<17) and cough frequency monitoring²³ (>2 coughs/h), there were 27 participants with abnormal cough. Laryngoscopic evidence of paradoxical vocal fold movement during respiration was present in 18 (69%) participants with abnormal cough and LMD-Phon was present in 22 (85%) participants. This finding was similar to the finding in those without abnormal cough where LMD-Resp was present in 31 (70.5%) participants, and 28 (63.6%) participants had evidence of abnormal laryngeal movement during phonation. Fifteen participants had both LMD-Phon and LMD-Resp. There was no correlation between the presence of cough and LMD-Resp ($r_s = -0.234$; $P = .062$) or between cough and LMD-Phon ($r_s = -0.018$; $P = .454$). Similarly, there was no significant correlation between LHQ scores and either LMD-Resp

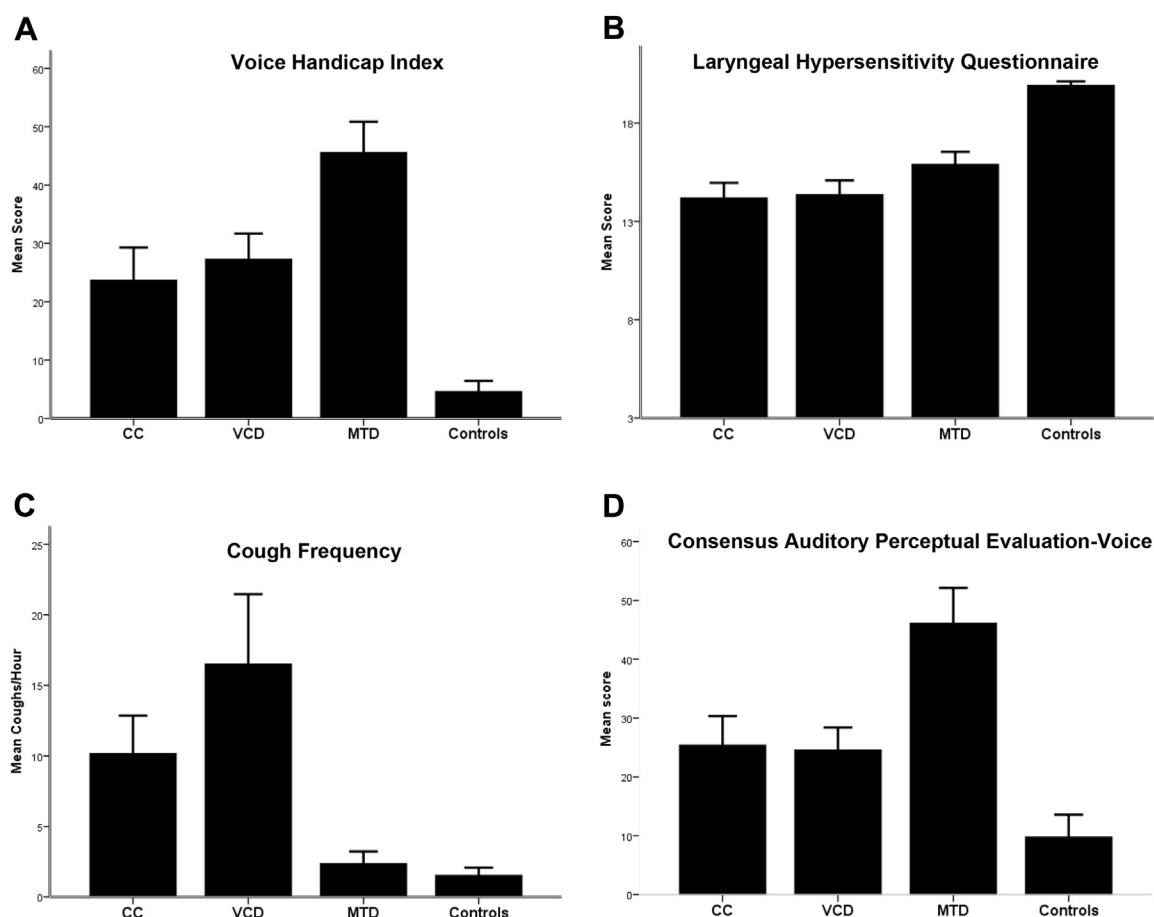


FIGURE 2. Comparison of key laryngeal measurements between groups. **A**, VHI scores. Normal scores are <10 (vs patient groups, $P < .001$; CC vs MTD, $P = .011$). **B**, LHQ scores. Normal scores are >17.1 (vs patient groups, $P < .001$). **C**, Cough frequency (coughs/h) during 24-h ambulatory cough monitoring (vs patient groups, $P < .001$; VCD vs MTD, $P = .010$). **D**, Auditory perceptual analysis of voice using CAPE-V. Higher scores are more severe (vs patient groups, $P < .001$; MTD vs CC, $P = .013$; MTD vs VCD, $P = .011$).

($r_s = -0.220$; $P = .269$) or LMD-Phon ($r_s = -0.217$; $P = .277$).

DISCUSSION

This study characterized laryngeal dysfunction in participants with CRC compared with those with VCD and MTD and is the first to conduct laryngoscopy and perform odor challenge on a cross section of patients with upper airway disorders. Laryngeal dysfunction was common in participants with CRC. The prevalence and severity of laryngeal hypersensitivity and the pattern of laryngeal motor dysfunction in CRC were similar to other well-recognized laryngeal disorders of VCD and MTD. Patients with CRC also demonstrated distinct patterns of laryngeal motor dysfunction affecting respiration, phonation, and/or swallowing. In particular, LMD-Resp was frequent in CRC and may represent an inherent laryngeal motor abnormality in this condition.

These findings provide insight into the mechanism of CRC and demonstrate that laryngeal dysfunction might be an important feature in CHS. This concept is shown in Figure 4, which outlines the components of CHS. In this model, cough hypersensitivity is associated with both laryngeal dysfunction and central sensitization.³² Laryngeal dysfunction affects sensory

pathways, causing laryngeal hypersensitivity, and also affects motor pathways, leading to laryngeal motor dysfunction. Laryngeal hypersensitivity causes cough and hypersensitivity to various stimuli, whereas laryngeal motor dysfunction manifests as abnormal laryngeal movement during phonation (LMD-Phon), respiration (LMD-Resp), or both. These features are well recognized in VCD and MTD, and we now describe LMD-Phon and LMD-Resp as features of CRC. Further research is needed to determine whether LMD-Phon and LMD-Resp have a distinct pathological basis. This model explains why a specific disease alone (eg, asthma, rhinitis, and GERD) may not be sufficient to cause cough. This model is explanatory and can also be used to direct therapy. The high prevalence of laryngeal dysfunction suggests that the clinical pathway for CC should include more systematic examination of laryngeal dysfunction particularly in patients who do not respond to traditional medical treatment.

Speech pathology intervention for CRC is successful in reducing cough frequency and cough severity and improving cough quality of life, cough reflex sensitivity, voice quality, and voice quality of life,³³⁻³⁷ but the mechanism behind improvement is unknown. Many patients with CRC have associated laryngeal symptoms that can be successfully targeted with speech pathology intervention.^{33-36,38-40} The high prevalence of

TABLE IV. Laryngoscopy results

Laryngoscopy finding	CRC	VCD	MTD
LMD-Resp during quiet respiration	47%	40%	27%
Inspiration			
Mild	8%	36%	25%
Moderate	23%	21%	17%
Severe		14%	8%
Expiration			
Mild		21%	
Moderate	15%	7%	
Severe		7%	9%
LMD-Resp during odor challenge	67%	100%	45%
Inspiration			
Mild	21%	14%	17%
Moderate	21%	35%	17%
Severe	21%	35%	17%
Expiration			
Mild	14%	36%	
Moderate	7%	21%	
Severe	14%		9%
Mediolateral constriction during phonation	45%	93%	64%
Mild	21%	6%	36%
Moderate	29%	63%	55%
Severe	7%	19%	9%
Anterior-posterior constriction during phonation	54%	76%	81%
Mild	36%	13%	18%
Moderate	27%	63%	54%
Severe	27%	13%	27%
Incomplete true vocal fold closure or abnormal vocal fold closure pattern during phonation	75%	87%	36%
Anterior gap	0%	6%	0%
Posterior gap	33%	31%	0%
Hourglass	8%	25%	0%
Spindle gap	0%	13%	9%
Irregular	0%	6%	0%
Incomplete	25%	0%	36%
Variable	8%	6%	0%
Abnormal mucosal wave during phonation	28%	54%	30%
Right vocal fold			
Restricted	14%	46%	30%
Excessive	14%	8%	
Left vocal fold			
Restricted	14%	46%	30%
Excessive	14%	8%	
Amplitude—right%, mean ± SD	34 ± 8	48 ± 17	27 ± 15
Amplitude—left%, mean ± SD	40 ± 11	54 ± 14	44 ± 12
Reduced vocal fold mobility—right	38%	31%	75%

(continued)

TABLE IV. (Continued)

Laryngoscopy finding	CRC	VCD	MTD
Reduced vocal fold mobility—left	38%	44%	50%
Pharyngeal constriction during phonation	63%	88%	99%
Mild	27%	50%	63%
Moderate	36%	38%	36%
Observations during quiet respiration			
Excess secretions	27%	25%	18%
Secretions-appearance	Sticky 40%	Sticky 60%	Sticky 50%
		Thick 13%	Thick 10%
Free edge-right vocal fold			
Smooth and straight	56	53	64
Convex	18	27	9
Concave	9	0	18
Irregular	9	20	0
Rough	9	0	9
Free edge-left left vocal fold			
Smooth and straight	55	73	63
Convex	18	20	18
Concave	18	0	9
Irregular	9	6	0
Rough	0	0	9

laryngeal motor dysfunction that we have identified in this study might explain why speech pathology intervention is successful for CRC.^{34,35} Speech pathology intervention may be targeting one of the key features of CRC because it addresses laryngeal dysfunction. Further research is needed to assess changes in laryngeal function after speech pathology intervention.

One clinical implication of this study is that patients with CRC may have coexisting laryngeal dysfunction including laryngeal hypersensitivity, abnormal voice function, impaired voice quality of life, and laryngeal motor dysfunction affecting either respiration or phonation. These issues may require assessment and treatment in addition to traditional cough management strategies. In particular, the high prevalence of LMD-Resp suggests that patients with CRC may need to be evaluated for signs and symptoms of VCD. Patients may also require voice screening and consideration of muscle tension patterns during phonation.

The odor challenge is used to detect VCD.²⁸ We found it to be useful in detecting LMD-Resp in CHS, and that odor challenge triggered more LMD-Resp than was present in quiet respiration. This result is consistent with other studies whereby the perception of odor increased laryngeal hyperresponsiveness.⁴¹ The odor challenge induced LMD-Resp in two-thirds of the participants with CRC, which demonstrates an overlap with VCD (Figure 3). It suggests that provocation is necessary to diagnose VCD in some patients and that laryngoscopy without provocation may lead to false negatives.

Cough quality of life and cough frequency were high in the VCD group and not readily distinguishable from the CRC group. This result suggests that patients with VCD may also require intervention and treatment for CC.^{34,35} Perhaps these 2

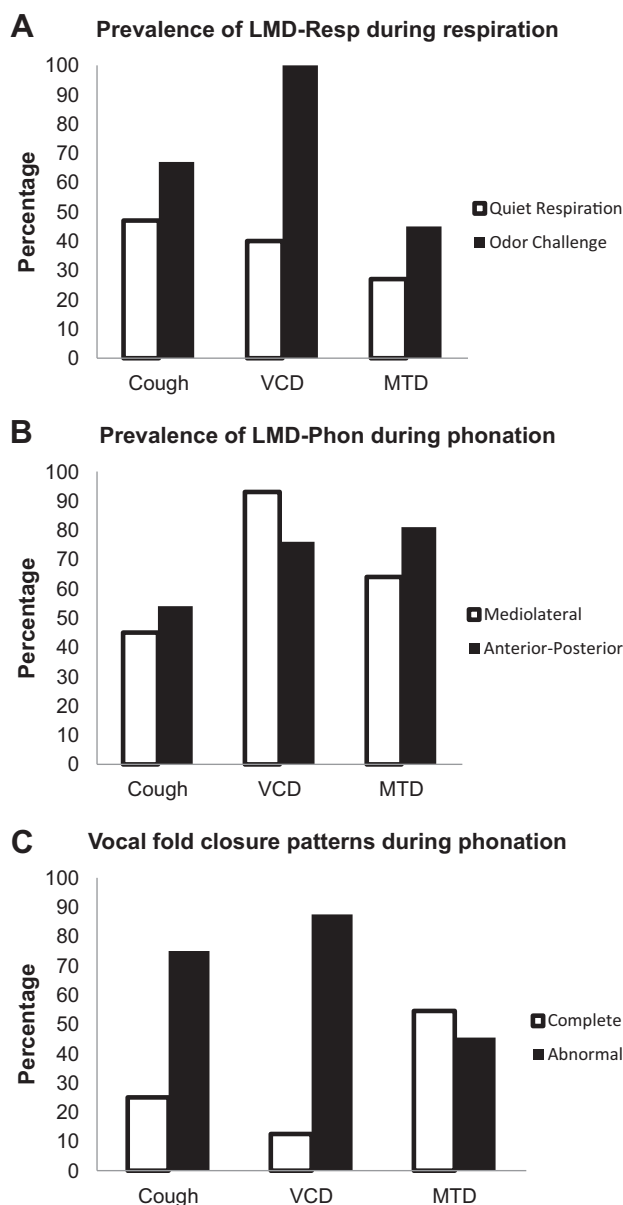


FIGURE 3. Comparison of laryngoscopy measures between the clinical groups. **A**, Prevalence of abnormal laryngeal (LMD-Resp) movement during quiet respiration and odor challenge. **B**, Prevalence of supraglottic constriction during phonation (LMD-Phon) in either mediolateral dimensions involving the false vocal folds or anterior-posterior dimensions. **C**, Comparison of complete versus abnormal vocal fold closure patterns during phonation.

conditions could be viewed as the same disorder with different manifestations, for example, cough alone, VCD alone, or both.

The prevalence of LMD-Resp and LMD-Phon was similar in those with and without abnormal cough. This suggests that these changes in laryngeal function are not the consequence of CC, but rather represent a common laryngeal hypersensitivity, as proposed in the irritable larynx syndrome hypothesis.^{42,43} This hypothesis involves neural plastic changes to brainstem laryngeal control networks. Furthermore, the concept of CHS could be expanded to include VCD. There was a distinct pattern of LMD-Phon (reduced

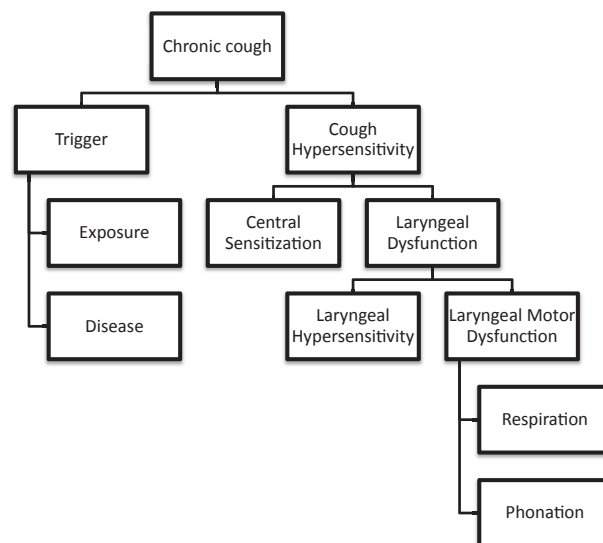


FIGURE 4. Proposed model of CC outlining the components of CC. In this model, CC is the result of a trigger plus underlying cough hypersensitivity. The trigger may be either external exposure or associated disease that affects the afferent limb of the cough reflex. Cough hypersensitivity includes central sensitization and laryngeal dysfunction. Laryngeal dysfunction may be due to a combination of laryngeal hypersensitivity and laryngeal motor dysfunction affecting phonation, respiration, or both.

vocal fold closure during phonation) in the CRC group, which may suggest a specific pattern characteristic of CHS. The motor basis is increased tension in the posterior cricoarytenoid muscle, which prevents full vocal fold closure during phonation. There was no significant correlation between LHQ and either LMD-Resp or LMD-Phon. This suggests that CRC and possibly CHS are related to laryngeal hypersensitivity rather than to laryngeal motor dysfunction; that is, it is the hypersensitivity that is related to cough. Furthermore, most participants (70%) with MTD did not have cough. Although there was a high degree of laryngeal motor dysfunction in participants with MTD, it primarily affected phonation and it is possible that any overlap between CRC/VCD and MTD affects only a proportion of those with MTD.

Study limitations

There are several potential limitations to this study. Participants underwent a single assessment and hence it is unclear whether these results would have been stable over time. Although participants with coexisting medical conditions were excluded from the study, it is possible that those coexisting conditions could have confounded results. The cross-sectional study design did not include assessment after speech pathology treatment, and further research is needed to examine changes in laryngeal dysfunction after treatment. Formal cough reflex sensitivity testing was not used in the present study.

Finally, we used moderate-severe ratings to identify LMD-Resp and LMD-Phon. It should, however, be remembered that mild abnormalities of laryngeal motor function can still be clinically significant.

The reported rates of antibiotics and over-the-counter medication appear to be low. It is possible that there was

underreporting of this medication. The medical treatment received before inclusion in this study was similar between patient groups, suggesting a spillover from the treatment recommended in cough guidelines to other related conditions.

CONCLUSIONS

CRC is a common and disabling problem that can be refractory to standard therapeutic approaches. Participants with CRC have evidence of laryngeal dysfunction on a range of measures, both subjective and objective. There is overlap in the degree of laryngeal dysfunction between CRC and other laryngeal disorders such as VCD and MTD. Laryngeal dysfunction is a significant and frequent problem in CRC. This may contribute to cough hypersensitivity syndrome and is a relevant target of treatment.

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