

Original Article

Paradoxical Vocal Fold Motion in Difficult Asthma Is Associated with Dysfunctional Breathing and Preserved Lung Function

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What is already known about this topic? Patients with “difficult-to-treat” asthma may also have comorbidities, such as vocal cord dysfunction, which are associated with worse asthma outcomes, such as exacerbation risk, high symptom burden, and poorer quality of life.

What does this article add to our knowledge? Clinical features associated with vocal cord dysfunction amongst patients with difficult asthma include dysfunctional breathing and preserved lung function.

How does this study impact current management guidelines? Identifying and treating dysfunctional breathing alongside vocal cord dysfunction should be included in management guidelines for patients with difficult asthma and is likely to be essential to improve patient outcomes.

BACKGROUND: Many patients with difficult asthma also have coexisting vocal cord dysfunction (VCD), evident by paradoxical vocal fold motion (PVFM) on laryngoscopy.

OBJECTIVE: Among patients with difficult asthma, we sought to identify clinical features associated with laryngoscopy-diagnosed PVFM.

METHODS: Consecutive patients with “difficult asthma” referred by respiratory specialists underwent systematic assessment in this observational study. Those with a high clinical suspicion for VCD were referred for laryngoscopy, either at rest or after mannitol provocation. Statistical analyses were performed to identify clinical factors associated with PVFM, and a multivariate logistic regression model was fitted to control for confounders.

RESULTS: Of 169 patients with difficult asthma, 63 (37.3%) had a high clinical probability of VCD. Of 42 who underwent

laryngoscopy, 32 had PVFM confirmed. Patients with PVFM more likely had preserved lung function (prebronchodilator forced expiratory ratio $74\% \pm 11$ vs $62\% \pm 16$, $P < .001$); physiotherapist-confirmed dysfunctional breathing (odds ratio [OR] = 5.52, 95% confidence interval [CI]: 2.4–12.7, $P < .001$), gastro-oesophageal reflux (OR = 2.6, 95% CI: 1.16–5.8, $P = .02$), and a lower peripheral eosinophil count (0.09 vs 0.23 , $P = .004$). On multivariate logistic regression, independent predictors for PVFM were dysfunctional breathing (OR = 4.93, 95% CI: 2–12, $P < .001$) and preserved lung function (OR = 1.07, 95% CI: 1.028–1.106, $P < .001$).

CONCLUSION: Among specialist-referred patients with difficult asthma, VCD pathogenesis may overlap with dysfunctional breathing but is not associated with severe airflow obstruction. Dysfunctional breathing and preserved lung function may serve

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Abbreviations used

ACT- Asthma Control Test
 AQLQ- Asthma-related quality of life
 CI- Confidence interval
 ENT- Ear, nose, and throat
 FER- Forced expiratory ratio
 FEV1- Forced expiratory volume in 1 second
 HADs- Hospital Anxiety and Depression Scale
 OR- Odds ratio
 PVFM- Paradoxical vocal fold motion
 VAO- Variable airflow obstruction
 VCD- Vocal cord dysfunction

as clinical clues for the presence of VCD. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Asthma; Larynx; Paradoxical vocal fold motion; Vocal cord dysfunction

“Difficult asthma” is a diagnosis applied to patients who despite high-dose preventer treatment continue to experience a high symptom burden or frequent exacerbations.¹ Misdiagnosis, coexisting comorbidities, nonadherence to medication, and biologically severe disease may all contribute to difficult asthma. Systematic multidisciplinary assessment is therefore beneficial to identify these contributory factors, distinguish biologically severe asthma from difficult asthma, and improve patient outcomes.²⁻⁵

Vocal cord dysfunction (VCD), also known as the glottic form of inducible laryngeal obstruction, is an important comorbidity in difficult asthma. Symptoms of dyspnoea, throat tightness, dysphonia, and stridor arise from intermittent airway obstruction caused by paradoxical vocal fold motion (PVFM), which can be visualized on laryngoscopy. This paradoxical adduction is thought to be due in part to laryngeal hypersensitivity,⁶ which may be triggered by irritants such as odors and strong emotions as well as risk factors such as laryngopharyngeal reflux or post-nasal drip.⁷ Patients with concomitant VCD and asthma have worse asthma outcomes including increased symptoms, poorer quality of life, and more exacerbations.⁸

VCD may affect as many as 30% to 50% of patients with difficult asthma in some series,⁹ serving either as a coexisting or alternative diagnosis. VCD is frequently under-recognized, even by respiratory specialists,¹⁰ leading to delays in diagnosis and inappropriate treatment.¹⁰⁻¹² We have previously reported on the challenges in distinguishing VCD from asthma, even with classic signs and symptoms such as stridor and inspiratory difficulty, which highlights the need to visualize PVFM on laryngoscopy to confirm VCD diagnosis.¹³

This study aimed to identify clinical features of laryngoscopy-diagnosed VCD, among patients with difficult asthma referred by respiratory specialists for systematic multidisciplinary assessment.

METHODS

Our tertiary hospital in Melbourne, Australia, undertakes systematic assessment of adults with difficult asthma referred by respiratory and allergy specialists. Specialists may refer patients with asthma that is difficult to control due to any of the following reasons:

TABLE I. Comorbidity questionnaires

Comorbidity	Questionnaire
Chronic rhinosinusitis	Sinonasal Questionnaire (SNQ) ¹⁹
	Sinonasal Outcome Test (SNOT-22) ²⁰
Allergic rhinitis	Rhinitis Control Assessment Test (RCAT) ²¹
Gastroesophageal reflux disease	Gastroesophageal Reflux Questionnaire (GERD-Q) ²²
Obstructive sleep apnoea	Berlin Questionnaire ²³
Depression	Hospital Anxiety and Depression Scale (HADs) ²⁴
Anxiety	HADs ²⁴
Dysfunctional breathing	Nijmegen score ²⁵
Vocal cord dysfunction	Pittsburgh VCD Index ²⁶
	Vocal Cord Dysfunction Questionnaire (VCD-Q) ²⁷

diagnostic dilemma; poor symptom control; frequent or serious exacerbations; poor lung function; or patient factors, such as poor adherence or psychosocial concerns.¹⁴

Patients are assessed over 3 visits conducted over a 6-month period, as previously described. Consecutive patients who completed assessment between June 1, 2014, and March 9, 2018, were eligible for inclusion in this analysis. This research was approved by the Alfred Health Ethics committee (Reference number 285/15).

Systematic assessment

A standardized electronic clinic template on REDCap (Research Electronic Data Capture), a secure web-based application,¹⁵ was used to collect baseline demographics and clinical data as previously described.¹⁶ The template included a comprehensive asthma history and questionnaires to assess asthma control (Asthma Control Test or ACT),¹⁷ asthma-related quality of life (AQLQ),¹⁸ and 8 comorbidities,¹⁶ as listed in Table I. Permission from questionnaire authors was obtained.

The diagnosis of asthma was confirmed by stepwise testing for the presence of variable airflow obstruction (VAO) using bronchodilator reversibility on spirometry, peak flow variability, or (when safe and appropriate) positive bronchial provocation challenge test with mannitol (Aridol; Pharmaxis, Sydney, Australia).

Further investigations for phenotyping included assessment of atopic status by skin prick testing or *in vitro* allergen specific IgE, fractional exhaled nitric oxide measurement, total serum IgE, and peripheral blood eosinophil count. All patients underwent asthma nurse assessment of inhaler technique, and were given a written asthma action plan and an electronic monitoring device for objective adherence monitoring if a device was compatible with their inhalers.²⁸

Patients were classified as having a high clinical probability of VCD if compatible clinical symptoms were present, the specialist clinician had a high index of suspicion after systematic assessment, and supported by an abnormal Pittsburgh VCD index. As a gold standard of VCD diagnosis, both compatible clinical history and objective paradoxical vocal cord adduction seen on laryngoscopy were required. Laryngoscopy was performed either by an ear, nose, and throat (ENT) specialist or through the specialized middle airway clinic protocol, which also included nasoendoscopy with laryngeal provocation using mannitol when required.^{13,29} Mannitol provocation was used if vocal cord examination was normal at rest. Paroxysmal movement was defined as abnormal adduction of the vocal cords on inspiration or greater than 50% and sustained adduction of vocal cords observed in expiration.

Patients were referred for further investigation of dysfunctional breathing if compatible clinical symptoms were present and the assessing clinician had a high index of suspicion. Dysfunctional breathing was diagnosed by specialized single physiotherapist assessment comprising assessment for mouth breathing, hyperventilation (resting elevated respiratory rate), thoracic dominance, thoracoabdominal asynchrony, and accessory muscle use.³⁰

The diagnoses of other comorbidities were made by criteria outlined by Tay et al³ and summarized as follows. Chronic rhinosinusitis was diagnosed by the presence of clinical symptoms and visible sinus opacification on computed tomography, or ENT examination. Allergic rhinitis was diagnosed by clinical assessment by an allergist and positive skin prick test or serum specific IgE to common aeroallergens. Obstructive sleep apnoea was indicated by the presence of clinical symptoms and Berlin questionnaire score greater than or equal to 2, or a previous positive polysomnogram. Gastroesophageal reflux disease was determined by the presence of reflux symptoms and gastroesophageal reflux questionnaire score greater than 2, or a known history of reflux disease on acid suppression treatment. Anxiety and depression were diagnosed based on clinical symptoms and Hospital Anxiety and Depression Scale (HADS) score (either anxiety, depression, or both) greater than or equal to 11, or a known history of anxiety or depression currently on medication.

Statistical analysis

Data analysis was performed using SPSS version 22 (IBM, Armonk, NY). Descriptive analyses included categorical variables that are presented as percentages and frequency, and continuous variables that are presented as mean or median values with standard deviation or interquartile range, respectively. Univariate analyses identified clinical factors associated with VCD. Unpaired *t*-tests or Wilcoxon rank sum tests were used to compare continuous variables, and χ^2 or Fisher's exact tests to compare categorical variables, depending on data distribution. Logistic regression was used to identify relationships between suspected clinical factors (from a previous study³¹) and VCD. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs), with a *P* value of less than .05 reported as significant. These factors were then adjusted for possible confounders, including age, gender, and forced expiratory ratio (FER), in a multivariate model, with results presented as adjusted ORs. Sensitivity analysis including patients with missing data was performed and included in the results.

RESULTS

Between May 1, 2015, and March 9, 2018, 169 consecutive patients were assessed for difficult asthma. Of these, 63 (37.3%) had a high clinical probability of VCD based on clinical assessment supported by questionnaire results. Of these, 17 patients did not proceed to laryngoscopy (Figure 1): 5 declined laryngoscopy, 7 failed to attend laryngoscopy, 1 was assessed by an ENT surgeon external to our hospital, and the remaining 4 were not thought to clinically have VCD on subsequent review, with symptom improvement after treatment of chronic rhinosinusitis, gastroesophageal reflux disease, obesity with bariatric surgery, or severe asthma with monoclonal antibody therapy.

The other 46 underwent laryngoscopy either at rest or after laryngeal provocation with mannitol,²⁹ and confirmed PVFM was observed in 32. Only these patients with confirmed paradoxical movement on laryngoscopy were included for primary statistical analysis. Among 14 patients with observable *normal* vocal fold movement despite provocation, 6 had alternative

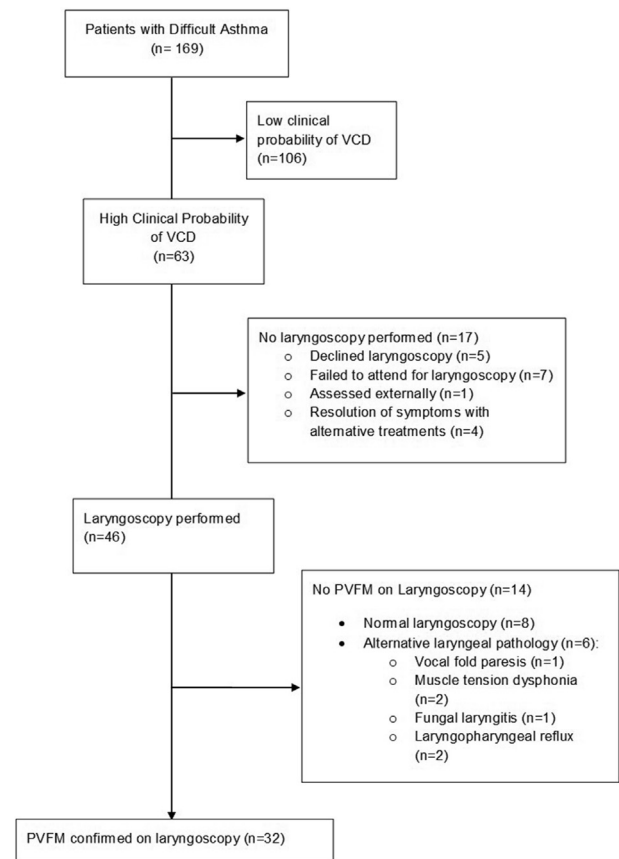


FIGURE 1. CONSORT diagram depicting flow of patients. *PVFM*, Paradoxical vocal fold motion; *VCD*, vocal cord dysfunction.

laryngeal pathology identified on laryngoscopy, including 1 with vocal fold paresis, 2 with muscle tension dysphonia, 1 with fungal laryngitis, and 2 with laryngeal pachydermia and laryngopharyngeal reflux. These patients were treated appropriately with speech, antifungal, and reflux therapy, respectively.

Baseline demographics of the patients are described in Table II. Clinical asthma characteristics and asthma comorbidities are described in Tables III and IV, respectively.

On univariate analysis, baseline demographics including age, gender, body mass index, and smoking status did not differentiate between patients with or without PVFM. VAO was demonstrated objectively in the majority (86%) of patients. The proportion of patients with VAO was not different among patients with and without demonstrable PVFM. Of the 23 patients without demonstrable VAO, 9 patients with negative bronchial provocation challenge tests had VCD as an alternative diagnosis to severe asthma and had their inhaled corticosteroid dose reduced or ceased. Three patients had dysfunctional breathing as an alternative diagnosis and also had asthma medication reduced. Five patients had severe fixed airflow obstruction consistent with chronic obstructive pulmonary disease and were not eligible for bronchial provocation challenge testing. One patient's symptoms were attributed to obesity with improvement in symptoms after bariatric surgery. The remaining 5 patients failed to return peak flow charts or declined bronchial provocation testing.

TABLE II. Baseline characteristics

Baseline characteristics	Total	Patients with PVFM on laryngoscopy (n = 32)	Patients without PVFM (n = 137)	P value
Age (y), mean (SD)	52 (14), range 19-80	50 (12.7)	52 (14.6)	.491
Gender, n (%)				
Female	112 (66%)	24 (75%)	88 (64%)	.246
BMI (kg/m ²), mean (SD)	32 (8.4)	33 (6.7)	31 (8.7)	.55
BMI ≥30, n (%)	91 (54%)	20 (63%)	71 (52%)	.275
Smoking status, n (%)				.830
Never	95 (57%)	16 (52%)	79 (58%)	
Ex-smoker	65 (39%)	14 (45%)	51 (37%)	
Current smoker	7 (4%)	1 (3.2%)	6 (4%)	
Unemployed	81 (49%)	14 (46.7%)	67 (49%)	.797

BMI, Body mass index; PVFM, paradoxical vocal fold motion; SD, standard deviation.

TABLE III. Asthma characteristics

	Total	Patients with PVFM on laryngoscopy (n = 32)	Patients without PVFM (n = 137)	P value
Asthma questionnaire results at visit 1				
ACT, mean (SD)	13.9 (5)	12.39 (5)	14.25 (5)	.064
AQLQ, mean (SD)	4.2 (1.24)	3.9 (1.24)	4.27 (1.24)	.136
Age at asthma diagnosis, mean (SD)	22 (20)	20 (13)	22 (20)	.64
Asthma diagnosis				
Variable airflow obstruction demonstrated, n (%)	146 (86)	28 (88)	118 (86)	.839
Peak flow variability, n (%)	30 (17.8)	7 (22)	23 (17)	.5
Bronchodilator reversibility, n (%)	98 (58)	16 (50)	83 (60)	.309
Bronchial provocation challenge, n (%)	17 (10.1)	5 (16)	12 (9)	.245
Lung function characteristics				
Prebronchodilator FEV ₁ (%predicted), mean (SD)	67 ± 23	79 (18)	65 (23)	<.001
Prebronchodilator FVC (%predicted), mean (SD)	81 ± 17	85 (16)	80 (17)	.130
Prebronchodilator FER, mean (SD)	64.5 ± 15.5	74 (11)	62 (16)	<.001
FER <70% (airflow obstruction), n (%)	96 (57)	13 (41)	83 (61)	.040
Severe airflow obstruction (FEV ₁ <40% predicted)	19 (11)	0 (0)	19 (14)	.026
Asthma phenotype				
Atopic, n (%)	95 (58)	17 (57)	78 (58)	.911
Blood eosinophils (×10 ⁹ /L), median (IQR)	0.19 (0.37)	0.09 (0.23)	0.23 (0.41)	.004
IgE (kU _A /L), median (IQR)	124.5 (422)	70 (371)	134 (475)	.119
FeNO (ppb), median (IQR)	24 (32)	23 (19)	24 (34)	.708
Asthma severity				
GINA treatment step 4 or 5,* n (%)	146 (86)	27 (84)	119 (86)	.772
Exacerbations, mean (SD)				
Burst of oral corticosteroids	2.5 (2)	2.9 (1.7)	2.4 (2)	.257
Unscheduled GP visit	2.3 (3.5)	2.9 (3)	2 (4)	.265
ED presentation	0.7 (1.4)	0.9 (1)	0.7 (1.4)	.329
Hospitalization	0.37 (0.9)	0.34 (0.5)	0.3 (0.5)	.513
Adherence to prescribed preventer				
Self-reported adherent >75%, n (%)	144 (85)	29 (94)	115 (84)	.190
Percentage adherent as measured by EMD (median, IQR)	75% (27)	53% (56)	77% (21)	.043

ACT, Asthma Control Test;¹⁷ AQLQ, asthma-related quality of life; ED, emergency department; EMD, electronic monitoring device; FeNO, fractional exhaled nitric oxide; FER, forced expiratory ratio; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; GP, general practitioner; ICS, inhaled corticosteroid; IQR, interquartile range; PVFM, paradoxical vocal fold motion; SD, standard deviation.

P values in bold indicate results significant to level of $P < .05$.

*GINA step 4: moderate-to-high dose ICS; GINA step 5: add on therapy including oral corticosteroids.

A higher forced expiratory volume in 1 second (FEV₁) was seen among patients with PVFM compared with those without (79% compared with 65% predicted, $P < .001$), with less airflow obstruction (mean FER 74% vs 62%, $P < .001$). Peripheral blood eosinophil count was lower among patients with PVFM

(median 0.09 compared with $0.23 \times 10^9/L$, $P = .004$). Despite these differences, exacerbation frequency was similar among patients with and without PVFM. Dysfunctional breathing (50% vs 15%, $P < .001$) and gastroesophageal reflux disease (66% vs 42%, $P = .017$) were key comorbidities more frequently present

TABLE IV. Comorbidities

	Total	Patients with PVFM on laryngoscopy (n = 32)	Patients without PVFM (n = 137)	P value
Allergic rhinitis	90 (53%)	20 (63%)	70 (51%)	.244
Chronic rhinosinusitis	65 (39%)	12 (38%)	53 (39%)	.901
Dysfunctional breathing	37 (22%)	16 (50%)	21 (15%)	<.001
Obstructive sleep apnoea	52 (31%)	11 (34%)	41 (30%)	.624
Gastroesophageal reflux disease	79 (47%)	21 (66%)	58 (42%)	.017
Chronic obstructive pulmonary disease	18 (11%)	1 (3%)	17 (13%)	.200
Anxiety	43 (26%)	11 (34%)	32 (24%)	.242
Depression	50 (30%)	13 (41%)	37 (28%)	.157
Comorbidity questionnaire results				
SNQ ¹⁹	1.44 (0.9)	1.4 (0.8)	1.5 (1)	.609
SNOT-22 ²⁰	39 (21)	39 (22)	39 (22)	.954
RCAT ³²	21 (5)	20 (5)	21 (5)	.424
Nijmegen score ²⁵	23 (12)	25 (13)	22 (14)	.168
VCD-Q ²⁷	40 (9)	44 (8)	38 (9)	.008
Pittsburgh VCD index ²⁶	2.6 (2.4)	4 (2)	2.3 (2.3)	<.001
HADs-A ²⁴	8 (5)	9 (6)	7 (5)	.091
HADs-D ²⁴	6 (4)	7.6 (5)	5 (4)	.006

All questionnaire results reported as mean (SD) unless otherwise stated.

P values in bold indicate results significant to level of $P < .05$.

HADs-A, Hospital Anxiety Scale; HADs-D, Hospital Depression Scale; PVFM, paradoxical vocal fold motion; RCAT, Rhinitis Control Assessment Test; SD, standard deviation; SNOT-22, Sinusoidal Outcome Test; SNQ, Sinusoidal Questionnaire; VCD-Q, Vocal Cord Dysfunction Questionnaire.

TABLE V. Clinical predictors for VCD

Clinical factor	Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	P (for adjusted OR)
Dysfunctional breathing	5.524 (2.4-12.7)	4.93 (2.0-11.96)	<.001
Depression	1.78 (0.8-4)	1.7 (0.724-3.998)	.222
Anxiety	1.64 (0.7-3.76)	1.38 (0.58-3.32)	.47
Gastroesophageal reflux disease	2.6 (1.16-5.8)	2.089 (0.871-5)	.099
Forced expiratory ratio	1.061 (1.027-1.097)	1.067 (1.028-1.106)	<.001

CI, Confidence interval; OR, odds ratio; VCD, vocal cord dysfunction.

*Adjusted for baseline demographics (Table I) including age, gender, spirometry parameters.

in the PVFM population. Patients with PVFM also had higher HADs-D scores ($P = .006$) although diagnoses of depression were not more frequent. Patients with PVFM had higher scores in both the Pittsburgh Vocal Cord Index²⁶ and the Vocal Cord Dysfunction Questionnaire.²⁷

Although self-reported adherence was similar among both patient groups (94% vs 84% of patients reported taking their inhalers more than 75% of the time, $P = .19$), when data from objective electronic monitoring devices were analyzed, patients with PVFM had lower rates of adherence to their preventer inhaler (median taking of prescribed doses 53% of the time) compared with those without PVFM (77%, $P = .043$).

Key clinical comorbidities (dysfunctional breathing, anxiety, depression and gastroesophageal reflux disease, lung function) were included in the multivariate logistic regression model, controlling for potential confounders of age and gender. Peripheral eosinophil count was not included in multivariate analysis because of collinearity with markers of airflow obstruction. Dysfunctional breathing was independently associated with VCD (OR = 4.93, 95% CI: 2.0-12.0, $P < .001$), as was preserved lung function: for every unit increase in FER, the odds of identified VCD increased by 3.8% (95% CI: 1.028-1.106, $P < .001$) (Table V).

We conducted a sensitivity analysis to include all 63 patients with a high index of clinical suspicion of VCD. This analysis

confirmed relationships between VCD and less severe FEV₁ and FER (72% predicted vs 64% predicted, $P = .025$, and 70% predicted vs 61% predicted, $P < .001$, respectively), dysfunctional breathing ($P = .005$), and gastroesophageal reflux disease ($P = .006$). In addition, there were also associations with female gender (76% vs 69%, $P = .036$), oral corticosteroid use in the prior 6 months (2.94 vs 2.24 courses, $P = .03$), and poorer asthma control (Asthma Control Questionnaire 6: 2.7 vs 2.2, $P = .027$) and quality of life scores (AQLQ: 3.87 vs 4.4, $P = .006$). However, there was no significant association with blood eosinophil level ($P = .16$).

DISCUSSION

Key findings

VCD is an important comorbidity among patients with difficult asthma, because it is frequently found in this population and its symptoms closely mimic those of asthma.¹³ VCD was found to often coexist with asthma, as demonstrated by the presence of objective VAO in most patients. In this sample, we examined the association between clinical factors and VCD. VCD was defined by laryngoscopic-visualized PVFM. Dysfunctional breathing was associated with VCD, as was preserved lung function. These findings have implications for the pathogenesis of VCD in difficult

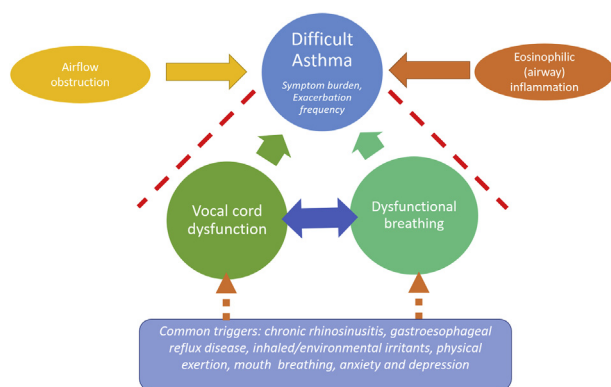


FIGURE 2. Proposed relationships between vocal cord dysfunction, dysfunctional breathing, and difficult asthma (as defined by symptom burden and exacerbation frequency). Dashed arrow = suspected clinical associations.^{33,37} Dashed red line = lack of association in this study.

asthma and may also help to identify patients in this cohort in whom VCD is most likely to be present.

Implications for VCD pathogenesis

The association of VCD with less severe airflow obstruction in this difficult asthma cohort was intriguing. It has previously been suggested that unstable and severe airflow obstruction in asthma may induce VCD through a variety of putative mechanisms including high inspiratory flow rates, enhanced perception of symptoms, hyperventilation-induced airway dryness, and emotion-triggered cholinergic and sympathetic activity.^{33,34} Our findings imply instead that severe lower airway obstruction may not be an essential part of VCD pathophysiology in difficult asthma.

The significant association of VCD with dysfunctional breathing in difficult asthma supports a relationship between the 2 conditions. Recognition of both comorbidities among patients with difficult asthma is increasing.³⁵ However, many studies have focused separately on either VCD or dysfunctional breathing. Some researchers have suggested that both conditions should be recognized as somatoform respiratory disorders—functional disorders of respiratory regulation.³⁶ Others have suggested that VCD represents an extrathoracic form of dysfunctional breathing.³⁷ In the context of our current data in difficult asthma, the relationship between VCD and dysfunctional breathing may well be bidirectional, with both conditions potentially increasing symptom burden and exacerbation frequency (Figure 2). The identification of one comorbidity should thus prompt a search for the other. Also, based on our data, these relationships appear unrelated to lower airway obstruction or eosinophilic airway inflammation (Figure 2). Interventional study designs are needed to explore these relationships further.

In addition, there may be triggers common to both dysfunctional breathing and VCD.⁶ Some of these potential triggers were examined in our study, namely chronic rhinosinusitis, gastroesophageal reflux disease, obstructive sleep apnoea, anxiety, and depression, but no significant relationships between these variables and the presence of VCD were found on multivariate analysis.

In this analysis, the Nijmegen score was a poor discriminator for the presence or absence of dysfunctional breathing. Previous work at our center has demonstrated the limitations of the

Nijmegen score in identifying dysfunctional breathing, highlighting the importance of a more objective diagnosis of dysfunctional breathing by an experienced physiotherapist, as undertaken in this and other studies.^{30,38} A sensitivity and specificity analysis comparing the performance of the Nijmegen score to physiotherapy assessment among this difficult patient population was 21% and 42%, respectively.

Implications for clinical practice

Despite significantly better lung function in patients with VCD, the symptoms and quality of life impairment, frequency of asthma exacerbations, and health care utilization were similar to those without VCD. This is consistent with previous studies indicating the impact of VCD on patient outcomes and health care utilization.³⁹ Patients with VCD were also more likely to have lower eosinophil counts. These findings together suggest that VCD may be more likely to contribute to symptom burden and exacerbation frequency in patients with preserved lung function and minimal (eosinophilic) airway inflammation. Although self-reported adherence to preventer asthma treatment was similar among patients with and without VCD, when examined objectively, patients with VCD had lower rates of adherence to their prescribed preventer. Although we have previously reported the inaccuracy of self-reported adherence within this population,²⁸ this discrepancy may reflect the poor response of VCD symptoms to inhaled asthma therapies.

Strengths and limitations of this study

This is the first study to demonstrate a substantial relationship between VCD and dysfunctional breathing in difficult asthma. Our patients with difficult asthma underwent a standardized and systematic assessment, and follow-up of patients was close to 100%. We defined the diagnosis of VCD with objective visualization of PVFM at laryngoscopy. The diagnosis of dysfunctional breathing was established by standardized physiotherapist assessment³⁰ rather than with the Nijmegen questionnaire, the use of which did not demonstrate a relationship with VCD in a previous analysis.⁴⁰ There is also an inherent limitation in defining these clinical entities, particularly dysfunctional breathing, due to a lack of agreed gold standard diagnostic criteria and definitions, which leads to reliance on consensus statements and expert opinions.

We also recognize the limitations inherent to an observational case series—that associations do not necessarily imply causation. In this pragmatic clinical protocol, only patients with a clinical suspicion of VCD or dysfunctional breathing were referred for laryngoscopy and/or physiotherapy assessment. Furthermore, not all patients referred for laryngoscopy underwent the procedure. Patients with more severe airflow obstruction may have been thought to be less likely to have VCD or may have been thought to poorly tolerate further investigation (ie, laryngoscopy and/or provocation). Thus, our results may represent an underestimation of the presence of PVFM in difficult asthma.

Future directions

Although observational studies in difficult asthma have highlighted both VCD and dysfunctional breathing as important comorbidities among this population, further studies are required to determine underlying pathophysiological mechanism(s) and to confirm this inter-relationship in a larger sample and within other difficult asthma groups. Furthermore, randomized controlled trials are needed to determine which patients would benefit most from therapy and which therapies

are the most effective, whether this would include speech therapy, physiotherapist directed breathing retraining, or both. Traditionally, patients with VCD are referred to speech therapists and patients with dysfunctional breathing are referred to physiotherapists, but other treatment paradigms may warrant exploration. Further item analyses of asthma symptom questionnaire scores (eg, ACT and AQLQ) may also help to further identify distinguishing symptoms among patients with VCD compared with asthma.

Conclusion

Among patients with difficult asthma, VCD and dysfunctional breathing are likely to overlap, suggesting that their pathogenesis may be related. Patients with difficult asthma and preserved lung function should be examined carefully for the presence of both dysfunctional breathing and VCD. They should also be considered for interventions such as breathing retraining or speech therapy, in addition to standard asthma management.

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REFERENCES

- GINA. Diagnosis and management of difficult-to-treat and severe asthma in adolescent and adult patients; 2019. Contract No.: 2. Available from: <https://ginasthma.org/severeasthma/>. Accessed January 14, 2020.
- Heaney LG. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax* 2003;58:561-6.
- Tay TR, Lee J, Radhakrishna N, Hore-Lacy F, Stirling R, Hoy R, et al. A structured approach to specialist-referred difficult asthma patients improves control of comorbidities and enhances asthma outcomes. *J Allergy Clin Immunol Pract* 2017;5:956-964.e3.
- Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003;22:478-83.
- van der Meer A-N, Pasma H, Kempenaar-Okkema W, Pelinck J-A, Schutten M, Storm H, et al. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. *Eur Respir J* 2016;48:726-33.
- Hull JH, Backer V, Gibson PG, Fowler SJ. Laryngeal dysfunction: assessment and management for the clinician. *Am J Respir Crit Care Med* 2016;194:1062-72.
- Sykes A, Menzies-Gow A. Clinical assessment of difficult asthma. In: Heaney LG, Menzies A, editors. *Difficult asthma*. S Narayan & Sons: Jaypee Brothers Medical Publishers Ltd.; 2013. p. 24-40.
- Tay TR, Radhakrishna N, Hore-Lacy F, Smith C, Hoy R, Dabscheck E, et al. Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life. *Respirology* 2016;21:1384-90.
- Low K, Lau KK, Holmes P, Crossett M, Vallance N, Phyland D, et al. Abnormal vocal cord function in difficult-to-treat asthma. *Am J Respir Crit Care Med* 2011;184:50-6.
- Radhakrishna N, Tay TR, Hore-Lacy F, Stirling R, Hoy R, Dabscheck E, et al. Validated questionnaires heighten detection of difficult asthma comorbidities. *J Asthma* 2017;54:294-9.
- Newman KB, Mason UG, Schmalig KB. Clinical features of vocal cord dysfunction. *Am J Respir Crit Care Med* 1995;152:1382-6.
- Tay TR, Hew M. Comorbid "treatable traits" in difficult asthma: current evidence and clinical evaluation. *Allergy* 2018;73:1369-82.
- Lee JW, Tay TR, Paddle P, Richards AL, Pointon L, Voortman M, et al. Diagnosis of concomitant inducible laryngeal obstruction and asthma. *Clin Exp Allergy* 2018;48:1622-30.
- Radhakrishna N, Tay TR, Hore-Lacy F, Hoy R, Dabscheck E, Hew M. Profile of difficult to treat asthma patients referred for systematic assessment. *Respir Med* 2016;117:166-73.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-81.
- Denton E, Hore-Lacy F, Radhakrishna N, Gilbert A, Tay T, Lee J, et al. Severe Asthma Global Evaluation (SAGE): an electronic platform for severe asthma. *J Allergy Clin Immunol Pract* 2019;7:1440-9.
- Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
- Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76-83.
- Dixon AE, Sugar EA, Zinreich SJ, Slavin RG, Corren J, Naclerio RM, et al. Criteria to screen for chronic sinonasal disease. *Chest* 2009;136:1324-32.
- Kennedy JL, Hubbard MA, Huyett P, Patrie JT, Borish L, Payne SC. Sinusnasal Outcome Test (SNOT-22): a predictor of post-surgical improvement in patients with chronic sinusitis. *Ann Allergy Asthma Immunol* 2013;111:246-251.e2.
- Schatz M, Meltzer EO, Nathan R, Derebery MJ, Mintz M, Stanford RH, et al. Psychometric validation of the Rhinitis Control Assessment Test: a brief patient-completed instrument for evaluating rhinitis symptom control. *Ann Allergy Asthma Immunol* 2010;104:118-24.
- Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009;30:1030-8.
- Netzer NC. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131:485.
- Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361-70.
- van Dixhoorn J, Folgering H. The Nijmegen Questionnaire and dysfunctional breathing. *ERJ Open Res* 2015;1: 00001-2015.
- Traister RS, Fajt ML, Landsittel D, Petrov AA. A novel scoring system to distinguish vocal cord dysfunction from asthma. *J Allergy Clin Immunol Pract* 2014;2:65-9.
- Fowler SJ, Thurston A, Chesworth B, Cheng V, Constantinou P, Vyas A, et al. The VCDQ—a questionnaire for symptom monitoring in vocal cord dysfunction. *Clin Exp Allergy* 2015;45:1406-11.
- Lee J, Ren Tay T, Radhakrishna N, Hore-Lacy F, Mackay A, Hoy R, et al. Non-adherence in the era of severe asthma biologics and thermoplasty. *Eur Respir J* 2018;51.
- Tay TR, Hoy R, Richards AL, Paddle P, Hew M. Inhaled mannitol as a laryngeal and bronchial provocation test. *J Voice* 2017;31:247.e19-23.
- Denton E, Bondarenko J, O'Hehir RE, Hew M. Breathing pattern disorder in difficult asthma: characteristics and improvement in asthma control and quality of life after breathing re-training. *Allergy* 2019;74:201-3.
- Low K, Ruane L, Uddin N, Finlay P, Lau KK, Hamza K, et al. Abnormal vocal cord movement in patients with and without airway obstruction and asthma symptoms. *Clin Exp Allergy* 2017;47:200-7.
- Nathan RA. The rhinitis control assessment test. *Curr Opin Allergy Clin Immunol* 2014;14:13-9.
- Bardin PG, Low K, Ruane L, Lau KK. Controversies and conundrums in vocal cord dysfunction. *Lancet Respir Med* 2017;5:546-8.
- Connett GJ, Thomas M. Dysfunctional breathing in children and adults with asthma. *Front Pediatr* 2018;6:406.
- McDonald VM, Hiles SA, Godbout K, Harvey ES, Marks GB, Hew M, et al. Treatable traits can be identified in a severe asthma registry and predict future exacerbations. *Respirology* 2018;24:37-47.
- Grüber C, Lehmann C, Weiss C, Niggemann B. Somatoform respiratory disorders in children and adolescents—proposals for a practical approach to definition and classification. *Pediatr Pulmonol* 2012;47:199-205.
- Barker N, Everard ML. Getting to grips with 'dysfunctional breathing'. *Paediatr Respir Rev* 2014;16:53-61.
- Todd S, Walsted ES, Grillo L, Livingston R, Menzies-Gow A, Hull JH. Novel assessment tool to detect breathing pattern disorder in patients with refractory asthma. *Respirology* 2018;23:284-90.
- Jain S, Bandi V, Officer T, Wolley M, Guntupalli KK. Role of vocal cord function and dysfunction in patients presenting with symptoms of acute asthma exacerbation. *J Asthma* 2006;43:207-12.
- Denton E, Bondarenko J, Tay T, Lee J, Radhakrishna N, Hore-Lacy F, et al. Factors associated with dysfunctional breathing in patients with difficult to treat asthma. *J Allergy Clin Immunol Pract* 2018;7:1471-6.