



Clinical associations in the diagnosis of vocal cord dysfunction

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ARTICLE INFO

Article history:

Received for publication April 23, 2016.

Received in revised form July 31, 2016.

Accepted for publication August 2, 2016.

ABSTRACT

Background: Diagnosis of VCD is complicated by its symptom similarities to asthma. Although clinical history, spirometry, and fiberoptic nasolaryngoscopy are used for VCD diagnosis, videostroboscopy is considered the gold standard. However, little is known about patient characteristics that might suggest a VCD diagnosis is more likely.

Objective: To identify clinical characteristics of patients suspected of having VCD that would increase the likelihood of an accurate diagnosis before videostroboscopy.

Methods: Records of 55 patients were reviewed for a cross-sectional, retrospective study. Individuals selected were suspected of having VCD because of poor clinical response to asthma medications, absence of objective criteria for diagnosis of asthma (eg, normal forced expiratory volume in 1 second without reversibility, normal exhaled nitric oxide, equivocal methacholine challenge test), or both. We used χ^2 analyses to determine significant univariate associations of various patient characteristics. Multivariate regression analysis was then performed using those variables identified as being significant predictors by univariate analysis.

Results: A significant association between VCD and age and between VCD and shortness of breath (SOB) was found. Further analysis revealed that at ages younger than 35 years, with every 5-year decrement in age, patients suspected of having VCD in which SOB is the presenting symptom are more likely to have a positive VCD diagnosis by a factor of 1.3.

Conclusion: Clinical presentation of younger patients with SOB in conjunction with lack of objective criteria for an asthma diagnosis, poor response to asthma medications, or both is highly predictive of VCD and should prompt an objective stroboscopic evaluation to confirm the diagnosis.

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Introduction

Diagnosis of vocal cord dysfunction (VCD) has perplexed clinicians for years, owing to its multifaceted nature. Symptoms that present as VCD have also been referred to as paradoxical vocal fold motion (PVFM),¹ Munchausen stridor,² factitious asthma,³ and functional laryngeal stridor,⁴ among other terms. This variety of monikers can be attributed to the historic lack of understanding about this heterogeneous condition. In VCD, the vocal folds usually adduct on inhalation but can also adduct on exhalation, thus restricting movement of breath through the glottic airway.^{5,6} Patients often report wheezing, which can manifest with

dyspnea, stridor, or both, a localized tightness in the throat often described as a sensation of throat swelling or choking.

The diagnosis of VCD has been confounded by many symptom similarities to asthma. Most patients with VCD are initially diagnosed as having asthma but are then unresponsive to asthma treatment.⁶ This can lead to inappropriate stepping up of medications to generate a better therapeutic response, which places the patient at risk for more potential adverse effects and greater costs. In addition, the multitude of triggers that induce an episode of VCD are frequently similar to those that exacerbate asthma,⁷ including physical exercise, extreme temperatures, airway irritants, and emotional stressors. Finally, the numerous comorbidities, including chronic allergic or nonallergic rhinitis with postnasal drainage, gastroesophageal reflux disease (GERD), and anxiety, make this condition challenging to diagnose.⁸ Morris and Christopher⁹ proposed a classification system that attempted to account for the variety of syndromes associated with VCD, including asthma,

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Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.08.002>

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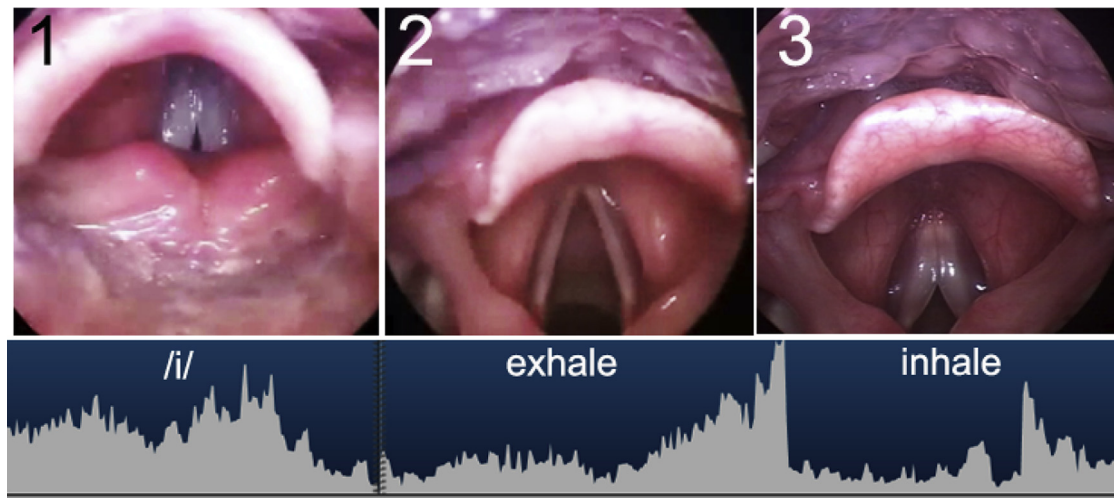


Figure 1. Videostroboscopy findings for a definite diagnosis of vocal cord dysfunction (VCD) demonstrating a characteristic pattern of incomplete vocal fold adduction with inhalation after the exposure to an ammonia inhalant capsule. Panel (1) represents /i/ phonation; panel (2) exhalation; and panel (3) inhalation with the characteristic glottic chink of the posterior vocal cords consistent with VCD.

chronic rhinitis with or without sinusitis, exertion irritant-induced respiratory symptoms associated with environmental exposures, GERD, and psychogenic syndrome. They also described criteria to establish the diagnosis of VCD, including clinical symptoms of noisy breathing and dyspnea, laryngoscopic evidence of vocal cord adduction, and confirmatory pulmonary function test findings of an abnormal flow volume loop, in particular the inspiratory limb. They concluded that laryngoscopic criteria were essential for accurately diagnosing VCD because spirometry findings and clinical symptoms were not independently confirmatory.⁹ Thus far, there are no consensus VCD guidelines that have been established, likely because of the heterogeneous clinical presentation of this condition, the paucity of data on its pathogenesis, and the lack of well-designed clinical trials demonstrating the best approach for diagnosis and treatment. Although clinical history, spirometry, and direct fiberoptic nasolaryngoscopy can all be used to support a diagnosis, there is consensus that a laryngoscopic examination that directly visualizes the vocal cords in response to different maneuvers and when necessary in response to irritant triggers to evoke VCD remains the gold standard for diagnosing VCD.^{5,10} Newer imaging modalities, including videostroboscopy, have been used to diagnose VCD and have an advantage over direct laryngoscopy by providing measurable recordings of vocal fold diseases.^{11,12} Investigators have previously attempted to categorize VCD based on clinical characteristics. For example, comparisons between VCD and chronic cough have been reported.^{13,14} However, in the adolescent–early adult age group, VCD manifesting as exertional dyspnea has been reported to be a predominant presentation.^{15–17} Although a number of clinical characteristics may lead the clinician to suspect a diagnosis of VCD, there is still a gap in knowledge regarding which features are most predictive of a positive videostroboscopy result. The primary objective of this study was to identify patient characteristics that were associated with a greater likelihood that a patient suspected of having VCD will have confirmatory videostroboscopy.

Methods

Study Design and Patient Selection

This was a cross-sectional, retrospective study reviewing a data set of patients with a suspected diagnosis of VCD referred for videostroboscopy. Because this database was historical and deidentified, institutional review board approval was not required. Medical records of 55 patients suspected of having VCD because of

a poor clinical response to asthma medications, absence of objective criteria for diagnosis of asthma (eg, normal forced expiratory volume in 1 second without reversibility, normal exhaled nitric oxide, negative or equivocal methacholine challenge test result), or both were reviewed. The potential bias in this retrospective study was reduced by masking of the medical record reviewers and data analysts on the results of videostroboscopy until the data interpretation from the medical records.

Videostroboscopy

All 55 patients were examined by a single speech pathologist (S.G.) under the supervision of an otolaryngologist using standard videostroboscopy.⁹ A rigid laryngoscope (model 9106; Kaypentax, Lincoln Park, New Jersey) paired with a laryngeal strobe (model 9400; Kaypentax) was used in the examination. The laryngoscope was placed in the posterior oral cavity with the lens just posterior to the base of the tongue. The 70° rigid endoscope was inserted into the oral cavity while the patient sustained the /i/ vowel at several frequencies and intensities and was instructed when to breathe. Each patient's larynx was evaluated both before and after provocation based on their respective trigger for shortness of breath (SOB). The triggers consisted of either aerobic or anaerobic exercise or exposure to a noxious odor based on their report of which trigger induces SOB (ie, ammonia). For those patients whose symptoms were induced through physical exertion, their provocation was dependent on the activity through which they became dyspneic. Depending on their relative fitness, this could range from walking on a flat surface to running sprints on a flat surface to running flights of stairs. The level of intensity necessary was gleaned from the pretesting interview with the patient. Typically, the exercise period continued until symptoms emerged. After provocation,

Table 1
Results of VCD Diagnosis Based on Stroboscopic Examination

Category	No. of patients	Patient age, y		
		Mean (SD)	Range	Median
Definite VCD diagnosis	27	30.1 (3.68)	11–68	20
Probable VCD diagnosis	5	24.4 (4.72)	13–35	26
Normal VC function with LPR presence	19	48.6 (3.33)	14–68	53
Negative VCD	4	54 (5.21)	41–66	54.5

Abbreviation: VCD, vocal cord dysfunction.

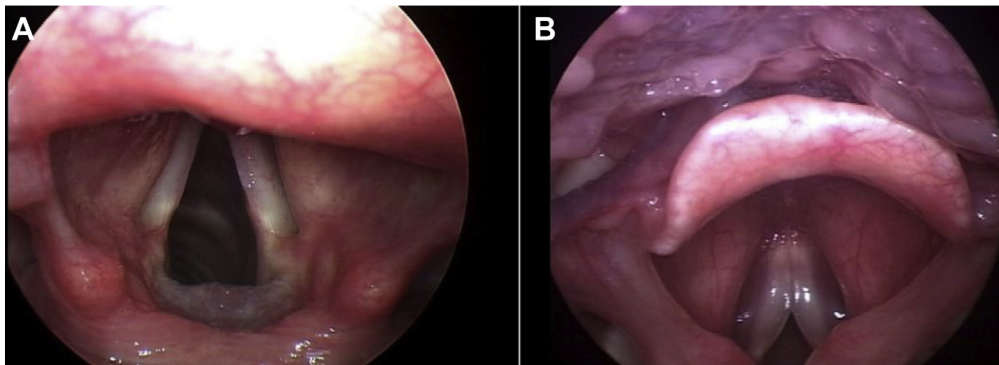


Figure 2. Laryngoscopic comparison of a patient with laryngopharyngeal reflux (A) and the same patient in Figure 1 with vocal cord dysfunction induced by exercise maneuver (B).

diagnosis was classified as (1) a definite diagnosis of VCD if patients had a characteristic pattern of vocal fold adduction with inhalation (Fig 1); (2) a probable diagnosis of VCD if patients had a high clinical suspicion for VCD, but neither adduction of the vocal folds on inhalation nor evidence of laryngopharyngeal reflux (LPR) could be observed on examination; (3) normal vocal cord movement with evidence of LPR; and (4) a negative VCD examination result.

Statistical Analysis

We performed χ^2 analyses to determine significant univariate associations. Multivariate regression analysis was then performed using those variables that were identified as significant predictors by univariate analysis. The association of severity of clinical characteristics of LPR, such as the erythema or edema of posterior arytenoid area or pachyderma in the interarytenoid space, with reflux symptom index (RSI) was determined by generalized linear modeling. SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina), was used for analysis. $P < .05$ was considered statistically significant.

Results

Patients included 45 females and 10 males ranging in age from 11 to 68 years, with a median age of 42 and a mean age of 37.6 years (Table 1). The mean age was 33.8 years (range, 11–57 years) for males and 38.6 years (range, 11–68 years) for females. Twenty-four

patients were younger than 37.6 years. All patients had a suspected diagnosis of asthma. The most frequent presenting clinical symptoms included SOB, chronic cough, and hoarseness. Other reported clinical conditions included in the analysis were stridor, chronic allergic and/or nonallergic rhinitis, GERD, and anxiety; workplace and home environmental exposures and smoking were also included in the analysis.

Thirty-two patients (58%) were diagnosed as having definite ($n = 27$) or probable ($n = 5$) VCD based on clinical presentation and stroboscopic examination. In the definite VCD group, the female to male ratio was 20:7, whereas the probable diagnosis group ($n = 5$) was all female. In the probable diagnosis group, patients presented clinically as having VCD but had normal vocal cord response despite different maneuvers to evoke paradoxical movement. Thirty-four of 55 total patients were observed to have LPR. A significant number of patients (19 of 55) were found to have normal vocal cord movement with evidence of LPR. There were no correlations between LPR and VCD findings in our analysis. Stroboscopic rating was compared with the RSI (Belafsky) in this study,¹⁸ which has high correlation with the Reflux Finding Score.¹⁹ Erythema and edema of the posterior arytenoid area on videostroboscopy was associated with a high RSI score ($P = .01$) and was suggestive of LPR (Fig 2 and Fig 3). Approximately one-third of patients (19 [34.5%] of 55) were found to have normal VC movement with evidence of LPR. No attempt was made to elicit VCD once LPR was identified. The 4 patients who were ruled out for VCD served as the reference level

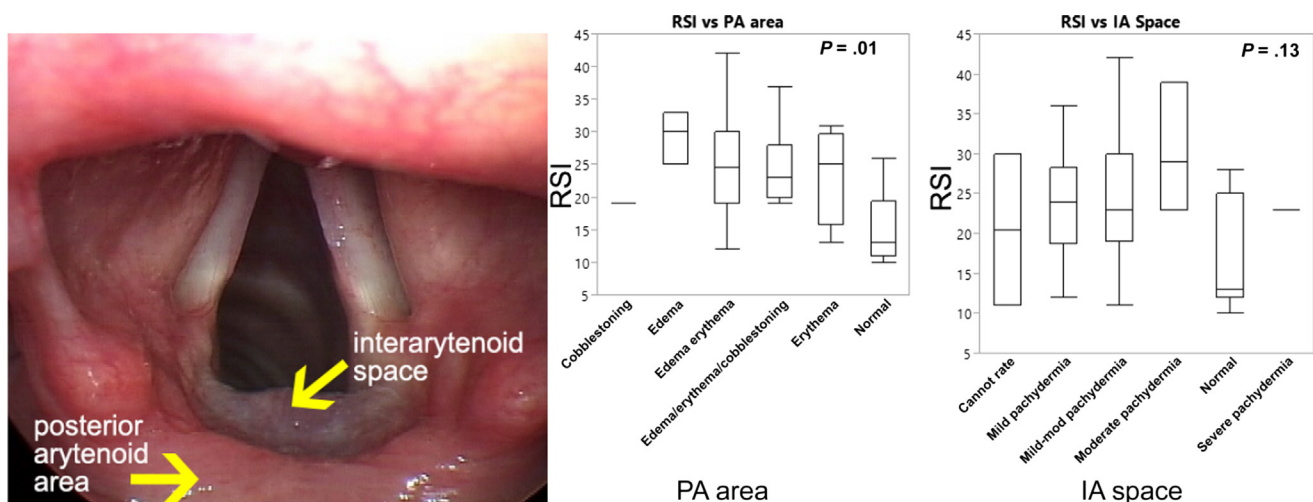


Figure 3. A high reflux symptom index (RSI) was significantly associated with edema and erythema of the posterior arytenoid (PA) area ($P = .01$) and to a lesser extent with pachyderma in the interarytenoid (IA) space ($P = .13$). These characteristics were used to differentiate normal vocal cord dysfunction function with laryngopharyngeal reflux from a definite VCD diagnosis.

for the outcomes during analysis (Table 1). Of the 55 patients, videostroboscopy results were positive in 27 (of 32 patients with truly positive VCD results) and negative in 28 (of 23 patients with truly negative VCD results) (Table 2). Thus, videostroboscopy diagnosis for VCD in our cohort had a sensitivity of 0.84 (ie, [27 positive videostroboscopy results]/[32 true-positive VCD results] or videostroboscopy detected 27 of 32 patients with true VCD and missed 5), a specificity of 1 (ie, [23 positive videostroboscopy results]/[23 true-positive VCD results]; negative videostroboscopy results for 28 patient included all 23 patients with truly negative VCD results), a positive predictive value of 1 (ie, [27 patients with true-positive VCD results]/[27 with positive videostroboscopy results] or all the 27 patients with positive videostroboscopy results were true VCD patients), and a negative predictive value of 0.82 (ie, [23 patients with true-positive VCD results]/[28 with positive videostroboscopy results]; of the 28 patients with positive videostroboscopy results, 23 had truly-negative VCD results).

Among all the presenting characteristics analyzed, SOB was significantly associated with VCD ($P < .01$). Age was also significantly associated with VCD ($P = .02$). Although the study included more female patients (45 of 55), no significant association was observed between sex and VCD ($P = .29$). For patients who presented with cough, hoarseness, or a diagnosis of asthma, no significant association was found with VCD (Table 3).

Multivariable analysis of SOB and age as independent variables compared with VCD as the dependent variable revealed a significant association between VCD and SOB combined with age, especially in the age group younger than 35 years. Analysis of the entire group irrespective of age demonstrated a trend but not a statistically significant association ($P = .07$) (Table 3) between VCD with SOB combined with age. Further analysis revealed a statistically significant association with VCD in the population younger than 35 years (odds ratio, 3.87; 95% CI, 1.20–12.54) (Table 3). In fact individuals younger than 35 years suspected of having VCD in which SOB was the presenting symptom were 1.3 times more likely to have a positive VCD diagnosis confirmed by videostroboscopy for every 5-year decrement in age (Table 4).

Discussion

The results of this study indicate a significant association between VCD and SOB consistent with previous studies that reported SOB to be the most common clinical presentation for VCD.^{9,20} Recently, Fowler et al²⁰ designed a specific VCD questionnaire to identify potential patients with VCD. The questionnaire included 12 items, such as location of symptoms, onset, and overall well-being. In their study, the overall score of VCD was significantly higher in patients with VCD than it was in those with asthma and in healthy volunteers. Although patients' symptoms were not defined in detail in their questionnaire, they found that breathless (or SOB) was the most common clinical presentation for VCD.

Although SOB is a nonspecific clinical symptom and difficult to use as a single predictor for VCD, if present as the predominant symptom in a patient for whom a diagnosis of asthma is unclear

Table 2
Determining Sensitivity, Specificity, PPV, and NPV of Videostroboscopy

	Positive VCD result	Negative VCD result	Predictive value
Positive videostroboscopy result	27	0	1.00 (PPV)
Negative videostroboscopy result	5	23	0.82 (NPV)
Sensitivity or specificity	0.84 (Sensitivity)	1.00 (Specificity)	

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; VCD, vocal cord dysfunction.

Table 3
Univariate Analysis of Significant Determinants of VCD Diagnosis

Determinant variable	Analysis of maximum likelihood estimates		OR estimate (Wald 95% CI)
	Estimate	P value	
Sex (female vs male)	−0.75	.29	0.47 (0.12–1.89)
Age	−0.04	.02	0.97 (0.94–0.99)
Shortness of breath	1.47	<.01	4.34 (1.47–12.84)
Cough	−0.81	.16	0.44 (0.14–1.34)
Hoarseness	0.55	.41	1.73 (0.47–6.35)
Asthma	−0.90	.23	0.41 (0.09–1.77)

Abbreviations: CI, confidence interval; OR, odds ratio.

and/or their response to medication is unsatisfactory, it may help guide clinical decisions about whether referral for videostroboscopy is appropriate. In our analyses, other clinical presentations, such as cough, stridor, and hoarseness, were not useful in predicting a diagnosis of VCD confirmed by videostroboscopy.

Our findings, in the univariate analysis, also indicate that patient age is a significant predictor for VCD. It has been previously reported that young female adults suspected of having VCD are more likely to have a confirmed diagnoses of VCD.^{6,9,10} Although our study found that more females received a confirmed diagnosis of VCD, this finding was not statistically significant, which likely reflects the small population size analyzed. Why younger individuals are more susceptible to having VCD is still unclear. However, it may simply reflect less comorbidity manifested by young adults and teenagers, making it easier to diagnose VCD based on the single presenting symptom. In contrast, elderly patients often present with multiple concomitant diseases that can have overlapping symptoms, making the clinical picture less clear. Previous reports noted that exertion and exercise appear to be a predominant trigger for VCD-related dyspnea in the young adult and adolescent group.^{15–17} However, exertion-induced dyspnea was not a common symptom in our patient population. The absence of exertion as a trigger may again reflect the cross-sectional study design and small sample size. However, the strong association between VCD and the SOB presentation in young adults, in our study, may also indicate SOB by itself is a stronger clinical predictor of VCD because it was not influenced by exertion.

Not surprisingly, a significant number of patients (19 of 55) were found to have normal vocal cord movement with evidence of LPR. This high percentage of patients with LPR further emphasizes the importance of objective testing to differentiate LPR from VCD because they often have a similar clinical presentation. However, in our analysis, SOB was not found to be a significantly associated with LPR as it was for VCD. Further investigation into the underlying mechanism(s) explaining the association between LPR and VCD is required.²¹

Table 4
Significant Determinants of Vocal Cord Dysfunction Diagnosis Using Multiple Logistic Regression Analysis Without and With Age Stratification

Determinant variable	Analysis of maximal likelihood estimates		OR estimate (Wald 95% CI)
	Estimate	P value	
Shortness of breath	3.26	.02	
Age × shortness of breath	−0.05	.07	
SOB (yes vs no)			15.10 (1.64–138.71)
Age 10 y			11.50 (1.61–82.2)
Age 15 y			8.76 (1.56–49.36)
Age 20 y			6.68 (1.47–30.22)
Age 25 y			5.10 (1.36–19.05)
Age 30 y			3.87 (1.20–12.54)
Age 35 y			2.95 (0.99–8.76)
Age 40 y			2.25 (0.76–6.62)
Age 45 y			

Abbreviations: CI, confidence interval; OR, odds ratio; SOB, shortness of breath.

Table 5
Results of Videostroboscopy for 4 Patients With Inspiratory Stridor

Glottic closure	Vocal fold edge left and right	Mucosal waveform propagation	Phase symmetry	Interarytenoid space	Posterior arytenoid area	RSI
Anterior/posterior gap	Bowed	Mild to moderate decreased 3	Always asymmetrical	Mild moderate pachydermia	Edema erythema	28
Anterior gap	Edema or erythema	Mild to moderate decreased 3	50% Asymmetrical	Mild pachydermia	Edema, erythema, or cobblestoning	28
Complete	Edema	Normal	50% Asymmetrical	Mild to moderate pachydermia	Edema or erythema	23
Posterior gap	Smooth straight	Mildly decreased 2	Irregular, frequently extreme	Normal	Normal	10

Abbreviation: RSI, reflux symptom index.

We also analyzed other important clinical characteristics, including stridor, chronic rhinitis, GERD, anxiety, and work or home environmental exposures. These characteristics were only reported by 24 patients. However, none of these clinical conditions revealed a significant association with VCD, further highlighting the important association of SOB with VCD in the younger population. Despite stridor being a strong historical feature of VCD, only 4 of 55 patients studied had inspiratory stridor, and thus a statistical significance with VCD was unlikely because of small number of patients in this category. The most common videostroboscopy findings in these patients were decreased mucosal waveform propagation, phase asymmetry, mild to moderate pachydermia of the interarytenoid space, edema or erythema of the posterior arytenoid area, and a median RSI of 26 (Table 5).

The strength of this study is that all patients underwent videostroboscopy after failure of asthma therapy by the same speech pathologist (S.G.). In addition to the small sample size and retrospective study design limitations of our study, there could also be a potential statistical bias of our analysis in that the 4 patients ruled out for VCD, who served as the dependent variable reference group to which other VCD-diagnosed groups were compared, were not aged matched (mean age, 54 years) to the groups confirmed to have VCD or with probable VCD. However, despite this potential bias, it was appropriate to use these patients as the internal control because they were randomly selected and underwent the same diagnostic procedures as the other groups. Videostroboscopy may not be the reference standard to diagnose VCD, and simple laryngoscopy may still be needed. Nonetheless, VCD lacks an objective gold standard because it occurs intermittently and is situational. Moreover, the provocative maneuvers to diagnose VCD may itself be heterogeneous. This has been the root of the problem with this clinical entity.

The results of this study emphasize several important points regarding VCD. First, more than half of the patients in our study were diagnosed as having VCD, suggesting that a high percentage of patients may carry a misdiagnosis of asthma confounded by VCD. Second, an accurate diagnosis of asthma is essential to prevent unnecessary persistent symptoms, which can affect the patient's quality of life and create an unnecessary economic burden if they are paying for monthly medications that are not indicated. Third, because asthma occurs at a young age, and patients with asthma commonly present with SOB in addition to wheezing, cough, chest tightness, and sometimes chest pain,^{22–24} physicians should include VCD in their differential diagnosis, especially when objective changes in lung function cannot be elicited and asthma medications are ineffective. Laryngeal visualization in emergency departments and urgent care clinics would enable proper diagnosis of more patients with VCD. Therefore, a serial follow-up and success in controlling symptoms without using asthma medications should be the standard of care for VCD.

In summary, our study found that a clinical presentation of younger patients with SOB in conjunction with lack of objective criteria for an asthma diagnosis, poor response to asthma

medications, or both is highly associated with VCD and should prompt an objective stroboscopic evaluation to confirm the diagnosis. These findings need to be confirmed in a larger study that includes a larger healthy control group, a patient population with suspected VCD, and a comparative asthma control group. Future such studies should include standardized methods for videostroboscopy as part of the VCD assessment criteria.

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