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Spirometry and provocation tests for vocal fold dysfunction diagnosis: a retrospective case series

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Summary

AIMS: Vocal cord dysfunction (VCD) is characterised by paradoxical inspiratory laryngeal motion and is often misdiagnosed as asthma. Definitive diagnosis of VCD is difficult, because laryngoscopy is positive only during symptomatic episodes or upon provocation with exercise or inhaled irritants. The aims of the study were to better characterise the symptomatology of patients with VCD and to evaluate the potential usefulness of less-invasive diagnostic tools, namely provocation tests and spirometry.

METHODS: Retrospective case series of 84 patients with a typical clinical history of VCD, in whom at least one of the three following diagnostic tests were performed: laryngoscopy, provocation testing, or spirometry.

RESULTS: The mean age of the patients was 51 years and 74% were women. The principal comorbidities were rhinosinusitis (60%), gastro-oesophageal reflux disease (56%) and atopy (54%). Diagnosis of VCD was confirmed in 73/84 cases (87%), by laryngoscopy (8%), spirometry (84%) and/or provocation tests (68%).

CONCLUSIONS: VCD remains an underdiagnosed condition. A negative finding on laryngoscopy can lead to false negative diagnosis if it is done when the patient is asymptomatic. Here we show that a clinical suspicion of VCD, evoked by medical history, can be confirmed in many cases by less invasive diagnostic tools such as spirometry and provocation tests. Future well-conducted prospective case-control studies are needed to draw firmer conclusions and to improve the diagnostic accuracy of this condition.

Keywords: *paradoxical vocal cord motion, extra-thoracic airway hyper-responsiveness, asthma, atopy, volume-flow loop, mannitol challenge test, exercise challenge test, laryngoscopy*

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Background

Vocal cord dysfunction (VCD) is an upper airway disorder characterised by a paradoxical inspiratory closure of the vocal cords. It is an under-recognised cause of wheezing and unexplained refractory cough, often misdiagnosed as asthma [1–3]. Many labels have been used for VCD in recent decades, including false croup, Munchausen's stridor, psychogenic stridor, hysterical stridor, factitious asthma, pseudo-asthma, emotional laryngeal wheezing, episodic laryngeal dyskinesia, irritable larynx syndrome, paradoxical vocal fold motion/movement [4–6] and, more recently, inducible laryngeal obstruction [7].

The prevalence of VCD in the general population is not known. It occurs in all age groups, frequently being reported in juvenile girls [8], and especially in athletic subjects [9]. A prospective evaluation of a military population with exertional dyspnoea revealed a diagnosis of VCD in 15% [10]. The prevalence of VCD in patients admitted to emergency services for breathlessness of acute onset varied between 2.5 and 22% depending on the study population, with a female predominance varying from 2:1 to 4:1 [11, 12]. VCD is related to a broad spectrum of underlying causes, including functional as well as organic conditions. Psychological disorders were initially believed to be the exclusive cause of VCD [13–15]. However, a role of various nonpsychological factors involving sensory mechanisms [16–18], such as gastro-oesophageal reflux [19], as well as upper respiratory tract conditions and infections (pharyngitis, laryngitis, rhinosinusitis), are progressively being recognised [20–25]. Paradoxical vocal fold movement has also been reported in the context of established neurological diseases, such as brain stem compression, severe cortical injury, nuclear or lower motor neurone injury movement disorders and neuroleptic abuse [24, 26].

The clinical presentation of VCD is that of airway obstruction with wheezing, inspiratory stridor, breathlessness and coughing, which are easy to confuse with symptoms of asthma [27, 28]. Cough as the sole presenting symptom raises the probability of extra-thoracic airway hyperresponsiveness (EAHR) [22, 29], which results in the same reduction of inspiratory flow as VCD, and therefore is difficult to distinguish from it [5, 22]. In general, the diagnosis is suspected in patients with atypical asthma presentation and refractory clinical course. Nevertheless, VCD and asthma can also present together, in half or more of the cas-

es, as demonstrated in several series of asthmatic patients [2, 3, 30, 31].

The principal difficulty in recognising and diagnosing VCD is that laryngeal endoscopic observation or video-laryngostroboscopy are conclusive only during a symptomatic episode [31, 32]. Therefore, the sensitivity of these examinations is only moderate [33, 34]. To overcome this problem, some authors have tried to challenge VCD patients with exercise [9], or inhaled irritants such as methacholine [35], histamine [20, 22] and mannitol [34]. An alternative diagnostic approach might be based on the combination of a typical clinical history, eventually using standardised questionnaires [36–38], with less-specific tests [39], consisting of volume flow loops, mannitol challenge test (MCT), and the exercise challenge test (ECT).

The aim of this study was to present a case series of patients with a strong clinical suspicion of VCD based on medical history and findings obtained by laryngoscopy, spirometry and provocation tests consistent with VCD. The potential diagnostic usefulness of the latter two non-invasive tests was evaluated.

Materials and methods

Population

Patients were identified by the senior allergist in charge (PT) when presenting with a typical clinical history of VCD, and were included when at least one of the following three complementary tests was performed in order to confirm the diagnosis: laryngoscopy, spirometry and respiratory challenge tests. Patients were recruited in the last 10 years in the Allergy Unit of the Geneva University Hospital (HUG) and in the Centre des Allergies et de l'Asthme de la Terrassière, in Geneva between 2004 and 2013. Data were collected retrospectively from medical records in 2014. Approval was obtained by the local ethics committee (HUG; protocol n°13-166). This study was purely observational; therefore written consent was not required.

Clinical parameters

Patient characterisation included age and gender; reason for consulting (asthma, cough, dyspnoea, dysphonia, or referral for VCD suspicion); triggering symptoms (anxiety, physical exertion, irritant inhalation, gastro-oesophageal reflux disease, rhinosinusitis), clinical symptoms and disease pattern (inspiratory or expiratory dyspnoea, cough, hoarseness, rhinosinusitis, gastro-oesophageal reflux disease [GORD], atopy, suspicion of asthma, rapid onset [<3 minutes] and resolution [<5 minutes] of symptoms, and β_2-antagonist responsiveness). Atopy was defined by the presence of at least one positive skin prick test for common aeroallergens, one positive specific IgE, or a positive Phadiatop test. Suspicion of asthma was based on recurrent attacks of breathlessness and wheezing associated with either a diminished FEV/FVC ratio (80% or less at age 20–39, 75% or less at age 40–59, and 70% or less at age 60–79), or a positive response to β_2-antagonists an increase in FEV_1 of 200 ml or greater and 12% or greater from baseline) [40].

Spirometry

Spirometry (EasyOne™, Zurich, Switzerland) was performed to measure forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) using the American Thoracic Society criteria [41]. Spirometry was performed until two comparable values of FEV_1 within 100 ml were obtained. The higher of the two values was recorded and the percentage of predicted values was calculated. We added a measure that pinpoints EAHR on the flow volume-loop: the forced expiratory flow over the forced inspiratory flow at 50% of inspiration ratio (FEF_{50}/FIF_{50}). In addition, we described three typical morphological aspects of the inspiratory flow curve that can be related to laryngeal hyper-reactivity: the *flattened aspect*, the *notched aspect* and the *steep slope aspect* of the second part of the inspiratory curve. If the inspiratory curve was not U-shaped and did not belong to one of these three typical morphological patterns, we referred to it as *undefined pathological aspect* [11, 12, 42]. In contrast to the measurement of FEV_1 [41], inspiratory measures such as FIF_{50} and FEF_{50}/FIF_{50} ratio are not yet standardised. We performed a minimum of three expiratory/inspiratory volume-flow loops and accepted it as abnormal if at least one of the three inspiratory curves had ≥1 of the typical morphologies described.

Exercise challenge test

Briefly, the ECT was performed according to the ATS guidelines for exercise challenge testing [41] by using an electronically braked cycle ergometer. Work rate (Watts) was adjusted in increments. Speed was chosen to produce 4–6 minutes of exercise at near-maximum levels (i.e. Borg effort scale 17–20/20) with a total duration of exercise of 8 min. Spirometry was performed before exercise and then serially at 2, 5, 10 and 15 min after cessation of exercise. A positive response to ECT was defined by a fall in FEV_1 of ≥15% after challenge, a positive ECT for VCD as a ≥20% fall in FIF_{50} from baseline.

Mannitol challenge test

The MCT was performed according to the protocol by Anderson et al [42]. Briefly, doses of 0 (empty capsule acting as a placebo), 5, 10, 20, 40, 80 and 160 mg of mannitol were administered via an inhaler device (Pharmaxis Ltd., Frenchs Forrest, NSW, Australia). After the inhalation, the patients were told to hold their breath for 5 seconds. Two FEV_1 manoeuvres were performed 60 seconds after each dose and the highest FEV_1 measurement was recorded. The value measured after the 0 mg capsule was taken as the pre-challenge FEV_1 and was used to calculate the percentage decrease in FEV_1 in response to mannitol challenge. The challenge was stopped when a 15% fall in FEV_1 was documented or a cumulative dose of 635 mg had been administered. The dose of mannitol to cause a 15% fall in FEV_1 was calculated by linear interpolation of the relationship between the percent fall in FEV_1 at the end of the MCT and the cumulative dose of mannitol required (in mg) to provoke this fall. Response to the MCT was considered positive when a fall in FEV_1 of ≥15% occurred after a cumulative mannitol dose of 635 mg or less. We also measured FIF_{50} and the drop of FIF_{50} from baseline, to document extra-thoracic hyper-reactivity. A positive MCT for VCD was defined as a ≥20% fall in FIF_{50} from baseline.

Hypertonic saline challenge tests

Spirometry was performed before hypertonic saline exposure (NaCl 6%), and then serially at 2, 5, 10 and 15 minutes after exposure. A positive test was defined by a fall in FEV_1 of ≥15% after challenge, a positive test for VCD as a ≥ 20% fall in FIF_{50} from baseline.

Statistical analysis

Data were analysed using R software (Vienna, Austria, version 3.1.1). Continuous outcomes (i.e. age) were reported with mean and standard deviation. Binary outcomes were reported with absolute values and percentages with their corresponding confidence intervals. Sample size was reported for each binary outcome of interest, because of the significant rate of missing values.

Results

Ninety patients with typical history of VCD were identified and 84 who had undergone laryngoscopy, spirometry or respiratory challenge test were included: 62 (74%) females and 22 (26%) males. The median age was 51 ± 18 years old. The reasons for consulting, reported for all patients, comprised asthma (18%), cough (19%), dyspnoea (23%), combined cough and dyspnoea (10%), dysphonia (7%), and referral for VCD suspicion (21%) (table 1). VCD triggers, evaluated in 53/70 patients, consisted of anxiety (23%), physical exertion (48%), irritants inhalation (16%), GORD (26%), and rhinosinusitis (20%) (table 2). Note that multiple triggers could be found on the same patient.

Associated symptoms and disease pattern were sometimes partially reported (table 3). The major associated symptom was dyspnoea (91%), with 78% being inspiratory. Other associated symptoms were cough (90%), hoarseness (70%) and rhinosinusitis (60%). The principal comorbidities were GORD (56%), atopy (54%) and asthma (45%). During an acute period, rapid onset (75%) and resolution (52%) of symptoms was frequent. Response to β_2-antagonists occurred in 53% of cases.

Thirty-six patients underwent laryngoscopy, which was positive in three (table 4). Provocation tests were performed in 37 patients and were positive in 68%, of which 81% were MCTs, 50% were ECTs and 43% with various irritant triggers. The only test performed with hypertonic saline was also positive. Spirometry was conducted in 76 patients and was positive in 84%. The inspiratory volume-flow loop was notched in 36% of cases, flattened in 42%, had a steep slope in 2%, and had multiple undefined pathological patterns in 10%. FEF_{50}/FIF_{50} ratio was >1 in 54% of cases. For the 73 patients presenting at least one complementary examination positive, contribution to the diagnosis was obtained by spirometry alone in 45 cases, by provocation tests alone in 6 cases, and by any combination of spirometry, provocation tests and laryngoscopy in 23 cases.

Table 1: Reason for consulting.

Asthma	15/84 18% (11–28%)
Cough	16/84 19% (12–29%)
Dyspnoea	19/84 23% (14–33%)
Cough and dyspnoea	8/84 10% (4–18%)
Dysphonia	6/84 7% (3–15%)
VCD suspicion	18/84 21% (14–32%)
Others	2/84 2% (0–9%)

Reported values for each outcome of interest: number of positive cases/sample size; percentage (percentage's confidence interval).

Table 2: Trigger symptoms.

Anxiety	14/61 23% (14–36%)
Physical exertion	29/61 48% (35–61%)
Irritant inhalation	10/61 16% (9–29%)
Gastro-oesophageal reflux disease	16/61 26% (16–39%)
Rhinosinusitis	12/61 20% (11–32%)

Reported values for each outcome of interest: number of positive cases/sample size; percentage (percentage's confidence interval).

Discussion

The current study describes a large case series of patients presenting with a strong clinical suspicion of VCD, a condition for which a sensitive or specific complementary examination does not yet exist. Our findings provide additional information on VCD patient characteristics and indicate the potential usefulness of noninvasive diagnostic tools.

Table 3: Associated symptoms and disease pattern.

Dyspnoea	73/80 91% (82–96%)
Inspiratory dyspnoea	47/60 78% (65–88%)
Cough	55/61 90% (79–96%)
Hoarseness	51/73 70% (58–80%)
Rhinosinusitis	50/84 60% (48–70%)
Gastro-oesophageal reflux disease	47/84 56% (45–67%)
Atopy	45/84 54% (42–64%)
Asthma suspicion	32/80 45% (35–56%)
Rapid symptom onset (<3 min.)	52/70 74% (62–84%)
Rapid symptom disappearance (<5 min.)	35/68 52% (39–64%)
Response to β_2-agonists	26/49 53% (38–68%)

Reported values for each outcome of interest: number of positive cases/sample size; percentage (percentage's confidence interval).

Table 4: Diagnostic tools.

Laryngoscopy	3/36 8% (2–24%)
Provocation test (overall)	25/37 68% (50–81%)
Mannitol trigger	17/21 81% (57–94%)
Effort trigger	6/12 50% (25–75%)
Irritant trigger	3/7 43% (12–80%)
Hypertonic saline trigger	1/1 100% (5–100%)
Spirometry (overall)	64/76 84% (74–91%)
Notched aspect	21/59 36% (24–49%)
Flattened aspect	25/59 42% (30–56%)
Steep slope aspect	1/59 2% (0–10%)
Undefined pathological aspect	6/59 10% (4–21%)
FEF_{50}/FIF_{50}	37/69 54% (41–66%)
Findings for diagnosis contribution	
Spirometry only	45/84
Provocation test only	6/84
Spirometry and provocation tests	19/84
Spirometry and laryngoscopy	2/84
Spirometry, provocation test, and laryngoscopy	1/84

Reported values for each outcome of interest: number of positive cases/sample size; percentage (percentage's confidence interval).

VCD characteristics and triggers

The observed female-to-male ratio of 3:1 was previously reported [11, 43], but we found a median age of 54 years, which is much older than usually reported [8]. This higher age can be partly explained by a referral bias, since paediatric and adolescent patients are rarely seen in our clinics. The second possible explanation is that nowadays, VCD diagnosis is more frequently thought of in older age groups.

VCD triggers include inhaled irritants, physical exertion, acid reflux, upper respiratory tract infection [44], cold air, laughing and anxiety, all causing EAHR. Interestingly, a Brazilian cohort of patients suffering from allergic rhinitis reported a VCD prevalence of 28.5% following nasal provocation test with the house dust mite allergen *Dermatophagoides pteronyssinus* [45]. Allergens could therefore represent another potential trigger in a specific VCD subgroup. We found an atopy prevalence of 54% in our cohort. In comparison, the atopy prevalence in the general population is 32.3% [43]. This difference might be explained either by potential associations between atopy and VCD ± asthma, or by a potential referral bias (patients were screened in allergy and asthma centres). Pulmonary symptoms were the reason for consulting in a high proportion of our case series (see table 1). This might also be the result of a potential referral bias, for example compared to patients presenting predominantly with dysphonia who preferentially consult with ear nose and throat (ENT) specialists.

VCD and asthma overlap

Most of the symptoms associated with VCD are not specific for this disease (see table 3) with the exception of rapid symptom onset and disappearance, which partially explains the difficulties in making a correct diagnosis. A recent validated tool, the Newcastle laryngeal hypersensitivity questionnaire [36–38], can differentiate VCD patients from healthy controls, but differentiating VCD from other respiratory conditions such as chronic cough remains challenging [46]. The prevalence of comorbidities such as asthma, rhinitis, and GORD was similar to previously reported findings [30]. Rhinosinusitis (60%) and GORD (56%) are direct contributors to extra-thoracic hyperreactivity, by either direct laryngeal deposition of mucus and its proinflammatory mediators, or acid irritation. We found a prevalence of asthma suspicion in 32/80 patients (45%), and a relatively high proportion of β_2-agonist responders (26/49 patients, 55%). A similar prevalence of asthma of 55% has been previously reported in a case series of 95 patients with laryngoscopically diagnosed VCD [30]. One can argue that we recruited patients suffering from asthma but not VCD. However, the potential coexistence of asthma and VCD and the overlap in their clinical presentation account for the diagnostic difficulties and delays in identifying VCD.

The potential association of asthma and VCD could widen the concept of "united airway disease" to a new global rhino-laryngo-bronchial respiratory entity including laryngeal hypersensitivity [47, 48]. In the future, the recognition of a high prevalence of asthma associated to VCD could lead to significant changes in current asthma guidelines with potentially an important reduction in the morbidity of a subgroup of patients.

Implications for clinical practice

Diagnosis of VCD not only requires a high level of suspicion, but also access to specialised ENT testing such as laryngoscopy or videolaryngostroboscopy. Albeit laryngoscopy is the historical gold standard [5], it can fail to demonstrate VCD because of the paroxysmal nature of this condition. Indeed, in our case series, laryngoscopy was positive in only 3/36 patients (8%), reflecting a low sensitivity outside an acute episode. Provocation manoeuvres may increase the sensitivity of the laryngoscopy, especially when adequate triggers are applied [49, 50]. Laryngoscopy remains of great importance in the management of recalcitrant VCD cases, in order to differentiate between supraglottic and infraglottic obstructions. Indeed, supraglottic obstruction might be effectively managed by endoscopic supraglottoplasty [51], and laryngomalacia might coexist in cases of infraglottic obstruction [52].

Various bronchial provocation tests using hypertonic saline, methacholine, histamine, effort or other irritants have been proposed to investigate both classical bronchial hyperreactivity and EAHR. The rationale for the use of these provocation tests is laryngeal sensory neuropathy; characterised by hypersensitivity to many specific or non-specific triggers. These provocation tests act as laryngeal irritants and prompt extrathoracic symptoms such as cough, dyspnoea and dysphonia. The recognition of laryngeal dysfunction has led to an emerging concept, which is now called the irritable larynx syndrome [53]. The most promising provocation test is the MCT, which was positive in 17/21 (81%) of our patients. MCT is simple to implement for an allergy or respiratory physician, takes less than 30 minutes and can be performed outside an acute attack. In our clinical practice, an MCT is performed when history does not reveal a specific trigger. ECT and irritant respiratory challenges tests were performed when the related VCD stimulus was revealed by the clinical history, and were positive in one half of the cases.

Spirometry was completed in 76 patients and results were consistent with VCD in 84% of the cases. Previous studies have reported conflicting results on abnormal inspiratory loops in patients with a confirmed diagnosis of VCD, the incidences ranging from 23 to 100% [54], as well as a limited usefulness of spirometry to predict the diagnosis of VCD [55]. We found a surprisingly high prevalence of positive spirometry for VCD (84%). This unexpected finding has to be confirmed by future studies with confirmed diagnosis of VCD, eventually in combination with trigger provocation manoeuvres in order to get results during an acute attack.

A proper diagnostic test for VCD is imperative, because this condition requires specific therapeutic modalities. Furthermore, it is important to identify and manage VCD triggers. The first line of treatment includes diet and lifestyle adaptations, proton pump inhibitors, intranasal corticosteroids, and if feasible avoidance of inhaled irritants. The cornerstone of specific VCD treatment is based on speech therapy, to provide instructions in techniques of throat relaxation as well as cough and throat clearing avoidance. We found a prevalence of anxiety of 21%. Psychological

interventions such as psychotherapy, behavioural therapy, biofeedback or hypnosis may be required for some patients [14, 56, 57].

Limitations and implications for further research

Our study has significant limitations including the retrospective design, the potential inherent selection bias, a moderate sample size, missing values, the absence of a control group and foremost, the absence of a robust gold-standard test to confirm the diagnosis. Sensitivity and specificity analysis were therefore not feasible. However, we consider our results as relevant and representative of the current clinical practice, since a validated diagnostic algorithm is not yet established [7]. Practically, the diagnosis of VCD was based on a combination of low-weighted clinical arguments including VCD symptoms, trigger factors, associated conditions and easy-to-perform and non-invasive diagnostic tests. We observed surprisingly high proportions of atopy, positive mannitol provocation testing and specific disease patterns on spirometry. Even if our results did not lead to clear clinical recommendations, they could be useful in paving the way for future prospective case-control studies, which should focus on sensitivity analysis for the various noninvasive diagnostic tools presented here, applied either separately or, more interestingly, in combination. Future studies focusing on VCD and on its association with allergies and asthma would be of great interest.

Conclusions

VCD remains an underdiagnosed condition despite being increasingly recognised. For the important proportion of VCD patients presenting with a false-negative laryngoscopy or videofluoroscopy, a combination of clinical history and less invasive diagnostic tools, especially provocation tests and spirometry, might contribute to a better diagnostic approach to VCD. Atopy could play a role in VCD. Future case-control studies using a reproducible diagnostic scoring or assessment system for this condition are needed in order to draw firm clinical recommendations.

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