

Inhaled Mannitol as a Laryngeal and Bronchial Provocation Test

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Summary: Objectives. Timely diagnosis of vocal cord dysfunction (VCD), more recently termed “inducible laryngeal obstruction,” is important because VCD is often misdiagnosed as asthma, resulting in delayed diagnosis and inappropriate treatment. Visualization of paradoxical vocal cord movement on laryngoscopy is the gold standard for diagnosis, but is limited by poor test sensitivity. Provocation tests may improve the diagnosis of VCD, but the diagnostic performance of current tests is less than ideal. Alternative provocation tests are required. This pilot study demonstrates the feasibility of using inhaled mannitol for concurrent investigation of laryngeal and bronchial hyperresponsiveness.

Methods. Consecutive patients with suspected VCD seen at our institution’s asthma clinic underwent flexible laryngoscopy at baseline and following mannitol challenge. VCD was diagnosed on laryngoscopy based on inspiratory adduction, or >50% expiratory adduction of the vocal cords. Bronchial hyperresponsiveness after mannitol challenge was also assessed. We evaluated the interrater agreement of postmannitol laryngoscopy between respiratory specialists and laryngologists.

Results. Fourteen patients with suspected VCD in the context of asthma evaluation were included in the study. Mannitol provocation demonstrated VCD in three of the seven patients with normal baseline laryngoscopy (42.9%). Only two patients had bronchial hyperresponsiveness. There was substantial interrater agreement between respiratory specialists and laryngologists, kappa = 0.696 (95% confidence interval: 0.324–1) ($P = 0.006$).

Conclusion. Inhaled mannitol can be used to induce VCD. It is well tolerated and can evaluate laryngeal and bronchial hyperresponsiveness at the same setting.

Key Words: Asthma–Larynx–Mannitol–Paradoxical vocal fold motion–Vocal cord dysfunction.

INTRODUCTION

Vocal cord dysfunction (VCD), otherwise known as inducible laryngeal obstruction based on a more recent consensus nomenclature,¹ commonly gives rise to symptoms such as dyspnea and wheezing.² These patients are often misdiagnosed as having asthma, resulting in a delayed VCD diagnosis for several years and inappropriate treatment with high-dose corticosteroids.³ It is estimated that 10% of the patients presenting to the emergency department with a diagnosis of asthma exacerbations actually have symptoms due to VCD.⁴

VCD can also coexist with asthma. In one study, 50% of patients with severe asthma were found to have concomitant VCD.⁵ Overlooking the diagnosis of VCD in patients with concomitant asthma can lead to symptom misattribution and inappropriate escalation of asthma treatment. It is, therefore, important to recognize and confirm VCD early in its course.

Objective diagnosis of VCD is challenging. Laryngoscopic visualization of paradoxical vocal fold movement during inspiration and/or expiration is the gold standard for VCD diagnosis.⁶ However, it has poor sensitivity, as laryngoscopy findings are often normal when patients are asymptomatic.⁷ VCD is thought to result from laryngeal hypersensitivity,⁸ and bronchial provocation agents such as methacholine have previously been shown

to induce VCD.⁷ However, the mechanism by which methacholine induces VCD remains unclear, and its reported test sensitivity is less than 50%.⁷ There is a need to develop alternative provocation tests for the diagnosis of VCD.

Dry powder mannitol is a hyperosmolar agent increasingly used for bronchial provocation testing due to its ease of administration. Apart from its bronchoconstrictive properties, mannitol also has an irritant effect and has previously been used as a cough stimulus in cough sensitivity testing.⁹ Despite its potential as a laryngeal irritant and its established role in bronchial provocation testing, no previous studies have investigated the use of mannitol in the diagnosis of VCD and bronchial hyperresponsiveness concurrently.

We hypothesized that mannitol could be used to provoke paradoxical vocal cord movement in patients suspected of having VCD. If so, its role as a laryngeal and bronchial provocation test would be particularly useful in distinguishing respiratory symptoms due to VCD versus asthma. We performed a pilot study on a cohort of patients with suspected VCD referred to our clinic.

METHODS

This study was performed at a tertiary university hospital in Melbourne, Australia. Consecutive patients seen at our asthma clinic between June 1, 2015 and February 29, 2016 with suspected VCD and no contraindications to bronchial provocation testing¹⁰ were included. Most of the patients in our clinic had confirmed asthma or were under evaluation for possible asthma. The study was approved by the Alfred Health Ethics Committee as a clinical audit (Reference Number 37/16). Written consent for mannitol challenge and flexible laryngoscopy was obtained from the patients.

The patients’ baseline characteristics and presenting symptoms were documented at the first clinic visit. Aggravating factors, if present, were classified as inhalational (odors, chemical

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solutions, and fumes), exercise, or psychological stress. The presence of comorbidities, including rhinitis, gastroesophageal reflux (GORD), sleep apnea, and anxiety or depression, was based on patients' self-report.

Mannitol challenge test

Patients performed three forced vital capacity with full inspiratory maneuvers at baseline, followed by dry powder mannitol challenge test according to the recommendations of the manufacturer (Aridol; Pharmaxis, NSW, Australia). The dosing protocol consisted of 0 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 160 mg, and 160 mg of mannitol, resulting in a cumulative dose of 635 mg of mannitol. Two forced expiratory volume during the first second (FEV₁) maneuvers were performed after each dose. The challenge was terminated when a drop in FEV₁ of greater than 15% was demonstrated, or after a cumulative mannitol dose of 635 mg had been administered. A forced vital capacity with a full inspiratory maneuver was performed at the end of the challenge. Patients were asked to describe any symptoms they experienced following the mannitol challenge.

Flexible laryngoscopy

A targeted flexible laryngoscopy was performed by a respiratory physician (TT) with 5 years of flexible bronchoscopy experience immediately after the mannitol challenge and before the patients had received any bronchodilator. Topical xylocaine spray was administered to the nasal cavity, and if required the posterior pharynx, to improve patients' tolerance of the procedure. The laryngoscope tip was positioned 2 cm above the glottis. The vocal cords were observed during quiet breathing through an open mouth, deep breathing, and while phonating "ee." Based on laryngoscopic findings, a preliminary diagnosis was provided by the respiratory specialist. The video recording was subsequently reviewed by a laryngologist (PP), who was blinded to the patients' history as well as the respiratory physician's impression.

Baseline laryngoscopy was performed by laryngologists (PP or AR) to look for paradoxical vocal fold movement and organic causes of upper airway obstruction on a different day. Not all patients had baseline laryngoscopy performed prior to the mannitol challenge due to logistic issues. In order to limit the number of flexible laryngoscopies for each patient, laryngoscopy just prior to mannitol challenge was not performed.

Diagnosis of VCD

VCD was considered to be present if there was inspiratory vocal cord adduction or >50% vocal cord adduction on expiration on laryngoscopy either at baseline or following mannitol challenge. The MIF₅₀/MEF₅₀ (maximum inspiratory flow at 50% of vital capacity to maximum expiratory flow at 50% of vital capacity) ratio was calculated from spirometry at the start and end of mannitol challenge. A ratio <1 suggested variable extrathoracic airflow obstruction,^{11,12} supporting a diagnosis of VCD.

Statistical analysis

Data analysis was performed using SPSS version 22 (IBM, Armonk, NY). Interrater agreement of the postmannitol laryngoscopy findings between the respiratory specialist and an ear, nose, and throat

TABLE 1.
Baseline Characteristics (n = 14)

Female, n (%)	12 (85.7)
Age, median (IQR) years	48 (36–54)
Duration of symptoms, median (IQR) years	10 (4–30)
Source of referral, n (%)	
Difficult asthma clinic	11 (78.6)
Allergy clinic	3 (21.4)
Symptoms, n (%)	
Dyspnea	12 (85.7)
Cough	6 (42.9)
Voice change	8 (57.1)
Throat tightness	7 (50)
Stridor	8 (57.1)
Wheeze	8 (57.1)
Triggers, n (%)	
Inhalational	10 (71.4)
Exercise	8 (57.1)
Stress	6 (42.9)
Comorbidities, n (%)	
Rhinitis	14 (100)
GORD	9 (64.3)
Anxiety or depression	10 (71.4)
OSA	4 (28.6)

Abbreviations: GORD, gastroesophageal reflux; IQR, interquartile range; OSA, obstructive sleep apnea.

(ENT) specialist was calculated using Cohen's kappa statistic. Discordant diagnoses (n = 2) were resolved by discussion.

RESULTS

Fourteen patients underwent baseline laryngoscopy and mannitol challenge testing. They were under evaluation for VCD as part of their asthma assessment in view of persistent respiratory symptoms. All patients underwent mannitol challenge regardless of baseline laryngoscopy results as bronchial provocation was necessary to determine whether uncontrolled asthma was contributing to symptoms. Seven patients had baseline laryngoscopy performed after the mannitol challenge due to the reasons mentioned in the Methods section. Twelve of the patients were female (85.7%) and the median age was 48 (interquartile range: 36–54) years. The baseline characteristics and presenting symptoms of the patients are described in Table 1. The median time taken by the respiratory physician (TT) to perform laryngoscopy following mannitol challenge was 3.3 (interquartile range: 2.7–4.3) minutes, and this procedure was well tolerated by all patients.

As shown in Table 2, VCD was visualized on laryngoscopy at baseline or following mannitol challenge in 10 of the 14 patients. Seven patients did not have evidence of VCD at baseline laryngoscopy. Three of the seven patients (42.9%) had VCD demonstrated following mannitol challenge.

Bronchial provocation was positive in only two patients (patients 10 and 11), at a mannitol dose of 315 mg and 155 mg, respectively. Both patients also demonstrated VCD on postmannitol laryngoscopy. Of the 12 patients with a negative bronchial provocation test, VCD was diagnosed in eight

TABLE 2.
Mannitol Challenge Findings

Patient	Gender	Age (years)	VCD on Baseline Laryngoscopy	VCD Postmannitol Laryngoscopy	MIF ₅₀ /MEF ₅₀ <1 Postmannitol	Positive Bronchoprovocation
1	Female	52	+	+	–	–
2	Female	53	+	+	–	–
3	Female	49	+	+	–	–
4	Female	36	–	–	–	–
5	Male	64	+	+	+	–
6	Female	23	+	+	+	–
7	Male	47	+	+	+	–
8	Female	69	–	–	–	–
9	Female	22	–	–	–	–
10	Female	36	–	+	–	+
11	Female	56	+	+	–	+
12	Female	39	–	–	–	–
13	Female	49	–	+	–	–
14	Female	39	–	+	–	–

Abbreviations: MEF₅₀, maximum expiratory flow at 50% of vital capacity; MIF₅₀, maximum inspiratory flow at 50% of vital capacity; VCD, vocal cord dysfunction.

patients (66.7%). No patients had MIF₅₀/MEF₅₀ < 1 on baseline spirometry. Three patients developed inspiratory loop flattening with MIF₅₀/MEF₅₀ < 1 after mannitol challenge. All three patients also had VCD demonstrated on postmannitol laryngoscopy. In short, only three of ten patients with VCD on laryngoscopy postmannitol challenge had abnormal MIF₅₀/MEF₅₀.

There was substantial interrater agreement between the respiratory specialist and the laryngologist for the postmannitol laryngoscopy findings, kappa = 0.696 (95% confidence interval: 0.324–1) ($P = 0.006$).

DISCUSSION

We have shown that mannitol challenge testing can be used to induce paradoxical vocal cord movement in patients suspected of having VCD. Inhaled mannitol provocation enabled demonstration of abnormal vocal cord movement in 42.9% of patients with normal baseline laryngoscopy.

VCD is a manifestation of laryngeal hypersensitivity.⁸ Other features of laryngeal hypersensitivity are chronic refractory cough, throat clearing, muscle tension dysphonia, and globus pharyngeus. These conditions share many overlapping features, and it has been proposed that they might also share a common mechanistic pathway involving sensory neural dysfunction.¹³ Chronic refractory cough is probably the best studied of the laryngeal hypersensitivity conditions.¹⁴ Given the common mechanistic pathways,¹³ the pathophysiology of paradoxical vocal cord movements following mannitol challenge in our study is most likely related to the cough response observed during inhalational challenge.

Mannitol is a hyperosmolar agent used widely in bronchial provocation testing.¹⁵ Mannitol induces lower airway hyperresponsiveness by exerting a tissue osmolar effect which stimulates the release of mast cell mediators.¹⁶ Other osmotic agents, such as hypertonic saline, act in a similar fashion on airways.¹⁷ Both mannitol and hypertonic saline have been used to evaluate chronic refractory cough.^{9,18} Their effect on cough appears separate from their effect on bronchoconstriction,¹⁹ suggesting local

activation of cough receptors and sensory fibers.^{20,21} Local irritation of the larynx and activation of sensory pathways are a highly plausible explanation for the ability of inhaled mannitol to induce VCD in susceptible patients, as observed in our study.

Although irritation from GORD, laryngopharyngeal reflux (LPR), and postnasal drip^{8,22} resulting in direct damage to the laryngeal mucosa and accentuation of the glottis closure reflex has been suggested as a possible mechanism underlying VCD, other pathophysiological roles that these irritants play in VCD and related respiratory symptoms should also be considered. GORD and LPR can give rise to upper airway symptoms, such as chronic cough, dysphonia, and globus pharyngeus, as well as respiratory symptoms from the lower airways²³ unrelated to the irritant effect on laryngeal mucosa. Postnasal drip due to sinusitis has also been shown to concurrently affect both upper and lower airways.²⁴ The increase in upper airway hyperresponsiveness can result in VCD, whereas the increase in bronchial hyperresponsiveness may cause other respiratory symptoms experienced by patients with VCD. In addition, postviral vagal neuropathy can have both local laryngeal effects and extralaryngeal effects. Postviral vagal neuropathy may result in laryngeal hypersensitivity due to neural plasticity, and increase LPR due to altered esophageal peristalsis and clearing.²⁵

Direct visualization of abnormal vocal cord adduction during respiration is the gold standard for VCD diagnosis.⁶ However, laryngoscopy is often normal especially if the patient is asymptomatic at the time of examination.^{3,26,27} Various provocative maneuvers and tests have been used in attempts to improve the diagnosis of VCD. Provocative vocal fold maneuvers are performed by the patient during laryngoscopy.² Tests include histamine challenge,^{11,12} methacholine challenge,^{7,28} exercise challenge,^{27,29} and odor provocation.³⁰

Methacholine is widely used in bronchial provocation testing. It acts directly on smooth muscles leading to bronchoconstriction. Methacholine has previously been shown to induce VCD, but its mechanism of action on the larynx is uncertain because

methacholine (and histamine) acts only on smooth muscle and is therefore not thought to have an effect on striated laryngeal muscles.²⁸ Although methacholine is able to improve the diagnosis of VCD, its diagnostic yield shown in previous studies was not high. Guss and Mirza²⁸ induced VCD in three of seven (42.9%) patients, whereas Perkins and Morris⁷ induced VCD using methacholine in two of eight (25%) patients with known VCD (previously demonstrated abnormal vocal cord movement on laryngoscopy) but normal laryngoscopy prior to provocation testing. Mannitol provocation may have a better diagnostic yield given its likely direct irritant effect on the upper airway.

Exercise challenge has been used to diagnose VCD in those with exercise-induced dyspnea, especially in elite athletes.^{27,28} The exercise challenge can be performed as part of a bronchial provocation test. This is particularly useful as exercise-induced asthma is an important differential diagnosis in patients with exercise-induced dyspnea. The major drawback is the cumbersome setup required. The cause of VCD during exercise is uncertain,² and although not tested in our study it will be interesting for future studies to examine whether mannitol can also be used to identify exercise-induced VCD. Mannitol has already been shown to be able to diagnose exercise-induced bronchoconstriction.²⁷

Patients with VCD often report aggravation of symptoms by strong odors.² The upper airway response may be both irritant and stress-mediated.³¹ The use of strong odors to elicit VCD has been described in case reports³⁰ and is an attractive option given that specific stimuli the patient is sensitive to can be used. One limitation of odor provocation testing is that airway hyperresponsiveness cannot be examined at the same setting. For patients such as those included our study where the differential diagnosis includes both VCD and asthma, a single provocation test to identify both bronchoconstriction and laryngeal hyper-sensitivity would be highly advantageous.

Inspiratory loop flattening represented by an MIF₅₀/MEF₅₀ ratio of less than one was demonstrated in only three of ten patients with VCD seen on laryngoscopy in our study. The poor diagnostic sensitivity of a flattened inspiratory loop was previously described by Yelken et al.³² and Forrest et al.³³ One possible explanation for the poor sensitivity is that patients may have excessive expiratory vocal cord adduction but normal inspiratory vocal cord abduction. Although changes in the flow volume loop may give an indication of the presence of VCD after mannitol challenge, direct visualization of the vocal cords postchallenge is preferable.

Our study also demonstrates the feasibility of respiratory specialist-performed flexible laryngoscopy targeting VCD diagnosis. There was substantial interrater agreement between the respiratory specialist and laryngologist. It is important to stress that laryngologist-performed endoscopy is still necessary to exclude structural and other neurologic causes of upper airway symptoms (eg, malignancy, vocal process granulomata, and vocal cord paresis/paralysis). However, if the technical efficacy of respiratory physician-performed flexible laryngoscopy can be replicated in future studies, provocation testing with laryngoscopy would become more accessible as such testing could be performed outside of an ENT setting. This would be particu-

larly advantageous in settings where rapid access to ENT services is limited as it facilitates earlier diagnosis and institution of treatment for VCD.

To our knowledge, our study is the first to demonstrate the utility of mannitol challenge to elicit VCD. The use of mannitol to objectively assess both laryngeal and bronchial hyperresponsiveness is useful in patient groups such as ours where asthma is a differential diagnosis. It has previously been shown that VCD can be misdiagnosed as difficult asthma.³⁴ This can result in unnecessary treatment with high-dose corticosteroids with their attending side effects.³ In our cohort, only a minority actually demonstrated bronchial hyperresponsiveness, indicating that uncontrolled asthma was probably not the cause of their respiratory symptoms. At the same time, the demonstration of VCD postprovocation provided an alternative explanation for their symptoms. We also showed that respiratory specialist-performed flexible laryngoscopy is feasible, time-efficient, and has good agreement with ENT video review.

We acknowledge several limitations to our study. First, without a control arm, we could not determine the diagnostic accuracy of mannitol challenge for VCD diagnosis. Second, laryngoscopy was not performed just prior to mannitol challenge, so it is possible that VCD was present prior to the mannitol challenge. However, we think this to be unlikely as all the patients were asymptomatic prior to mannitol challenge, whereas symptoms were elicited by mannitol challenge. Ideally, all patients should have had baseline laryngoscopy prior to mannitol challenge. However, this would have resulted in management delay in a substantial proportion of patients due to logistic issues. Moreover, unique to our cohort, we felt that all patients would benefit from bronchial provocation testing as part of their clinical assessment regardless of baseline laryngoscopy results. Last, the number of patients in this series was small. However, our aim was to determine the feasibility of mannitol challenge testing in VCD diagnosis rather than the diagnostic accuracy of the test.

In conclusion, mannitol challenge can induce VCD. Its utility in “laryngeal provocation” as well as bronchial provocation lies in its ability to diagnose the cause of respiratory symptoms in patients who may have coexisting asthma and VCD. Formal studies to evaluate the diagnostic accuracy of mannitol-induced VCD are warranted.

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