Inhaled Mannitol as a Laryngeal and Bronchial Provocation Test

***Tunn Ren Tay, *Ryan Hoy, †Amanda L. Richards, †Paul Paddle, and *Mark Hew,** *†*Melbourne, Australia*

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 testing[10] 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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From the *Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, Melbourne, Victoria, Australia; and the †Department of Otolaryngology, Head and Neck Surgery, The Alfred Hospital, Melbourne, Victoria, Australia.
Address correspondence and reprint requests to Tunn Ren Tay, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, 55 Commercial Road, Prahran, VIC 3181, Australia. E-mail: tunn_ren_tay@cgh.com.sg
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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 (FEV_1) maneuvers were performed after each dose. The challenge was terminated when a drop in FEV_1 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 MIF_{50}/MEF_{50} (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 (ENT) specialist was calculated using Cohen's kappa statistic. Discordant diagnoses ($n = 2$) were resolved by discussion.

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.

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 laryngoscope. 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