Laryngeal Mucosal Reaction during Bronchial Histamine Challenge Test Visualized by Videolaryngostroboscopy

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Summary: Objectives/Hypothesis. To examine the changes in the larynx, as well as self-reported voice and throat symptoms, among patients undergoing a histamine challenge test. Thus, to understand the possible clinical effects of histamine on the larynx.

Study design. Controlled, open prospective study.

Methods. Thirty adult patients with prolonged cough and suspicion of bronchial asthma underwent a histamine challenge test. Videolaryngostroboscopy was performed immediately before and after the challenge. Voice and throat symptoms immediately before and after the challenge test were assessed using a visual analog scale.

Results. Videolaryngostroboscopy after exposure showed significant increases in edema ($P < 0.001$) as well as redness ($P < 0.001$) of the vocal folds after the exposure. Self-reported voice complaints increased significantly for 8 of 11 symptoms. A moderate positive correlation was found between the increase in edema of the vocal folds and reported heartburn/regurgitation symptoms ($r = 0.42$, $P < 0.05$). Atopy, asthma, nasal symptoms, or bronchial hyperreactivity during the histamine challenge test were not associated with laryngeal reactions.

Conclusions. According to the results, the laryngeal mucosal reaction during a histamine challenge test can be objectively visualized. Videolaryngostroboscopy findings, together with an increase in self-reported voice and throat symptoms, show that histamine has potential effects on vocal folds. The mucosal reaction seems to be pronounced among patients with reflux symptoms, probably reflecting the permeability features of the vocal folds.

Key Words: Permeability–Edema–Vocal fold–Allergy–Reflux.

INTRODUCTION

The histamine challenge test is a method used to demonstrate nonspecific bronchial hyperreactivity in asthma diagnostics. Histamine challenge has also been used in some studies to distinguish laryngeal hyperreactivity from bronchial hyperreactivity among the patients with cough, wheezing, and dyspnea by measuring the decrease in inspiratory flows during the challenge test.[1–3] In another study, voice reactions to histamine provocation were studied among asthmatic and nonasthmatic subjects.[4] In that study population, histamine provocation induced voice changes in some asthmatic patients; voice reactions were not related to the degree of bronchial obstructions, however, leading authors to suggest that laryngeal and bronchial reactions may occur independently of each other. A more recent *in vitro* study on freshly excised porcine vocal fold epithelium demonstrated that histamine compromises the tight junction-related paracellular barrier needed in vocal fold hydration.[5]

These findings support the clinical observation that some patients develop voice and throat symptoms after exposure to histamine. These symptoms are temporary and tend to disappear within a few hours of exposure. This reaction mimics the clinical picture of the laryngeal allergic reaction, which gave us the motivation to investigate the voice symptoms and reactions of the vocal folds during a histamine challenge test, along with the possible background factors.

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Aim of the study

To examine changes in the larynx and self-reported voice and throat symptom changes among patients undergoing a histamine challenge test.

SUBJECTS AND METHODS

Subjects

The study population comprised 30 randomly selected adult patients presenting to the Skin and Allergy Hospital of Helsinki University Hospital with a prolonged cough and suspicion of bronchial asthma. Patients underwent the histamine challenge test in 2012 (May–December). Subjects were either steroid naïve or had not used inhaled glucocorticosteroids in the previous 4 weeks.

Methods

Bronchial hyperresponsiveness (BHR) was evaluated with a dosimetric histamine challenge test; the procedure is described elsewhere.[6] An inhalation-synchronized dosimeter with controlled tidal breathing (Spira Elektro 2, Respiratory Health Care Centre, Hämeenlinna, Finland) was used to nebulize increasing inhaled doses (0.025, 0.1, 0.4, and 1.6 mg) of buffered histamine diphosphate. By using the dose-response curve, the provocative dose of inhaled histamine producing a decrease of 15% in FEV_1 ($PD_{15}FEV_1$) was determined. The severity of BHR was classified as mild ($PD_{15}FEV_1$ 0.41–1.6 mg) or moderate ($PD_{15}FEV_1$ 0.11–0.40 mg), the latter being indicative of asthma. If a patient's FEV_1 was near the 15% decrease but did not reach it after a particular histamine dose, only half the amount of the next dose was given (ie, 0.2 or 0.8 mg).

Before the challenge test, subjects filled in a questionnaire regarding their medical history and airway symptoms. To describe their voice and the effects of their voice in their life, subjects answered the Voice Handicap Index (VHI). This is a 30-item questionnaire assessing the functional, emotional, and psychosocial

consequences of a possible voice disorder, with a frequency scale ranging from 0 to 4 (from never to always) for each question.[7]

Videolaryngostroboscopy was performed immediately before and after the challenge test with a portable videolaryngoscope (rpSzene-Mobile, Rehder/Partner GmbH, Germany) composed of a small 1/3″ CCD camera (model rpCam250, Rehder/Partner GmbH) mounted with a 28- to 35-mm focus zoom lens, combined with a 70° laryngeal telescope (model 4450,47, Richard Wolf, Germany) and a light source (model rp 150, Rehder/Partner GmbH).

Recordings were made digitally on a personal laptop that included rpSzene software. The subjects were seated leaning forward with their chin up during the examination. The recording was performed during an intermittent and sustained "ee" vocalization. Laryngoscopy was done without local anesthesia to avoid the effects that may result from it on the voice and throat symptom questionnaire (visual analog scale [VAS], see below).

Videolaryngoscopy videos were assessed by two experienced phoniatricians and one specializing phoniatrician during the final phase of the training. Videos were assessed in a blinded manner but the samples were presented in a paired arrangement (each pair of samples belonged to the same subject but the timing of the samples and identification of the patient were blinded). The physicians assessed edema and redness of the vocal folds, edema of the interarytenoid area, edema elsewhere in the larynx, and the amount of mucus in the larynx using a four-point scale from none to severe, with the option to label as nonassessable as well. Other possible laryngeal findings were also recorded with an open question.

The interrater reliabilities were $r = 0.77$ (when ratings of redness before the challenge test by raters 1 and 2 were compared), $r = 0.54$ (for raters 1 and 3), and $r = 0.46$ (for raters 2 and 3). Accordingly, the grading of the most experienced rater (rater 1) was chosen for analysis of the data.

Voice and throat symptoms immediately before and after the challenge test were assessed using a VAS composed of 11 parameters; each parameter was assessed using a continuous point scale from 0 to 10, with 0 being no symptom and 10 being the worst possible symptom[8] (Table 3).

Ethical considerations

The study design was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District, Department of Surgery Dnr 61/13/03/02/2012. The participants received information concerning the study at the time of recruitment and gave their written consent for study participation.

Statistical analysis

Statistical analyses were carried out using SPSS for Windows, Version 21.0.0 Statistical Software (SPSS Inc., Chicago, IL, USA). Descriptive statistics served to describe the demographic characteristics of the study and control groups. Subjects served as their own controls pre- and postchallenge.

Differences in the results before and after the challenge test were compared using the Wilcoxon signed-rank test. Spearman correlation tests were used to statistically analyze the correlation between the patient-reported symptoms and medical history in relation to laryngeal findings. Interrater reliability of the videolaryngostroboscopy was measured using Spearman correlation between each pair of reviewers. The previously mentioned tests were chosen due to the skewed distribution of the parameters.

RESULTS

The mean age of the 30 subjects (22 females) was 40.9 years, ranging from 21 to 66. The mean body mass index (BMI) was 26.1 (standard deviation [SD] 4.8). In the study population, never-smokers were 67% (n = 20), ex-smokers were 20% (n = 6), and current smokers were 13% (n = 4). Based on the clinical diagnostic examinations, 40% of the study subjects (n = 12) were diagnosed with probable or clear asthma, and 63% (n = 19) were atopic (skin prick test positive to common aeroallergens). A variety of airway symptoms was also reported by patients (Table 1).

Out of 30 subjects, 12 (40%) did not have heartburn or regurgitation, whereas 13 (43%) reported to have it occasionally and 5 (17%) reported it often. Regarding reflux medication, most subjects (n = 23, 77%) never took medication, although five took it occasionally and two used it regularly.

Out of 30 patients, three (10%) had moderate bronchial hyperreactivity according to the histamine challenge test and seven (23%) had mild bronchial hyperreactivity, whereas the others did not show any hyperreactivity (ie, $PD_{15}FEV_1 > 1.6$ mg). The maximum histamine dose (1.6 mg) was inhaled by 25 subjects. In five subjects, a significant histamine-induced bronchoconstriction was reached with a lower histamine dose (two with 0.8 mg, two with 0.4 mg, and one with 0.2 mg).

VHI scores varied from 0 to 59 (out of 120), with a mean value of 16 points ± SD 17.7. The mean scores of the subscales were "functional" 4.3 ± SD 5.6, "physical" 8.1 ± SD 7.6, and "emotional" 3.6 ± SD 6.0.

Assessment of the videolaryngostroboscopy recording of the subjects

Two subjects showed unexpected laryngeal findings: one with a small vocal fold polyp and one with vocal fold paralysis. These two subjects were not excluded from the analysis, however, because we were interested in the change in laryngeal function. Three other patients' stroboscopy videos, however, were not assessable due to throat sensitivity resulting from local anesthesia not being used. These patients were excluded from analyses of videolaryngostroboscopy results.

TABLE 1.
Airway Symptoms Reported by the Patients (n = 30)

Symptom	n (%)
Exercise-induced dyspnea	20 (67)
Dyspnea during inspiration	12 (40)
Wheezing during inspiration	8 (27)
Wheezing during expiration	5 (17)
Hoarseness during or after physical exercise	5 (17)
Choker around the neck during exercise	3 (10)
Nasal congestion or runny nose	19 (63)