

Voice reactions to histamine inhalation in asthma

Leinonen L, Poppius H. Voice reactions to histamine inhalation in asthma. *Allergy* 1997; 52: 27–31. © Munksgaard 1997.

Susceptibility to voice reactions during a histamine provocation test was studied in 21 asthmatics and 21 healthy subjects. Speech samples were recorded before, and 5 and 15 min after histamine inhalation, and the samples were rated by six speech pathologists. Deterioration of voice quality occurred in 2/12 asthmatic men and in 3/9 asthmatic women within 5 min after histamine inhalation; no change was observed between 5 and 15 min. Voice reactions were not related to the degree of bronchial obstruction: the subjects with the most pronounced decrease in peak expiratory flow (PEF) (60–61% in three subjects) did not develop voice reactions, and PEF did not decrease in one subject with voice reactions. No voice reactions were observed in the healthy subjects.

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Key words: asthma; histamine provocation test; voice disorders.

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Accepted for publication 4 July 1996

Professional voice users with asthma or allergic rhinitis often experience deterioration of voice quality in association with other symptoms. Non-asthmatic phoniatric patients also suffer from similar fluctuating voice problems together with slight long-lasting cough (1). It has been suggested that such voice disorders are due to laryngeal hyperreactivity (1–3).

Histamine may induce dysphonia both in asthmatic and nonasthmatic subjects (2), but the frequency of voice changes during the routine histamine provocation test is not known. In the present study, asthmatic and healthy subjects were compared with respect to their susceptibility to voice changes during histamine provocation. The voice samples were evaluated by six experienced speech pathologists. Speaking volume, fundamental frequency, and jitter, the common acoustic index for laryngeal pathology, were also monitored to evaluate their contribution to the evaluation of voice.

Material and methods

Subjects

Forty-two subjects, nine asthmatic women aged 26–46 years (mean 34 years), 12 healthy women aged 22–52 years (mean 31 years), 12 asthmatic

men aged 17–58 years (mean 34 years), and nine healthy men aged 24–66 years (mean 38 years) participated in the study. The diagnosis of asthma was based on the criteria of the American Thoracic Society. All asthmatics reported episodes of wheezing and shortness of breath; asthmatic symptoms were reported to be mild or occasional. Reversible airway obstruction (increase in forced expiratory volume in 1 s [FEV₁] by 15% or more after inhalation of a β_2 -agonist drug), bronchial hyperreactivity (fall in FEV₁ or peak expiratory flow [PEF] by 15% or more after inhalation of 16 or fewer tidal breaths of an aerosol of 1.6% histamine diphosphate from a DeVilbiss nebulizer no. 40 with an output of 0.2 ml/min [4]), or increased diurnal variability in PEF (morning dips repeatedly in excess of 20%) was demonstrated in all asthmatics. The asthmatic subjects were selected on the basis of being adults under 60 years of age and not using oral or inhaled corticosteroids. In some subjects, symptoms had begun in childhood; in some subjects, only a few months before the study (the symptoms had lasted less than 1 year in five, less than 5 years in seven, and more than 5 years in nine subjects).

Nineteen of the 21 asthmatics were being treated with inhaled sympathomimetics and two with short-acting antihistamines. The subjects stopped the antihistamine medication 3 days before the

experiment, and they used no inhalers during the day of the experiment. The healthy subjects were recruited from clinical and university research laboratories. Smoking was reported by one asthmatic and three healthy subjects. No subject reported respiratory viral infection during the past 6 weeks. None of the subjects reported symptoms indicative of gastroesophageal reflux, which may also induce hoarseness (5). Informed consent was obtained from all subjects. The study was approved by the ethics committee of the Department of Pulmonary Diseases, Helsinki University Central Hospital.

Histamine provocation

Histamine (1.6% histamine diphosphate in buffered saline) was given in increasing doses: one, four, eight, or 16 inhalations during slow tidal breathing with a DeVilbiss nebulizer no. 40 (output 0.2 ml/min) according to the PEF response (4). PEF was measured with a Wright peak-flow meter after the recording of the first speech sample before the histamine provocation test, and 90 s after each dose of histamine. The highest value of three similar records was noted before the test and after the last dose of histamine. When a significant decrease of PEF took place (15% or more), its recovery after the administration of a metered-dose inhaler bronchodilator drug after the last speech sampling was also monitored. All tests were performed between 5 and 7 p.m.

Speech samples were recorded at the beginning of the experiment, and 5 and 15 min after the last dose of histamine. The subjects were asked to utter the following word list */kaari, saari, kaari, saari, kaari, saari, kaari/* (Finnish words meaning "bow" and "island") at a comfortable volume and inspire before each word. In this manner, the words were spoken at a rather steady pitch and volume. Then the subjects were asked to utter the sentence */Saarinen nousee syömään aamiaista ennen neljää aamulla/* ("Saarinen gets up to have breakfast before four o'clock in the morning") three times.

Speech recording and signal sampling

The speech samples were recorded with an AKG-C568EB microphone and a Sony TCD-D3 DAT-recorder. The lips-to-microphone distance was 20 cm. The recorded samples were fed through the audio port to an Iris Indigo workstation (Silicon Graphics) and digitized at a 22.05-kHz sampling frequency and 16-bit quantization. The weak signals were amplified so that the peak loudness of the first long [a] of the tokens varied within 10 dB(A). The original volume of the utterance was evaluated

with simultaneous recording of a calibration signal of 1 kHz.

Analysis of F0 and jitter

The fundamental frequency (F_0) was determined by a combination of autocorrelation and cepstral analysis. The maximum of the autocorrelation function, computed from a 46-ms Hamming windowed signal, was the first estimate for F_0 . After median filtering of the consecutive F_0 estimates, they were used to calculate the duration of three F_0 periods, which was the window length used in the computation of the cepstra. The cepstral maxima differing 5% at the most from the first F_0 estimates yielded the final F_0 values. The frequency perturbation quotient (FPQ) (6, 7) and mean F_0 were calculated with these values for the [aa]-segments (of 100–220-ms duration). The seven-word samples recorded in the three situations were compared for significant differences in F_0 , jitter, and peak volume (in dB(A) at the microphone 25 cm from the mouth).

Auditory ratings

The speech samples of the 42 subjects, which were scattered among the samples of 67 other subjects (23 men and 43 women) were evaluated in two listening experiments at a 1-week interval by six experienced speech pathologists (8). The listening tapes were constructed from the digitized samples.

The sentence */Saarinen nousee syömään aamiaista ennen neljää aamulla/* was used to judge whether the two samples of the same subject differed in degree of pathology. The sentences were compared pairwise: a sentence recorded before histamine inhalation was compared with a sentence recorded 5 min after the inhalation, and a sentence recorded 5 min after histamine inhalation was compared with a sentence recorded 15 min after the inhalation. The two sentences were heard without a pause between them, and the different pairs were separated by 4 s. The samples of one subject were presented in succession; two different sentences for each of the three situations. The order of the samples was random. The speech pathologists judged whether the two sentences were equal, or which of them was worse. The listeners also indicated (by underlining) whether a difference was due to roughness or breathiness. One listening test included all pairs of one sex, and 10 pairs of the other sex (repeated samples from five subjects). Nine or more agreeing judgments (out of 12) were regarded as indicative of change.

Word lists, for each subject two different tokens of *[kaari]* and two tokens of *[saari]* repeated three

times /kaari, kaari, kaari, saari, saari, saari, kaari, kaari, kaari, saari, saari, saari/, were rated with 50-mm visual analog scales for the degree of pathology, roughness, breathiness, strain, asthenia (commonly used clinical terms (9, 10), and pitch. The utterances of different subjects, including the prehistamine sample and the sample 15 min after histamine inhalation, were separated by a 6-s pause. One listening test included all samples of the same sex, and 17 randomly selected samples of the other sex. The six-dimensional ratings were used to categorize voices for the development of acoustic feature extraction. Dimension pathology and its main determinants, breathiness and roughness, are described in the following.

The judges' performance was evaluated with the samples of 110 subjects (8). There was a significant correlation between the repeated ratings of all judges and of individual judges for each of the three dimensions (Spearman's correlation coefficient was 0.73 for pathology, 0.65 for roughness, and 0.70 for breathiness; all differed from zero at $P < 0.001$, chi-square statistics). The concordance among the judges was relatively high for all dimensions both for the male and female data (Kendall's coefficients were, for pathology, 0.73/0.70; for roughness, 0.65/0.67; and for breathiness, 0.70/0.60). Spearman's partial correlation coefficients, calculated for different dimension pairs, showed that the judges distinguished between the dimensions roughness and breathiness (they did not correlate), and breathiness was more often than roughness regarded as an indicator of pathology.

Results

The ranges of baseline PEF values in the histamine provocation test were 395–733 l/min (median 615 l/min) in men and 305–570 l/min (median 463 l/min) in women, corresponding to 65–118% (median 96%) and to 69–116% (median 100%) of the predicted values (11). PEF decreased significantly ($>15\%$) in seven asthmatic men and eight women (Table 1).

Pairwise comparison of the sentences showed that the voice quality of five asthmatics, two men and three women (indicated by boldface in Table 1), deteriorated within 5 min after histamine inhalation; no difference was observed between 5 and 15 min. All six judges characterized the deteriorations as both increased roughness and breathiness. In the rating of word lists, when the pre- and posthistamine utterances of the same subject were not presented in succession, the scores for pathology, breathiness, and roughness increased substantially for two subjects only. Thus, the deterioration of voice quality, observed in sentence

comparisons, was probably severe in two subjects and relatively mild in the three other subjects. The prehistamine scores for pathology, roughness, and breathiness show that most subjects had normal voice quality, and that there was no significant difference between the scores of healthy subjects and asthmatics (Mann-Whitney U test). Table 1 shows that the voice reactions were not related to the degree of bronchial obstruction: the subjects with the most pronounced decrease in PEF (man a21, women a10 and a15) did not develop voice reactions, and PEF did not decrease significantly in one subject with voice reaction (man a14). That the voices of two subjects with extremely low PEF values (women a10 and a15) received low scores for pathology suggests that bronchial obstruction interfering with speech breathing did not disturb voice evaluation.

$F0$ and speaking volume, measured for the [aa]-segments in the word list, did not distinguish between the healthy subjects and asthmatics, or between normal (scores for pathology below 10) and pathologic (scores over 10) voice qualities. During the provocation test, small changes, usually increases, in the speaking volume and $F0$ occurred in six men and eight women (prehistamine values with significant alterations are indicated by asterisks in Table 1). These alterations were apparently not related to perceived deterioration of voice quality or PEF.

Before histamine inhalation, the lowest values for jitter were encountered for samples with low scores for pathology, and the highest values were encountered for samples regarded as somewhat pathologic (Table 1). Pre- and posthistamine jitter values differed in the samples of two subjects only, one of them without audible increase in dysphonia (Table 1). No significant changes in jitter, not even in the [aa]-segments of the compared sentences, were encountered for four subjects with audible voice reactions.

Discussion

Histamine provocation induced voice changes in five of 21 asthmatics but in none of 21 healthy subjects. This meets the expectation that the susceptibility to voice reactions is higher in asthmatics than in healthy subjects (who have not been treated for voice problems). The deterioration of voice occurred within 5 min after histamine inhalation and did not subside during the 15-min follow-up. The degree of expiratory obstruction did not relate to the susceptibility to voice reactions, suggesting that laryngeal and bronchial reactions may occur independently of each other. This is in line with the results of Bucca et al. (2) showing that laryngeal

Table 1. Prehistamine PEF (percentage of predicted), posthistamine change in PEF, and deterioration of voice quality in sentenced speech described by number of comparisons (out of 12) with observed increase in dysphonia; prehistamine scores (mean scores of six judges) for pathology (path), roughness (rough), and breathiness (breath), significantly (Mann-Whitney *U*-test; $P < 0.02$) changed scores at 15 min after histamine inhalation, are given in parentheses; prehistamine peak volume, *F0*, and jitter (FFQ [frequency perturbation quotient]), significant (Friedman test with Dunn test $P < 0.02$) changes after histamine inhalation are indicated by asterisk. Subjects with asthma are indicated by "a". In each subject index, number in parentheses gives maximum number of histamine inhalations. Results of subjects with voice reactions are in boldface

Subject	Prehistamine PEF % of pred.	Decrease in PEF %	Increase in dysphonia, 0–50 scale	path	Prehistamine rough 0–50 scale	breath	Prehistamine		
							Volume dB (A)	F0 Hz	Jitter FFQ
Men									
1(16)	95	0	7	1	0	1	80	80	0.30
2(16)	115	2	0	1	0	6	79	112*	0.31
a3(16)	104	6	0	3	3	4	72*	100	0.26
a4(16)	116	3	0	3	9	5	71*	92	0.21
5(16)	115	8	0	4	5	1	84	101	0.21
6(16)	98	6	0	5	10	7	71	93	0.21
7(16)	95	7	0	6	3	5	81*	113	0.19
8(16)	104	7	0	8	13	9	68	88	0.27
a9(4)	90	23	1	8	4	8	69	122	0.29
a10(4)	111	19	2	9	5	16	72*	111	0.30
a11(8)	100	30	9	4	1	3	71	107	0.25
12(16)	100	7	2	10	4	4	64*	81*	0.43
a13(16)	86	23	1	16	21	16	76	107	0.32
a14(16)	78	13	9	18	14	8	65	113	0.46
a15(4)	114	16	0	22	18	19	65	113	0.34
16(16)	94	13	0	25	16	27	62	89	0.34
a17(16)	116	17	2	28	4	8	77	191	0.25
a18(16)	103	13	1	29	30	20	75	110	0.86
19(16)	83	14	0	32	31	17	65	82	0.55
a20(16)	103	13	1	35	25	33	58	122	0.60
a21(1)	69	61	3	32	30	29	74	113	0.76
Women									
1(16)	115	4	0	2	1	4	79	213	0.31
2(16)	100	5	1	2	6	2	73*	162	0.23
3(16)	95	4	0	3	1	3	74	218	0.34
a4(16)	103	5	1	2	1	4	71	195	0.46
5(16)	88	5	0	3	2	5	82	189	0.39
6(16)	75	2	0	3	2	6	72	191	0.19
7(16)	98	5	0	3	4	7	72	194	0.31
8(16)	95	11	2	5	1	8	71*	235	0.32
a9(16)	118	16	3	5(22)	4(11)	6(21)	71	207*	0.42
a10(4)	104	60	0	5	6	7	72	204	0.32
11(16)	104	1	1	6	2	9	62	188	0.37
12(16)	90	2	0	6	6	10	71*	182	0.38
a13(4)	107	19	8	5	6	5	68	227	0.17**
14(16)	87	10	1	8	5	17	69	207	0.29
a15(1)	67	60	0	8	8	4	70	164*	0.32
16(16)	108	4	0	9	9	10	61	188*	0.48
a17(16)	81	28	12	9(46)	11(45)	8(37)	62	147	0.47**
a18(16)	96	30	12	10	1	21	67*	189	0.31
a19(1)	65	34	0	12	3	16	63	178	0.59
20(16)	108	6	0	9	6	11	67	198	0.38
a21(4)	92	49	11	18(47)	8(46)	23(41)	76*	212	0.72

reactions (decreased maximal midinspiratory flow, pharyngolaryngeal edema) may be induced by histamine inhalation in some nonasthmatics with long-lasting cough and mild dysphonia.

During the test, small increases and decreases in the speaking volume and fundamental frequency were encountered in many subjects but they were unrelated to voice reactions or bronchial obstruc-

tion. Increase in jitter was encountered in only one of the five subjects with voice reactions. The results suggest that histamine inhalation does not affect *F0*, and that voice changes induced by histamine may occur without deterioration of the periodicity of glottal vibration.

The design of provocation tests for the identification of voice disorders has been prevented by the

lack of objective acoustic measures of voice quality. The reliability of perceptual ratings is relatively low because of considerable intra- and interjudge variation (12). The reliability may be improved by using reference voice samples in the training of judges and during the listening test (9, 12, 13). At present, however, there are no internationally approved standards. The two types of listening tests used in the present study served two different purposes. The resolution of intraspeaker variations was maximized in the pairwise comparison of sentences, and the ratings of word lists depicted voice with respect to the judges' shared frame of reference of voice pathology. Two sentences, especially when uttered at an interval of several minutes, are never exactly similar; i.e., for some reason one usually sounds "better". The results suggest that the expert listeners were aware of natural variation of speech and distinguished it from the effects of histamine.

Due to the problems of perceptual rating tests, many attempts have been made to find acoustic measures for voice evaluation. The current acoustic indices, derived from glottal wave periodicity (jitter and shimmer) and from speech spectrum (e.g., signal-to-noise ratios or distribution of spectral energy over predefined spectral bands), may detect deterioration of the phonatory mechanism, but they are poor predictors of the degree and quality of perceived voice changes. For the jitter quotient, this was demonstrated also in the present study. The extraction of perceptually significant acoustic features is difficult because of the high intra- and interspeaker variability and the multidimensionality of the acoustic signal. We have previously applied the self-organizing map (14) to the recognition of spectral variation in speech of subjects with or without dysphonia (15, 16). The speech samples recorded in the present work were included in the database used for the improvement of acoustic feature selection for the clustering of voice samples with the self-organizing map. An objective method of voice evaluation would benefit the diagnosis of phonation disorders and the comparison of therapeutic maneuvers.

As suggested by the study of Bucca et al. (2), the histamine provocation test may be useful in the diagnosis of laryngeal hyperreactivity in patients with voice problems. The present study suggests that histamine provocation also reveals susceptibility to voice reactions in asthmatic subjects.

However, a wide survey of healthy subjects, voice patients, and asthmatics is needed to determine the significance of histamine-induced voice reactions for the diagnosis of voice disorders.

Acknowledgments

We thank Prof. Teuvo Kohonen, head of the Neural Networks Research Centre, for providing technical facilities for the work. Dr Ilkka Linnankoski provided linguistic aid. Financial support was provided by the Academy of Finland.

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