Quantification of Vocal Fold Vibration in Various Laryngeal Disorders Using High-Speed Digital Imaging

*Akihito Yamauchi, †Hisayuki Yokonishi, *Hiroshi Imagawa, ‡Ken-Ichi Sakakibara, *Takaharu Nito, §Niro Tayama, and *Tatsuya Yamasoba, *Bunkyo-Ku, †Nakano-Ku, and §Shinjuku-Ku, Tokyo, and ‡Ishikari-Gun, Hokkaido, Japan

Summary: Objective. To quantify vibratory characteristics of various laryngeal disorders seen by high-speed digital imaging (HSDI).

Methods. HSDI was performed on 78 patients with various laryngeal disorders (20 with polyp, 16 with carcinoma, 13 with leukoplakia, 6 with vocal fold nodule, and 33 with others) and 29 vocally healthy subjects. Obtained data were quantitatively evaluated by frame-by-frame analysis, laryngotopography, digital kymography, and glottal area waveform.

Results. Overall, patients with laryngeal pathologies showed greater asymmetry in amplitude, mucosal wave and phase, smaller mucosal wave, and poorer glottal closure than vocally healthy subjects. Furthermore, disease-specific vibratory disturbances that generally agreed with the findings in the literature were quantified: comparing polyp with nodule, differences were noted in longitudinal phase difference, amplitude, and mucosal wave. In comparison with leukoplakia and cancer, nonvibrating area was more frequently noted in cancer.

Conclusions. The HSDI analysis of various voice disorders using multiple methods can help phonosurgeons to properly diagnose various laryngeal pathologies and to estimate the degree of their vocal disturbances.

Key Words: Vocal fold polyp–Vocal fold nodule–Laryngeal leukoplakia–Laryngeal cancer–Reinke edema–Laryngeal granuloma–Laryngeal papilloma–Vocal fold cyst–High-speed digital imaging.

INTRODUCTION

Direct observation and objective assessment of vocal fold vibration are essential for reaching an appropriate diagnosis and determining the best therapeutic approach to various voice disorders. For this purpose, videostroboscopy is used most frequently because it provides full color images with high spatial resolution at a relatively low cost. However, videostroboscopy can only be applied to the assessment of stable and periodic vocal fold vibration, whereas high-speed digital imaging (HSDI) is a superior method for assessing irregular or aperiodic vocal fold vibration that is commonly associated with voice pathology.[1–3] Quantification of oscillatory characteristics is also essential to enhance the objectivity and validity of assessment, and HSDI is superior to videostroboscopy with regard to quantification of data because it allows the registration of true intracycle or intercycle vibratory behavior and offers a wider variety of analytical methods.[1–3]

Until recently, HSDI studies of voice disorders had been conducted in a small number of patients for each voice disorder.[4–15] Only in the past few years, several HSDI studies have been published that differentiate voice disorders and quantify their oscillatory characteristics.[16–22] However, the HSDI parameters reported in these reports have been focused on temporal aspects or left-right asymmetry, and size parameters that are routinely investigated by stroboscopic examination (such as amplitude and mucosal wave) have not been fully explored. Furthermore, HSDI research has been focused on vocal fold polyps and nodules, and there is a paucity of knowledge regarding other voice disorders. Additionally, the association between HSDI-derived vibratory parameters and conventional aerodynamic or acoustic parameters in patients with voice disorders has not fully been investigated. Making a connection between HSDI parameters and common vocal function parameters should be beneficial for improving our understanding of the pathophysiological aspects of various clinical entities.

Accordingly, the purpose of the present study was to quantitatively elucidate the vibratory characteristics of various vocal fold disorders by using multiple HSDI analytical methods, including an assessment form, single-line and multiline digital kymography (SLK and MLK, respectively), laryngotopography (LTG), and glottal area waveform (GAW) analysis. In addition, the aim was to clarify the relationship between HSDI parameters and perceptual/aerodynamic/acoustic measures.

MATERIALS AND METHODS

Subjects

Patients who visited the Voice Outpatient Clinic of the Department of Otolaryngology and Head and Neck Surgery at the University of Tokyo Hospital (Tokyo, Japan) between 2006 and 2013 were included in this study. In each patient, the diagnosis was based on a detailed history, acoustic and aerodynamic evaluation, videostroboscopy, and histologic examination and was made by agreement among three or four certified otorhinolaryngologists specializing in vocal treatment. Patients with vocal fold polyp, laryngeal carcinoma, laryngeal leukoplakia,

Accepted for publication April 28, 2015.

From the *Department of Otolaryngology, University of Tokyo Hospital, Bunkyo-Ku, Tokyo, Japan; †Department of Otolaryngology, Tokyo Metropolitan Police Hospital, Nakano-Ku, Tokyo, Japan; ‡Department of Communication Disorders, Health Sciences University of Hokkaido, Ishikari-Gun, Hokkaido, Japan; and the §Department of Otolaryngology and Tracheo-Esophagology, National Center for Global Health and Medicine, Shinjuku-Ku, Tokyo, Japan.

Address correspondence and reprint requests to Akihito Yamauchi, Department of Otolaryngology, University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: drachilles23@yahoo.co.jp

Journal of Voice, Vol. ■, No. ■, pp. 1-10
0892-1997/$36.00

http://dx.doi.org/10.1016/j.jvoice.2015.04.016

laryngeal papillomatosis, laryngeal granuloma, vocal fold nodule, Reinke edema, or vocal fold cyst were included in this study. As a control group, healthy subjects were recruited who had no vocal complaints, no history of laryngeal disorders, and no signs of laryngeal abnormality on laryngoendoscopy. All subjects signed a consent form that was approved by our institutional review board.

A total of 78 patients (23 women and 55 men) aged between 22 and 87 years with various laryngeal pathologies were enrolled along with 29 vocally healthy subjects (12 women and 17 men) aged between 21 and 81 years. Twenty patients had vocal fold polyps, 16 patients had laryngeal carcinoma, and 13 patients had laryngeal leukoplakia. In addition, there were eight patients with laryngeal papillomatosis, eight with laryngeal granuloma, six with vocal fold nodule, five with Reinke edema, and four with vocal fold cyst.

Background data

Vocal function and voice quality were evaluated by measuring aerodynamic and acoustic parameters. Aerodynamic parameters, including the maximum phonation time and mean flow rate, were measured with a Nagashima PE-77E Phonatory Function Analyzer (Nagashima Medical Inc., Tokyo, Japan). Acoustic parameters, including the fundamental frequency (AA-F_0), amplitude perturbation quotient, period perturbation quotient, and harmonics-to-noise ratio, were measured at the University of Tokyo with a dedicated software program. Perceptual voice ratings were also determined by using the GRBAS scale.

Table 1 summarizes the results of perceptual, aerodynamic, and acoustic studies. The maximum phonation time, mean flow rate, period perturbation quotient, and harmonics-to-noise ratio, as well as the grade, roughness, and breathiness on the GRBAS scale, showed significant intergroup differences. The Voice Handicap Index-10 and voice-related quality of life scores were 10.8 ± 7.3 and 14.3 ± 10.8, respectively, and the rate of synchronization of videostroboscopy (LS-3A, Nagashima Medical Inc., Tokyo, Japan) was achieved in 60.6% of the patients.

High-speed digital imaging

For HSDI, a high-speed digital camera (FASTCAM-1024PCI; Photron, Tokyo, Japan) was connected to a rigid endoscope (#4450.501, Richard Wolf, Vernon Hills, Illinois, USA) via an attachment lens (f = 35 mm, Nagashima Medical Inc., Tokyo, Japan). Illumination was provided by a 300-W xenon light source, and recording was performed at a frame rate of 4500 fps and a spatial resolution of 512 × 400 pixels with an 8-bit grayscale and a recording duration of 1.86 seconds. High-speed digital images were recorded during sustained phonation of the vowel /i/ at a comfortable frequency and comfortable intensity. Then, an image sequence with stable vocal fold vibrations was selected for further analysis.

Aerodynamic and acoustic studies were performed approximately 30 minutes before HSDI because simultaneous recording was not available at our institution. Both evaluations were done under conditions that were as similar as possible to allow comparison between HSDI parameters and perceptual/aerodynamic/acoustic parameters.

HSDI analysis

The recorded HSDI data were evaluated by frame-by-frame analysis,[23] LTG,[24] SLK and MLK,[25,26] and GAW analysis.[27] The details of these methods have been described elsewhere.[23–27]

Size parameters normalized by the vocal fold length were signified by the term "N_L-" (eg, N_L-amplitude mean), whereas time parameters normalized by the glottal cycle were signified by "N_G-" (eg, N_G-lateral phase difference). In addition, size and time parameters normalized by both the glottal cycle and vocal fold length were signified by "N_{GL}-" (eg, N_{GL}-lateral phase difference).[25]

TABLE 1.
Clinical Data of All Participants Are Summarized

Parameter (U)	Control Group (n = 29)	Pathologic Group (n = 78)	*P* Value
Age (y)	59 ± 21	59 ± 16	0.973
Gender (n)	Male (17), female (12)	Male (55), female (23)	0.248
MPT (s)	22.3 ± 9.7	15.9 ± 8.1	0.002**
MFR (mL/s)	135 ± 37	220 ± 80	<0.001***
AA-F_0 (Hz)	160 ± 51	175 ± 46	0.232
APQ (%)	2.8 ± 1.5	3.6 ± 1.8	0.066
PPQ (%)	0.26 ± 0.39	0.74 ± 0.84	<0.001***
HNR (dB)	22.1 ± 3.9	14.5 ± 4.8	<0.001***
Grade	0.62 ± 0.62	1.48 ± 0.57	<0.001***
Roughness	0.62 ± 0.62	1.48 ± 0.57	<0.001***
Breathiness	0.38 ± 0.49	0.71 ± 0.65	<0.002**

Abbreviations: MPT, maximum phonation time; MFR, mean flow rate; AA-F_0, fundamental frequency in acoustic analysis; APQ, amplitude perturbation quotient; PPQ, period perturbation quotient; HNR, harmonics-to-noise ratio.
Notes: Values signify "mean ± standard deviation." The column for *P* value shows the *P* values of chi-squared test (gender) and Student *t* test (the rest) between control and various vocal fold pathology groups.
**P < 0.01; ***P < 0.001.

In the present study, analysis focused on parameters that were considered to be related to the vibratory characteristics of the various laryngeal pathologies, including the symmetry, periodicity, supraglottal hyperactivity, amplitude, mucosal wave, phase, and glottal closure (open quotient, speed index, maximal/minimal glottal area, and glottal area difference). A sequence of 512 frames was evaluated.

Frame-by-frame analysis was performed using an assessment form for HSDI developed by the authors, which was designed for evaluation of vibratory parameters on a two- or four-point scale, including the symmetry, periodicity, supraglottal hyperactivity, amplitude, mucosal wave, phase difference, and glottal closure.[23]

LTG involves Fourier transformation of the brightness versus time curve for each pixel across images, allowing quantitative evaluation of the spatial characteristics of amplitude, frequency, and phase. In the present study, the presence or absence of a nonvibrating region and the phase (N_G-lateral/longitudinal phase difference^{LTG}) were evaluated.[24]

SLK involves analysis of mediolateral vocal fold movements at a midglottal level. In the present study, mediolateral and temporal vibratory characteristics were evaluated, including the magnitude of the amplitude (N_L-amplitude mean) and the mucosal wave (N_L-mucosal wave magnitude mean, N_G-mucosal wave persistence mean), the asymmetry of the amplitude (N_L-amplitude difference), mucosal wave (N_L-mucosal wave magnitude difference, N_G-mucosal wave persistence difference), and phase (N_G-lateral phase difference^{SLK}), and glottal closure (O_q^{SLK}, SI^{SLK}).[25] MLK involves data acquisition from five different longitudinal levels for assessment of temporal and longitudinal oscillatory features such as the open quotient (O_q^{MLK}) and speed index (SI^{MLK}).[26]

Finally, GAW analysis provides information on the general dynamics of the glottal area by tracing the vocal fold edges and displaying temporal changes of the glottal area, with which open quotient (O_q^{GAW}), speed index (SI^{GAW}). It allows assessment of the minimal glottal area (N_L-minimal glottal area), maximal glottal area (N_L-maximal glottal area), and glottal area difference index ((N_L-maximal glottal area − N_L-minimal glottal area)/N_L-maximal glottal area).[27] Additionally, N_L-glottal outlet, the normalized supraglottal area outlined by the ventricular fold, arytenoid, and epiglottis was calculated as a parameter of supraglottal hyperactivity.

All HSDI analyses were performed with custom *MATLAB* software programmed at our institution (Version 2014a; Mathworks Inc., Natick, MA, USA). An example of HSDI analysis is displayed in Figure 1.

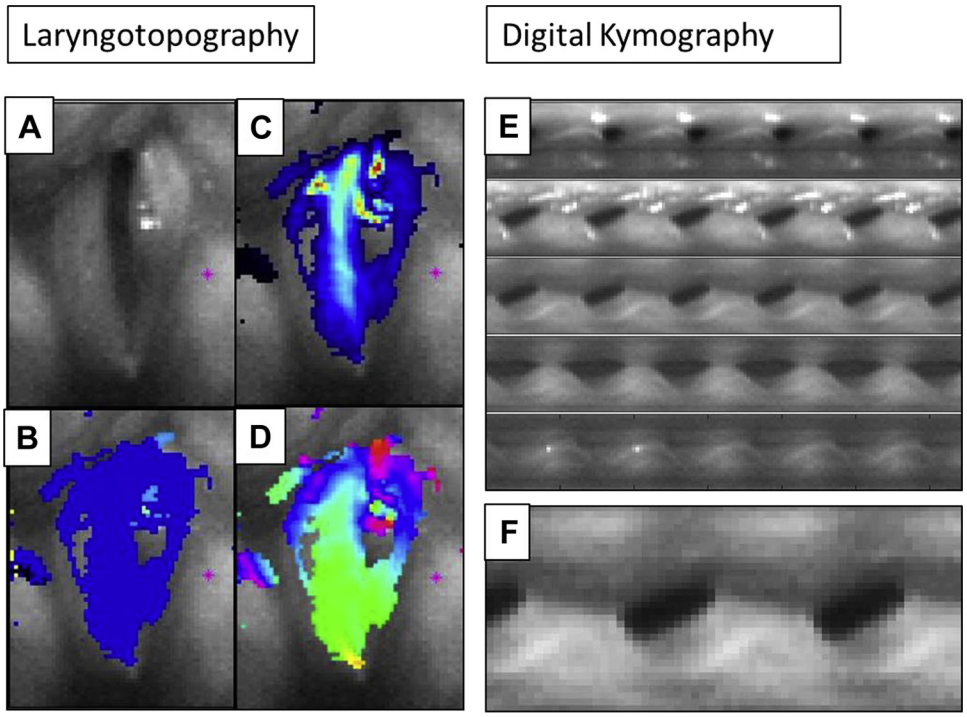

FIGURE 1. An example of the analysis of high-speed digital image is shown. *Panels A through D* show laryngotopography: *panel A* is a static laryngeal image to be superimposed by analyzed topographic data, and *panels B through D* are a spatial distribution of frequency, amplitude, and phase of the maximum-amplitude components, respectively. This 52-year-old male patient with left vocal fold polyp has a topographic F_0 of 198 Hz, right-to-left lateral phase difference (12.5% of a glottal cycle), and anterior-to-posterior longitudinal phase difference (37.5% of a glottal cycle). There is a signal void (a nonvibrating area) where the polyp exists. *Panel E* shows a five-line multiline kymogram, and *panel F* shows a single-line kymogram at the midglottal level. The left vocal fold with a polyp shows reduced amplitude and mucosal wave, lateral phase delay, large speed index (an opening phase is longer than a closing phase), and a rounded lateral peak. Open quotient is larger in the anterior glottis, and O_q^{MLK} and SI^{MLK} are 0.49 and −0.17, respectively.

Statistics

Differences of clinical and HSDI parameters between the control and laryngeal pathology groups or between the control group and each vocal disorder group were evaluated by Student *t* test for normally distributed parameters or by either the Mann-Whitney *U* test or chi-square test for other parameters. To investigate the correlations between HSDI parameters and aerodynamic/acoustic data, as well as those among HSDI parameters, Pearson or Spearman correlation analysis was performed for normally distributed or the other parameters, respectively. In all analyses, $P < 0.05$ was considered significant. Calculations were performed with custom *MATLAB* software.

RESULTS

Overall HSDI parameters

Interpretation of vocal fold vibration by HSDI was feasible in 85.9% of the patients, and the successful interpretation rate was significantly higher for HSDI than for videostroboscopy (60.6%) with chi-square test ($P < 0.001$).

Subjective analysis of vocal fold vibration using the assessment form revealed that the laryngeal pathology group had more asymmetry ($P < 0.001$), a greater mucosal wave difference ($P < 0.001$), and a greater lateral phase difference ($P = 0.003$) than the control group. There were no significant differences in the other parameters such as supraglottal hyperactivity or amplitude.

Quantitative evaluation using LTG, SLK, MLK, and GAW revealed more severe vocal disturbance in the patients than in the control group (Table 2). There was significantly greater asymmetry with a larger N_G-lateral phase difference^{LTG} ($P < 0.001$), longer N_G-longitudinal phase difference^{LTG} ($P < 0.001$), larger N_G-mucosal wave persistence difference ($P = 0.028$), and larger N_G-lateral phase difference ($P = 0.028$). The patients also had a smaller mucosal wave with a smaller N_L-mucosal wave magnitude mean ($P = 0.020$) and smaller N_G-mucosal wave persistence mean ($P = 0.019$). Moreover, patients had worse glottal closure with a larger O_q^{SLK} ($P = 0.032$), larger O_q^{MLK} ($P < 0.001$), larger SI^{MLK} ($P = 0.041$), larger O_q^{GAW} ($P < 0.001$), and larger N_L-minimal glottal area ($P = 0.012$), as well as a smaller glottal area difference index ($P = 0.006$). On the other hand, supraglottal hyperactivity was milder in the patients than in the control group, as was reflected in N_L-glottal area outlet ($P = 0.006$).

Specific disease findings

Vocal fold polyp. The vocal fold polyp group had more evident asymmetry than the control group (larger N_G-longitudinal phase difference^{LTG}, N_G-mucosal wave persistence difference, and N_G-lateral phase difference^{SLK}), as well as a smaller mucosal wave (smaller N_L-mucosal wave magnitude mean) and worse glottal closure (larger O_q^{MLK}, N_L-minimal glottal area and smaller glottal area difference index; Table 3). Vocal folds with polyps had a smaller amplitude, mucosal wave magnitude, and mucosal wave persistence than vocal folds without polyps, as well as a larger speed index (Figure 2). Phase delay was frequently observed at the level of a polyp, with elevated O_qs at adjacent levels (Figure 2).

Vocal fold nodule. Compared with the control group, the vocal fold nodule group showed greater asymmetry (larger N_G-lateral phase difference^{LTG}, N_G-longitudinal phase difference^{LTG}, N_G-lateral phase difference^{SLK}, and N_G-mucosal wave persistence difference), a smaller mucosal wave (smaller N_L-mucosal wave magnitude mean), and worse glottal closure (larger O_q^{SLK}, O_q^{MLK}, O_q^{GAW}, and N_L-minimal glottal area and smaller glottal area difference index; Table 4). The vibrating zone tended to be confined to the vocal fold edge (Figure 2). Supraglottal hyperactivity was milder in the the vocal fold nodule group than in the control group (Table 4).

Laryngeal cancer. In the laryngeal cancer group, vibratory evaluation was only feasible in 50.0% by HSDI due to poor glottal exposure because of supraglottal hyperactivity and the presence of a tumor. Among the cancer patients in whom vibratory assessment was successful, LTG showed more evident asymmetry (larger N_G-lateral phase difference^{LTG} and N_G-mucosal wave persistence difference) than the control group (Table 3), as well as more frequently having a nonvibrating area (50.0%) than the control group (0.0%; Figure 2). Vocal folds with cancer demonstrated a smaller amplitude, mucosal wave magnitude, mucosal wave persistence, and speed index than vocal folds without cancer (Figure 2).

Laryngeal leukoplakia. The laryngeal leukoplakia group showed greater asymmetry (larger N_G-lateral phase difference^{LTG}) and poorer glottal closure (larger O_q^{SLK}, O_q^{MLK}, O_q^{GAW}, and N_L-minimal glottal area) compared with the control group (Table 3). Vocal folds with leukoplakia also demonstrated a smaller amplitude, mucosal wave magnitude, and mucosal wave persistence than vocal folds without leukoplakia, as well as having a larger speed index. However, a nonvibrating area was infrequent (8.3%; Figure 2).

Other disorders. The other laryngeal pathologies demonstrated similar oscillatory characteristics, and all showed greater asymmetry and poorer glottal closure compared with the control group (Tables 3 and 4). Although the difference was not significant, both amplitude and mucosal wave were reduced, except in the Reinke edema group with comparable mucosal wave parameters (Tables 3 and 4). LTG showed a massive nonvibrating area in patients with vocal fold cyst, whereas smaller nonvibrating areas were noted in papillomatosis and Reinke edema (Figure 3). Vocal folds with lesions demonstrated a smaller amplitude, mucosal wave magnitude, and mucosal wave persistence than vocal folds without lesions, as well as having a larger speed index (Figure 3).

Correlation study

A strong correlation ($r > 0.7$) was not found between HSDI parameters and conventional parameters. However, several moderate correlations ($0.4 < |r| \leqq 0.7$) were identified between the mean flow rate and N_L-mucosal wave magnitude difference ($r = 0.40$; $P < 0.001$), between AA-F_0 and N_G-longitudinal

TABLE 2.
Comparisons of High-Speed Digital Image Parameters Between the Control and Various Vocal Fold Pathology Groups Were Summarized

Parameter (U)	Control Group (29)	Pathologic Group (78)	*t* Test
Laryngotopography			
N_G-lateral phase difference-LTG (%)	3.5 ± 4.3	9.2 ± 7.0	<0.001***
N_G-longitudinal phase difference-LTG (%)	−13.2 ± 15.0	−2.6 ± 10.5	<0.001***
Single-line digital kymography			
N_L-amplitude mean (%)	8.1 ± 2.7	7.3 ± 3.3	0.237
N_L-amplitude difference (%)	2.5 ± 2.1	2.7 ± 2.9	0.748
N_L-mucosal wave magnitude mean (%)	18.0 ± 8.5	13.6 ± 7.8	0.020*
N_L-mucosal wave magnitude difference (%)	4.6 ± 3.3	6.1 ± 6.7	0.268
N_G-mucosal wave persistence mean (%)	54.3 ± 18.7	45.8 ± 17.1	0.019*
N_G-mucosal wave persistence difference (%)	13.5 ± 10.1	21.1 ± 20.9	0.028*
N_G-lateral phase difference-SLK (%)	8.7 ± 6.3	15.5 ± 14.5	0.020*
OQ-SLK	0.57 ± 0.14	0.66 ± 0.21	0.032*
SI-SLK	−0.14 ± 0.18	−0.05 ± 0.23	0.083
Multiline digital kymography			
OQ-MLK	0.49 ± 0.13	0.68 ± 0.18	<0.001***
SI-MLK	−0.18 ± 0.21	−0.08 ± 0.22	0.041*
Glottal area waveform			
OQ-GAW	0.78 ± 0.18	0.87 ± 0.16	0.020*
SI-GAW	0.11 ± 0.20	−0.08 ± 0.18	0.429
N_L-maximal glottal area (%)	9.2 ± 2.9	8.1 ± 4.1	0.216
N_L-minimal glottal area (%)	0.13 ± 0.45	0.86 ± 1.51	0.012*
Glottal area difference index (%)	97.6 ± 7.0	87.2 ± 19.2	0.006**
N_L-glottal area outlet (%)	58.3 ± 22.7	71.7 ± 31.4	0.042*

Abbreviations: N_G-, normalized by glottal cycle; LTG, laryngotopography; N_L-, normalized by vocal fold length; OQ, open quotient; SLK, single-line digital kymography; SI, speed index; MLK, multiline digital kymography; GAW, glottal area waveform.
Notes: Values for control and various vocal fold pathology columns show "mean ± standard deviation," and the value of *t* test column shows the *P* value of Student *t* test between all control and various vocal fold pathology groups.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

phase difference^{LTG} ($r = 0.52$; $P < 0.001$), between AA-F_0 and N_L-amplitude mean ($r = -0.51$; $P < 0.001$), and between AA-F_0 and $O_q{}^{GAW}$ ($r = 0.51$; $P < 0.001$).

Table 5 summarizes the correlations among HSDI parameters. A strong correlation ($r > 0.7$) was found between N_L-mucosal wave magnitude mean and N_L-amplitude mean ($r = 0.75$; $P < 0.001$), between $O_q{}^{MLK}$ and $O_q{}^{GAW}$ ($r = 0.71$; $P < 0.001$), and between N_L-minimal glottal area and glottal area difference index ($r = -0.78$; $P < 0.001$). In addition, multiple moderate correlations ($0.4 < |r| \leqq 0.7$) were identified between pairs of parameters.

DISCUSSION

Vocal fold polyp and nodule

The quantitative vibratory characteristics of vocal fold polyps demonstrated in the present study generally agreed with those reported previously, including asymmetry of amplitude, mucosal wave, and phase,[4,5,16,19–22] with a decreased amplitude[4,5,16,19] and mucosal wave[5] on the affected side, phase delay at the site of the polyp,[5] elevation of O_qs especially in the levels adjacent to the polyp,[5,6,20] and an increased speed index.[5,9,21,22] The reduction of amplitude and mucosal wave, as well as the phase delay, may originate from the mass effect of the polyp. Asymmetry of amplitude, mucosal wave, and phase may result from asymmetry in mass, tension, and mucoelasticity because most of the vocal fold polyps were unilateral in the present study.[5,16]

Although differentiation between vocal fold polyp and vocal fold nodule is easy in most cases, it can sometimes be challenging, especially in patients who have bilateral vocal fold polyps or nodules with edematous degeneration. Chodara et al,[16] Krausert et al,[20] and Bohr et al[21] have attempted to differentiate between these two pathologies on the basis of HSDI findings. According to all three studies, both pathologies were associated with more abnormal vibratory parameters compared with normal subjects.[16,20,21] However, both conditions generally caused similar vibratory disturbance, and a limited range of parameters was proposed for differentiation (eg, the lateral phase difference in the posterior glottis[16]). In the present study, the vibratory aberrations associated with nodules were also noted with polyps (asymmetry, reduced amplitude and mucosal wave, and impaired glottal closure). However, there was a conspicuous longitudinal phase difference (posterior-to-anterior in patients with nodules), as well as differences of the amplitude and mucosal wave (greater reduction in patients with nodules). Longitudinal phase difference may be related to gender or age rather than the pathology

TABLE 3.
Comparisons of High-Speed Digital Image Parameters Between the Control and Various Vocal Fold Pathology Groups Were Summarized

Parameter (U)	Polyp (20)	Cancer (16)	Leukoplakia (13)	Papilloma (8)
Laryngotopography				
N_G-lateral PD-LTG (%)	5.9 ± 5.6	11.1 ± 8.7***	11.5 ± 7.0***	7.1 ± 4.3**
N_G-longitudinal PD-LTG (%)	−3.3 ± 12.1*	−4.2 ± 6.4	−6.3 ± 6.8	1.3 ± 5.7*
Single-line digital kymography				
N_L-amplitude mean (%)	6.9 ± 4.1	6.8 ± 2.9	8.8 ± 3.4	7.0 ± 2.9
N_L-amplitude difference (%)	2.4 ± 2.5	1.2 ± 1.4	1.4 ± 1.7	2.5 ± 2.0
N_L-MWM mean (%)	11.0 ± 7.0**	15.0 ± 8.2	17.4 ± 8.2	14.5 ± 10.4
N_L-MWM difference (%)	6.3 ± 6.6	5.5 ± 3.1	8.5 ± 10.9	2.8 ± 2.7
N_G-MWP mean (%)	43.1 ± 16.7	52.5 ± 24.3	49.8 ± 15.0	38.7 ± 20.9
N_G-MWP difference (%)	22.6 ± 20.3*	33.0 ± 27.5**	22.1 ± 25.8	4.2 ± 4.1
N_G-lateral PD-SLK (%)	15.8 ± 15.0*	15.5 ± 15.7	14.5 ± 17.2	10.2 ± 8.6
OQ-SLK	0.61 ± 0.25	0.69 ± 0.22	0.74 ± 0.18**	0.62 ± 0.23*
SI-SLK	0.00 ± 0.28*	0.02 ± 0.90	−0.11 ± 0.19	−0.22 ± 0.23
Multiline digital kymography				
OQ-MLK	0.66 ± 0.19***	0.50 ± 0.17	0.68 ± 0.16***	0.72 ± 0.22***
SI-MLK	−0.01 ± 0.22**	−0.05 ± 0.16	−0.05 ± 0.16	−0.21 ± 0.15
Glottal area waveform				
OQ-GAW	0.85 ± 0.18	0.75 ± 0.21	0.90 ± 0.13*	0.84 ± 0.16
SI-GAW	0.05 ± 0.18	0.13 ± 0.16	0.02 ± 0.22	0.09 ± 0.15
N_L-maximal GA (%)	6.9 ± 5.0	7.5 ± 2.1	10.6 ± 3.8	7.5 ± 2.7
N_L-minimal GA (%)	0.79 ± 1.41*	0.13 ± 0.35	0.68 ± 1.08*	0.33 ± 0.62
GA difference index (%)	83.5 ± 21.1**	98.2 ± 4.9	92.3 ± 13.4	88.0 ± 27.2
N_L-glottal area outlet (%)	63.4 ± 32.5	71.8 ± 33.7	67.7 ± 25.9	84.3 ± 52.6

Abbreviations: N_G-, normalized by glottal cycle; PD, phase difference; LTG, laryngotopography; N_L-, normalized by vocal fold length; MWM, mucosal wave magnitude; MWP, mucosal wave persistence; OQ, open quotient; SLK, single-line digital kymography; SI, speed index; MLK, multiline digital kymography; GAW, glottal area waveform; GA, glottal area.
Notes: Values for control and various vocal fold pathology columns show "mean ± standard deviation," and the value of *t* test column shows the *P* value of Student *t* test between all control and various vocal fold pathology groups.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

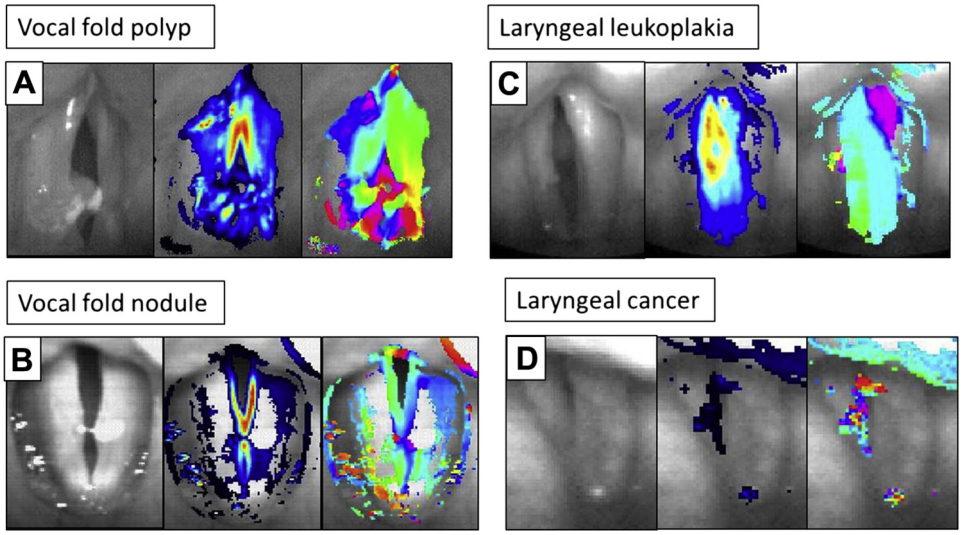

FIGURE 2. Laryngotopograms of representative cases with vocal fold polyp (*panel A*), nodule (*panel B*), leukoplakia (*panel C*), and laryngeal cancer (*panel D*) are shown. Each *panel* consists of a static HSDI image in the left, a window for amplitude in the middle, and a window for a phase in the right. *Panel A* is a 62-year-old male with left vocal fold polyp, and *panel B* is a 22-year-old female with bilateral vocal fold nodules. Compared with vocal fold polyp, vibrating area is limited to vocal fold edge (reduced amplitude and mucosal wave), and posterior-to-anterior longitudinal phase difference is noted. *Panel C* is a 72-year-old male with right laryngeal leukoplakia with a broad and symmetrical vibrating area. In contrast, *panel D* is a 71-year-old male with laryngeal cancer (left vocal fold, T1aN0M0), demonstrating signal void in the affected vocal fold (nonvibrating area).

TABLE 4.
Comparisons of High-Speed Digital Image Parameters Between the Control and Various Vocal Fold Pathology Groups Were Summarized

Parameter (U)	Granuloma (6)	Nodule (6)	Reinke edema (5)	Cyst (4)
Laryngotopography				
N_G-lateral PD-LTG (%)	8.3 ± 5.1*	8.3 ± 8.5*	15.6 ± 8.1***	15.6 ± 4.4***
N_G-longitudinal PD-LTG (%)	−10.4 ± 13.9	10.4 ± 10.0***	3.1 ± 4.4*	−7.8 ± 2.2
Single-line digital kymography				
N_L-amplitude mean (%)	9.5 ± 3.3	5.8 ± 1.9	6.9 ± 2.3	5.8 ± 2.2
N_L-amplitude difference (%)	5.0 ± 4.7*	1.1 ± 1.4	6.5 ± 3.8***	5.5 ± 3.8**
N_L-MWM mean (%)	18.8 ± 7.9	7.7 ± 4.2*	15.5 ± 7.3	11.4 ± 3.7
N_L-MWM difference (%)	5.6 ± 3.7	1.6 ± 1.7*	5.0 ± 5.1	11.8 ± 4.3***
N_G-MWP mean (%)	46.6 ± 11.5	44.7 ± 10.9	55.6 ± 15.9	25.0 ± 20.2
N_G-MWP difference (%)	15.9 ± 10.4	23.3 ± 23.1*	23.2 ± 13.6*	10.7 ± 15.2
N_G-lateral PD-SLK (%)	6.4 ± 5.3	21.4 ± 15.6**	26.6 ± 13.4***	3.6 ± 0.0
OQ-SLK	0.75 ± 0.21*	0.75 ± 0.16**	0.52 ± 0.06	0.50 ± 0.30
SI-SLK	−0.25 ± 0.12	−0.01 ± 0.14	0.04 ± 0.22	0.28 ± 0.32**
Multiline digital kymography				
OQ-MLK	0.78 ± 0.19***	0.78 ± 0.12***	0.62 ± 0.07	0.71 ± 0.00
SI-MLK	−0.27 ± 0.18	−0.04 ± 0.07	0.05 ± 0.29	0.18 ± 0.42*
Glottal area waveform				
OQ-GAW	0.92 ± 0.13	0.95 ± 0.12*	0.92 ± 0.13	1.00 ± 0.00
SI-GAW	0.05 ± 0.26	0.13 ± 0.14	0.21 ± 0.08	0.29 ± 0.00
N_L-maximal GA (%)	9.0 ± 4.7	9.4 ± 4.5	6.6 ± 2.2	7.0 ± 0.0
N_L-minimal GA (%)	1.9 ± 2.4***	2.1 ± 2.6***	0.95 ± 1.53*	0.42 ± 0.80
GA difference index (%)	79.0 ± 22.6***	77.7 ± 19.9***	86.3 ± 23.5*	96.7 ± 6.0
N_L-glottal area outlet (%)	83.2 ± 14.7*	79.2 ± 32.1*	63.0 ± 13.8	83.5 ± 29.9

Abbreviations: N_G-, normalized by glottal cycle; PD, phase difference; LTG, laryngotopography; N_L-, normalized by vocal fold length; MWM, mucosal wave magnitude; MWP, mucosal wave persistence; OQ, open quotient; SLK, single-line digital kymography; SI, speed index; MLK, multiline digital kymography; GAW, glottal area waveform; GA, glottal area.
Notes: Values for control and various vocal fold pathology columns show "mean ± standard deviation," and the value of *t* test column shows the *P* value of Student *t* test between all control and various vocal fold pathology groups.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

per se because vocal fold nodule usually occurs in young women who frequently show a posterior-to-anterior longitudinal phase difference.[23,24,26] The reduction of amplitude and mucosal wave in patients with nodules may be due to increased stiffness resulting from callous degeneration of the vocal fold edge.[16]

Laryngeal leukoplakia and cancer

Little is known about the HSDI vibratory characteristics of laryngeal leukoplakia or cancer. Although there have been several reports about postoperative patients,[6,9,11,17,28] there has been only one case report by Svec et al[11] on the preoperative status, which stated that the affected side demonstrated absence of vibration. In the present study, detection of a nonvibrating area was more frequent in the cancer group than in the leukoplakia group (50.0% vs 8.3%). Both groups had similar vibratory features (asymmetry and poor glottal closure), whereas reduction of the amplitude and mucosal wave were not observed (Table 3). A reduced amplitude and mucosal wave are conventionally considered to be synonymous with laryngeal malignancy. However, recent studies reported that both cancer and leukoplakia were associated with a diminished amplitude and mucosal wave,[29–31] and the presence of a nonvibrating area was also reported to be the only warning sign of malignancy on stroboscopic evaluation.[32] The findings of the present study are compatible with the results of these recent videostroboscopic studies. For the detection of such nonvibrating areas, LTG is considered to be effective. This technique involves analysis of the brightness versus time curve of each pixel, with the calculated data being superimposed on a still glottal picture. In a nonvibrating area, changes in the brightness of the corresponding pixels are absent or minimal, so the area becomes a signal void. This technique cannot be applied in patients with inadequate glottal exposure, such as those with supraglottal hyperactivity or a massive tumor. However, LTG can be a powerful tool for assessment of laryngeal cancer and leukoplakia in suitable cases.

Other disorders

In the present study, both papilloma and granuloma showed a similar pattern of vibratory disturbance (increased asymmetry and poorer glottal closure). Various degrees of left-right or anterior-posterior asymmetry of mass, stiffness, and mucoelasticity associated with laryngeal papillomatosis or massive granuloma may explain these results.

In the patients with Reinke edema, there were no significant differences of mucosal wave parameters compared with the control group, although we expected to find increased lateral

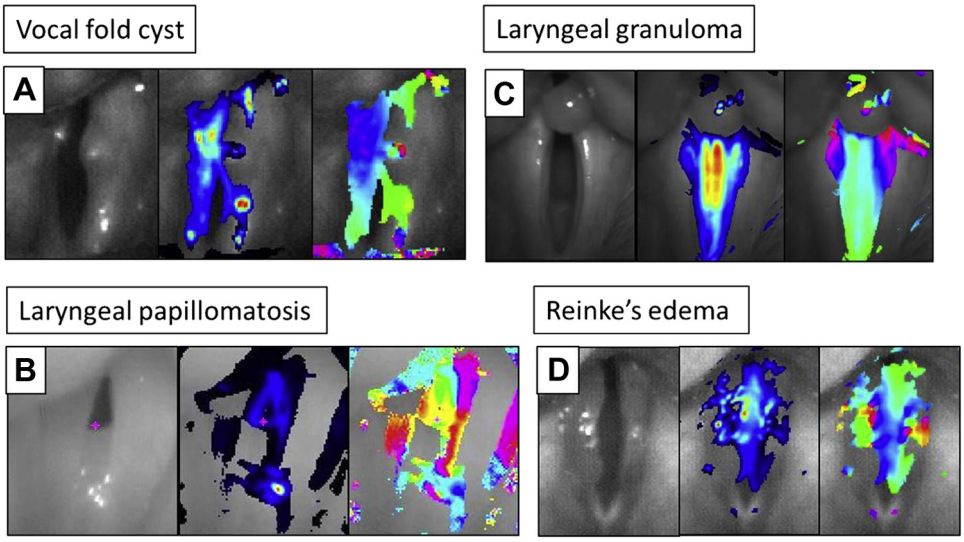

FIGURE 3. Laryngotopograms of representative cases with vocal fold cyst (*panel A*), laryngeal papillomatosis (*panel B*), laryngeal granuloma (*panel C*), and Reinke edema (*panel D*) are shown. Each panel consists of a static HSDI image in the left, a window for amplitude in the middle, and a window for a phase in the right. *Panel A* is a 24-year-old male with right vocal fold cyst, demonstrating signal void in the affected vocal fold (nonvibrating area). *Panel B* is a 28-year-old female with left laryngeal papilloma, demonstrating signal void in the affected vocal fold (nonvibrating area). *Panel C* is a 61-year-old male with left moderate laryngeal granuloma. Although granulomas cover the posterior glottis, the visible parts of vocal folds demonstrate intact vibration. The affected side of vocal fold manifests a phase delay. *Panel D* is a 22-year-old female with bilateral Reinke edema, demonstrating broad vibrating area spreading throughout the superior surface of vocal fold, with left-right and anterior-posterior asymmetry.

propagation or a prolonged mucosal wave duration because of the increased mass in Reinke space. Therefore, investigation of more patients is needed, or novel parameters that reflect the mucosal wave mass may be considered in the future.

The vocal fold cyst[9,10,21,22] group showed marked reduction of mucosal wave parameters, especially the temporal parameter (N_G-mucosal wave persistence mean), although the differences were not statistically significant because of the small sample size. Accordingly, evaluation of further patients with vocal fold cyst is required. Reduction of the mucosal wave was also observed in patients with polyps and nodules, indicating that mucosal wave improvement is not necessarily synonymous with a diagnosis of cyst. However, if there is marked mucosal wave reduction, especially shortened persistence of the visible mucosal wave, vocal fold cyst should be suspected.

TABLE 5.
Correlation Coefficients (*r*) Among High-Speed Digital Image Parameters Are Listed

Parameter	N_L-Amplitude Mean	OQ-GAW	N_L-Minimal GA
N_L-mucosal wave magnitude mean	0.75		
OQ-MLK		0.71	
GA difference index			−0.78

Abbreviations: N_L-, normalized by vocal fold length; OQ, open quotient; GAW, glottal area waveform; GA, glottal area; MLK, multiline digital kymography.
Note: Only the pairs with statistical significance ($P < 0.001$) and with strong correlations ($|r| \geq 0.7$) were selected.

Advantages of HSDI

One major advantage of HSDI over videostroboscopy is the broader range of application, which was demonstrated in the present study by the higher successful interpretation rate for HSDI compared with videostroboscopy. Another advantage is that more advanced analysis is possible with HSDI. Data from videostroboscopy are usually evaluated subjectively[29–34] or by glottal area waveform analysis[35,36] or kymography,[37,38] whereas HSDI allows the use of a variety of methods such as LTG,[24] phonovibrography,[12,13,19,21,22] time series analysis,[15] and others. The third advantage of HSDI is that it allows more reliable quantitative analysis. In the present study, most of the vibratory parameters that are routinely evaluated in a subjective manner by videostroboscopy could be quantified by HSDI, allowing objective documentation of the severity of vocal disturbance. The results obtained for each laryngeal disorder were generally compatible with the disease-specific vibratory characteristics reported in the literature, as discussed previously, supporting the validity of the analytical methods used in the present study.

Limitations

The first limitation of this study was the small sample size for some of the laryngeal disorders, especially cyst and Reinke edema, which presumably led to failure to demonstrate

statistical significance of our findings. Another limitation is that we only evaluated data obtained with sustained phonation. Because the evaluation was limited to steady-state vibration, vocal disturbance may have been underestimated.[21,39] Therefore, future investigations should focus on modification of tasks to include changes of the fundamental frequency,[23–27,39] sound pressure level,[35] and type of phonation (eg, pressed, breathy phonation),[40] as well as assessing a mixture of vowels and consonants to allow estimation of vocal disturbance during speech.[7] In addition, the method of analysis used in this study requires some manual measurement and thus is rather labor intensive; thus, improvement of the analytical technique with more automation would be desirable. Furthermore, there were only moderate correlations between conventional voice parameters and HSDI parameters. This may have occurred because HSDI and acquisition of other voice data were not performed simultaneously, leading to minor variations in frequency and sound pressure level. Implementation of a system to simultaneously acquire HSDI and other voice data has been attempted[40,41] and should be developed for use in the clinical setting.

CONCLUSIONS

Investigation of various voice disorders by HSDI using digital kymography, LTG, and GAW analysis revealed disease-specific vibratory disturbances that generally agreed with the findings reported in the literature.

Acknowledgments

This research was not funded by any organization or grants. There are no conflicts of interest to be disclosed.

REFERENCES

1. Olthoff A, Woywod C, Kruse E. Stroboscopy versus high-speed glottography: a comparative study. *Laryngoscope*. 2007;117:1123–1126.
2. Patel R, Dailey S, Bless D. Comparison of high-speed digital imaging with stroboscopy for laryngeal imaging of glottal disorders. *Ann Otol Rhinol Laryngol*. 2008;117:413–424.
3. Kendall KA. High-speed laryngeal imaging compared with videostroboscopy in healthy subjects. *Arch Otolaryngol Head Neck Surg*. 2009;135:274–281.
4. von Leden H, Moore P, Timcke R. Laryngeal vibrations: measurements of the glottic wave. Part III. The pathologic larynx. *Arch Otolaryngol*. 1960;71:16–35.
5. Hirano M, Gould WJ, Lambiase A, Kakita Y. Vibratory behavior of the vocal folds in a case with a unilateral polyp. *Folia Phoniatr.* 1981;33:275–284.
6. Schutte HK, Svec JG, Sram F. First results of clinical application of videokymography. *Laryngoscope*. 1998;108:1206–1210.
7. Wittenberg T, Tigges M, Mergell P, Eysholdt U. Functional imaging of vocal fold vibration: digital multislice high-speed kymography. *J Voice*. 2000;14:422–442.
8. Niimi S, Miyaji M. Vocal fold voice quality. *Folia Phoniatr Logop*. 2000;52:32–38.
9. Verdonck-de Leeuw I, Festen JM, Mahieu H. Deviant vocal fold vibration as observed during videokymography: the effect on voice quality. *J Voice*. 2001;15:313–322.
10. Qiu Q, Schutte HK, Gu L, Yu Q. An automatic method to quantify the vibration properties of human vocal folds via videokymography. *Folia Phoniatr Logop*. 2003;55:128–136.
11. Svec JG, Sram F, Schutte HK. Videokymography in voice disorders: what to look for? *Ann Otol Rhinol Laryngol*. 2007;116:172–180.
12. Lohscheller J, Eysholdt U, Toy H, Döllinger M. Phonovibrography: mapping high-speed movies of vocal fold vibrations into 2-D diagrams for visualizing and analyzing the underlying laryngeal dynamics. *IEEE Trans Med Imaging*. 2008;27:300–309.
13. Lohscheller J, Eysholdt U. Phonovibrogram visualization of entire vocal fold dynamics. *Laryngoscope*. 2008;118:753–758.
14. Voigt D, Döllinger M, Eysholdt U, Yang A, Gürlek E, Lohscheller J. Objective detection and quantification of mucosal wave propagation. *J Acoust Soc Am*. 2010;128:EL347–355.
15. Zhang Y, Shao J, Krausert CR, Zhang S, Jiang JJ. High-speed image analysis reveals chaotic vibratory behaviors of pathological vocal folds. *Chaos Solitons Fractals*. 2011;44:169–177.
16. Chodara AM, Krausert CR, Jiang JJ. Kymographic characterization of vibration in human vocal folds with nodules and polyps. *Laryngoscope*. 2012;122:58–65.
17. Piazza C, Mangili S, del Bon F, et al. Quantitative analysis of videokymography in normal and pathological vocal folds: a preliminary study. *Eur Arch Otorhinolaryngol*. 2012;269:207–212.
18. Mehta DD, Zeitels SM, Burns JA, Friedman AD, Deliyski DD, Hillman RE. High-speed videoendoscopic analysis of relationships between cepstral-based acoustic measures and voice production mechanisms in patients undergoing phonomicrosurgery. *Ann Otol Rhinol Laryngol*. 2012;121:341–347.
19. Kunduk M, Döllinger M, McWhorter AJ, Svec JG, Lohscheller J. Vocal fold vibratory behavior changes following surgical treatment of polyps investigated with high-speed videoendoscopy and phonovibrography. *Ann Otol Rhinol Laryngol*. 2012;121:355–363.
20. Krausert CR, Liang Y, Zhang Y, Rieves AL, Geurink KR, Jiang JJ. Spatiotemporal analysis of normal and pathological human vocal fold vibrations. *Am J Otolaryngol*. 2012;33:641–649.
21. Bohr C, Kraeck A, Eysholdt U, Ziethe A, Döllinger M. Quantitative analysis of organic vocal fold pathologies in females by high-speed endoscopy. *Laryngoscope*. 2013;123:1686–1693.
22. Bohr C, Kraeck A, Dubrovskly D, et al. Spatiotemporal analysis of high-speed videolaryngoscopic imaging of organic pathologies in males. *J Speech Lang Hear Res*. 2014;57:1148–1161.
23. Yamauchi A, Imagawa H, Yokonishi H, et al. Evaluation of vocal fold vibration with an assessment form for high-speed digital imaging: comparative study between healthy young and elderly subjects. *J Voice*. 2012;26:742–750.
24. Yamauchi A, Imagawa H, Sakakibara K-I, et al. Phase difference of vocally healthy subjects in high-speed digital imaging analyzed with laryngotopography. *J Voice*. 2013;27:39–45.
25. Yamauchi A, Yokonishi H, Imagawa H, et al. Quantitative analysis of digital videokymography: a preliminary study on age- and gender-related difference of vocal fold vibration in normal speakers. *J Voice*. 2015;29:109–119.
26. Yamauchi A, Imagawa H, Sakakibara K-I, et al. Characteristics of vocal fold vibrations in vocally healthy subjects: analysis with multi-line kymography. *J Speech Lang Hear Res*. 2014;57:648–657.
27. Yamauchi A, Yokonishi H, Imagawa H, et al. Age- and gender-related difference of vocal fold vibration and glottal configuration in normal speakers: analysis with glottal area waveform. *J Voice*. 2014;28:525–531.
28. Mehta DD, Deliyski DD, Zeitels SM, Quatieri TF. Voice production mechanisms following phonosurgical treatment of early glottic cancer. *Ann Otol Rhinol Laryngol*. 2010;119:1–9.
29. Colden D, Jarboe J, Zeitels SM, Bunting G, Hillman RE, Spanou K. Stroboscopic assessment of vocal fold keratosis and glottic cancer. *Ann Otol Rhinol Laryngol*. 2001;110:293–298.
30. Ganboa J, Echeverria L, Molina B, Cobeta I. Stroboscopic assessment of chronic laryngitis. *Acta Otorrinolaryngol Esp*. 2006;57:266–269.
31. Gugatschka M, Kiesler K, Beham A, Rechenmacher J, Friedrich G. Hyperplastic epithelial lesions of the vocal folds: combined use of exfoliative cytology and laryngostroboscopy in differential diagnosis. *Eur Arch Otorhinolaryngol*. 2008;265:797–801.
32. Djukic V, Milovanovic J, Jotic AD, Vukasinovic M. Stroboscopy in detection of laryngeal dysplasia effectiveness and limitations. *J Voice*. 2014;28:e13–21.

33. Hirano M, Bless D. *Videostroboscopic Examination of the Larynx*. San Diego, CA: Singular Publishing Group; 1993.
34. Woo P, Casper J, Colton R, Brewer D. Aerodynamic and stroboscopic findings before and after microlaryngeal phonosurgery. *J Voice*. 1994;8:186–194.
35. Woo P. Quantification of videostrobolaryngoscopic findings—Measurements of the normal glottal cycle. *Laryngoscope*. 1996;106:1–27.
36. Noordzu JP, Woo P. Glottal area waveform analysis of benign vocal fold lesions before and after surgery. *Ann Otol Rhinol Laryngol*. 2000;109: 441–446.
37. Sung MW, Kim KH, Koh TY, et al. Videostrobokymography: a new method for the quantitative analysis of vocal fold vibration. *Laryngoscope*. 1999; 109:1859–1863.
38. Kim DY, Kim LS, Kim KH, et al. Videokymographic analysis of benign vocal fold lesions. *Acta Otolaryngol*. 2003;123:1102–1109.
39. Wurzbacher T, Schwarz R, Döllinger M, Hoppe U, Eysholdt, Lohscheller J. Model-based classification of nonstationary vocal fold vibration. *J Acoust Soc Am*. 2006;120:1012–1027.
40. Orlikoff RF, Golla ME, Deliyski DD. Analysis of longitudinal phase differences in vocal-fold vibration using synchronous high-speed videoendoscopy and electroglottography. *J Voice*. 2012;26: e13–20.
41. Larsson H, Hertegard S, Lindestad P-A, Hammarberg B. Vocal fold vibrations: high-speed imaging, kymography, and acoustic analysis: a preliminary report. *Laryngoscope*. 2000;110:2117–2122.