Acoustic Analysis Findings in Objective Laryngopharyngeal Reflux Patients

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Summary: Objective: The aim of this study was to identify the effects of objective laryngopharyngeal reflux (LPR) on the acoustic parameters of patients by comparing their voice samples with that of control subjects. Study Design: Prospective study in two tertiary reference hospitals. Methods: 48 consecutive patients with symptoms related to LPR and 64 control subjects were included in the study. Suspected LPR patients underwent a 24-hour ambulatory pH monitoring, and 25 (52%) of them were shown to have objective LPR. Acoustical evaluation results of objective LPR patients were compared with that of symptomatic LPR patients and control subjects. Results: All frequency perturbation values obtained from objective and symptomatic LPR patients were higher than the control subjects ($P < 0.01$). Mean fundamental frequency, amplitude perturbation measures, and noise-to-harmonics ratio were not significantly different between groups. Conclusion: LPR patients have significantly different frequency perturbation values than control subjects.


INTRODUCTION

Gastroesophageal reflux (GER) is defined as the backflow of gastric contents into the esophagus. GER is a well-known entity and accepted to be physiological, up to 50 episodes a day, especially if it occurs after meals.1,2 It is estimated that between 18% and 40% of the central and northern European population suffers from this condition.3 Main symptoms that are related to GER are heartburn, chest pain, indigestion, and the feeling of stomach acid coming up. Laryngopharyngeal reflux (LPR), however, is the backflow of gastric contents above upper esophageal sphincter (UES), into the pharynx, larynx, and upper aerodigestive system. Even a single reflux episode above the UES is considered pathological.2 The incidence of LPR in the population is estimated at 1%.3 Symptoms that are related with LPR are hoarseness or other voice problems, coughing after meals, throat clearing, globus pharyngeus, sore throat, dysphagia, tongue burning, and breathing difficulties.3

The aim of this study was to identify the effects of objective LPR on the acoustic parameters of patients by comparing their voice samples with that of symptomatic patients and control subjects.
MATERIALS AND METHODS

Forty-eight consecutive, nonsmoking, new patients with symptoms related to LPR were included in this prospective study between July 2004 and May 2005. Besides a complete otolaryngological examination, the patients were evaluated with videolaryngostroboscopy to confirm that they do not have any additional laryngeal findings such as nodule, polyp, and dysplasia that may cause voice changes, by using a 90° rigid scope (Karl Storz Laryngostrobe, Tuttingen, Germany). The laryngeal changes related with LPR were evaluated according to reflux finding score (RFS), an eight-item, weighted instrument developed by Center for Voice Disorders, Wake Forest University (Table 1).4,5 An RFS above 7 was defined as positive, and a RFS below or equal to 7 was defined as negative.4,5

Then, a 24-hour double-channel ambulatory pH monitoring study was performed using a Digitrapper MK III (Synectics Medical AB, Stockholm, Sweden) ambulatory pH monitor and a Zinetics 24 TM (Zinetics Medical Inc, Salt Lake City, Utah) double-channel pH catheter. PW version 2.04 Esophagram (Synectics Medical AB, Stockholm, Sweden) software was used for analysis. Immediately before use, each probe was calibrated in solutions of pH 7 and pH 1. The catheters were placed transnasally under local anesthesia, with the lower sensor located 5 cm above the endoscopically determined LES. The upper sensor was located 15 cm above the first one. The catheter was then secured to the nasal dorsum. The patients were asked to continue their usual daily activities and eat their usual meals except gaseous, spicy, acidic food, and drinks. They were required to keep a timetable of meals, body positions, and symptoms. All pH recordings were performed for 24 hours. PH recordings for both sensors were recorded; however, only the values for the upper sensor are discussed in this article. The accepted cutoff values for the upper sensor measurements were as follows6: 1.4% for the percent total time pH > 4, 1.9% for the percent upright time pH > 4, and 1.3% for the percent supine time pH < 4. Patients with values above these limits were considered as having objective LPR. Other patients were defined as symptomatic LPR patients.

A control group was formed by 64 subjects. These subjects had no history of laryngeal irritation as any kind of tobacco use, endotracheal intubation, neurological disease, or toxic fume inhalation. The control group subjects had no history of laryngeal surgery or trauma, radiation exposure to head and neck, or reflux treatment. They were questioned about GER and LPR symptoms and underwent a complete otolaryngological and videolaryngostroboscopic examination, to confirm that they do not have any reflux symptoms or asymptomatic reflux-related laryngeal changes.

The acoustic data of the LPR patients and the control subjects were recorded by the same examiner under identical conditions in a sound-treated room with an ambient noise below 50 dB. According to National Center for Voice and Speech recommendations,7 10 samples of sustained vowel /a/ at a comfortable pitch, constant amplitude, and flat tone were obtained, by using a Shure C606N cardioid microphone (Shure Inc, Niles, IL) placed on

<table>
<thead>
<tr>
<th>Videolaryngoscopic Findings</th>
<th>Scoring Points</th>
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<tbody>
<tr>
<td>Subglottic edema</td>
<td>0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = polypoid</td>
</tr>
<tr>
<td>Ventricular obliteration</td>
<td>0 = absent, 1 = partial, 2 = complete</td>
</tr>
<tr>
<td>Erythema/hyperemia</td>
<td>0 = absent, 1 = arytenoids only, 2 = diffuse</td>
</tr>
<tr>
<td>Vocal cord edema</td>
<td>0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = obstructing</td>
</tr>
<tr>
<td>Diffuse laryngeal edema</td>
<td>0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = obstructing</td>
</tr>
<tr>
<td>Posterior comissure hypertrophy</td>
<td>0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = obstructing</td>
</tr>
<tr>
<td>Granuloma/granulation</td>
<td>0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = obstructing</td>
</tr>
<tr>
<td>Thick endolaryngeal mucus/other</td>
<td>0 = absent, 2 = present</td>
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</table>
a stand 8 cm apart and with an angle of 45 degrees to the patient’s mouth to decrease aerodynamic noise from the mouth. The acoustic parameters were evaluated by Praat software (Version 4.2.17, Paul Boersma and David Weenink, Phonetic Sciences Department, University of Amsterdam, the Netherlands) in a personal computer with a sampling rate of 22050 Hz. To exclude irregularities associated with onset and offset of phonation, the stable 3 seconds of the midvowel segment of the voice samples was evaluated. The most stable three voice samples were used to minimize intra-subject variability. The data reported for each subject in this article corresponds to overall mean of these three evaluated samples. Mean fundamental frequency and measures of phonatory stability, namely local jitter, absolute jitter, relative average perturbation (rap) jitter, period perturbation quotient (ppq) jitter, local shimmer, dB shimmer, amplitude perturbation quotient 3 (apq3) shimmer, amplitude perturbation quotient 5 (apq5) shimmer, amplitude perturbation quotient 11 (apq11) shimmer, and mean noise-to-harmonics ratio (NHR) values, were obtained for each subject.

The distribution pattern within groups was tested with the Kolmogorov–Smirnov test and the comparison of means between patient and control groups were tested with an independent sample t test. The difference of RFS results between groups was tested with the Fisher exact test. SPSS for Windows 10.0 (SPSS Corporation, Chicago, IL) and StatCrunch 4.0 computer programs (Integrated Analytics LLC) were used to perform summary statistics, tables, and graphics.

**RESULTS**

Upper probe results of 25 patients (52.1%) were defined as positive for LPR according to the above-mentioned criteria. These patients were described as “objective” LPR patients. Remaining LPR patients were defined as “symptomatic” LPR patients (n = 23, 47.9%).

Mean age of objective LPR patients, symptomatic LPR patients, and controls were 59.56 (standard deviation 9.96, range 40–78), 50.88 (standard deviation 15.42, range 22–85), and 50.09 (standard deviation 12.61, range 23–72), respectively.

Fifteen (60.0%) of the 25 objective LPR patients had a positive reflux finding score (RFS > 7) and 10 (40.0%) had a negative score. These numbers were 16 (69.6%) positive patients and 7 (30.4%) negative patients for the symptomatic LPR group. By definition, none of the control subjects had a positive RFS. This distribution was statistically insignificant between objective and symptomatic LPR patients. The difference was significant for both groups, when each of them was compared with the control group (P < 0.001).

Acoustic evaluation results of objective LPR patients, symptomatic LPR patients, and controls are given at Table 2.

All four examined frequency perturbation measures (jitter local, jitter absolute, jitter rap, and jitter

![Table 2](image-url)

**Table 2. Mean ± Standard Deviation Results of Analyzed Acoustic Parameters for Objective LPR Patients, Symptomatic LPR Patients, and Control Subjects**

<table>
<thead>
<tr>
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<th>Objective LPR Patients</th>
<th>Symptomatic LPR Patients</th>
<th>Control Subjects</th>
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<tbody>
<tr>
<td>Jitter local (%)</td>
<td>0.43 ± 0.20</td>
<td>0.39 ± 0.14</td>
<td>0.29 ± 0.11</td>
</tr>
<tr>
<td>Jitter absolute (μs)</td>
<td>26069 ± 15671</td>
<td>20571 ± 8298</td>
<td>17172 ± 9473</td>
</tr>
<tr>
<td>Jitter rap (%)</td>
<td>0.25 ± 0.13</td>
<td>0.21 ± 0.09</td>
<td>0.16 ± 0.07</td>
</tr>
<tr>
<td>Jitter ppq (%)</td>
<td>0.24 ± 0.10</td>
<td>0.22 ± 0.08</td>
<td>0.17 ± 0.07</td>
</tr>
<tr>
<td>Shimmer local (%)</td>
<td>4.10 ± 2.12</td>
<td>4.39 ± 2.22</td>
<td>4.54 ± 2.57</td>
</tr>
<tr>
<td>Shimmer dB (dB)</td>
<td>0.36 ± 0.18</td>
<td>0.39 ± 0.20</td>
<td>0.40 ± 0.23</td>
</tr>
<tr>
<td>Shimmer apq3 (%)</td>
<td>2.30 ± 1.32</td>
<td>2.50 ± 1.40</td>
<td>2.59 ± 1.63</td>
</tr>
<tr>
<td>Shimmer apq5 (%)</td>
<td>2.46 ± 1.26</td>
<td>2.65 ± 1.35</td>
<td>2.70 ± 1.54</td>
</tr>
<tr>
<td>Shimmer apq11 (%)</td>
<td>2.96 ± 1.30</td>
<td>3.03 ± 1.26</td>
<td>3.18 ± 1.49</td>
</tr>
<tr>
<td>NHR</td>
<td>0.181 ± 0.165</td>
<td>0.152 ± 0.104</td>
<td>0.157 ± 0.131</td>
</tr>
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*Abbreviations: NHR, noise-to-harmonics ratio; LPR, laryngopharyngeal reflux.*
ppq) were higher than the control group in objective LPR patients. The difference between objective LPR patients and control group was statistically significant ($P < 0.01$) (Table 2 and Figure 1). All four jitter parameters were also higher in subjective LPR patients than controls. The difference was also significant ($P < 0.01$) (Table 2 and Figure 1). The mean values of all four jitter parameters were higher in objective LPR patients than symptomatic LPR patients; however, this difference was not significant.

There were not any statistical difference between objective LPR patients and control subjects in any of the five amplitude perturbation parameters (shimmer local, shimmer dB, shimmer apq3, shimmer apq5, and shimmer apq11) (Table 2 and Figure 2). This was also true for symptomatic LPR patients and controls (Table 2 and Figure 2). The difference between objective LPR patients and subjective LPR patients was also insignificant (Table 2 and Figure 2).

Objective LPR patients had a higher mean noise-to-harmonics ratio than the other two groups, but the differences between groups were insignificant (Table 2 and Figure 3).

When we compared fundamental frequency values of three groups according to gender of the participants, we found that objective LPR patients and symptomatic LPR patients have lower mean values than control subjects in both genders. Mean fundamental frequency and standard deviation values were $224.42 \pm 26.78$ for objective LPR patients ($n = 12$), $221.02 \pm 28.25$ for symptomatic LPR patients ($n = 16$), and $241.84 \pm 34.76$ for control group ($n = 28$), in women. These values were $143.31 \pm 23.57$ for objective LPR patients ($n = 13$), $134.78 \pm 17.62$ for symptomatic LPR patients ($n = 7$), and $151.42 \pm 32.71$ for control group.

**FIGURE 1.** Graphic representation shows mean ± two standard deviation values of jitter local (Jlocal), jitter rap (Jrap), and jitter ppq (Jppq) for objective (L) laryngopharyngeal reflux (LPR) patients, symptomatic (S) laryngopharyngeal reflux (LPR) patients, and control (C) subjects.

**FIGURE 2.** Graphic representation shows mean ± two standard deviation values of shimmer local (Slocal), shimmer apq3 (Sapq3), shimmer apq5 (Sapq5), and shimmer apq11 (Sapq11) for objective (L) laryngopharyngeal reflux (LPR) patients, symptomatic (S) laryngopharyngeal reflux (LPR) patients, and control (C) subjects.

**FIGURE 3.** Graphic representation shows mean ± two standard deviation values of noise-to-harmonics ratio (NHR) for objective (L) laryngopharyngeal reflux (LPR) patients, symptomatic (S) laryngopharyngeal reflux (LPR) patients, and control (C) subjects.
(n = 36), in men. The difference between groups was statistically insignificant for both genders.

**DISCUSSION**

Gastroesophageal reflux disease (GERD) has been implicated in the pathogenesis of reflux esophagitis, Barrett’s esophagus, esophageal stricture, and esophageal adenocarcinoma. Similarly, LPR is being implicated in the etiopathogenesis of reflux laryngitis, subglottic stenosis, laryngeal carcinoma, contact ulcer, granuloma, vocal nodules, and arytenoid fixation. Larynx is more susceptible to reflux injury than the esophagus, because it lacks both the extrinsic and the intrinsic epithelial defenses (anti-reflux barrier) of the esophagus. Histological findings have frequently shown the laryngeal mucosa to be keratinized and to have many similarities to the esophageal mucosa noted in patients with GERD.

Laryngeal examination findings related with LPR are interarytenoid erythema or hyperemia, infraglottic edema (pseudosulcus), vocal cord or diffuse laryngeal edema, ventricular obliteration, posterior comissure hypertrophy/pachydermia, granuloma or granulation tissue formation, and thick and excessive endolaryngeal mucus. Observation of these findings with previously mentioned symptoms gives important information for the diagnosis of LPR.

The usual gastroenterological investigations such as esophagogastroduodenoscopy and barium swallow are usually normal in LPR patients and provide no information. Although probe placement has some controversies as wrong test results secondary to loss of mucosal contact, pH changes caused by oral intake, intermittent drying, and moistening of the proximal probe, 24-hour double-probe ambulatory pH monitoring is still the current gold standard for the diagnosis of LPR.

The importance of LPR in the pathogenesis of laryngeal disorders is better understood everyday; however, its implications on human voice is not well established. Hoarseness is one of the main symptoms of LPR, and LPR may be present in up to 50% of patients with voice problems. Literature lacks information on voice changes of LPR patients whose diagnosis are confirmed with 24-hour double-probe pH monitoring (objective LPR patients). This is the first study in the literature about the effects of reflux on acoustic parameters in objective LPR patients.

A positive upper probe in 24-hour monitorization confirms the diagnosis of LPR, but a negative result does not exclude the diagnosis. False-negative test results have been reported as high as 20–50% in the literature and when the time period at which pH < 4 is taken into consideration for both upper and lower probes, Bilgen et al reported that there were no statistically significant difference between LPR and control groups. Because of this reported high false negativity, in our study, we compared the acoustical analysis results of objective LPR patients confirmed with 24-hour pH monitoring with that of symptomatic LPR patients that have negative pH monitoring results and normal subjects who do not have any sign or symptom of LPR.

In two previous studies by Ross et al and Selby et al, perceptual and acoustic measures of suspected LPR patients were evaluated. Increased muscular tension, hard glottal attack, glottal fry, restricted tone placement, and hoarseness were recorded as the perceptual differences compared with the control group. Although used at the evaluation of patients in the outpatient setting, perceptual measures may have the problems of interpersonal and intrapersonal variability. Acoustic parameters obtained from voice evaluation, on the other hand, provide objective measures for vocal cord function. Fundamental frequency, jitter, shimmer, and noise-to-harmonic values determine the basic elements of voice quality. Our study was based on sustained vowels. Working on sustained vowels is easy to perform and is free from articulatory and dialectical variations among speakers. It also requires minimum patient compliance.

Mean fundamental frequency is the overall mean of all extracted period-to-period fundamental frequency values in the analyzed voice sample. Most laryngeal disorders may not have a significant influence on mean fundamental frequency. Murry studied the change of mean fundamental frequency in patients with a spectrum of laryngeal disorders and found that only vocal cord paralysis patients had different mean fundamental frequencies than controls. In their recent comparison study between
suspected LPR patients diagnosed according to laryngeal and esophageal findings and controls, Pribuisiene et al. found no difference for mean fundamental frequency in both female and male groups.

Jitter is one of the main measures for micro-instability in vocal cord vibrations. It refers to a cycle-to-cycle, short-term perturbation in the fundamental frequency of the voice. Jitter absolute is the average absolute difference between consecutive periods and is defined in microseconds. Jitter local is the average absolute difference between consecutive periods, divided by the average period. It is the relative evaluation of the very short-term variability of the pitch within the analyzed voice sample. Jitter rap is the average absolute difference between a period and the average of it and its two neighbor periods (smoothing factor of 3 periods), divided by the average period. Jitter ppq is the average absolute difference between a period and the average of it and its four closest neighbor periods (smoothing factor of 5 periods), divided by the average period. Jitter local, jitter rap, and jitter ppq are defined in percentages. Pribuisiene et al. did not find significant differences in shimmer values in the male group; however, there was a difference in the female group.

Increased jitter and shimmer may reflect both the diminished laryngeal control and the degenerative changes in laryngeal tissue. In addition to short-term period and amplitude variations, inconsistent or absent vocal cord closure leads to an air leakage through the glottis, which is acoustically characterized as noise. Shimmer is a cycle-to-cycle, short-term perturbation in amplitude of voice. It increases with poor and inconsistent contact between the vocal cord edges. It was reported to relate with the perception of breathiness. Shimmer dB is the average absolute base-10 logarithm of the difference between the amplitudes of consecutive periods, multiplied by 20. It is defined in decibels. Shimmer local is the average absolute difference between the amplitudes of consecutive periods, divided by the average amplitude. It is the relative evaluation of very short-term variability of peak-to-peak amplitude within the analyzed voice sample. Shimmer apq3 is the three-point amplitude perturbation quotient, the average absolute difference between the amplitude of a period and the average of the amplitudes of it, and its two closest neighbors (smoothing factor of 3 periods), divided by the average amplitude. Shimmer apq5 is the five-point amplitude perturbation quotient, the average absolute difference between the amplitude of a period and the average of the amplitudes of it, and its four closest neighbors (smoothing factor of 5 periods), divided by the average amplitude. Shimmer apq11 is the 11-point amplitude perturbation quotient, the average absolute difference between the amplitude of a period and the average of the amplitudes of it, and its 10 closest neighbors (smoothing factor of 11 periods), divided by the average amplitude. Shimmer local and Shimmers apq3, apq5 and apq11 are defined in percentages. Pribuisiene et al. did not find significant differences in shimmer values in the male group; however, there was a difference in the female group.

Increased jitter and shimmer may reflect both the diminished laryngeal control and the degenerative changes in laryngeal tissue. In addition to short-term period and amplitude variations, inconsistent or absent vocal cord closure leads to an air leakage through the glottis, which is acoustically characterized as noise. The noise-to-harmonics ratio is the average ratio of the inharmonic energy to the harmonic spectral energy. It is not specific to any cyclic parameter. It includes contributions from both perturbations of amplitude and frequency. The measure correlates best with the overall perception of noisiness or roughness in the signal, and it provides objective information on the presence of breathiness. In their study, Ross et al. did not find any difference in NHR values. However, Pribuisiene et al. found increased glottal noise in patients with laryngeal and esophageal changes attributed to LPR. Although both studies were based on laryngeal findings, the inconsistency between two studies needs further investigation. Selby et al. studied the effects of proton pump inhibitors on the voices of suspected LPR patients. They did not find any statistically significant
changes for any of the frequency- and amplitude-related measures. The only statistically significant change was observed in harmonics-to-noise ratio values. The statistically insignificant noise-to-harmonics ratio findings in our comparison groups may be explained by the difference of our objective diagnosis method than the subjective diagnosis methods of previous studies. The time period and/or severity of LPR that results in laryngeal findings may be longer than the period needed to initiate symptoms, and the patients of two previous studies may be later stage LPR patients with more pronounced voice symptoms than our patients. Further studies are necessary to establish the effects of short- or long-term LPR on voice parameters.

From a child’s initial cry to his/her final words, voice is one of the most important ways for people to express their feelings. A healthy voice is critical for every person either at work or during his/her social life for his/her well being. In a previous study, LPR patients were reported to have significantly lower quality-of-life scores than GERD patients. Discrimination of these two entities and defining the effects of LPR to patient’s voice and quality of life may positively affect the patient compliance to the long-term medical therapy required to treat LPR. Having these objective values on hand may also encourage the physician to treat this disorder effectively where the symptomatic relief usually precedes objective relief of signs of the disease.

Our future perspective on this study is to show that these results are repeatable by making studies with different probe positions, with other diagnosis methods suggested for LPR and showing that these results are reversible with medical or surgical treatment modalities.

CONCLUSION

To our knowledge, this is the first study that shows LPR patients, objectively diagnosed by 24-hour pH monitorization, have significantly different acoustic analysis values than control subjects. All frequency perturbation measures were higher in objective LPR patients than control counterparts. This difference was also valid for symptomatic LPR patients that have negative results with pH monitorization. Defining this objective voice difference and its effects on patient’s quality of life may positively affect both the compliance of patient and the motivation of physician during the long-term medical therapy required to treat LPR.

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REFERENCES