Evaluating the Autonomic Nervous System in Patients with Laryngopharyngeal Reflux
Wan-Ju Huang, Chih-Hung Shu, Kun-Ta Chou, Yi-Fen Wang, Yen-Bin Hsu, Ching-Yin Ho and Ming-Ying Lan

Otolaryngology -- Head and Neck Surgery 2013 148: 997 originally published online 21 March 2013
DOI: 10.1177/0194599813482103

The online version of this article can be found at:
http://oto.sagepub.com/content/148/6/997

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
AMERICAN ACADEMY OF
OTOLARYNGOLOGY--
HEAD AND NECK SURGERY

American Academy of Otolaryngology- Head and Neck Surgery

Additional services and information for Otolaryngology -- Head and Neck Surgery can be found at:

Email Alerts: http://oto.sagepub.com/cgi/alerts
Subscriptions: http://oto.sagepub.com/subscriptions
Reprints: http://www.sagepub.com/journalsReprints.nav
Permissions: http://www.sagepub.com/journalsPermissions.nav

Version of Record - May 20, 2013
OnlineFirst Version of Record - Mar 21, 2013

What is This?
Evaluating the Autonomic Nervous System in Patients with Laryngopharyngeal Reflux

Wan-Ju Huang, MD1,2, Chih-Hung Shu, MD, PhD1,2, Kun-Ta Chou, MD2,3,4, Yi-Fen Wang, MD, PhD1,2, Yen-Bin Hsu, MD1,2,4, Ching-Yin Ho, MD, PhD1,2, and Ming-Ying Lan, MD1,2,4

Abstract

Objectives. The pathogenesis of laryngopharyngeal reflux (LPR) remains unclear. It is linked to but distinct from gastroesophageal reflux disease (GERD), which has been shown to be related to disturbed autonomic regulation. The aim of this study is to investigate whether autonomic dysfunction also plays a role in the pathogenesis of LPR.

Study Design. Case-control study.

Setting. Tertiary care center.

Subjects and Methods. Seventeen patients with LPR and 19 healthy controls, aged between 19 and 50 years, were enrolled in the study. The patients were diagnosed with LPR if they had a reflux symptom index (RSI) ≥13 and a reflux finding score (RFS) ≥7. Spectral analysis of heart rate variability (HRV) analysis was used to assess autonomic function. Anxiety and depression levels measured by the Beck Anxiety Inventory (BAI) and Beck Depression Inventory II (BDI-II) were also conducted.

Results. In HRV analysis, high frequency (HF) represents the parasympathetic activity of the autonomic nervous system, whereas low frequency (LF) represents the total autonomic activity. There were no significant differences in the LF power and HF power between the 2 groups. However, significantly lower HF% (P = .003) and a higher LF/HF ratio (P = .012) were found in patients with LPR, who demonstrated poor autonomic modulation and higher sympathetic activity. Anxiety was also frequently observed in the patient group.

Conclusion. The study suggests that autonomic dysfunction seems to be involved in the pathogenesis of LPR. The potential beneficial effect of autonomic nervous system modulation as a therapeutic modality for LPR merits further investigation.

Keywords
laryngopharyngeal reflux, heart rate variability, autonomic nervous system, autonomic dysfunction, gastroesophageal reflux

Received November 23, 2012; revised January 30, 2013; accepted February 20, 2013.

Laryngopharyngeal reflux (LPR) is the backflow of gastric contents (refluxate) to the laryngopharynx and upper aerodigestive tract. This term was adopted by the American Academy of Otolaryngology—Head and Neck Surgery in its 2002 position statement on LPR.1 The symptoms include throat clearing, chronic cough, globus pharyngeus, hoarseness, postnasal drip, dysphagia, dyspnea, laryngospasm, and sore throat. The signs are laryngeal edema, hyperemia, postcommissure hypertrophy, ventricular obliteration, granulation, and pseudosulcus.2,3 Up to 10% of patients visit an otolaryngologist’s office due to symptoms of LPR.2

Establishing the diagnosis of LPR is difficult because of the lack of pathognomonic findings and the variety of other disease states causing similar symptoms. Three approaches have been used to confirm the diagnosis of LPR: (1) response of symptoms to behavioral and empirical medical treatment, (2) endoscopic observation of mucosal injury, and (3) demonstration of reflux events by multichannel impedance and pH monitoring studies.4 The first 2 methods have been shown to lack specificity,5 and pH monitoring also seems to be unreliable, although it was once the gold standard for diagnosing reflux.6 Moreover, studies found that patients with pharyngeal reflux documented by pH monitoring were no more likely to respond
to acid-suppressive therapy than patients with no documented reflux.7,8

Thus far, the pathogenesis of LPR has not been conclusively described. Currently proposed mechanisms include transient relaxation of the lower esophageal sphincter (LES),9 direct damage of gastric juices (acid and pepsin),10,11 more vulnerable laryngeal tissues than esophageal epithelium,2 and pepsin-depleting carbonic anhydrase III of the laryngopharynx, which buffers the gastric acid.12 Laryngopharyngeal reflux and gastroesophageal reflux disease (GERD) are distinct but interlinked diseases.2,13-15 It has been established that the vagus nerve provides parasympathetic control of the gastrointestinal tract.16 Decreased vagal nerve activity, caused by disturbed autonomic regulation, would appear to be responsible for functional LES failure and increased transient lower esophageal sphincter relaxations seen in GERD,17 which results in increasing volume of acidic gastric contents refluxing into the esophagus.18 Whether autonomic dysfunction is also involved in the pathogenesis of LPR remains unknown at this time.

Heart rate variability (HRV) tests are noninvasive methods of evaluating the integrity and functional state of the autonomic nervous system and may be carried out using short-term electrocardiogram (ECG) recordings or long-term measurement (Holter’s ECG). Either the time domain method or frequency domain method in HRV analysis has been used in studies for evaluating the relationship between specific disease and autonomic function.19 Abnormalities in autonomic nervous regulation have been demonstrated in patients with GERD.17,20-23 Since LPR and GERD are interlinked diseases, autonomic nerve dysfunction may play a role in LPR as in GERD pathogenesis.

Patients with anxiety or depression may exaggerate LPR symptoms.24 However, the mental status of LPR patients is rarely assessed. Only limited studies have pointed out that LPR patients were more anxious and had a higher depression score.25,26 In addition, lower HRV has been shown in patients with anxiety or depressive disorders.27,28 To determine the autonomic nervous function and mental status of LPR patients, we evaluated HRV and anxiety and depression status in this study.

Materials and Methods

Patients and Controls

This was a prospective case-control study. The institutional review boards of Taipei Veterans General Hospital approved this study. From April 2011 to August 2011, we prospectively enrolled 2 groups of adult patients (between 19 and 50 years old). One was the healthy control group consisting of 19 healthy employees of our hospital without subjective symptoms. The other group was the patient group (17 subjects) diagnosed with LPR and who had a reflux symptom index (RSI) $\geq 13$ and a reflux finding score (RFS) $\geq 7$. Patients were all newly diagnosed with LPR symptoms for more than 3 months or were patients with relapse and not under current treatment. Those who had diabetes mellitus, glucose intolerance, malignancy, hypertension, cardiac arrhythmia, chest pain with cardiac origin, recent stroke, upper gastrointestinal pathology, or upper abdominal surgery were excluded. Furthermore, all participants denied the usage of drugs with a potential effect on autonomic nervous function, such as antiserotonin drugs, synthetic prostaglandin analogues, cholinergic agonists or antagonists, adrenergic agonists or antagonists, or antiemetic or prokinetic drugs. They also denied smoking and alcohol intake in the 1 month prior to the study. Sex- and age-matched healthy subjects without LPR symptoms represented the control group. Each subject gave written informed consent prior to any study procedures being conducted.

Reflux Symptom Index

All enrolled subjects were asked to complete the RSI proposed by Belafsky et al.29 The RSI is a 0- to 5-point scale that grades the following symptoms: (1) hoarseness or voice problems, (2) throat clearing, (3) excess throat mucus or postnasal drip, (4) difficulty swallowing, (5) coughing after eating or lying down, (6) breathing difficulties or choking spells, (7) troublesome or annoying cough, (8) sensation of something sticking or a lump in the throat, and (9) heartburn, chest pain, indigestion, or stomach acid coming up. The RSI was performed by the enrolled subjects and the result was calculated by an otolaryngologist. On the basis of the analysis by Belafsky et al,29 one can be 95% certain that a patient with an RSI greater than 13 has LPR. Therefore, the patients having an RSI greater than 13 were given further fiber laryngoscopic examination.

Reflux Finding Score

Another otolaryngologist blinded to the result of the RSI performed fiber laryngoscopic examination on the enrolled subjects. The RFS, proposed by Belafsky et al.30 was calculated for each patient. The RFS is an 8-item clinical severity scale for judging laryngoscopic findings. Eight LPR-associated findings were rated on a scale from 0 to 4: subglottic edema, ventricular obliteration, erythema/hyperemia, vocal-fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma, and thick endolaryngeal edema. On the basis of the analysis by Belafsky et al.30 one can be 95% certain that a patient with an RFS of 7 has LPR. The patients with an RFS score less than 7 were excluded from the study. The patients with both RSI greater than 13 and RFS greater than 7 were considered as having LPR.

Heart Rate Variability Analysis

Both the LPR patient group and control group received the heart rate variability analysis. The subjects were instructed to sit quietly in a chair for 10 minutes for adaptation to the environment, which was air-conditioned at a temperature of 25°C. A blood volume pulse (BVP) sensor, placed on the first joint of any finger of the subject in a supine position for 5-minute recordings, detected heart beat by measuring the pulse in a fingertip. The heartbeat signals were recorded in digital format using a BVP amplifier and an 8-bit analog-to-digital converter.
with a sampling rate of 256 Hz. The BVP signals were then processed using a specially designed software algorithm that identified each beat and rejected noise according to their likelihood. The interbeat interval was retrieved, resampled, and interpolated at the rate of 7.11 Hz to construct an evenly sampled smooth contour of heartbeat in the time domain.

The power spectrogram of heartbeat was acquired using the fast Fourier transform of the heartbeat contour. The power spectrum was subsequently quantified into standard power values and frequency domain measurements as defined in the related literature, including a very low-frequency power (VLF, ≤0.04 Hz), low-frequency power (LF, 0.04-0.15 Hz), high-frequency power (HF, 0.15-0.40 Hz), and the ratio of LF to HF (LF/HF). In general, the HF represented the parasympathetic activity of the autonomic nervous system, whereas the LF represented the total autonomic activity. The LF and HF were also presented as a percentage (%), which was the LF or HF component in proportion to the total power. The LF/HF and LF% represented the sympathetic modulation. The HF% represented autonomic modulation. Mean heart rate, individual LF and HF power, LF%, HF%, and LF/HF power ratio were individually measured for all subjects for statistical analysis.

Evaluation of Anxiety and Depression Status
Anxiety was evaluated by the Beck Anxiety Inventory (BAI), a self-reported rating system. The BAI consists of 21 questions about how the subject has been feeling during the past week, expressed as common symptoms of anxiety (such as numbness and tingling, sweating not due to heat, and fear of the worst happening). Each item was scored as 0 = not at all, 1 = mildly, 2 = moderately, and 3 = severely. The BAI has a maximum score of 63. The total scores indicate the following: 0 to 7 = minimal level of anxiety, 8 to 15 = mild anxiety, 16 to 25 = moderate anxiety, and 26 to 63 = severe anxiety. In addition, depression was evaluated by the Beck Depression Inventory II (BDI-II), a self-reported rating system. The BDI-II consists of 21 questions about how the subject has been feeling in the past week. Each question has a set of at least 4 possible answers, ranging in intensity. The item was scored as 0 = I do not feel sad, 1 = I feel sad, 2 = I am sad all the time and I can’t snap out of it, and 3 = I am so sad or unhappy that I can’t stand it. When the test is scored, a value of 0 to 3 is assigned for each answer and then the total score is compared to a key to determine the depression severity. The standard cutoffs are as follows: 0 to 13 = minimal depression, 14 to 19 = mild depression, 20 to 28 = moderate depression, and 29 to 63 = severe depression.

Statistical Analysis
Quantitative data were summarized as mean ± standard deviation (SD) and categorical variables as percentages. Because of skewed distributions, LF and HF were transformed to a logarithm of the absolute units. The Student t test was used to compare parametric variables and the Mann-Whitney U test was used for comparing nonparametric variables between the LPR group and the control group. Statistical comparisons were analyzed using SPSS 12.0 software (SPSS, Inc, an IBM Company, Chicago, Illinois). A P < .05 was considered statistically significant.

Results
The demographic and clinical characteristics of the patients are summarized in Table 1. The average age of the LPR group (11 men, 6 women) was 35.8 years (range, 19-46 years). The average age of the control group (8 men, 11 women) was 32.7 years (range, 25-50 years). There were no statistical differences in age and sex between the 2 groups (P > .05). In the patient group, the average RSI score was 21.5 and the average RFI score was 10.8. In the control group, the average RSI score was 0 and the average RFI score was 1.4. There were statistical differences in RSI and RFS between the 2 groups (P < .05).

Baseline heart rates and parameters of HRV are listed in Table 2. In the patient group, heart rate was 73.45 ± 10.37 beats/min and the interbeat (RR) interval was 13.59 ± 3.12 ms. In the control group, heart rate was 69.62 ± 8.43 beats/min and the RR interval was 14.46 ± 2.16 ms.
no significant difference in baseline heart rate and the RR interval between the 2 groups ($P > .05$).

The LF power of the control and patient groups was $1.93 \pm 0.58$ and $1.88 \pm 0.36$, respectively; the HF power of the control and patient groups was $1.79 \pm 0.74$ and $2.00 \pm 0.40$, respectively. No significant differences in LF power and HF power were noted between the 2 groups ($P > .05$). The LF% of the control and patient groups was $31.11\% \pm 9.26\%$ and $35.62\% \pm 9.47\%$, respectively, and there was also no significant difference in LF% among these 2 groups ($P > .05$). However, the HF% of the control and patient groups was $44.60\% \pm 14.17\%$ and $30.46\% \pm 12.83\%$, respectively, with a significantly higher HF% in the control group ($P = .003$). This implied that poor autonomic modulation was noted in the patient group. The LF/HF ratio of the control and patient groups was $0.87 \pm 0.40$ and $1.79 \pm 0.33$, respectively, and it was significant higher in the LPR group ($P = .013$). This showed that higher sympathetic activity was noted in patients with LPR.

The results of depression and anxiety evaluations by the BDI-II and BAI are shown in Table 1. The depression scores of controls and LPR patients were $3.5 \pm 4.9$ and $8.2 \pm 9.0$, respectively. The scores were not significantly different between these 2 groups. However, the anxiety scores of the controls and LPR patients were $3.2 \pm 4.6$ and $8.1 \pm 6.4$, respectively, which were significantly different ($P = .011$). Patients with LPR appeared to be more anxious than those individuals from the control group.

### Discussion

In 1991, Cunningham et al.\(^{20}\) first showed a high prevalence of autonomic nervous dysfunction among patients with endoscopic esophagitis or abnormal ambulatory pH recordings. The accompanying delayed esophageal transit and abnormal peristalsis were probably due to an abnormality in parasympathetic tone. In 2004, Lee et al.\(^{21}\) found that autonomic tonus was lower in patients with endoscopically confirmed esophagitis (even without symptoms), in comparison with patients with nonerosive esophagitis (NERD). Dobrek et al.\(^{17}\) showed that both GERD and NERD present abnormally lower HF and LF components in resting conditions as compared with healthy controls. Chen et al.\(^{22}\) found that the HF power was significantly lower in patients with erosive esophagitis (ERD) than in NERD patients and controls, and LF% and the LF/HF ratio were significantly lower in NERD patients compared with ERD patients and controls. Similarly, autonomic dysfunction was noted in our LPR patients, who presented with a higher LF/HF power ratio and a lower HF% compared with controls. Since autonomic nerve function controls the gastrointestinal system, disturbed autonomic function will influence esophageal peristalsis, LES function, and gastrectomy motility. Therefore, this may support the hypothesis that transient relaxation of the LES, which might be related to autonomic dysfunction, is one of the factors causing LPR.\(^{9}\)

Laryngopharyngeal reflux and GERD are thought of as a continuum with a similar underlying pathophysiologic mechanism with some overlapping presenting symptoms. However, controversial and longstanding differences between them still exist.\(^{33}\) Most patients with LPR-related laryngitis deny classic symptoms of GERD, particularly heartburn. On the other hand, many LPR patients report lack of endoscopic reflux esophagitis, and the severity of endoscopic esophagitis does not predict the level of LPR symptoms and signs.\(^{13}\) The difference in some symptoms and results of HRV analysis between the 2 diseases may be partly explained by the different severity of autonomic dysfunction. Nevertheless, a disturbed autonomic nervous system could be observed in both LPR and GERD.

The high prevalence of some psychiatric symptoms and abnormal personality traits, such as functional dysphonia, globus hystericus, psychogenic cough, and psychogenic dysphagia, has been reported in conversion disorder, anxiety, and depressive disorder.\(^{34,37}\) Some of the symptoms are similar to those of LPR. Whether or not mental status influences the LPR disease process has seldom been studied. As in our daily practice, conditions of anxiety are frequently observed in LPR patients. This was also shown in our study. However, whether it was the primary cause or secondary consequence of LPRD cannot be proven at this time. Some authors have proposed that stress and anxiety are associated with an increased sympathetic activity and decreased vagal activity.\(^{38,39}\) These and related findings imply that anxiety may lead to unbalanced autonomic function, corresponding to the higher LF/HF ratio as shown in our LPR patients as compared with controls.

### Table 2. Statistical comparison of HRV variables in the control group and patient group.

<table>
<thead>
<tr>
<th>Parameters of HRV</th>
<th>Control (n = 19), Mean ± SD</th>
<th>Patient (n = 17), Mean ± SD</th>
<th>P Value</th>
<th>Mean Difference</th>
<th>95% CI of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>69.62 ± 8.43</td>
<td>73.45 ± 10.37</td>
<td>.230</td>
<td>−3.83</td>
<td>−10.20 to 2.55</td>
</tr>
<tr>
<td>RR interval, ms</td>
<td>14.46 ± 2.16</td>
<td>13.59 ± 3.12</td>
<td>.330</td>
<td>0.87</td>
<td>−0.93 to 2.67</td>
</tr>
<tr>
<td>LF</td>
<td>1.93 ± 0.58</td>
<td>1.88 ± 0.36</td>
<td>.783</td>
<td>−0.05</td>
<td>−0.38 to 0.29</td>
</tr>
<tr>
<td>HF</td>
<td>1.79 ± 0.74</td>
<td>2.00 ± 0.40</td>
<td>.280</td>
<td>0.21</td>
<td>−0.18 to 0.61</td>
</tr>
<tr>
<td>LF %</td>
<td>31.11 ± 9.26</td>
<td>35.62 ± 9.47</td>
<td>.158</td>
<td>−4.51</td>
<td>−10.86 to 1.84</td>
</tr>
<tr>
<td>HF %</td>
<td>44.60 ± 14.17</td>
<td>30.46 ± 12.83</td>
<td>.003(^a)</td>
<td>14.15</td>
<td>4.96 to 23.35</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.87 ± 0.40</td>
<td>1.79 ± 1.33</td>
<td>.013(^a)</td>
<td>−0.92</td>
<td>−1.63 to −0.22</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HF, high-frequency power; HRV, heart rate variability; LF, low-frequency power; LF/HF, ratio of LF to HF; RR interval, interbeat interval. LF and HF are expressed in logarithmic scale of ms\(^2\).\(^{6}\)

\(\*P < .05\) indicates a statistically significant difference.
Treatment of LPR includes diet and lifestyle changes and proton pump inhibitor usage. If the autonomic system is related to the etiology of LPR, restoration of autonomic dysfunction could be a possible treatment for these patients. Some authors have claimed that regular exercise, including tai chi, and HRV biofeedback have had a positive impact on both the sympathetic and parasympathetic nervous activities. Restoration of the autonomic dysfunction may be implemented into therapeutic programs for patients with LPR.

Although few studies have investigated the relationship between GERD and autonomic function, this is the first preliminary study to identify the relationship between LPR and autonomic function. We discovered that autonomic dysfunction may play a role in the pathogenesis of LPR. Currently, there is still not a standard method to diagnose LPR. The limitation of this study is that the approach in which we enrolled LPR patients with an RSI greater than 13 and an RFS greater than 7 may not be the best method. Simultaneous 24-hour HRV analysis with multichannel impedance and pH monitoring that demonstrates both acid and non–acid reflux in the laryngopharyngeal region may help to confirm a causal relationship between LPR and disturbed autonomic nervous function. Further studies with a large series of patients may show more significant differences in HRV analysis between the 2 groups. Furthermore, the HRV analysis could be performed again in patients who show improvement with regard to symptoms after a course of treatment to better determine if there are any changes in autonomic function. The potential beneficial effect of autonomic nervous system modulation in patients with LPR also merits further investigation.

**Conclusion**

The results of this study suggest that autonomic dysfunction may appear to play a role in the pathogenesis of LPR. Enrollment with a large series of patients and implementation of autonomic modulation as a therapeutic method for patients with LPR are needed in the future to confirm our initial findings and to expand on this research.

**Author Contributions**

Wan-Ju Huang, conducting HRV analysis, manuscript writing; Chih-Hung Shu, study design; Kun-Ta Chou, statistical analysis; Yi-Fen Wang, conducting the laryngoscope examination; Yen-Bin Hsu, conducting the laryngoscope examination; Ching-Yin Ho, conducting the laryngoscope examination; Ming-Ying Lan, study design, statistical analysis, article revision.

**Disclosures**

Competing interests: None.

Sponsorships: None.

Funding source: None.

**References**


