Esophageal Functional Changes in Obstructive Sleep Apnea/Hypopnea Syndrome and Their Impact on Laryngopharyngeal Reflux Disease

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Background: Obstructive sleep apnea/hypopnea syndrome (OSAHS) and laryngopharyngeal reflux (LPR) disease have a high comorbidity rate, but the potential causal relation between the two diseases remains unclear. Our objectives were to investigate the esophageal functional changes in OSAHS patients and determine whether OSAHS affects LPR by affecting esophageal functions.

Methods: Thirty-six OSAHS patients and 10 healthy controls underwent 24-h double-probed combined esophageal multichannel intraluminal impedance and pH monitoring simultaneously with polysomnography. High-resolution impedance manometry was applied to obtain a detailed evaluation of pharyngeal and esophageal motility.

Results: There were 13 OSAHS patients (36.1%) without LPR (OSAHS group) and 23 (63.9%) with both OSAHS and LPR (OSAHS and LPR group). Significant differences were found in the onset velocity of liquid swallows (OVL, \( P = 0.029 \)) and the percent relaxation of the lower esophageal sphincter (LES) during viscous swallows (\( P = 0.049 \)) between the OSAHS and control groups. The percent relaxation of LES during viscous swallows was found to be negatively correlated with upright distal acid percent time (\( P = 0.016, R = −0.507 \)), and OVL was found to be negatively correlated with recumbent distal acid percent time (\( P = 0.006, R = −0.557 \)) in the OSAHS and LPR group.

Conclusions: OSAHS patients experience esophageal functional changes, and linear correlations were found between the changed esophageal functional parameters and reflux indicators, which might be the reason that LPR showed a high comorbidity with OSAHS and why the severity of the two diseases is correlated.

Key words: Esophageal Function; Laryngopharyngeal Reflux Disease; Obstructive Sleep Apnea/Hypopnea Syndrome

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Accepted for publication by the American Academy of Otolaryngology – Head and Neck Surgery in 2002, laryngopharyngeal reflux (LPR) is the backflow of gastric contents to the laryngopharynx and upper aerodigestive tract.\(^{[4,7]}\) LPR was believed to be a manifestation of gastroesophageal reflux disease (GERD),\(^{[3]}\) causing hoarseness, globus, dysphagia, cough/throat clearing, and excessive throat mucus. LPR affects 4–10% of patients in otolaryngology.\(^{[9]}\)

Both OSAHS and LPR are extremely harmful to human health, and the coexistence of the two diseases is 45.4%;\(^{[2]}\) however, the potential causal relation between the two diseases remains under debate. It has been reported that OSAHS patients have more reflux events than the healthy controls, and continuous positive airway pressure therapy can reduce the occurrence of nocturnal reflux events;\(^{[10,11]}\) but no explicit correlation was found between reflux...
events and apnea. Our team also found a correlation between the severity of OSAHS and reflux, but no clear corresponding relation was found between reflux events and apnea.

It was proved that chronic neuromuscular injury exists in the genioglossus muscle of OSAHS patients, and reduction in the activity of the upper-airway dilators contribute to OSAHS development. In addition, esophageal motility abnormalities are among the main factors implicated in the pathogenesis of GERD. Our aims for this study were to investigate the esophageal functional changes in OSAHS patients and determine whether OSAHS affects LPR by affecting esophageal functions.

**Methods**

**Subjects and study design**

This study was conducted at Department of Otolaryngology, Beijing Tongren Hospital, China, between January 2011 and December 2014. Signed informed consent was received from all study participants, and the study protocol was approved by the ethics committee of the hospital.

Ten healthy volunteers (mean age 45 ± 4 years, 5 females) and 36 OSAHS patients (mean age 47 ± 2 years, 5 females) were enrolled in this study. All healthy volunteers were between 18 and 70 years old and none had any snoring issues or LPR symptoms, such as hoarseness, dysphagia, globus, regurgitation, heartburn, cough/throat clearing, or excessive throat mucus, within 2 months of the study or experienced these conditions only very mildly. All OSAHS patients also ranged in age from 18 to 70 years and had symptoms of apnea and daytime sleepiness. Patients with a history of severe systemic diseases, laryngopharyngeal surgery, or hiatal hernia were excluded from the study. Those who had received any treatments for OSAHS or LPR were also excluded.

The medical history of all participants was carefully recorded by one ENT doctor to obtain a reflux symptom index. A complete endoscopic examination of the upper-airway was performed by the same ENT doctor while the reflux finding scores of the patients were determined. High-resolution impedance manometry was used to obtain a detailed evaluation of pharyngeal and esophageal motility, and the location of the upper esophageal sphincter (UES), and the lower esophageal sphincter (LES). All patients underwent polysomnography (PSG) testing on the same night with double-probed 24-h combined esophageal multichannel intraluminal impedance and pH (MII-pH) monitoring.

Patients with OSAHS were divided into two groups according to the 24-h MII-pH monitoring as follows: OSAHS only and both OSAHS and LPR (OSAHS and LPR). Eighty-four esophageal functional indicators were compared among the OSAHS groups and the control. Correlations were tested between the selected esophageal functional indicators and reflux parameters in the OSAHS and LPR group.

**Esophageal function testing**

High-resolution impedance manometry using the Sandhill esophageal function test (EFT) catheter 38-channel probe (Sandhill Scientific Inc., Highlands Ranch, CO, USA) was inserted into all study participants after an overnight fast for an EFT. The 4.5 mm – diameter catheter has 32 circumferential solid-state pressure sensors spaced at 1.0-cm intervals. Impedance measuring segments consisted of two metal rings placed 2.0 cm apart, centered at 10, 15, 20, and 25 cm from the tip [Figure 1]. Each catheter was put into the esophagus passing through the nose to a depth of 60 cm. It was then pulled slowly upward until the most distal sensor was seated in the high-pressure zone of LES. The intraesophageal pressure sensors and impedance measuring segments were subsequently located 5 (distal), 10 (midway 2), 15 (midway 1), and 20 (proximal) cm above LES. Following at least a 30-s baseline reading to identify UES and LES, 105.0-ml saline and 105.0-ml viscous swallows at least 30 s apart were performed with the patient in a supine position. The esophageal functional indicators of saline and viscous swallows were analyzed separately.

**Ambulatory pH monitoring**

Ambulatory 24-h MII-pH monitoring was applied to all participants using a ZepHR recorder and the Sandhill ZAI-BL-48E double-probed catheter (Sandhill Scientific Inc., Highlands Ranch, CO, USA). Each probe carried one antimony pH electrode and several impedance electrodes. Each pair of adjacent electrodes represents an impedance-measuring segment (2.0 cm long). EFT was performed before MII-pH monitoring to detect the locations of LES and UES. A pharyngeal probe was placed 1 cm above the superior border of UES, and the esophageal probe was placed 5 cm above LES through the nose. Data were stored in a portable receiver with an impedance amplifier. Participants were required to record their meals, body position changes, and any symptoms.

LPR was considered to be positive when at least one of the following criteria was met: (1) Total acid exposure time (%) >0.1%, (2) acid exposure time (%) in upright position >0.2%, (3) acid exposure time (%) in supine position >0.0%, and (4) acid reflux number ≥4.

![Figure 1: High-resolution impedance manometry catheter.](image)
Polysomnography
All the participants underwent diagnostic sleep studies during the 24-h MII-pH monitoring period using an ambulatory Embla S4000 recorder (SASN Medical Supplies Co., Ltd., China). Nasal airflow, oxyhemoglobin saturation, body position, and thoracic and abdominal movements were recorded overnight. Apnea episodes were defined as complete cessation of airflow lasting at least 10 s. Hypopnea was defined as at least a 50% reduction in airflow for at least 10 s accompanied by a reduction in SO2 of at least 4%. AHI was defined as the number of events of apnea or hypopnea per hour during sleep time based on the results of the overnight PSG. The participants with an AHI ≥5 events/h and with associated symptoms were considered to be OSAS-positive cases, according to the American Association of Sleep Medicine criteria.[1]

Statistical analyses
Statistical analyses were performed using SPSS 20.0 (IBM Corporation, Chicago, IL, USA). Data having a normal distribution were presented as the mean ± standard deviation (SD). The data having nonnormal distribution were presented as the median (M) and the 25% and 75% percentiles (P25, P75). For normally distributed data, independent t-tests were used to compare the esophageal functional parameters among the OSAHS groups and the control and one-way analysis of variance (ANOVA) was used to compare the normally distributed parameters among the three groups. For data in nonnormal distribution, the Mann–Whitney U-test was used to compare the differences among the groups. Pearson’s coefficient and Spearman’s coefficient were used to analyze the associations between normally distributed and nonnormally distributed variables of interest with reflux indicators, respectively. P < 0.05 was considered to be statistically significant.

Results
Demographics and characteristics
Thirteen patients were diagnosed with having only OSAHS (49 ± 2 years old, 1 female), and 23 patients were diagnosed with having both OSAHS and LPR (46 ± 2 years old, 4 females). The demographic characteristics, main PSG, and reflux indicators of the participants are provided in Table 1. No significant differences were found in the mean ages among the three groups. The body mass index (BMI) in the OSAHS and LPR disease group was significantly higher than that in the control (P = 0.01).

Esophageal functional parameters
Eighty-four esophageal functional parameters were compared between the OSHAS group and the control. To exclude the impact of LPR, the esophageal functional indicators were compared between the patients with OSAHS only and the control instead of all 36 OSAHS patients and the control. Table 2 shows the comparison of some main indicators of esophageal function in the healthy controls and the OSAHS patients. Other parameters of esophageal function were also compared, but no significant differences were found.

Correlation between esophageal function and reflux parameters
Correlations were tested between the indicators selected above and the indicators for reflux severity in patients in the OSAHS and LPR group. Significant correlations were found among these parameters and some of the reflux indicators. Table 3 shows the correlation among the selected parameters and the severity of reflux in the OSAHS and LPR group. Figure 2 shows the correlation between onset velocity of liquid (OVL) swallows and the percent time of recumbent distal acid episodes. Figure 3 shows the correlation between LES percent relaxation of viscous swallows and the longest upright distal acid episodes.

Correlation between esophageal function and obstructive sleep apnea/hypopnea syndrome severity
Correlations were tested between OSAHS severity and the selected esophageal functional parameters in the OSAHS group and the OSAHS and LPR group; however, no significant correlations were found between the severity of OSAHS and the changed esophageal functional indicators. Table 4 shows the correlations between OSAHS severity and

| Parameters       | Control (n = 10) | OSAHS (n = 13) | OSAHS and LPRD (n = 23) | P      |
|------------------|-----------------|----------------|-------------------------|--------|
| Age (years)      | 44.70 ± 11.86   | 49.23 ± 8.64   | 46.22 ± 10.49           | 0.552  |
| Height (m)       | 1.67 ± 0.078    | 1.72 ± 0.053   | 1.70 ± 0.067            | 0.259  |
| Weight (kg)      | 65.50 ± 12.37   | 77.54 ± 9.01   | 81.22 ± 14.21           | 0.008* |
| BMI (kg/m²)      | 23.33 ± 2.81    | 26.31 ± 2.70   | 28.03 ± 3.52            | 0.001* |
| AHI (events/h)   | 1.20 (0.15, 4.28)| 21.55 (15.25, 29.65) | 36.7 (9.80, 54.90)      | 0.000** |
| ODI (events/h)   | 0.80 (0.15, 3.00)| 20.70 (15.75, 28.73) | 33.12 ± 5.40            | 0.000** |
| ASAT (%)         | 96.74 ± 0.34    | 95.20 (94.23, 96.05) | 94.4 (93.60, 95.60)      | 0.000** |
| LSAT (%)         | 93.20 ± 0.70    | 82.67 ± 1.94   | 79.26 ± 1.74            | 0.000* |
| RSI              | 6.00 (2.75, 10.75)| 6.83 ± 1.23   | 15.79 ± 2.36            | 0.008** |
| RFS              | 3.80 ± 0.70     | 4.25 ± 0.50    | 8.11 ± 0.79             | 0.000* |
| PARN (events)    | 0.00 (0.00, 0.03)| 2.25 ± 0.81   | 15.05 ± 2.03            | 0.026** |

*Statistically significant (P<0.05); †Mann-Whitney U-test was used for the comparison. Normally distributed data were presented as the mean ± SD, nonnormally distributed data were presented as median (P25, P75). BMI: Body mass index; AHI: Apnea-hypopnea index; ODI: Oxygen desaturation index; ASAT: Average oxygen saturation; LSAT: Lowest oxygen saturation; RSI: Reflux symptom index; RFS: Reflux finding score; PARN: Proximal acid reflux number; SD: Standard deviation; OSAHS: Obstructive sleep apnea/hypopnea syndrome; LPRD: Laryngopharyngeal reflux disease.
esophageal function in the OSAHS group. The correlations between OSAHS severity and esophageal functions in the OSAHS and LPR group are provided in Table 3.

**Polysomnography parameters**

Polysomnography parameters were compared between the OSAHS and OSAHS and LPR groups. The percentage of time with oxygen saturation below 90% was significantly different between the OSAHS and OSAHS and LPR groups; however, there were no significant differences in other OSAHS severity indicators between the two groups.

Table 2: Esophageal functional parameters in the control and OSAHS groups

| Variables                              | Control (n = 10) | OSAHS (n = 13) | P  |
|----------------------------------------|-----------------|----------------|----|
| Onset velocity of liquid swallowing (cm/s) | 5.78 ± 1.83     | 4.31 ± 1.16    | 0.029* |
| UES recovery of viscous swallowing (ms) | 610.10 ± 106.20 | 527.23 ± 171.50 | 0.195 |
| LES percent relaxation of viscous swallowing (%) | 66.90 ± 8.56     | 93.00 (72.50, 99.00) | 0.049* |
| Liquid amplitude of mid 1 esophagus (mmHg) | 44.90 ± 7.74     | 67.39 ± 8.55   | 0.073 |
| Viscous amplitude of mid 1 esophagus (mmHg) | 75.50 ± 15.70    | 74.00 (64.00, 88.00) | 0.067* |

*Statistically significant (P<0.05); †Mann-Whitney U-test was used for the comparison. Normally distributed data were presented as the mean ± SD, nonnormally distributed data were presented as median (P25, P75). UES: Upper esophageal sphincter; LES: Lower esophageal sphincter; Amplitude of mid 1 esophagus: The amplitude of contraction at 15 cm above LES; SD: Standard deviation; OSAHS: Obstructive sleep apnea/hypopnea syndrome.

**Table 3: Correlations between esophageal function and disease severity in OSAHS and LPR**

| Parameters          | Onset velocity of liquid swallowing | LES percent relaxation of viscous swallowing |
|---------------------|------------------------------------|---------------------------------------------|
|                     | P       | r       | P       | r       |
| DeMeester score     | 0.051   | −0.412  | 0.031   | −0.452* |
| UDAE time (%)       | 0.508   | −0.149  | 0.016   | −0.507* |
| RDAE time (%)       | 0.006   | −0.557† | 0.259   | −0.245  |
| Longest RDAE        | 0.009   | −0.530† | 0.397   | −0.185  |
| Longest UDAE        | 0.259   | −0.246  | 0.008   | −0.541† |
| AHI                 | 0.395   | −0.186  | 0.698   | −0.085  |
| ODI                 | 0.605   | −0.117  | 0.584   | −0.124  |
| LSAT                | 0.743   | 0.072   | 0.719   | −0.079  |
| ASAT                | 0.554   | 0.134   | 0.587   | 0.122   |
| CT90                | 0.886   | 0.034   | 0.886   | −0.034  |
| BMI                 | 0.749   | −0.071  | 0.274   | −0.238  |

*Statistically significant (P<0.05); †Statistically significant (P<0.01); Pearson’s coefficient was used to analyze the associations. AHI: Apnea-hypopnea index; ODI: Oxygen desaturation index; LSAT: Lowest oxygen saturation; ASAT: Average oxygen saturation; CT90: Percentage of time with oxygen saturation below 90%; UDAE: Upright distal acid episodes; RDAE: Recumbent distal acid episodes; OSAHS: Obstructive sleep apnea/hypopnea syndrome; LPR: Laryngopharyngeal reflux; LES: Lower esophageal sphincter; BMI: Body mass index.

Table 5 shows the comparison of PSG parameters between both groups.

**Discussion**

This study focused mainly on the potential correlation between OSAHS and LPR in esophageal function. We found that some of the esophageal functional parameters were significantly different between OSAHS patients and the controls and were significantly correlated with some of the reflux parameters when OSAHS and LPR coexisted.

Researchers have pointed out that OSAHS has a high comorbidity with LPR,[23] however, the relation between OSAHS and LPR remains under debate. It was found that there were certain consistencies between the severity of reflux and OSAHS based on a questionnaire,[20] whereas studies have not shown a direct temporal link between apneic and LPR events.[13] Mechanisms by which the two diseases are associated include large negative intrathoracic pressure swings generated during obstructive apneas and respiratory-related arousals, which appear to be associated with LES relaxation, and laryngeal sensory dysfunction.[10,11,21] It has been reported that the prevalence of LPR among OSAHS patients is higher than that in the general population.[12,13,14] Our study had similar findings. A 63.9% LPR coexist rate was found among patients with snoring problems.

Given that upper-airway muscular hypotonia exists in OSAHS patients,[3,12] and esophageal motility abnormalities were found in reflux diseases,[8,16] we suspect that OSAHS patients might have esophageal functional disorders, which might be the reason that LPR showed a high comorbidity with OSAHS, and esophageal function might be one of the points that join the two diseases together. Kuribayashi et al.[10] simultaneously applied high-resolution manometry, impedance and pH recordings, and PSG to 26 patients with OSAHS and/or GERD to obtain the pressure changes in UES and the gastroesophageal junction during apneic periods, but the transmission and clearance functions of the esophagus were not measured.

![Figure 2: Correlation between onset velocity of liquid swallowing and recumbent distal acid episodes percent time.](Image 314x85 to 534x261)
Onset velocity of viscous swallowing and longest upright distal acid episodes.

**Figure 3:** Correlation between lower esophageal sphincter percent relaxation of viscous swallowing and longest upright distal acid episodes.

**Table 4: Correlations between esophageal functional parameters and OSAHS severity in OSAHS patients**

| Parameters                      | Onset velocity of liquid swallowing | LES percent relaxation of viscous swallowing |
|---------------------------------|------------------------------------|---------------------------------------------|
|                                 | \( P \) | \( r \) | \( P \) | \( r \) |
| AHI (events/h)                  | 0.459  | 0.225  | 0.303  | −0.310 |
| ODI (events/h)                  | 0.590  | 0.165  | 0.327  | −0.296 |
| LSAT (%)                        | 0.786  | 0.084  | 0.152  | 0.421  |
| ASAT (%)                        | 0.595  | −0.163 | 0.695  | 0.120  |
| CT90 (%)                        | 0.931  | 0.028  | 0.982  | −0.007 |
| BMI                             | 0.180  | −0.396 | 0.345  | −0.285 |

Statistically significant \( P < 0.05 \). AHI: Apnea-hypopnea index; ODI: Oxygen desaturation index; LSAT: Lowest oxygen saturation; ASAT: Average oxygen saturation; CT90: Percentage of time with oxygen saturation below 90%; OSAHS: Obstructive sleep apnea/hypopnea syndrome; LES: Lower esophageal sphincter; BMI: Body mass index.

**Table 5: Polysomnography parameters in patient groups**

| Parameters                      | OSAHS \((n = 13)\) | OSAHS and LPRD \((n = 23)\) | \( P \) |
|---------------------------------|---------------------|-------------------------------|--------|
| AHI (events/h)                  | 21.55 (15.25, 29.65) | 36.7 (9.80, 54.90) | 0.434  |
| ODI (events/h)                  | 20.70 (15.75, 28.73) | 33.12 ± 5.40 | 0.601  |
| ASAT (%)                        | 95.11 ± 1.40        | 94.4 (93.60, 95.60) | 0.159  |
| LSAT (%)                        | 82.67 ± 6.71        | 79.26 ± 1.74 | 0.893† |
| CT90 (%)                        | 1.05 (0.05, 4.25)   | 6.65 (0.93, 11.90) | 0.032* |

*Statistically significant \( P < 0.05 \). †Independent \( t \)-test was used for the comparison. Normally distributed data were presented as mean ± SD, nonnormally distributed data were presented as median (P25, P75). AHI: Apnea-hypopnea index; ODI: Oxygen desaturation index; ASAT: Average oxygen saturation; LSAT: Lowest oxygen saturation; OSAHS: Obstructive sleep apnea/hypopnea syndrome; LPRD: Laryngopharyngeal reflux disease; CT90: Percentage of time with oxygen saturation below 90%; SD: Standard deviation.

In this research, the OVL swallows was found significantly different between the healthy control and OSAHS groups. Calculated from the two most distal analysis channels, the OVL swallows is an indicator for the distal esophageal contraction. Although this parameter could be accepted as normal in OSAHS patients, the two diseased groups appeared to have an OVL lower than that of the healthy control. In addition, OVL showed a linear relation with some of the reflux indicators that appears to prevent reflux in the patients with both LPR and OSAHS. Similarly, LES percent relaxation of viscous swallows was found significantly different between OSAHS patients and healthy people and was also found correlated with some of the reflux parameters when OSAHS and LPR coexist. These results revealed that esophageal functional changes exist in OSAHS patients, and some of the changed esophageal functional parameters are correlated with reflux indicators in patients with both OSAHS and LPR. This might explain why the occurrence of LPR in OSAHS patients is high, and why the severity of the two diseases is correlated; however, the changed parameters were considered to be normal according to the normal range. In addition, individual differences exist among OSAHS patients. In our study, BMI was significantly higher in the OSAHS and LPR group than in the OSAHS and control groups. However, BMI showed no correlation with the changed esophageal functional parameters.

To our knowledge, the esophageal functional changes and the reason that they changed in OSAHS patients remain unclear, but it has been proved that the upper-airway dilator dysfunction exists in OSAHS patients. Upper-airway dilators are mainly innervated by the pharyngeal branch of vagus and trigeminal nerves. Composed of the cricopharyngeus and inferior pharyngeal constrictor, UES is mainly innervated by the glossopharyngeal nerve and branches of the vagus and accessory nerves, and LES is innervated by the enteric nervous system of the vagus nerve. Thus, the upper-airway dilators and the esophageal sphincters are affected by the vagus nerve and might share the same regulatory mechanisms. Repeated apnea, oxygen desaturation, and sleep fragmentation during sleep might cause autonomic dysfunction, which might impact vagus nerve function and subsequently, impact esophageal functions. Further researches are needed to reveal the mechanism by which the function or dysfunction of the vagus nerve influences the function of the esophageal sphincter.

This study was limited by sample size. Additional larger, long-term studies are needed to determine whether a causal relationship exists between the two diseases. There are also several deficiencies in this study. First, sex differences were not excluded in this study. Because we had female patients with OSAHS, we also enrolled female volunteers into the control group.

In conclusion, obstructive sleep apnea/hypopnea syndrome patients exhibit esophageal functional changes, which might be why LPR showed a high comorbidity with OSAHS. Linear correlations were found between some of the changed esophageal functional parameters and reflux indicators, which might explain why the severity of these two diseases is correlated.
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