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Original Article

Correlation analysis of gastroesophageal reflux disease and obstructive sleep apnea hypopnea syndrome

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Abstract: Objective: This study aimed to investigate the sleep quality and sleep respiratory conditions at night in patients with various level of gastroesophageal reflux disease (GERD) before and after conventional treatments. Methods: 40 patients with GERD were further divided into the non-erosive reflux disease (NERD) group and the reflux esophagitis (RE) group. 20 healthy people were enrolled as control group. The Pittsburgh Sleep Quality Index (PSQI) was used for evaluate sleep quality and video polysomnography (PSG) was used to assess the sleep respiratory conditions in all patients. PSG was rechecked at the third month after treatment, and the variation of apnea hypopnea index (AHI), the lowest oxygen saturation ($LSaO_2$), mean oxygen saturation ($MSaO_2$), and wakening times (WT) before and after treatments were detected. Results: There were significant differences of PSQI scores between GERD group and healthy control group ($P<0.05$). GERD could increase the incidence of obstructive sleep apnea-hypopnea syndrome (OSAHS), but its severity was not associated with the degree of OSAHS. There was no significant difference of OSAHS incidence and severity between RE group and NERD group ($P>0.05$). Furthermore, there was significant difference of the variation of $MSaO_2$, frequency of awakening and apnea hypopnea, $LSaO_2$ and AHI in RE and NERD group before and after treatments, but no significant difference of the OSAHS incidence. Conclusion: There is sleep apnea with variant degrees in GERD patients, and the sleep apnea can be improved after the GERD controlled.

Keywords: Gastroesophageal reflux disease, obstructive sleep apnea hypopnea syndrome, Pittsburgh sleep quality index, lowest oxygen saturation

Introduction

Gastroesophageal reflux disease (GERD) is an uncomfortable symptom or complication caused by stomach and duodenal content reflux. GERD is one of the most common gastrointestinal diseases worldwide [1, 2]. It has been recognized that GERD can be classified as non-erosive reflux disease (NERD) and reflux esophagitis (RE). NERD is characterized by some symptoms related to sick reflux without evidence of endoscopic mucosa lesions. RE refers to esophageal mucosa damage seen with endoscope. Except typical manifestations including heartburn and reflux, GERD patients may also represent extra-esophageal symptoms such as retrosternal pain, non-cardiogenic chest pain, sphagitis, cough, asthma and sleep disorder [3]. Currently, GERD has been proved to have a relationship with insomnia, but the relationship between GERD and other sleep disorders such as obstructive sleep apnea-hypopnea syndrome (OSAHS) is still unclear [4]. The latest research suggested that OSAHS was a kind of sleep disorders associated with GERD [5]. Therefore, this study investigated the correlation between GERD and OSAHS.

Patients and methods

Patients and treatment

A total of 40 patients with GERD from gastroenterology clinics in the second affiliated hospital of Nanchang university from June 2014 to October 2015 were enrolled. All the GERD patients were with symptoms such as heart-

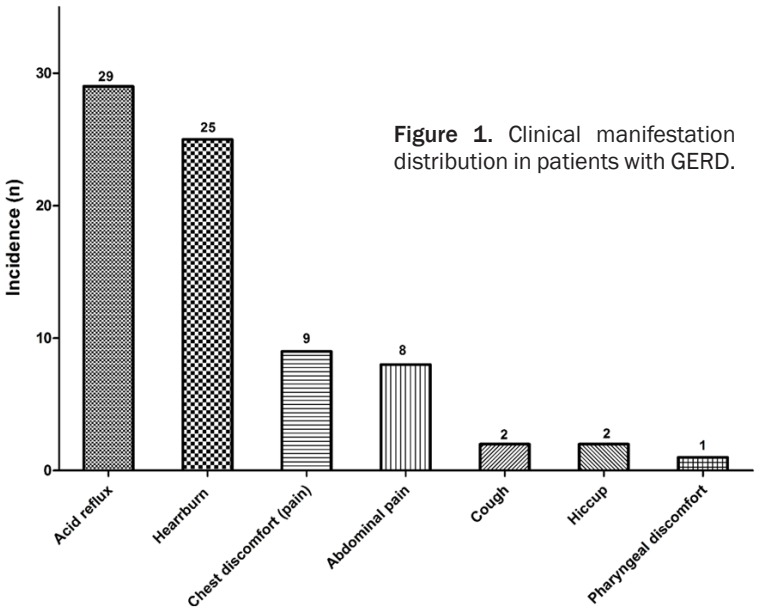

Figure 1. Clinical manifestation distribution in patients with GERD.

Table 1. Demographic characteristics

	GERD (n=40)	Control group (n=20)	*P* value
Age (years)	52.45±11.31	50.05±12.30	0.455
Gender (n, %)			
Male	19 (47.5%)	10 (50.0%)	0.536
Female	21 (52.5%)	10 (50.0%)	
Smoking (n, %)	13 (32.5%)	5 (25.0%)	0.388
Drinking (n, %)	11 (37.5%)	6 (30.0%)	0.534
Education level (above junior school)	29 (72.5%)	10 (50.0%)	0.076
Body mass index (kg/m^2)	24.63±3.89	23.01±3.63	0.127

Notes: GERD: Gastroesophageal reflux disease.

burn and reflux, or with reflux esophagitis through gastroscopy or patients with Barrett esophagus. Meanwhile, patients with a history of gastrointestinal surgery, peptic ulcer, stomach and duodenal neoplasm, psychological illness or mental disorders, and other chronic systemic diseases were excluded. All GERD patients were divided into NERD (n=20) and RE (n=20) group according to the 2013 International GERD Guideline, clinical manifestation and endoscopic results. In RE group, two patients were with Barrett esophagus. A total of 20 healthy adults were enrolled as control group. All patients in three groups were tested with PSQI sleep quality evaluation and polysomnography (PSG) sleep monitoring. GERD patients were continuously treated by proton-pump inhibitors, and then they were rechecked with PSG after three months.

Criteria of PSQI score

PSQI scale was used to evaluate the sleep conditions of patients, which consisted of seven contents: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disorders, medication and functional state in the daytime [6]. The time for falling asleep over 30 min represented the prolonged sleep latency, and the frequency of awakening at night for at least twice or early morning awakening represented sleep disorders. Superficial sleep and dreaminess represented the decrease of sleep quality, and sleep time less than 6 h daily represented shorten of total sleep duration. Diurnal residual effect was presented with dizzy, depressed, drowsiness, weak and so on at the following morning. Any abnormality of sleep quality indicated sleep disorders. Each factor was marked by 0-3 scores with the total of 0-21 scores. The higher the score was, the worse the sleep quality was. In addition, PSQI≥8 score indicated sleep disorders.

PSG

The present measures to diagnose GERD related sleep disorders cannot embody the sleep condition of GERD patients directly. Here, video PSG is a sleep monitoring instrument, which can be able to monitor, record and analyze electroencephalogram, electrocardiogram, leg myoelectricity, jaw electromyography (EMG), electromyogram, mouth-nose flow, breathing movement, position, snore, and finger oxygen saturation during evening sleep (monitoring duration>7 h). Now, the golden standard to diagnose OSAHS is PSG. Specifically, OSAHS can be confirmed in case, more than 30 times of recurrent apnea and hypopnea occur during at least 7 hours sleep at every night, or AHI≥5, and apnea is mainly obstructive. OSAHS guideline should be referenced to judge its severity.

Table 2. Demographic characteristics in NERD, RE and control group

	NERD (n=20)	RE (n=20)	Control (n=20)	*P* value
Age (years)	50.45±9.75	54.45±12.61	50.05±12.30	0.144
Gender (n, %)				
Male	8 (40.0%)	11 (55.0%)	10 (50.0%)	0.627
Female	12 (60.0%)	9 (45.0%)	10 (50.0%)	
Smoking (n, %)	4 (20.0%)	9 (45.0%)	5 (25.0%)	0.189
Drinking (n, %)	6 (30.0%)	5 (25.0%)	6 (30.0%)	0.534
Education level (above junior school)	12 (60.0%)	6 (30.0%)	10 (50.0%)	0.076
Body mass index (kg/m^2)	24.63±3.89	23.01±3.63	23.01±3.63	0.127

Notes: NERD, Non-erosive reflux disease; RE, Erosive reflux disease.

Table 3. PSQI scores in each group

Group	n	PSQI score
GERD group	40	5.97±3.64
NERD group	20	5.45±3.33
RE group	20	6.50±3.94
Control group	20	2.85±2.18

Notes: GERD, Gastroesophageal reflux disease; NERD, Non-erosive reflux disease; RE, Erosive reflux disease; PSQI, Pittsburgh Sleep Quality Index; P1 represented GERD group and control group; P2 represented NERD group and RE group; P3 represented RE group and healthy control group; P4 represented NERD group and control group. When PSQI comparing in each group P valves were P1=0.001, P2=0.309, P3=0.001 and P4=0.014. When GERDQ comparing in each group, *P* values were P1=0.001, P2=0.309, P3=0.001 and P4=0.014.

mild: AHI 5~15, $LSaO_2$>86%; moderate: AHI15-30, $LSaO_2$ of 80%-85%; Severe: AHI>30, $LSaO_2$≤79% [7].

Statistical methods

Data were statistically analyzed with SPSS13.0 software, and measurement data was presented as mean ± standard deviation. Besides, one-way analysis of variance, multiple comparisons, independent-samples T test, Pearson relevant analysis, chi-square test, Bonferroni test, and paired T test were used for data analysis. Non-parametric test was used to analyze the ranked data. *P* values were two-sided with a level of significance of 0.05.

Results

Clinical manifestations in patients with GERD

The heartburn (n=25) and acid reflux (n=29) were the major clinical manifestations in GERD patients (n=40). However, plenty of patients were often accompanied with retrosternal pain/discomfort, epigastric pain/distention, cough, hiccup, throat discomfort and so on. The specific manifestation distribution was shown in **Figure 1**.

Demographic characteristics

A total of 40 patients were enrolled in GERD group in which male/female ratio was 19/21 with an age range of 52.45±11.31 years old and the body mass index (BMI) was 24.63±3.89 kg/m^2. In control group, male/female ratio was 10/10 with an age range of 50.05±12.30 years old and the BMI was 23.01±3.63 kg/m^2. There was no statistically significant difference of gender, smoking, drinking and education between GERD group and control group (all *P*>0.05) (**Table 1**). Comparing with control group, there was no significant difference of age, weight index, gender, smoking, drinking, and education in NERD and RE group (all *P*>0.05) (**Table 2**).

PSQI scores

PSQI scores in GERD group and control group were 5.97±3.64 and 2.85±2.18 respectively, and the difference was significant (*P*<0.05) (**Table 3**). There was no significant difference between NERD group and RE group (*P*>0.05).

Sleep apnea before and after treatment

The incidence rates of OSAHS in NERD group, RE group and healthy control group were 65%, 70% and 0% respectively, and the incidences of OSAHS in NERD group and RE group were approximate (*P*>0.05). PSG was followed up at third months after conventional treatments.

Table 4. Incidence of OSAHS before and after treatment in NERD and RE group

Group	NERD (n=20)			RE (n=20)		
	Pre-treatment	Post-treatment	*P* value	Pre-treatment	Post-treatment	*P* value
OSAHS	13 (65.0%)	9 (45%)	0.17	14 (70.0%)	12 (60.0%)	0.371
Non-OSAHS	7 (35.0%)	11 (55.0%)		6 (30.0%)	8 (40.0%)	

Notes: NERD, Non-erosive reflux disease; RE, Erosive reflux disease; OSAHS, Obstructive sleep apnea-hypopnea syndrome.

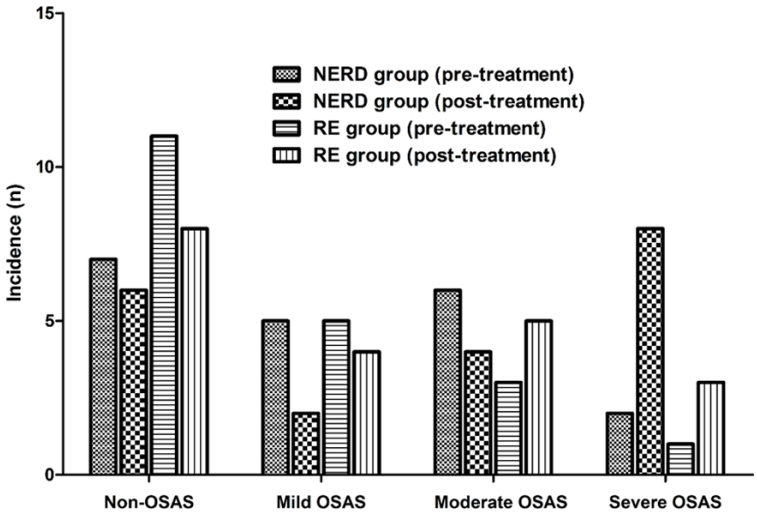

Figure 2. Incidences of OSAHS before and after treatment in NERD and RE group.

Table 5. Incidence of OSAHS before and after treatment in NERD group and RE group

Group	NERD (n=20)		RE (n=20)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Mild	5 (25%)	5 (25%)	2 (10%)	4 (20%)
Moderate	6 (30%)	3 (15%)	4 (20%)	5 (25%)
Severe	2 (10%)	1 (5%)	8 (40%)	3 (15%)

Notes: GERD, Gastroesophageal reflux disease; NERD, Non-erosive reflux disease; RE, Erosive reflux disease; Mild, AHI 5~15, $LSaO_2$>86%; moderate: AHI15-30, $LSaO_2$ 80%-85%; Severe: AHI>30, $LSaO_2$≤ 79%. P1 represented mild-moderate group; P2 represented moderate-severe group; P3 represented mild-severe group. The severity in NERD group was that P1=0.395, P2=0.764 and P3=0.563; severity in RE group was that P1=0.545, P2=0.205 and P3=0.145.

The incidence rates of OSAHS in NERD group and RE group were 45% and 60% respectively, and the differences were not significant comparing with pre-treatment incidences (*P*>0.05) (**Table 4** and **Figure 2**).

Incidences of mild, moderate and severe OSAHS in NERD group were 5 (25%), 6 (30%) and 2 (10%); mild, moderate and severe OSAHS in RE group were 2 (10%), 5 (25%) and 8 (40%) respectively. There was no significant difference between NERD and RE group (*P*>0.05). After conventional treatments, incidences of mild, moderate and severe OSAHS in NERD group became 5 (25%), 3 (15%) and 1 (5%); mild, moderate and severe OSAHS in RE group turned into 4 (20%), 5 (25%) and 3 (15%) respectively. There were no significant differences of OSAHS severity in both groups comparing with the pre-treatment data (P>0.05) (**Table 5**).

The differences of $MSaO_2$, number of awakening, and the $LSaO_2$ among three groups were not significant (*P*>0.05). However, there was significant difference of the $LSaO_2$ between RE group and control group (*P*<0.05) (**Table 6**). Besides, the differences of the $LSaO_2$, $MSaO_2$ and frequency of awakening in NERD group and RE group were significant (*P*<0.05) (**Table 7**). There were significant differences of hypopnea numbers and apnea index among three groups (*P*<0.05), so did the difference before and after treatments (P<0.05).

Discussion

GERD is a disease with motility disorder of gastrointestinal tract, which is caused by variant factors. The relevant mechanism is that scavenging activity of esophagus for stomach and duodenal reflux decreased and excessive gastric acid, pepsin and cholic acid led to damages of esophageal epithelium [8]. Except sour regurgitation and heartburn, GERD may also arouse non-cardiogenic chest pain, spha-

Table 6. Comparison of the lowest oxygen saturation, mean oxygen saturation and awakening incidence in each group

	NERD	Control	*P* value	RE group	Control	*P* value	NERD	RE	*P* value
$LSaO_2$ (%)	84.1±7.0	85.0±6.0	0.745	78.7±13.0	85.0±6.0	0.034	84.1±7.0	78.7±13.0	0.071
$MSaO_2$ (%)	96.9±1.1	97.2±0.8	0.18	96.7±1.5	97.2±0.8	0.418	96.9±1.1	96.7±1.5	0.589
WT	8.2±3.7	7.6±3.4	0.577	6.6±3.8	7.6±3.4	0.416	8.2±3.6	6.6±3.8	0.173

Notes: NERD, Non-erosive reflux disease; RE, Erosive reflux disease; $LSaO_2$, The lowest oxygen saturation, $MSaO_2$, Mean oxygen saturation, WT, Awakening times.

Table 7. PSG in NERD group and RE group before and after treatment

Group	NERD			RE		
	Pre-treatment	Post-treatment	*P* value	Pre-treatment	Post-treatment	*P* value
$LSaO_2$ (%)	84.1±7.0	85.5±6.3	< 0.001	78.7±13.0	83.5±9.4	<0.001
$MSaO_2$ (%)	96.9±1.1	97.0±0.1	0.006	96.7±1.5	97.0±0.9	<0.001
Awakening times	8.200±3.736	5.850±1.814	< 0.001	6.600±3.830	5.500±2.460	<0.001

Notes: NERD, Non-erosive reflux disease; RE, Erosive reflux disease; $LSaO_2$, The lowest oxygen saturation, $MSaO_2$, Mean oxygen saturation, WT, Awakening times.

gitis, respiratory disorder, sleep disorders and so on. Sleep disorders may be caused by stomach content reflux at night specifically. To date, the relationship between GERD and insomnia has been confirmed, but the relationship between GERD and other sleep disorders such as OSAHS needs to be further investigated. The latest research revealed that OSAHS was a kind of sleep disorders related to gastroesophageal reflux. It referred to sleep apnea generated by constraining of mouth-nose flow, according to partially or completely blocked upper respiratory tract . Until now more and more studies have proved that GERD had potential relationship with OSAHS. However, insufficient evidence has yet been found to support causal relationship between GERD and OSAHS. It is known that sour regurgitation at night, micro-arousal and vague reflex irritation may result in OSAHS. Firstly, at the beginning of sleep, the pressure of sphincter in upper esophagus starts to decline, and it decreases to the lowest point at phase III of non-rapid eye movement when the gastric acid is easy to reflux [9]. Secondly, under normal conditions, sphincter in upper esophagus still keeps perfect contractility during sleep even in the period of rapid eye movement. Whereas, the pressure of lower sphincter is basically constant during sleep and excitability threshold of vague increases during stable sleep, which is difficult to dominate sphincter in lower esophagus. When reflux occurs, clearing time is extended, excitability of vague decreases, and sphincter in lower esophagus is relax that leads to awakening. Retrogressive reflux is easy to occur during sleeping. Thirdly, gastric secretion is rare during sleeping. When reflux occurring, GERD patients need more night swallow behaviors to accelerate esophageal clearance and gastric peristalsis in the period of sleep and awakening is thus realized. During sleeping, disorders of stomach physiological rhythm may prolong gastric emptying time which can lead to awakening. Besides, several body movements and sleep apnea may induce GERD related sleep disorders, which include difficult to fall asleep, disorder of maintaining sleep, early awakening, wake up frequently at night, light sleep, and residual effects in the day time such as excessive sleepiness [10].

There may be two possibilities of the correlation between GERD and OSAHS. One is that both diseases have common risk factors such as obesity and alcoholism. As obese patients often possess a higher intra-abdominal pressure, and differentials between intra-esophageal pressure and intra-abdominal pressure is dropped, which may increase the occurrence of gastroesophageal reflux. Furthermore, upper airways of obese patients is so narrow because of fat deposition in neck that uvula become thick and long during sleep with soft palate being relax and hypertrophy, and of tongue root being post-positioned, all of which may increase the incidence of OSAHS. The second explanation is that pressure variation in esophagus and gastral cavity may also have dramatic influence on the obstruction of upper airway, and symp-

toms such as sour regurgitation and heartburn are associated with OSAHS [11-13]. Through comparison between control group and GERD group (including RE and NERD group), this study showed that there was no statistically significant difference of smoking, education, age and gender among all groups, which was consistent with other researches. However, unlike other researches, differences of inter-group BMI and alcoholism among all groups were not statistically significant, which indicated that BMI and alcoholism were the common risk factors for two diseases [14]. This study showed that morbidity of OSAHS patients in GERD group was significant higher than that in control group with eliminating the impact of BMI and alcoholism, which indicated that gastroesophageal reflux symptoms such as sour regurgitation and heartburn increased the occurrence of OSAHS except BMI and alcoholism. GERD patients in this research were identified with endoscopic, and there was no significant difference of OSAHS morbidity between RE and NERD group. Meanwhile, occurrence rate of OSAHS was not associated with the severity of GERD that was not consistent with other research results abroad [15]. When patients were grouped according to severity of OSAHS, it could be observed that the seriousness of OSAHS was not associated with serious degree of endoscopic examination.

Except that, this research made contrast about sleep respiratory for GERD patients combined with OSAHS before and after treatment, and the results showed that improving GERD symptoms cannot reduce the morbidity of OSAHS patients. However, improving GERD symptoms could reduce apnea index and obstruction events to change sleep quality, which was consistent with other researches in which the improvement of reflux symptoms in GERD patients with OSAHS may improve sleep quality [16]. Treatment by proton-pump inhibitors can reduce obstructive events and apnea index. Fass *et al* [17] also confirmed that for GERD patients were accompanied with sleep disorders, and the sleep condition could also be improved and work efficiency in the daytime can be increased with treatment of GERD. However, the long-term prognosis and result data were rare.

It was also found that the prevalence of OSAHS incidence in GERD patients was 67.5%. In these patients with OSAHS, only 33.3% was diagnosed with sleep disorders measured by PSQI. That means PSQI test is not enough for GERD patients with sleep disorders. It is necessary for those patients measured by PSG to make sure whether they had OSAHS. It is important for treatments to account for OSAHS when the association between GERD and sleep quality was examined. OSAHS can disrupt sleep, and treatments with continuous positive airway pressure can increase sleep quality in OSAHS patients [18]. GERD may play a role in the development of OSAHS by causing upper airway inflammation and obstruction [19]. OSAHS may lead to GERD because of increased intrathoracic pressure [20] and treatment with continuous positive airway pressure has been shown to improve nocturnal heartburn and regurgitation [21], as well as distal esophageal acid exposure and frequency of acid reflux episodes [22]. Irrespective of the nature of the association between GERD and OSAHS, it is important to account and adjust for the presence of OSAHS when studying sleep quality in GERD patients. So PSG is an important method for clarifying he association between GERD and OSAHS.

In conclusion, GERD is associated with OSAHS, and it is essential to note the sleep quality during GERD therapy. Moreover, well sleep quality can be regarded as the mark of effective treatment for GERD [23]. The disease without standard treatment will be further developed even bring serious complications such as esophagitis, esophageal erosion, esophageal ulcer, esophageal stenosis, Barrett esophagus, esophagus cancer and lung related diseases. Although the relative research may indicate that GERD patients are usually complicating OSAHS, as limited samples in this study, it cannot be confirmed that whether relationship between sleep disorder and GERD exists. Therefore, more clinical researches are needed in the future to investigate their relationships further.

Disclosure of conflict of interest

None.

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