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Original Article

A possible pathophysiology of GERD in OSAS patients: the roles of decreased lung volume and increased lung elastic resistance

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Abstract: Background: To study the relationship between GERD and OSAS in overweight and obese populations. Methods: A total of 196 patients (143 males and 53 females) who developed snoring or suspected OSAS participated in the study. All the patients were divided into the OSAS and non-OSAS groups based on their nocturnal polysomnographies (PSG). Their lung volumes (LV) and respiratory mechanical performances (RMPs) were assessed using impulse oscillometry (IOS) without the dysfunction of pulmonary ventilation in the patients. The esophageal function and degree of reflux were evaluated by monitoring their esophageal pressure and testing their 24-hour esophageal pH. Results: The incidence of pathological GERD in overweight and obese OSAS patients is higher than it is in age-, gender-, and BMI-matched non-OSAS overweight and obese patients ($P > 0.05$). The FRC and ERV are significantly decreased in the OSAS with GERD patients compared to the non-OSAS with GERD patients ($P < 0.05$). The absolute value of the inspiratory-expiratory pressure gradient was also significantly higher in the OSAS patients than it was in the controls ($P < 0.001$). Through a multiple linear stepwise regression analysis, we found that the Rcentral airway resistance in a supine position ($P < 0.001$) and AHI ($P = 0.002$) correlated with the DeMeester score. Conclusions: Regarding the pathophysiological prevalence of GERD in overweight and obese OSAS patients, in addition to the abnormal esophageal motility, a potential mechanism may be negative intrathoracic pressure fluctuations caused by increased lung elastic resistance and decreased lung volume (FRC, ERV) and an induced lower intraesophageal pressure gradient that results in sucking the gastric contents into the esophagus.

Keywords: Lung volume, functional residual capacity, lung elasticity, gastroesophageal reflux disease

Introduction

Gastroesophageal reflux disease (GERD) is a common chronic disorder [1]. The GERD incidence is about 20%, and, in the USA, 10% of the population reports symptoms of nocturnal reflux [2, 3]. Obesity has noticeably augmented in recent years, and many studies show that obesity is related to the increased incidence of obstructive sleep apnea syndrome (OSAS) [4].

The predictive mechanism underlying the tight correlation of increased BMI and GERD involves increased intragastric and gastroesophageal pressure, esophageal motor and sensory abnormalities, hiatal hernias, transitory relaxation of the lower esophageal sphincter, serum hormone levels, diet, and comorbidities [5-7]. It is speculated that various factors are involved in the increased GERD incidence in obese patients. There are also some hypotheses regarding obese patients with OSAS which posit that negative intra-aortic pressure causes GERD symptoms [8, 9]. In addition, autonomic nervous system dysfunction is a major component of GERD and obesity. Weight change caused by exercise or dietary modifications leads to increases in the vagal efferent flow [10].

Regarding the mechanism of GERD in overweight and obese OSAS patients, no study has evaluated the pathophysiology of GERD in obese patients. So, there are only some hypotheses about the pathophysiology of the high incidence rate of GERD (there is no data to prove them) in overweight and obese OSAS patients or in overweight and obese patients. The aim of this study is to confirm the hypothesis that reeducated intraesophageal pressure (which represents the intrathoracic pressure) is caused by reduced LV and augmented pulmonary elastic resistance in overweight and obese OSAS patients.

Materials and methods

A total of 196 overweight or obese patients (143 males and 53 females) who had never contracted lung diseases before but were bothered by snoring or suspected OSAS, were recruited as the study cohort for this cross-sectional study from March 2015 to April 2016. All the patients were diagnosed with OSAS after respiratory monitoring using polysomnography overnight. All the subjects were classified as overweight or morbidly obese based on the established criteria [11]. Among the patients in the cohort, 59 were non-OSAS and 137 were OSAS.

The exclusion criteria were: (1) patients who underwent CPA*P* or urolo patopharyhgo plast for snoring or OSA in the past, (2) patients developing an upper airway disturbance, (3) patients who have contracted a cardiopulmonary diseases or who have suffered from them in the past, (4) patients with an airway obstruction (FEV1/FVC) < 80% of the predictive value, patients with hyperinflation signs in pulmonary function examinations and MEFV curves, (5) and patients who have having neuromuscular diseases (like kaliopenia or AIDP). The study was approved by the Ethics Committee of the First People's Hospital of Kashi District, and all the patients signed an informed consent prior to their participation in the study.

Study design

Based on the nocturnal PSG, 5 males and 3 females were excluded from the study because they had an AHI ≥ 5/h after being placed in the OSAS group for limited expiratory flow (EF), as recorded by pneumotachographs, with a FEV1/FVC < 70% of predictive value, leaving the group with 96 males and 41 females. Other subjects, including 51 males and 14 females (AHI < 5/h), who simultaneously met the inclusion and exclusion criteria, constituted the non-OSA group. A total of 6 subjects (4 males, 2 females) without OSA were eliminated because of limited EF. Consequently, 47 males and 12 females were remained in the non-OSAS group. All the subjects received standardized spirometry and LV measurements according to the guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [12]. Maximum flow-volume loops were performed via a pneumotachograph. Three loops were required by each pulmonary function examination to measure the FVC and FEV1, and the largest one was used for calculating the FEV1/FVC. The thoracic gas volume at the FRC level was determined when the subjects made gentle pants against the shutter at a rate of < 1/s. ERV and their inspiratory and vital capacities (hereinafter abbreviated as IC and VC, respectively) were determined in the same way. The average of three eligible FRC determinations was used for calculating the total LV (TLV) and the residual volume as FRC + IC and TLV - VC, accordingly.

Sleep studies

All the subjects received a nocturnal PSG, involving EEG, EOG, chin EMG, ECG, and snoring and body position records, and their breathing force was measured with thoracic and abdominal piezo belts and oxygen saturation via pulse oximetry, according to the AASM guidelines [13]. Their airflow was measured through a nose-pressure sensor and an oronose thermal sensor. For 7-hour sleeping period, a nose pressure decrease ≥ 30% of baseline accompanied by ≥ 4% desaturation and ≥ 10 s duration was considered hypopnea, and no less than a 10 s decrease in a thermistor peak signal drift ≥ 90% of baseline and no airflow recorded in a nose-pressure sensor were considered apnea. The duration in ≥ 90% of events fulfilled the amplitude attenuation criteria. The OSA severity was presented as the overall apnea number + hypopneas per hour of sleep (AHI). Based on the apnea hypopnea index (AHI), 5-20 is the lowest oxygen saturation ($LSaO_2$), ≥ 86 is mild OSAS, AHI 20-40, ($LSaO_2$) 80%-85% is moderate OSAS, and RDI ≥ 40, $LSaO_2$ ≤ 79% is severe OSAS [13].

The IOS mechanical performance determination and quality control were performed as ER guidance through IOS [14]. The IOS determination was conducted in the subjects in a neutral sitting position with their cheeks supported by nose clips. The subjects closed their lips tightly around the mouthpiece and breathed calmly. Incessant rectangular electric pulse signals gathered on the airway after the steady airflow and natural volume were determined, and at least three successive determinations of > 0.5 h were conducted. We applied the respiratory system impedance (Zrs) at 5 Hz (Zrs5) and average whole-breath values of Rrs and reactance (Xrs) ranging from 5 to 35 Hz with 5 Hz as an increment (R5-35 and X5-35, accordingly). The IOS determination was conducted by two skilled technicians who were unfamiliar with the groupings. Any artifacts we found, like unsteady breathing and swallowing, were eliminated. IOS is able to assess Rrs and Xrs which are computed through software that takes advantages of Fourier transform analysis to measure Raw in the lung and chest wall elasticity, together with the extra- and intra-thoracic airways.

Esophageal motility monitoring

The patients had to fast for one day before the esophageal motility examination. The monitoring was performed using a 36-channel ManoScan360™ solid-state high-resolution gastrointestinal motility examination system (Sierra Scientific Instruments, USA). Through the patients' nasal cavities, a solid esophageal manometry catheter was placed by swallowing 10 ml liquid 10 times, and the esophageal body peristalsis pressure wave and the esophageal sphincter contraction, dilatation, and position were observed using the ManoView fully automatic gastrointestinal dynamic analysis software that collects and analyzes data, and the dynamic pressure distribution of the esophagus was described. A separation of the diaphragm and lower esophageal sphincter more than 2 cm is defined as a hiatal hernia.

Esophageal pH monitoring

The patients had to fast for one day before the examination and had to stop using the PPI treatment for one week before the examination. Using a 24-hour multi-channel air cavity resistance meter and a pH monitoring system (Given Imaging, Israel) and model ZAI-BL-48E electrode catheters, 6 impedance receptors were placed in the lower esophageal sphincter (LES) above 3 cm, 5 cm, and 7 cm, 9 cm, 5 cm below the upper esophageal sphincter (UES), the pH feeling is placed 2 cm above the UES and is 5 cm above the LES. A pH recorder was connected to the patient's body for 24 h, and the ManoView software was used for the data acquisition, analysis, and recording of the reflux episodes of frequency, duration, and explicitly changed reflux of acid alkali degrees according to the pH value. The results were divided into three grades, namely acidic, weak acid, and non-acidic. Acid reflux is defined as a decline in esophageal pH more than or equal to 1 and the following four things; at the occurrence of the reflux, the esophageal pH value is less than 4; weakly acidic reflux is an esophageal pH decline more than or equal to 1, but the esophageal pH value is still in-between 4 and 7; the non-acid reflux is a reflux event that cannot make the esophageal pH value fall below 7. According to the different reflux materials, in terms of reaching a different level in the esophagus, the reflux events that achieve 5 cm below the UES are described as proximal esophageal reflux. According to the American Society for Gastroesophageal Reflux Disease guidelines, a patient meeting the standard definition for pathological gastroesophageal reflux has a DeMeester score ≥ 14.7 and must also maintain a normal diet in addition to smoking and drinking alcoholic, acidic, or alkaline beverage [15].

Statistical analyses

The data were presented as the average value ± SD and the non-normal distribution data as the median ± quartile. The data from the males and females were investigated separately because gender distinctions exist in LV size and airway resistance and OSAS incidence which are all well-recorded. Independent-sample *t* tests were conducted to analyze the intergroup differences. The relationships between the variables were analyzed using the least-square linear regression method. A multiple regression analysis was conducted to evaluate the link between OSA severity and LV and the RMPs and anthropometry. The statistical analysis was carried out using SPSS 19.0. $P < 0.05$ indicated statistical significance.

Table 1. General properties of the non-OSAS and OSAS groups (mean ± SD), n (%)

	Non-OSAS	OSAS	Statistics	*P*
Age	46.95 ± 10.61	49.66 ± 11.59	-1.53	0.13
Gender				
Male	47 (79.70)	96 (70.10)	1.92	0.17
Female	12 (20.30)	41 (29.90)		
Ethnic group				
Uyghur	19 (32.20)	66 (48.20)	4.98	0.08
Chinese	35 (59.30)	58 (42.30)		
Other	5 (8.50)	13 (9.50)		
Height (cm)	169.17 ± 7.04	167.45 ± 8.84	1.45	0.15
Weight (kg)	81.36 ± 14.53	84.53 ± 17.26	-1.23	0.22
Body mass index	28.53 ± 4.28	29.82 ± 5.47	-1.61	0.11
FEV/VCMAX	79.38 [78.25-82.44]	80 [75.55-83.00]	-0.04	0.97
TLV-B	6.07 ± 0.84	5.72 ± 1.01	-1.80	0.07
IC-B	2.29 ± 0.55	2.91 ± 5.18	-0.50	0.62

Table 2. The occurrence of pathological GERD in the OSAS and non-OSAS groups

		Non-OSAS	OSAS	Total	Chi square	
D-score	< 14.7	43 (72.90)	45 (32.80)	88 (44.90)	26.72	< 0.001
	≥ 14.7	16 (27.10)	92 (67.20)	108 (55.10)		

Results

Baseline characteristics

196 patients without pulmonary ventilation dysfunction were ultimately included in the study cohort. The two groups, in terms of age, gender, nationality, body weight, height, body mass index, FEV/TLV-B, VCMAX, IC-B, pulmonary function indexes, etc., had no statistically significant differences. The two sets of data are comparable statistically and clinically as shown in **Table 1**.

Occurrence of pathological GERD in the OSAS and non-OSAS groups

In the two groups of patients, the occurrence of pathological GERD in the OSAS group was significantly higher than it was in the non-OSAS group ($P < 0.001$), as shown in **Table 2**.

Comparison of the lung volumes and absolute IEPG values between the OSAS and non-OSAS patients among the overweight and obese patients

In the patients who were included in the case and control groups in a sitting position, their total LV had no significant statistical differences ($P = 0.07$) in functional residual capacity expiratory reserve volume, but the absolute values of the inspiratory-expiratory pressure gradient (IEPG) of the esophagus had a significant difference ($P < 0.05$), as shown in **Table 3**.

Mechanical properties of the lungs of the OSAS and non-OSAS patients among the overweight and obese patients

In this study, we also found that, in the sitting position, in the case and control groups, Zat5Hz elastic resistance, pulmonary Rcentral and Rperipheral elastic resistances, and Rat5Hz~Rat25Hz and Xat5Hz~Xat25Hz elastic resistances had significant differences ($P < 0.05$). However, the Xat35Hz elastic resistance in the sitting position had no statistical difference ($P < 0.09$) as shown in **Table 4**.

In the supine position, the Zat5Hz elastic resistance, the pulmonary Rcentral and Rperipheral elastic resistances, Rat5Hz~Rat35Hz, and Xat5Hz~Xat35Hz have very significant differences ($P < 0.001$) as shown in **Table 5**.

Relationship among the pulmonary functional indexes, AHI, and DeMeester scores

We performed a univariate analysis for all the patients with respiratory disturbance indexes, TLV-B, RVB-b, FRC, ERV, Zat5HZ, Rcentral, and

Table 3. Comparison of the lung volumes and the absolute IEPG values between the OSAS and non-OSAS patients among the overweight and obese patients

	Non-OSAS	OSAS	Z	*P*
TLV	6.04 [5.61-6.76]	5.84 [5.11-6.56]	-1.8	0.07
FRC	3.68 [3.20-4.18]	3.29 [2.76-3.92]	-3.01	0.003
ERV	1.39 [0.96-1.84]	1.29 [0.73-1.64]	-2.11	0.04
IEPG (absolute value)	3.70 [4.30-2.90]	5.80 [8.30-4.23]	-5.65	< 0.001

Table 4. The mechanical lung properties of the OSAS and non-OSAS patients among the overweight and obese patients (sitting position)

	Non-OSAS	OSAS	Z	*P*
Zat5HZ	0.38 [0.30-0.54]	0.45 [0.37-0.59]	-2.71	0.01
Rcentral	0.15 [0.13-0.27]	0.22 [0.14-0.30]	-2.2	0.03
Rperipheral	0.25 [0.10-0.25]	0.29 [0.18-0.35]	-2.74	0.01
Rat5HZ	0.37 [0.28-0.51]	0.44 [0.35-0.55]	-2.7	0.01
Rat10HZ	0.35 [0.27-0.43]	0.39 [0.32-0.48]	-2.57	0.01
Rat15	0.32 [0.26-0.38]	0.34 [0.29-0.42]	-2.19	0.03
Rat20	0.32 [0.26-0.39]	0.35 [0.29-0.42]	-2.27	0.02
Rat25	0.32 [0.27-0.39]	0.36 [0.30-0.42]	-2.19	0.03
Rat35	0.34 [0.29-0.42]	0.39 [0.33-0.46]	-2.41	0.02
Xat5	-0.09 [-0.15-0.06]	-0.11 [-0.19-0.08]	-2.31	0.02
Xat10	-0.03 [-0.08-0.00]	-0.05 [-0.11-0.02]	-2.31	0.02
Xat15	-0.01 [-0.04-0.02]	-0.03 [-0.08-0.00]	-2.49	0.01
Xat20	0.03 [0.00-0.05]	0.01 [-0.02-0.04]	-2.21	0.03
Xat25	0.06 [0.04-0.08]	0.05 [0.02-0.07]	-2.18	0.03
Xat35	0.12 [0.09-0.13]	0.11 [0.08-0.13]	-1.71	0.09

Table 5. Mechanical lung properties of the OSAS and non-OSAS patients among the overweight and obese patients (supine position)

	Non-OSAS	OSAS	Z	*P*
Zat5HZ	0.40 [0.32-0.59]	0.70 [0.53-0.90]	-6.87	< 0.001
Rcentral	0.17 [0.14-0.29]	0.41 [0.28-0.56]	-7.48	< 0.001
Rperipheral	0.26 [0.15-0.31]	0.49 [0.34-0.70]	-6.88	< 0.001
Rat5HZ	0.40 [0.31-0.55]	0.68 [0.53-0.82]	-6.82	< 0.001
Rat10HZ	0.36 [0.29-0.45]	0.57 [0.46-0.73]	-7.42	< 0.001
Rat15	0.33 [0.28-0.39]	0.54 [0.43-0.70]	-7.78	< 0.001
Rat20	0.34 [0.28-0.39]	0.55 [0.42-0.71]	-7.68	< 0.001
Rat25	0.34 [0.29-0.40]	0.55 [0.43-0.71]	-7.49	< 0.001
Rat35	0.36 [0.31-0.44]	0.58 [0.44-0.74]	-7.12	< 0.001
Xat5	-0.10 [-0.17-0.08]	-0.37 [-0.47-0.20]	-7.02	< 0.001
Xat10	-0.05 [-0.11-0.02]	-0.26 [-0.36-0.13]	-7.52	< 0.001
Xat15	-0.03 [-0.07-0.00]	-0.21 [-0.33-0.09]	-7.75	< 0.001
Xat20	0.01 [-0.02-0.04]	-0.16 [-0.28-0.05]	-7.67	< 0.001
Xat25	0.04 [0.02-0.07]	-0.12 [-0.24-0.01]	-7.53	< 0.001
Xat35	0.11 [0.07-0.12]	-0.07 [-0.18-0.07]	-7.13	< 0.001

Rperipheral lung resistances at the sitting and supine positions with the DeMeester scores.

The statistical analysis showed that the AHI ($P < 0.001$), FRC ($P = 0.03$), sitting ZAT5Hz ($P = 0.03$), and supine ZAT5Hz ($P < 0.001$), Rcentral ($P < 0.001$) and Rperipheral pulmonary elastic resistances ($P < 0.001$), and the IEPG (absolute value) ($P < 0.001$) were associated with the DeMeester score. It is known that AHI, FRC, and total pulmonary resistance at the sitting and supine positions, and Rcentral and Rperipheral airway resistances at the supine position correlated with gastroesophageal reflux degree (see **Table 6**).

Multiple linear stepwise regression analysis among the pulmonary functional indexes, AHI, and DeMeester scores

In a multiple linear stepwise regression analysis of the previously mentioned indicators, the results show that the Rcentral airway resistance at the sitting position ($P = 0.02$) and the absolute value of the inspiratory-expiratory pressure gradient (IEPG) ($P < 0.001$) correlated with the DeMeester score. So, we can say that the Rcentral airway resistance and absolute value of IEPG were related to the degree of gastroesophageal reflux in pre-obese and obese patients. For the majority of the inspiratory-expiratory pressure gradient values that are negative, we take their absolute value in the statistical analysis (see **Table 7**).

Discussion

Regarding the mechanism of GERD in overweight or obese OSAS patients, no study has

Table 6. The relationships among the pulmonary functional indexes, AHI, and the DeMeester scores

	Correlation coefficient	P
AHI	0.34	< 0.001
IEPG (absolute value)	0.367	< 0.001
TLV-B	-0.04	0.63
FRC	-0.022	0.002
ERV	-0.10	0.18
Sitting Zat5Hz	0.16	0.03
Sitting Rcentral	0.11	0.12
Sitting Rperipheral	0.11	0.12
Supine Zat5Hz	0.25	< 0.001
Supine Rcentral	0.38	< 0.001
Supine Rperipheral	0.24	0.00

explored the general mechanism of the occurrence of gastroesophageal reflux or laryngopharyngeal reflux disease, like the increase in the prevalence of hiatal hernias, increased transient lower esophageal sphincter relaxation, lower LES pressure, increased intragastric pressure, increased gastroesophageal pressure gradient and some theoretical hypotheses regarding the enlarged negative pressure fluctuations in the thorax [16]. In the supine position, all the IOS indexes in the OSAS groups in our study were significantly higher than the non-OSAS groups ($P < 0.001$). The reasons we consider are that in the supine position, a reduction of the diaphragmatic muscle movement may increase more respiratory efforts to overcome the pulmonary elastic resistance and cause more negative intrathoracic and intraesophageal pressures in their respiration. We proved this idea using the esophageal motility monitoring system, measuring the pressure of the middle and lower segments of the esophageal inspiratory and expiratory period separately, and calculating the IEPG. In the results, we found that the absolute IEPG value was significantly higher in the OSAS patients than in the controls. So, the more negative the IEGP, the higher the DeMeester score.

We used a single-factor analysis for all the patients with AHI and some of the lung-resistant indexes at the sitting and supine positions with the DeMeester scores. Our statistical analysis showed that the AHI, FRC, and total lung elastic resistance at the sitting position and the total lung elastic resistance and Rcentral and Rperipheral pulmonary elastic resistances at the supine position are correlated with the degree of gastroesophageal reflux. We performed a multiple-linear stepwise regression analysis of these indicators and found that the Rcentral elastic resistance in the supine position and IEPG are related to the degree of gastroesophageal reflux in overweight and obese patients. So, we can say that the increased lung elastic resistance and decreased lung volume may cause increased negative intrathoracic pressure fluctuations in overweight and obese OSAS patients. Thus, more negative intrathoracic pressure fluctuation and lower intraesophageal pressure or gastroesophageal pressure gradient cause the reflux events. So, we can say that there may be a casual relation between OSAS and GERD.

We think that laryngopharyngeal reflux disease (LPRD) is a special type of GERD, and there are some similar mechanisms that occur in OSAS patients. Eskiizmir and Kezirian [17] hypothesized that the causal relationship between OSA and LPRD depends on the vicious cycle that is initially triggered by respiratory efforts which cause a greater negative intrathoracic pressure. This negative intrathoracic pressure promotes the reflux of the gastric contents.

In order to further find the relationship between the changes in the pulmonary functions and GERD in OSAS patients, more intensive studies about the relationship between the pulmonary elastic resistance indexes and the esophageal functional indexes are needed.

In conclusion, there is high prevalence of pathological GERD in OSAS overweight and obese patients. The potential mechanism may be negative intrathoracic pressure fluctuation caused by increased lung elastic resistance and decreased lung volumes (FRC, ERV) that affect the esophageal function and reduce the intraesophageal pressure.

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Table 7. A multiple linear stepwise regression analysis among the pulmonary functional indexes, AHI, and the De-Meester scores

	B	Standard deviation	Beta value	t	P
Constant	2.886	2.541	-	1.136	0.258
IEPG (absolute value)	1.521	0.387	0.357	3.932	< 0.001
Supine Rcentral	19.658	6.422	0.278	3.061	0.003

Disclosure of conflict of interest

None.

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