Effect of Continuous Positive Airway Pressure on Chronic Cough in Obstructive Sleep Apnea Concomitant Gastroesophageal Reflux Patients: A Retrospective Observational Study

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Research

Keywords: chronic cough, gastroesophageal reflux, obstructive sleep apnea, continuous positive airway pressure

Posted Date: July 14th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-694754/v1>

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Abstract

Background:

Chronic cough is common in obstructive sleep apnea. The aetiology of chronic cough in obstructive sleep apnea patients could be multifactorial. Several studies have reported high incidence rates of gastroesophageal reflux in obstructive sleep apnea patients, and gastroesophageal reflux may be one of causes of chronic cough in OSA patients. This study aimed to investigate the effect of continuous positive airway pressure on chronic cough in obstructive sleep apnea concomitant gastroesophageal reflux patients.

Methods:

Obstructive sleep apnea concomitant gastroesophageal reflux patients who also suffered chronic cough were enrolled. Patients who accepted continuous positive airway pressure as treatment group, and the patients who accepted general treatment (diet control, moderate exercise, sleeping on your side, limiting alcohol consumption and proton pump inhibitor±mosapride) as control group. Effects of different treatment modalities on chronic cough were assessed, and the correlation between chronic cough, obstructive sleep apnea and gastroesophageal reflux were performed by Pearson correlation analyses.

Results:

All Patients had poor sleep quality, severe daytime sleepiness, moderate-severe sleep apnea, significant weak acid reflux and moderate coughing events at the baseline. Compared with the baseline, PSQI and ESS score were improved in treatment group after 1 week's treatment, the improvement became stronger with duration of therapy ($P<0.05$). GERD-Q score, VAS score, daytime and night cough symptom score were all significantly improved in these two groups after treatment ($P<0.05$), while this improvement was more pronounced in the treatment group ($P<0.05$). There were significant correlation between AHI and VAS score ($r=0.612$, $P<0.05$), weak acid reflux and VAS score ($r=0.429$, $P<0.05$), weak acid reflux and AHI ($r=0.366$, $P<0.05$).

Conclusion:

The improvement in chronic cough and gastroesophageal reflux was due to the resolution of obstructive sleep apnea. AHI and weak acid reflux may be critical factors affecting the therapeutic effect of chronic cough in obstructive sleep apnea concomitant gastroesophageal reflux patients.

Background

Chronic cough, which affects 2.3–33% of the adult population^[1, 2], is one of the most common complaints in respiratory outpatient clinic visits. A significant fraction of chronic cough remains undiagnosed, and the percentage of unexplained cough has ranged up to 42%^[3]. Obstructive sleep apnea (OSA) is being increasingly recognized as cause of chronic cough. The aetiology of chronic cough in OSA

patients could be multifactorial. The incidence of gastroesophageal reflux (GER) is high in OSA patients, and GER may be one of the causes of chronic cough in OSA patients.

OSA is characterized by repetitive collapse of the upper airway during sleep, with the development of larger negative intrathoracic pressures during inspiratory efforts against the occluded airway. Recent evidence points to a link between chronic cough and OSA. OSA is being increasingly recognized as cause of chronic cough^[4–6]. Similar to OSA, GER which can co-exist or not in the same individual, is a common cause of chronic cough. The prevalence of GER was significantly higher in OSA patients than general population^[6–8]. Gastroesophageal reflux (GER) may be one of the causes of chronic cough in OSA patients. Previous study have concluded that proton pump inhibitor (PPI) therapy for GER can not improve cough in GER patients^[9]. Continuous positive airway pressure (CPAP) has been shown to improve GER events in OSA patients^[10]. Unfortunately, as far as OSA and GER-related cough is concerned, the therapeutic management remains largely empirical. This study aimed to determine the effect of different treatment modalities on chronic cough in OSA concomitant GER patients, and the possible mechanism of these association.

Methods

Subjects

This study was a retrospective observational study. Adult patients with chronic cough seen at Department of Respiratory and Sleep Medicine of First affiliated Hospital of Zhengzhou University were given the option to enroll into this study between Mar. 2017 and Nov. 2020. This study was carried out in accordance with the WMA Declaration of Helsinki, and approved by the grass-roots ethics committee of First affiliated Hospital of Zhengzhou University and the ethics committee of Zhengzhou University.

Exclusion criteria: (1) Any other diseases that resulted in chronic cough. (2) Chronic disease states such as congestive heart failure, chronic kidney disease, cancer, need for immunosuppressive therapy, or diabetes mellitus. (3) History of hypertension, and poor blood pressure control.

Inclusion criteria: (1) Cough more than 8 weeks. (2) Normal spirometry and provocation test. (3) Normal chest radiographs and/or CT scans of the chest. (4) Normal acidophilic granulocyte count of induced sputum. (5) Normal skin phadiatop test. (6) Normal paranasal sinus computed tomography. (7) No history of ACEI drugs.

Pittsburgh Sleep Quality Index (PSQI)

Sleep quality was assessed using the Chinese version of the PSQI^[11]. The PSQI is a self-rated questionnaire that can assess sleep quality and sleep disturbances over one-month period. It consists of 18 items which are divided into 7 aspects: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. Each answer is graded on a four-point scale ranging from 0 to 3. The score ranges from 0 to 21. Higher PSQI score, poorer sleep quality.

Epworth sleepiness scale (ESS)

Daytime sleepiness was assessed using the Chinese version of the ESS ^[12]. It consists of eight questions regarding how often an individual dozes during daily activities. Each answer is graded on a four-point scale ranging from 0 to 3. The ESS score ranges from 0 (never dozed) to 24 (high chance of dozing). Higher ESS score, greater sleep propensity during the day.

GERD - Questionnaire (GERD-Q)

Gastroesophageal reflux symptom was evaluated using the Chinese version of GERD-Q ^[13]. It consists of six questions which are divided into three aspects: heartburn and reflux, epigastric pain and nausea, sleep disorder and PPI use within the past one week. The total score of 8 or greater indicates GERD.

Visual Analogue Scale (VAS)

VAS for cough ^[14] is used for assess the severity of cough by linear integral method. It ranges from 0 to 10. 0 indicates asymptomatic, and 10 indicates the most severity of cough. It can be used for the longitudinal comparison before and after the treatment.

Cough symptom score

Daytime and nighttime cough symptom was assessed using Chinese version of cough symptom score according to the 2015 guideline for the diagnosis and treatment of cough in China ^[14]. This scale is divided into 2 parts, daytime and nighttime cough symptom scores. The score ranges 0 to 3, with 0 being no cough and 3 being the most severe cough.

24h esophageal Multichannel Intraluminal Impedance-pH (24h MII-pH)

- 24h MII-pH (Medtronic, Inc. USA) monitoring was used to diagnose GER. Patients were not treated with antacid during the examination or within 8 weeks before the examination. Abnormal GER was defined when the DeMeester score ≥ 14.72 ^[15] and/or meet the criteria of Lyon Consensus ^[16].

Polysomnography

Overnight polysomnography monitoring were performed using Compumedics systems. Categorisation of sleep stage and respiratory events were performed according to American Academy of Sleep Medicine criteria (AASM Version 2.4) ^[17]. The severity of sleep disordered breathing was defined by the apnea-hypopnea index (AHI).

24h MII-pH (Medtronic, Inc. USA) combined with polysomnography monitoring was performed for each patient. A synchronisation signal of pH was recorded in both the reflux system and the Compumedics system to allow accurate analysis of the temporal relationship between apnea and reflux events.

Protocol

Based on the above inclusion-exclusion criteria, patients with chronic cough were enrolled. After relevant auxiliary examinations, OSA concomitant GER patients were further collected. General treatment includes diet control, moderate exercise, sleeping on your side, limiting alcohol consumption and medications (PPI $\pm$ mosapride). According to the patient preference and compliance, the patients were divided into two groups, treatment group (CPAP + general treatment) and control group (general treatment). The study protocol is as follows (Fig. 1).

Statistical analysis

Results are presented as mean $\pm$ SD. For the analysis of PSQI, ESS, GERD-Q, VAS, cough symptom score between treatment group and control group, we performed a repeated measures multivariate analysis of variance (MANOVA). For the analysis of AHI, the longest time of apnea, the lowest oxygen saturation, Demeester score, acid reflux, weak acid reflux and non-acid reflux between treatment group and control group, we performed independent sample t-test. Pearson correlation coefficients were used to examine the correlation between variables and chronic cough. $P < 0.05$ was considered statistically significant. All statistical analysis was performed in SPSS 16.0.

Results

Baseline characteristics

Out of a total of 86 patients who meet the criteria were enrolled into the study between Mar. 2017 and Nov. 2020, 40 patients accepted general treatment as control group and 46 patients accepted CPAP as treatment group. The baseline data of this study are shown in Table 1. Patients in both groups had poor sleep quality, severe daytime sleepiness, sleep structural disorder, decreased sleep efficiency, moderate-severe sleep apnea, significant weak acid reflux, and moderate coughing events. These parameters were no statistical difference between control group and treatment groups at the baseline.

Table 1
The baseline data of this study.

	Treatment group(n=46)	Control group(n=40)
Age	36.91 ± 5.55	37.52 ± 5.92
Sex(M/F)	26/20	24/16
BMI(kg/m ²)	27.48 ± 4.75	28.38 ± 4.94
Smoking:		
Yes	26	25
No	20	15
Drinking:		
Yes	28	27
No	18	13
PSQI	12.09 ± 2.49	11.63 ± 2.36
ESS	14.33 ± 2.46	14.08 ± 2.28
GERD-Q	4.09 ± 2.98	4.43 ± 2.51
TST/min	398.33 ± 23.03	404.18 ± 23.15
Sleep efficiency(%)	73.15 ± 5.59	75.18 ± 4.47
Sleep structure:		
N1(%)	15.04 ± 2.09	13.15 ± 2.52
N2(%)	68.28 ± 5.00	70.53 ± 2.14
N3(%)	8.56 ± 2.51	10.05 ± 2.01
R(%)	7.89 ± 3.02	6.03 ± 3.07
AHI(/h)	30.24 ± 5.45	29.73 ± 4.03
Longest time of apnea(min)	43.12 ± 8.29	41.26 ± 4.60
LSaO ₂ (%)	81.09 ± 3.33	80.08 ± 4.35
Demeester score	18.23 ± 7.77	17.71 ± 5.15
Acid reflux	29.33 ± 11.34	27.77 ± 13.84
Weak acid reflux	24.60 ± 9.14	23.89 ± 7.95
Non-acid reflux	2.14 ± 1.30	1.12 ± 1.09

	Treatment group(n=46)	Control group(n=40)
VAS	55.76 ± 10.59	52.38 ± 8.09
Daytime cough symptom	2.13 ± 0.81	2.03 ± 0.80
Nighttime cough symptom	1.83 ± 0.77	1.73 ± 0.82

Compared with the baseline, PSQI (Fig. 2a) and ESS (Fig. 2b) were improved in treatment group after 1 week treatment, and the improvement became stronger with duration of therapy ($P \leq 0.05$). GERD-Q (Fig. 3), VAS (Fig. 4a), daytime (Fig. 4b) and night cough symptom score (Fig. 4c) were all significantly improved after treatment ($P \leq 0.05$), the improvement were more pronounced in the treatment group ($P \leq 0.05$). Furthermore, there were significant correlation between AHI and VAS (Fig. 5a, $r = 0.612$, $P \leq 0.05$), weak acid reflux and VAS (Fig. 5b, $r = 0.429$, $P \leq 0.05$). Weak acid reflux was significantly correlated with AHI (Fig. 5c, $r = 0.366$, $P \leq 0.05$).

Discussion

The major findings of this study were as follows: (1) CPAP improved symptoms of chronic cough and GER in OSA concomitant GER patients. (2) AHI and weak acid reflux were both significantly correlated with chronic cough, AHI was also correlated with weak acid reflux. This findings are consistent with other studies that CPAP treatment can improve GER^[10, 18] and daytime sleepiness^[10]. Previous studies investigated the effect of CPAP on GER and OSA, but there had been no analysis focus on the effect of CPAP on chronic cough in OSA concomitant GER patients. The present study is the first to explore the effects of different treatment modalities on chronic cough in OSA concomitant GER patients.

OSA and GER are being increasingly recognized as causes of chronic cough. Previous study found that GER symptom was improved after 1 week's CPAP treatment in OSA concomitant GER patients^[18]. Tamanna et al. further found that GER and daytime sleepiness were improved after 6 months' CPAP treatment in OSA concomitant GER patients^[10]. However, no studies have yet confirmed the efficacy of CPAP on chronic cough in OSA concomitant GER patients. Thus, 86 OSA concomitant GER patients who also suffered from chronic cough were collected in present study. We assessed the association between cough, GER, and treatment response in OSA concomitant GER patients and found that the sleep quality, daytime sleepiness, symptoms of cough and GER were all markedly improved after 3 months' CPAP treatment in these patients. Previous study suggested that PPI can not improve cough symptom in GER patients, while lifestyle modifications and weight loss may be beneficial for chronic cough in GER patients^[9]. In our study, we further found that general treatment and PPI improved the symptoms of cough and GER, while the improvement was more pronounced after CPAP treatment. Unfortunately, general treatment and medications had no effect on sleep quality and daytime sleepiness in OSA concomitant GER patients.

- The 24h MII-pH monitoring can accurately distinguish and analyze forms of reflux, such as acid reflux, weak acid reflux, and non-acid reflux^[19]. OSA concomitant GER patients were diagnosed using 24h MII-pH combined with overnight PSG monitoring in present study. We discovered an association between AHI and VAS, weak acid reflux and VAS, AHI and weak acid. These findings are consistent with several, but not all, previous studies^[8, 20, 21]. Previous studies have reported the relationship between AHI and GER using symptoms^[6], responses to anti-GER medication^[22], 24h pH monitoring^[22] or endoscopic findings^[8] to define GER, rather than 24h MII-pH. The symptoms of GER, such as weak acid reflux, may have been masked by the severity of the cough and not considered by the physician. With 24h MII-pH monitoring is widely used, clinicians find that not all forms of reflux can cause symptoms in GER patients. The diagnostic yield of 24h esophageal pH monitoring in patients with extra-esophageal symptoms is probably far from perfect. Previous study has found that the frequency of weak acid reflux is significantly higher in GER patients with cough than in patients without cough^[23]. It probable reveal why some reflux episodes in the GER patient causes cough while others do not. Our study indicates that both AHI and weak acid reflux may play important roles in the the pathogenesis of chronic in OSA concomitant GER patients.

Several studies have suggested that OSA causes GER, rather than the reverse, while there was no objective parameters to assess AHI and reflux episodes in these studies^[24, 25]. The mechanism by which CPAP reduces the symptom of chronic cough in OSA concomitant GER patients is not fully understood. Several studies have demonstrated that CPAP can make lower esophageal sphincter (LES) less susceptible to reflux by increasing barrier pressure to reflux and decreasing the duration of LES relaxation^[26, 27]. We speculated that the probable mechanism of cough resolution with CPAP is through the improvement of upper airway collapse, further promoting the barrier function of LES, and then alleviating weak acid reflux in OSA patients.

The limitations of the present study are as follows. First, there was no blank control group. We believed that it would not be ethical to withhold therapy from patients. Second, the subjective parameters such as sleep quality, daytime sleepiness, GER related questionnaire and cough related questionnaires could be influenced by patients' judgment. These questionnaires are simple and practicable to perform, and there is no objective cough-related monitoring up to now. Moreover, professional technicians operate these questionnaires strictly and accurately according to the instructions in our study. Third, our study is a retrospective observational study, further fundamental research and large-scale prospective studies are needed to draw a more definitive conclusion.

Conclusions

In summary, this results indicates that the improvement in chronic cough and GER was due to the resolution of OSA. AHI and weak acid reflux may be critical factors affecting the therapeutic effect of chronic cough in OSA concomitant GER patients. We speculated that the probable mechanism of cough resolution with CPAP is through the improvement of upper airway collapse, further promoting the barrier

function of LES, and then alleviating weak acid reflux in OSA patients. Further fundamental research and large-scale prospective studies are needed to draw a more definitive conclusion in the future.

Abbreviations

obstructive sleep apnea OSA

gastroesophageal reflux GER

proton pump inhibitor PPI

continuous positive airway pressure CPAP

apnea-hypopnea indices AHI

Pittsburgh Sleep Quality Index PSQI

Epworth sleepiness scale ESS

GERD - Questionnaire GERD-Q

Visual Analogue Scale VAS

24h esophageal Multichannel Intraluminal Impedance-pH 24h MII-pH

repeated measures multivariate analysis of variance MANOVA

lower esophageal sphincter LES

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the WMA Declaration of Helsinki, and approved by the grass-roots ethics committee of First affiliated Hospital of Zhengzhou University and the ethics committee of Zhengzhou University.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Supported by grant No. U1804195 from National Natural Science Foundation of China.

Authors' contributions

JS participated in the design of the study, analyzed data, interpreted data and drafted manuscript. CZ, YM and YF carried out the study. YL, LS, and MW analyzed data, drafted manuscript. LD completed statistical analysis. SO conceived of the study, participated in the design of the study, edited and revised manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

Figure 1

The protocol of this study.

Figure 2

Comparisons of PSQI score [a] and ESS score [b] between treatment group and control group. *Indicates a significant difference between treatment group and control group at the same measurement time ($P \leq 0.05$). #Indicates a significant improvement in treatment group when compared with the data of baseline ($P \leq 0.05$).

Figure 3

Comparisons of GERD-Q score between treatment group and control group. *Indicates a significant difference between treatment group and control group at the same measurement time ($P \leq 0.05$). #Indicates a significant improvement in treatment group when compared with the data of baseline ($P \leq 0.05$). &Indicates a significant improvement in control group when compared with the data of baseline ($P \leq 0.05$).

Figure 4

Comparisons of VAS score [a], day cough symptom score [b], and night cough symptom score [c] between treatment group and control group. *Indicates a significant difference between treatment group and control group at the same measurement time ($P \leq 0.05$). #Indicates a significant improvement in treatment group when compared with the data of baseline ($P \leq 0.05$). &Indicates a significant improvement in control group when compared with the data of baseline ($P \leq 0.05$).

Figure 5

The correlation between AHI and VAS score^a, weak acid reflux and VAS score^b, weak acid reflux and AHI^c.