Postprint of an Observational Study on the Efficacy of Continuous Positive Airway Pressure Therapy in Patients with Obstructive Sleep Apnea Comorbid with Gastroesophageal Reflux

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Abstract

Background Gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA) are both common clinical conditions with increasing prevalence. Whether continuous positive airway pressure (CPAP) can improve GERD while treating OSA remains controversial.

Objective To investigate the therapeutic efficacy of CPAP in patients with OSA complicated by GERD.

Methods A total of 169 patients with OSA complicated by GERD who were admitted to the Geriatrics Department and Respiratory Medicine Department of Peking University People's Hospital from September 2020 to January 2023 were enrolled as study subjects. General patient data were collected and regular follow-up was conducted, with the follow-up endpoint being GERD resolution or 8 weeks of treatment; patients without treatment compliance were excluded. Patients were divided into PPI-nonusers and PPI-users according to whether they took proton pump inhibitors (PPI), and then the PPI-nonusers were further divided into a CPAP group (n=43) and a no-treatment group (n=53) according to whether they received CPAP therapy, while PPI-users were divided into a CPAP+PPI group (n=32) and a PPI group (n=41). Kaplan-Meier method was used to plot survival curves for GERD resolution rates between the CPAP group and no-treatment group, as well as between the CPAP+PPI group and PPI group, with differences compared using Log-rank test. Multivariate Cox proportional hazards regression model analysis was employed to investigate the effect of CPAP on GERD resolution in patients with OSA complicated by GERD.

Results The median time to resolution was 6 weeks in the CPAP group and 7.5 weeks in the no-treatment group; the cumulative GERD resolution rate in the

CPAP group was higher than that in the no-treatment group, with a statistically significant difference (2=4.182, P=0.041). The median time to resolution was 3.9 weeks in the CPAP+PPI group and 6.1 weeks in the PPI group; the cumulative GERD resolution rate in the CPAP+PPI group was higher than that in the PPI group, with a statistically significant difference (2=14.333, P<0.001). Multivariate Cox proportional hazards regression model results showed that CPAP was an influencing factor for GERD resolution in patients with OSA complicated by GERD who did not use PPI [HR=2.360, 95%CI (1.044, 5.338)), P<0.05]. CPAP was also an influencing factor for GERD resolution in patients with OSA complicated by GERD who used PPI [HR=6.123; 95%CI (2.562, 14.635), P<0.05].

Conclusion CPAP therapy can improve GERD symptoms in patients with OSA complicated by GERD, and CPAP+PPI treatment is superior to PPI alone for GERD.

Full Text

The Efficacy of Continuous Airway Positive Pressure Ventilation on OSA Complicated with GERD: An Observational Study

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Abstract

Background: Gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA) are both common clinical conditions with increasing prevalence year by year. Whether continuous positive airway pressure (CPAP) can improve both OSA and GERD simultaneously remains controversial.

Objective: To investigate the efficacy of CPAP in patients with OSA complicated with GERD.

Methods: A total of 169 patients diagnosed with OSA complicated with GERD in the geriatric and respiratory departments of Peking University People's Hospital from September 2020 to January 2023 were enrolled. General patient data were collected, and participants were followed up regularly with the endpoint defined as GERD remission or completion of 8 weeks of treatment; those without treatment compliance were excluded. Patients were divided into PPI (proton pump inhibitor) users and non-users, then further stratified by CPAP treatment status: non-PPI patients were divided into CPAP group (n=43) and non-treatment group (n=53), while PPI users were divided into CPAP+PPI group

(n=32) and PPI group (n=41). Kaplan-Meier survival curves were plotted to compare GERD remission rates between CPAP and non-treatment groups, and between CPAP+PPI and PPI groups, with differences assessed using Log-rank tests. Multivariate Cox proportional hazards regression models were used to analyze the effect of CPAP on GERD remission in OSA patients.

Results: The median time to GERD remission was 6 weeks in the CPAP group versus 7.5 weeks in the non-treatment group, with the CPAP group showing a significantly higher cumulative GERD remission rate (^{2}=4.182, P=0.041). In the CPAP+PPI group, the median remission time was 3.9 weeks compared to 6.1 weeks in the PPI group, with the CPAP+PPI group demonstrating a significantly higher cumulative GERD remission rate (^{2}=14.333, P<0.001). Multivariate Cox regression revealed that CPAP was an independent factor for GERD remission in OSA patients without PPI use [HR=2.360, 95%CI (1.044, 5.338), P<0.05] and also in those using PPI [HR=6.123, 95%CI (2.562, 14.635), P<0.05].

Conclusion: CPAP therapy can improve GERD symptoms in patients with OSA complicated with GERD. CPAP combined with PPI is superior to PPI alone for treating GERD.

Keywords: Sleep apnea, obstructive; Gastroesophageal reflux; Continuous positive airway pressure; Proton pump inhibitors; Proportional hazards models

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1. Methods

1.1 Study Subjects and Inclusion/Exclusion Criteria

This study enrolled patients with OSA complicated with GERD who underwent polysomnography (PSG), portable monitoring (PM), and completed the gastroesophageal reflux disease questionnaire (GERDQ) in the geriatric and respiratory departments of Peking University People's Hospital between September 2020 and January 2023. Inclusion criteria were based on the "Guidelines for Primary Care of Obstructive Sleep Apnea in Adults" (2018), which defines OSA as apnea-hypopnea index (AHI) $ $5 events/hour, and the "Guidelines for Primary Care of Gastroesophageal Reflux Disease" (Practice Version 2019), which defines GERD as GERDQ score $ $8. The study was approved by the Medical Ethics Committee of Peking University People's Hospital (approval number: JKCJ202102).

Exclusion criteria included: (1) active malignancy, acute infection, severe cardiopulmonary dysfunction, Parkinson's disease, hypothyroidism, or other conditions affecting neuromuscular function; (2) history or current diagnosis of peptic ulcer, upper gastrointestinal malignancy, or pyloric obstruction; (3) prior diagnosis of OSA or GERD with ongoing CPAP or PPI treatment at enrollment; and (4) incomplete clinical data.

1.2 Grouping

This observational cohort study initially included 192 patients with OSA complicated with GERD. Patients were first divided into PPI users (n=85) and non-users (n=107) based on proton pump inhibitor administration. They were then further stratified by CPAP treatment status: PPI users were divided into CPAP+PPI group (n=38) and PPI group (n=47), while non-PPI users were divided into CPAP group (n=48) and non-treatment group (n=59). Treatment compliance was assessed at 4 weeks: CPAP compliance was defined as regular nightly use >4 hours, and PPI compliance as adherence to prescribed therapy. Patients who discontinued or added CPAP or PPI treatment on their own were excluded. After 8 weeks, 10 patients were excluded and 13 were lost to follow-up, leaving final cohorts of 32 in CPAP+PPI group, 41 in PPI group, 43 in CPAP group, and 53 in non-treatment group. Comparative analyses of GERD remission and medication discontinuation rates were then performed between CPAP+PPI versus PPI groups, and CPAP versus non-treatment groups.

1.3 Data Collection

Baseline data collected included gender, age, height, weight, BMI, smoking and alcohol history (defined as continuous or cumulative use $ $1 year), baseline GERDQ score, and sleep monitoring parameters [AHI, oxygen desaturation index (ODI3, number of nocturnal oxygen drops >3%), lowest nocturnal oxygen saturation (LSpO2), and mean nocturnal SpO2 (MSpO2)]. Patients were followed up by telephone at 2, 4, 6, and 8 weeks to assess GERDQ scores, PPI discontinuation time, and compliance with CPAP and PPI therapy. GERD remission was defined as GERDQ score <8 with positive symptom score <1, based on the "Guidelines for Primary Care of Gastroesophageal Reflux Disease" (2019), with follow-up ending at symptom remission or 8 weeks.

1.4 Statistical Analysis

Data were analyzed using SPSS 26.0. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared between groups using independent samples t-tests. Non-normally distributed variables were expressed as median (P25, P75) and compared using rank-sum tests. Categorical data were expressed as frequencies and compared using ^{2} tests. Kaplan-Meier survival curves were plotted with 8 weeks or GERD symptom remission as the endpoint to calculate cumulative GERD remission rates, with between-group differences assessed using Log-rank tests. Cox proportional hazards regression models were used to analyze the association between CPAP treatment and GERD remission, calculating hazard ratios (HR) and 95% confidence intervals (CI). Statistical significance was defined as $P<0.05$.

2. Results

2.1 CPAP Group Versus Non-Treatment Group

2.1.1 Baseline Characteristics The CPAP group had significantly higher proportions of males and alcohol users, higher positive symptom scores, AHI, and ODI3 compared to the non-treatment group (P<0.05). The CPAP group was significantly younger with lower GERDQ scores, LSpO2, and MSpO2 (P<0.05). No significant differences were observed in BMI or smoking history between groups (P>0.05) .

2.1.2 Treatment Outcomes No significant difference in GERD remission rates was observed at 2 weeks between groups (P>0.05). However, the CPAP group showed significantly lower GERDQ scores and positive symptom scores at 8 weeks, and significantly higher GERD remission rates at 4, 6, and 8 weeks compared to the non-treatment group (P<0.05) .

2.1.3 Survival Analysis Kaplan-Meier survival curves comparing GERD remission between groups showed a median remission time of 6 weeks in the CPAP group versus 7.5 weeks in the non-treatment group. The CPAP group demonstrated a significantly higher cumulative GERD remission rate (^{2}=4.182, P=0.041) [Figure 1: see original paper].

2.1.4 Multivariate Cox Regression Analysis in Non-PPI Patients Using GERD remission (no=0, yes=1) as the dependent variable and CPAP use (no=0, yes=1) as the independent variable, with adjustment for gender (female=0, male=1), age (<60 years=0, $ 60$years = 1), BMI(< 28$kg/m^{2}$=0, $ 28kg/m^{2}=1), AHI (<30 events/h=0, $ 30$events/h = 1), and alcohol/tobacco use(no = 0, yes = 1), multivariate Cox proportional hazards regression revealed that CP 0.859, SE = 0.416, Wald χ^{2}=4.254, HR=2.360, 95%CI (1.044, 5.338), P<0.05].

2.2 CPAP+PPI Group Versus PPI Group

2.2.1 Baseline Characteristics No significant differences were observed between CPAP+PPI and PPI groups in gender, age, BMI, smoking history, alcohol history, GERDQ score, AHI, ODI3, LSpO2, or MSpO2 (P>0.05) .

2.2.2 Treatment Outcomes While no significant differences were found in 8-week GERDQ scores or positive symptom scores between groups (P>0.05), the CPAP+PPI group demonstrated significantly higher GERD remission rates at 2, 4, and 6 weeks, and a significantly higher medication discontinuation rate at 8 weeks compared to the PPI group (P<0.05) .

2.2.3 Survival Analysis Kaplan-Meier survival analysis with GERD remission or 8 weeks as the endpoint showed a median remission time of 3.9 weeks

in the CPAP+PPI group versus 6.1 weeks in the PPI group. The CPAP+PPI group had a significantly higher cumulative GERD remission rate (^{2}=14.333, P<0.001) [Figure 2: see original paper].

2.2.4 Multivariate Cox Regression Analysis in PPI Users Multivariate Cox regression analysis (with the same variable definitions as above) showed that CPAP treatment was an independent factor for GERD remission in OSA patients using PPI [B=1.812, SE=0.445, Wald ^{2}=16.612, HR=6.123, 95%CI (2.562, 14.635), P<0.05].

3. Discussion

Current research suggests that OSA and GERD influence each other, creating a vicious cycle where treating one condition can positively impact the other. CPAP is the first-line treatment for OSA, yet its effect on reflux remains controversial. This study demonstrates that CPAP therapy improves GERD symptoms in patients with OSA complicated with GERD. A 2021 Chinese meta-analysis incorporating two GERD symptom scores and four pH monitoring indices confirmed that CPAP treatment improves various reflux-related parameters while treating OSA, consistent with our findings. Similarly, Kerr et al. reported reduced reflux symptoms in OSA patients after CPAP treatment.

This therapeutic effect may relate to increased intrathoracic pressure from CPAP, which reduces inspiratory effort, increases esophageal pressure, and decreases airway obstruction, leading to fewer arousals and movements, thereby reducing gastroesophageal reflux (GER) risk. Studies using simultaneous polysomnography and esophageal impedance-pH monitoring found that nocturnal GER events primarily occur after nighttime arousals; by improving upper airway obstruction, CPAP reduces these arousals and consequently reflux events. Jung et al. suggested that CPAP-induced reflux improvement results from increased esophageal pressure and lower esophageal sphincter (LES) pressure, though this mechanism may not be specific to OSA patients. In contrast, Kerr et al. found LES pressure was not crucial in GER reduction. Nocturnal CPAP therapy reduces acid contact time, indicating an independent positive effect on GER. Other research shows CPAP can reduce transient lower esophageal sphincter relaxation (TLESR) frequency by nearly half without changing baseline esophageal or LES pressure. Recent studies also indicate CPAP therapy improves not only GER symptoms but also GERD-related chronic cough and laryngopharyngeal reflux.

However, some studies report CPAP increases GER. Watson et al. observed increased GER frequency in 22 OSA patients on CPAP, possibly related to aerophagia during treatment. Shepherd et al. found high GER frequency in aerophagic patients, and CPAP can cause aerophagia. Some researchers propose that aerophagia may exacerbate GER, particularly nocturnal GER, by causing gastric distension that triggers transient esophageal relaxation. During sleep, upper esophageal pressure decreases, allowing air to move more easily into

the esophagus under CPAP pressure; increased upper esophageal intraluminal pressure may trigger non-swallowing esophageal peristalsis and air movement into the stomach. Esophageal dilation by air has been shown to trigger LES relaxation, promoting further air entry. Resulting gastric distension can trigger vagally-mediated TLESR, and since GER events primarily occur during increased TLESR, aerophagia-induced GER may result from increased TLESR frequency. Conversely, Bredenoord et al. monitored esophageal impedance, pH, and pressure in patients with and without GERD before and after gastric air insufflation, finding that while air perfusion increased gas reflux, acid reflux events did not increase. Sifrim et al. also found that the liquid component of GER occurs as the primary event, independent of gas, suggesting aerophagia may not cause GERD. Ozcelik et al. compared mean lower esophageal sphincter pressure and DeMeester scores before and after CPAP, finding no significant differences ($P>0.05$), concluding CPAP does not trigger GERD.

Our study found that CPAP significantly improves subjective reflux symptoms in shorter time, with higher PPI discontinuation rates after 8 weeks. Regarding symptom improvement and medication discontinuation, CPAP combined with PPI is significantly superior to PPI alone, and CPAP alone can improve or even cure GERD in some patients.

However, this study has limitations. First, treatment selection was made by patients after physician consultation, so baseline characteristics were not perfectly matched. Some patients refused CPAP due to gastrointestinal bloating, dry mouth, inability to sleep, poor adherence, or perceived minimal OSA impact, opting for PPI alone. Others refused PPI due to mild reflux symptoms or preference for milder antacids, choosing CPAP alone. Some with mild OSA and GERD attempted lifestyle modifications, refusing both treatments. These baseline differences may have affected outcomes. Second, this study relied primarily on questionnaires and subjective reflux assessments, without objective parameters such as esophageal pressure or pH changes before and after treatment. Large-sample, prospective studies with objective measures are needed for further validation.

In conclusion, CPAP therapy improves reflux symptoms in OSA patients complicated with GERD and increases PPI discontinuation rates. In OSA patients with GERD, CPAP combined with PPI is significantly superior to PPI alone, and CPAP alone shows better GERD symptom improvement than no treatment. Clinically, CPAP should be actively added when managing OSA complicated with GERD to achieve better and faster symptom relief.

Author Contributions

DENG Jingjing and WANG Jingtong designed the study protocol. DENG Jingjing selected participants and collected data. DENG Jingjing, XUE Qian, and DENG Lihua performed statistical analysis and created figures. DENG Jingjing, LI Xia, and WANG Jingtong drafted the manuscript. DENG Jingjing

and WANG Jingtong revised the final version and take responsibility for the paper.

Conflicts of Interest: None declared.

References

[1] WANG L, HAN H L, WANG G, et al. Relationship between reflux diseases and obstructive sleep apnea together with continuous positive airway pressure treatment efficiency analysis[J]. Sleep Med, 2020, 75:151-155. DOI:10.1016/j.sleep.2020.07.024.

[2] WOLF S M, FURMAN Y. Sleep apnea and gastroesophageal reflux disease[J]. Ann Intern Med, 2002, 136(6):490. DOI:10.7326/0003-4819-136-6-200203190-00020.

[3] ON Z X, GRANT J, SHI Z M, et al. The association between gastroesophageal reflux disease with sleep quality, depression, and anxiety in a cohort study of Australian men[J]. J Gastroenterol Hepatol, 2017, 32(6):1170-1177. DOI:10.1111/jgh.13650.

[4] MAHFOUZ R, BARCHUK A, OBEIDAT A E, et al. The relationship between obstructive sleep apnea (OSA) and gastroesophageal reflux disease (GERD) in inpatient settings: a nationwide study[J]. Cureus, 2022, 14(3):e22810. DOI:10.7759/cureus.22810.

[5] PENZEL T, BECKER H F, BRANDENBURG U, et al. Arousal in patients with gastro-oesophageal reflux and sleep apnoea[J]. Eur Respir J, 1999, 14(6):1266-1270. DOI:10.1183/09031936.99.14612669.

[6] GUDA N, PARTINGTON S, VAKIL N. Symptomatic gastro-oesophageal reflux, arousals and sleep quality in patients undergoing polysomnography for possible obstructive sleep apnoea[J]. Aliment Pharmacol Ther, 2004, 20(10):1153-1159. DOI:10.1111/j.1365-2036.2004.02263.x.

[7] YANG Y X, SPENCER G, SCHUTTE-RODIN S, et al. Gastroesophageal reflux and sleep events in obstructive sleep apnea[J]. Eur J Gastroenterol Hepatol, 2013, 25(9):1017-1023. DOI:10.1097/MEG.0b013e32836282cf.

[8] HE J, WANG C M, LI W C. Laryngopharyngeal reflux in obstructive sleep apnea-hypopnea syndrome: an updated meta-analysis[J]. Nat Sci Sleep, 2022, 14:2189-2201. DOI:10.2147/NSS.S390272.

[9] JECKER P, RASSOULI S, SELIVANOVA O, et al. No correlation between reflux of gastric contents and obstructive sleep apnea[J]. HNO, 2008, 56(11):1122-1128. DOI:10.1007/s00106-008-1733-y.

[10] TAMANNA S, CAMPBELL D, WARREN R, et al. Effect of CPAP therapy on symptoms of nocturnal gastroesophageal reflux among patients with obstructive sleep apnea[J]. J Clin Sleep Med, 2016, 12(9):1257-1261. DOI:10.5664/jcsm.6126.

[11] SHEPHERD K, HILLMAN D, EASTWOOD P. Symptoms of aerophagia are common in patients on continuous positive airway pressure therapy and are related to the presence of nighttime gastroesophageal reflux[J]. J Clin Sleep Med, 2013, 9(1):13-17. DOI:10.5664/jcsm.2328.

[12] SHEPHERD K, HILLMAN D, EASTWOOD P. CPAP-induced aerophagia may precipitate gastroesophageal reflux[J]. J Clin Sleep Med, 2013, 9(6):633-634. DOI:10.5664/jcsm.2776.

[13] LIM K G, MORGENTHALER T I, KATZKA D A. Sleep and nocturnal gastroesophageal reflux: an update[J]. Chest, 2018, 154(4):963-971. DOI:10.1016/j.chest.2018.05.030.

[14] IZCI BALSERAK B. Special issue: the diagnosis and management of OSA[J]. Diagnostics (Basel), 2022, 12(8):1919. DOI:10.3390/diagnostics12081919.

[15] LI C, WU Z H, PAN X L, et al. Effect of continuous positive airway pressure on gastroesophageal reflux in patients with obstructive sleep apnea: a meta-analysis[J]. Schlaf Atmung, 2021, 25(3):1203-1210. DOI:10.1007/s11325-020-02224-5.

[16] KERR P, SHOENUT J P, MILLAR T, et al. Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome[J]. Chest, 1992, 101(6):1539-1544. DOI:10.1378/chest.101.6.1539.

[17] JAIMCHARIYATAM N, TANTIPORNSINCHAI W, DESUDCHIT T, et al. Association between respiratory events and nocturnal gastroesophageal reflux events in patients with coexisting obstructive sleep apnea and gastroesophageal reflux disease[J]. Sleep Med, 2016, 22:33-38. DOI:10.1016/j.sleep.2016.04.013.

[18] JUNG H K, CHOUNG R S, TALLEY N J. Gastroesophageal reflux disease and sleep disorders: evidence for a causal link and therapeutic implications[J]. J Neurogastroenterol Motil, 2010, 16(1):22-29. DOI:10.5056/jnm.2010.16.1.22.

[19] TAWK M, GOODRICH S, KINASEWITZ G, et al. The effect of 1 week of continuous positive airway pressure treatment in obstructive sleep apnea patients with concomitant gastroesophageal reflux[J]. J Clin Sleep Med, 2016, 12(9):1257-1261. DOI:10.5664/jcsm.6126.

[20] SHEPHERD K, HILLMAN D, HOLLOWAY R, et al. Mechanisms of nocturnal gastroesophageal reflux events in obstructive sleep apnea[J]. Schlaf Atmung, 2011, 15(3):561-570. DOI:10.1007/s11325-010-0404-x.

[21] SU J, FANG Y F, MENG Y, et al. Effect of continuous positive airway pressure on chronic cough in patients with obstructive sleep apnea and concomitant gastroesophageal reflux[J]. Nat Sci Sleep, 2022, 14:13-23. DOI:10.2147/NSS.S341400.

[22] WATSON N F, MYSTKOWSKI S K. Aerophagia and gastroesophageal reflux disease in patients using continuous positive airway pressure: a preliminary observation[J]. J Clin Sleep Med, 2008, 4(5):434-438.

[23] EASTWOOD P R, KATAGIRI S, SHEPHERD K L, et al. Modulation of upper and lower esophageal sphincter tone during sleep[J]. Sleep Med, 2007, 8(2):135-143. DOI:10.1016/j.sleep.2006.08.016.

[24] SCHOEMAN M N, HOLLOWAY R H. Stimulation and characteristics of secondary oesophageal peristalsis in normal subjects[J]. Gut, 1994, 35(2):152-158. DOI:10.1136/gut.35.2.152.

[25] BREDENOORD A J, WEUSTEN B L A M, TIMMER R, et al. Relationships between air swallowing, intragastric air, belching and gastro-oesophageal reflux[J]. Neurogastroenterol Motil, 2005, 17(3):341-347. DOI:10.1111/j.1365-2982.2004.00626.x.

[26] SIFRIM D, SILNY J, HOLLOWAY R H, et al. Patterns of gas and liquid reflux during transient lower oesophageal sphincter relaxation: a study using intraluminal electrical impedance[J]. Gut, 1999, 44(1):47-54. DOI:10.1136/gut.44.1.47.

[27] OZCELIK H, KAYAR Y, DANALIOGLU A, et al. Does CPAP treatment lead to gastroesophageal reflux in patients with moderate and severe OSA?[J]. Eur Arch Otorhinolaryngol, 2017, 274(3):1223-1229. DOI:10.1007/s00405-016-4116-0.

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Note: Figure translations are in progress. See original paper for figures.