

Impact of Treatment of Gastroesophageal Reflux on Obstructive Sleep Apnea-Hypopnea Syndrome

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Objectives: We test the hypothesis that treatment of gastroesophageal reflux disease (GERD) can improve obstructive sleep apnea-hypopnea syndrome (OSAHS).

Methods: One hundred forty-six patients with OSAHS underwent a complete history-taking, physical examination, and laboratory testing, including questions related to GERD symptoms. Full-night attended polysomnography, 24-hour wireless pH study at the upper esophagus, snoring level evaluation, Epworth Sleepiness Scale, and quality-of-life surveys were completed for each patient. Patients who tested positive for GERD were treated with esomeprazole magnesium 40 mg once daily for 2 to 12 months. The 24-hour pH study was repeated, and those patients with elimination of GERD were reevaluated by polysomnography, snoring level evaluation, Epworth Sleepiness Scale, quality-of-life surveys, and subjective data collection.

Results: Forty-one patients completed single-dose treatment with esomeprazole, but the repeat 24-hour pH study showed that 9 patients had persistent GERD. In the 29 patients who completed phase 2 with normal pH study findings, the snoring level decreased from 9.7 ± 0.5 to 7.9 ± 1.3 ($p < .0001$), the Epworth Sleepiness Scale score decreased from 14.2 ± 2.5 to 11.1 ± 2.4 ($p < .0001$), the apnea-hypopnea index decreased from 37.9 ± 19.1 to 28.8 ± 11.5 ($p = .006$), and the minimum saturation of oxygen increased from $84.1\% \pm 7.8\%$ to $86.9\% \pm 5.0\%$ ($p = .055$).

Conclusions: Treatment of GERD had a significant impact on the reduction of the apnea-hypopnea index, snoring, and daytime sleepiness. Elimination of GERD should be part of a comprehensive treatment plan for patients with OSAHS.

Key Words: adjunctive treatment, gastroesophageal reflux, laryngopharyngeal reflux, obstructive sleep apnea-hypopnea syndrome, proton pump inhibitor therapy.

INTRODUCTION

Gastroesophageal reflux disease (GERD) and obstructive sleep apnea-hypopnea syndrome (OSAHS) are common comorbid conditions that share risk factors.^{1,2} It is well documented that each of these diseases adversely affects both the symptoms and the severity of the comorbid condition. Many studies have looked at the impact of OSAHS treatment on elimination or reduction of reflux disease.³⁻⁶ Other studies have looked at the opposite approach, treating reflux with the hope of improving symptoms of OSAHS.⁷⁻¹²

Gastroesophageal reflux disease and laryngopharyngeal reflux disease (LPR) may increase the symptoms and findings of OSAHS in several ways. Arousals caused by reflux may increase daytime somnolence.^{1,13,14} In addition, repeated reflux

causes tissue swelling, and this contributes to further airway obstruction.

Theoretically, therefore, control of reflux may improve both subjective and objective findings of OSAHS. Several attempts have been made by different investigators to determine whether antireflux treatment may indeed improve OSAHS, with variable results.⁷⁻¹² This study was designed to further test the hypothesis that elimination of GERD may improve the subjective and objective findings of OSAHS. Patients with comorbid conditions of GERD and OSAHS proven by 24-hour pH-monitoring studies and overnight polysomnograms (PSGs) were treated with a proton pump inhibitor (PPI) for 2 to 6 months and then retested and reevaluated for assessment of both subjective and objective changes.

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METHODS

This is phase 2 of a 2-part study designed as a prospective clinical trial in a tertiary care academic center approved by our Institutional Review Board (Advocate Illinois Masonic Medical Center). Phase 1 of this study, which has been previously reported, assessed the incidence of upper esophageal reflux disease in unselected patients with OSAHS.¹⁵ One hundred forty-six patients who were seeking treatment for snoring and other symptoms of OSAHS were recruited to participate in this study. Eighty-nine patients with OSAHS documented by means of full-night attended PSGs with or without symptoms of LPR or GERD were selected as candidates to undergo transnasal wireless 24-hour pH monitoring studies (Bravo, Medtronic, Shoreview, Minnesota) and were prospectively studied. The Bravo capsule was placed in the upper esophagus 5 cm below the cricopharyngeus in order to study upper esophageal reflux. Confirmation of its location was performed by transnasal esophagoscopy. Of these 89 patients, 77 successfully completed a 24-hour pH study, and 52 were found to have evidence of GERD. These 52 patients were enrolled in this second phase of the study, which involved treatment with PPI therapy (esomeprazole magnesium, 40 mg once daily) for 2 to 6 months. Although the minimum treatment was designed as 2 months, many patients extended this treatment course until they were available to undergo the repeat testing. All patients, however, were kept on therapy until their posttreatment testing could be completed. Forty-one of these patients eventually underwent their posttreatment pH monitoring study. Of these 41 patients, 9 were found to have persistent evidence of GERD after once-daily treatment with 40 mg of esomeprazole and were therefore excluded from the study. Thirty-two of the patients were found to have negative pH studies after treatment. Of these 32 patients, 29 completed a second-night PSG and questionnaires regarding quality of life (QOL) and symptoms associated with snoring and OSAHS. These 29 patients were the basis of our study.

The outcome data that were assessed included the following points: change in apnea-hypopnea index (AHI) and minimum saturation of oxygen (Min SaO₂), change in snoring visual analog scale (VAS; 0 to 10) as assessed by bed-partner, Epworth Sleepiness Scale (ESS), and QOL surveys (SF-36 v2).

All statistical analyses were performed with SPSS version 11.0.1 (SPSS, Inc, Chicago, Illinois). Continuous data are displayed as mean \pm SD. Statistical significance was accepted when the *p* value was less than .05. Intention-to-treat analysis was performed.

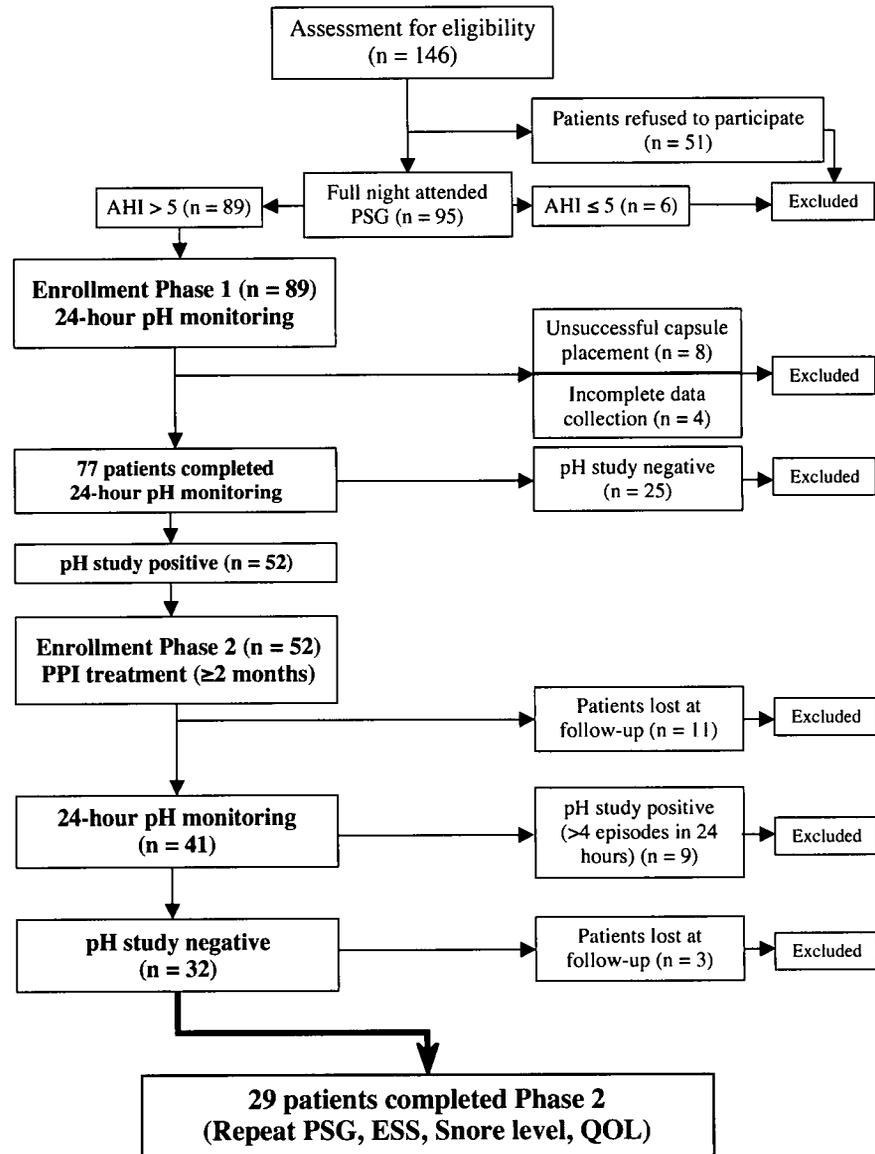
Levine's test for equality of variances was used to determine statistically significant variances. The paired Student's *t*-test was used to compare preoperative versus postoperative mean values within each group. The χ^2 test was used to test the association between categorical variables.

RESULTS

A flowchart of this study is illustrated in the Figure. Twenty-four-hour pH monitoring data were collected on 77 patients. The pH study was negative (fewer than 4 episodes of pH of 4 or less during the 24-hour period) in 25 patients. These patients were excluded from the study. Thus, 52 patients entered into phase 2, in which GERD was treated for a minimum period of 2 months with esomeprazole. The patients were kept on therapy until their posttreatment pH study and PSGs were completed. The duration of therapy therefore ranged from 60 to 360 days (mean \pm SD, 155.45 \pm 91.80 days). Eleven patients were lost to follow-up during the treatment phase. Posttreatment pH monitoring revealed positive findings for GERD in 9 patients despite treatment, leaving 32 patients negative for GERD. Three additional patients were lost to follow-up before undergoing the posttreatment PSG and QOL survey. Nevertheless, an intention-to-treat analysis looking at objective treatment success was performed on all 52 patients who received the initial study treatment. The 14 patients who were lost to follow-up, as well as the 9 patients with positive GERD despite treatment, were considered treatment failures and analyzed accordingly. Table 1 displays the results of that analysis. The true purpose of this study, however, was not an attempt to cure OSAHS with PPI therapy, but to assess the impact of complete elimination of GERD on signs and symptoms of OSAHS. Therefore, all additional results are reported on the remaining 29 patients (12 men and 17 women) who had normalized pH studies and completed the follow-up. Their mean age was 44.8 \pm 13.3 years, and their mean body mass index was 33.0 \pm 7.8 kg/m².

Complications and Long-Term Morbidity. There was no morbidity or complications in phase 2 of the study.

Subjective Symptom Elimination. Patients' and bed-partners' subjective assessments of disease severity (snoring level and ESS) were collected before treatment and at the time of follow-up after a minimum of 2 months' treatment with PPIs. When we compared the snoring VAS and ESS scores obtained before treatment with the posttreatment values, we found that both had decreased significantly. The mean snoring VAS score decreased from 9.7



Flowchart of study. AHI — apnea-hypopnea index; PSG — polysomnogram; PPI — proton pump inhibitor; ESS — Epworth Sleepiness Scale; QOL — quality of life.

± 0.5 before treatment to 7.9 ± 1.3 after treatment. The mean ESS score decreased from 14.2 ± 2.5 before treatment to 11.1 ± 2.4 after treatment. Both of these decreases were statistically significant ($p < .0001$; Table 2). This represented a mean $18.5\% \pm 14.9\%$ reduction in snoring level and a mean $21.3\% \pm 15.6\%$ reduction in ESS score.

Because nearly all of the patients originally sought treatment for loud snoring, we also determined a subjective improvement of the patients' snoring symptoms using strict criteria, which required a 50% decrease in snoring level after therapy. Subjective improvement was encountered in 2 of 29 patients (6.9%).

SF-36 v2 Quality-of-Life Health Survey. All 29 patients completed the SF-36 v2 Health Survey before and after treatment. Scores from 0 to 100 (100 being the best health) were obtained for all 29 pa-

tients in each of the 8 domains both before and after treatment (Table 3). The posttreatment improvement in mean scores was statistically significant ($p < .05$) for 4 of the 8 domains. These included the domains for bodily pain, general health, vitality/energy, and mental health.

Objective Polysomnographic Changes. Objective measures of clinical improvement of OSAHS were based on data collected during PSG. Table 2 compares the AHI, apnea index (AI), and Min SaO₂ obtained before treatment with those obtained after treatment. The mean AHI and AI improved significantly after PPI therapy. No significant change in Min SaO₂ was identified.

Using the classic definition of the successful treatment of OSAHS¹⁶ (which requires a 50% or greater reduction in posttreatment AHI as compared with the pretreatment value, and a posttreatment AHI of

TABLE 1. INTENT-TO-TREAT ANALYSIS FOR SUCCESSFUL TREATMENT OF OBSTRUCTIVE SLEEP APNEA-HYPOPNEA SYNDROME

	Apnea-Hypopnea Index Criteria	Lost to Follow-Up	Positive Posttherapy pH Study	Total
Success	2	0	0	2 (3.9%)
No success	27	14	9	50 (96.1%)

Data are numbers of patients.

less than 20), we determined the success or failure of PPI treatment of LPR in each patient. Objective cure of OSAHS was encountered in 2 of 29 patients (6.9%), the same 2 patients who experienced subjective improvement as noted above.

DISCUSSION

Previous studies have implicated both GERD and LPR as factors in causing or exacerbating OSAHS.^{1,17,18} Several mechanisms are postulated to take place in that chain of events; acid reflux to the esophagus stimulates the vagus nerve and causes bronchoconstriction that starts the short-term damage.^{13,14} Also, irritation and damage of the upper airway mucosa caused by acid reflux begins an exudative mucosal reaction, causing a long-term effect.¹⁰

Although some studies have demonstrated that GERD causes OSAHS, other studies have demonstrated that OSAHS may cause or aggravate GERD.¹⁴ The increase in the negative intrathoracic pressure created by OSAHS causes a vacuum-like effect on the gastric contents, leading to GERD and LPR. Also, the phrenoesophageal ligament, connecting the diaphragm to the lower esophageal sphincter, experiences increased tension during upper airway resistance and obstructive sleep-disordered breathing. When the force transmitted to the lower esophageal sphincter exceeds the threshold, the lower esophageal sphincter will open and allow gastric contents to enter the esophagus.^{19,20} Several studies

TABLE 2. COMPARISON OF PRETREATMENT AND POSTTREATMENT DATA

Parameter	Before Treatment	After Treatment	p
Apnea-hypopnea index	37.9 ± 19.1	28.8 ± 11.5	.006*
Apnea index	5.9 ± 7.2	3.8 ± 4.7	.04*
Minimum saturation of oxygen (%)	84.1 ± 7.8	86.9 ± 5.0	.055
Epworth Sleepiness Scale (1-24)	14.2 ± 2.5	11.1 ± 2.4	<.0001*
Snoring level (visual analog scale, 0-10)	9.7 ± 0.5	7.9 ± 1.3	<.0001*

Data are mean ± SD for 29 patients.
*Statistically significant difference (p < .05).

TABLE 3. COMPARISON OF PRETREATMENT VERSUS POSTTREATMENT QUALITY-OF-LIFE VALUES FOR EACH OF EIGHT SF-36 v2 HEALTH DOMAINS

Parameter	Before Treatment	After Treatment	p
Physical function	84.8 ± 20.4	90.0 ± 20.5	.455
Role limitation/physical problem	71.3 ± 23.3	73.4 ± 16.7	.737
Bodily pain	84.1 ± 16.0	100.0 ± 0.0	<.0001*
General health	51.5 ± 17.5	86.3 ± 14.6	<.0001*
Vital energy/fatigue	32.8 ± 16.8	57.8 ± 11.1	<.0001*
Social function	78.9 ± 17.2	78.9 ± 8.4	1.000
Role limitation/emotional problem	67.1 ± 25.9	72.9 ± 16.2	.386
Mental health	44.5 ± 20.2	59.7 ± 11.2	.008*

Score of 0 to 100 is calculated for each domain according to patient responses; score of 100 represents best possible health. Data are mean ± SD.
*Statistically significant (p < .05).

have shown that the incidence of GERD is statistically higher in patients with OSAHS.^{3,9,11,13,15,18,21} This is the second phase of a study of the senior author's (M.F.). In the first study, our group investigated the incidence of GERD based on upper esophageal monitoring in patients with OSAHS; 71.4% of OSAHS patients had positive pH studies, and 10.4% of these patients reported no symptoms and had no signs of upper esophageal reflux, ie, had occult disease.¹⁵

Continuous positive airway pressure (CPAP), when used to treat OSAHS, has been found to have a positive impact on the control of GERD. Some researchers have postulated that the treatment of OSAHS breaks the OSAHS-GERD loop, and several studies have shown a statistically significant reduction of GERD in patients on CPAP therapy.³⁻⁶ Others postulate that in addition to eliminating OSAHS, CPAP may have a direct beneficial effect in reduction of GERD by applying a positive pressure through the upper airway to the esophagus and preventing the contents of the stomach from entering the upper airway.^{2,6} This study was designed to determine whether elimination of reflux disease as an isolated treatment can affect the signs and symptoms of OSAHS. Therefore, no additional treatment was given during the studied time period. This study was designed for 60 days. The patients who registered for this study were given a full explanation that this study would not offer them traditional treatment such as CPAP for this period of time. The patients all agreed to this isolated form of treatment as part of this study. Many of the patients delayed their posttreatment studies beyond the 2-month recommendation of the study and stayed on PPI therapy until the study was completed. The patients were not asked to make any other

change in their lifestyle, diet, or medical care during the period of this study. Therefore, the raw data indicate no significant difference between pretreatment and posttreatment body mass indices.

Just as treatment of OSAHS has a positive impact on GERD, other studies have shown that treatment of GERD has a positive impact on control of OSAHS. In 2001, Senior et al¹¹ reported a study on 10 patients with OSAHS confirmed by overnight PSGs and GERD confirmed by pH monitoring. Patients received 20 mg of omeprazole twice a day for 30 days. Assessment of the AHI and AI showed a statistically significant difference between the pretreatment and posttreatment states, favoring the latter by 25% for the AHI and showing a 31% decline in AI for the experimental group. This pilot study was the stimulus for many other projects to confirm these initial findings.¹¹

In 2004, Steward⁷ treated 27 symptomatic GERD patients with mild to moderate OSAHS for 3 months with pantoprazole 40 mg daily. Pretreatment PSGs were performed, but acid reflux was determined by symptom questionnaire only. Posttreatment daytime somnolence, total reflux symptoms, and bed-partner assessment of snoring were shown to be significantly improved, but the snoring quantification, AI, and AHI remained unchanged.⁷ No pretreatment or posttreatment pH studies were performed. It is therefore difficult to determine whether AHI reduction was not achieved because of failure to eliminate LPR and GERD or because elimination of GERD does not improve AHI.

Chand et al¹² studied 18 patients with GERD to determine whether elimination of GERD would improve their sleep. They used the Pittsburgh Sleep Quality Index questionnaire in assessing OSAHS. Esomeprazole (40 mg) was given once daily for 8 weeks. The posttreatment Pittsburgh Sleep Quality Index decreased after 8 weeks, showing that OSAHS symptoms can be treated by antireflux therapy. They, however, did not perform pretreatment or posttreatment PSGs for evaluating OSAHS, nor did they perform pH studies.

In 2006, Bortolotti et al⁸ treated 20 patients with OSAHS (confirmed by PSGs) and GERD (confirmed by pH monitoring) divided into 2 groups as study and control. The study group received omeprazole 20 mg twice daily while the control group received a placebo twice daily for 6 weeks. They found that the weekly frequency of apnea attacks decreased by 73% in the 6 weeks, and concluded that the occurrence of apnea attacks progressively decreased in the study group with respect to the basal period and was significantly lower than that of the control

group. They reported no data on the AHI.

An adequate treatment period for upper esophageal reflux disease is considered to be 4 weeks to 6 months,²² and although the short-term treatment protocols are effective, the rate of relapse within 1 year is as high as 90%. Within 2 to 3 months of treatment, most patients report significant symptomatic improvement; however, it takes 6 months or longer for the laryngeal findings of upper esophageal reflux to resolve.^{23,24} We used once-daily esomeprazole on the basis of studies that showed it to be effective in achieving adequate reflux suppression in clinical trials.^{25,26} Thus, we treated our patients with 40 mg of esomeprazole once daily for 2 to 12 months. After treatment, 24-hour esophageal pH monitoring was repeated. Although symptoms of GERD were eliminated in all patients, 9 of 41 patients (21.9%) who had persistently positive pH studies were excluded. Patients with normalized posttreatment pH studies achieved improvement in both subjective and objective data that indicated improvement but not cure of OSAHS. We arbitrarily chose 4 episodes of upper esophageal reflux as being positive for "GERD" on the basis of pharyngeal reflux studies.²⁷ All previous studies focused on the effect of GERD treatment on symptoms of OSAHS. This is the first study to focus on patients with negative upper esophageal monitoring indicating the elimination of GERD. It is well known that patients may have residual GERD even in the absence of classic symptoms.

This study has many limitations. Although it was designed and planned as a prospective study, it did not include a placebo-controlled arm. This would have been ideal, and such a study is ongoing. The initial study was designed to determine whether there is a positive effect on signs and symptoms of OSAHS with the elimination of reflux disease as an isolated treatment.

This study clearly supports some of the earlier work indicating the benefit of PPI therapy for patients with OSAHS. Although the incidence of occult GERD was over 10% in our patient population, the routine use of pH monitoring without subjective symptoms or physical findings is probably not warranted. In addition, routine treatment with PPI therapy for all patients with OSAHS cannot be recommended on the basis of this study. From a clinical stance, however, it becomes apparent that aggressive control of signs or symptoms of reflux disease is an important component in treatment of patients with OSAHS. Although patients with classic symptoms of GERD are willing to take medication to prevent the symptoms, most patients with only mild symptoms and no classic symptoms of heartburn of-

ten are noncompliant with ongoing treatment for reflux. Otolaryngologists are also often unconvinced of the benefit of PPI therapy for patients who have only laryngeal findings suggestive of LPR and no symptoms. According to this study, the combination of OSAHS with clinical evidence of GERD should be a basis for either pH monitoring studies or ongoing treatment with PPIs.

An ideal study would have been double-blinded and randomized. Although this study was prospective, the patients served as their own control group in the pretreatment phase. A randomized control group would have been ideal. Another limitation of this study is that the minimum treatment duration was as low as 60 days. It is possible that further improvement might have occurred in a more extended study. The mean duration, however, of treatment was 155 days, and therefore most patients probably did achieve maximal improvement. The study was difficult for patients because of the required pH monitoring studies. The discomfort associated with the studies caused a considerably large number of patients

to drop out of the study before completion.

CONCLUSIONS

Gastroesophageal reflux disease and OSAHS are common comorbid conditions. In patients with both conditions, adequate treatment of GERD with esomeprazole was effective in reduction of the subjective and objective findings of OSAHS. When pretreatment and posttreatment snoring VAS and ESS scores were compared, both snoring scores were seen to have decreased significantly. The mean snoring VAS score decreased from 9.7 ± 0.5 before treatment to 7.9 ± 1.3 after treatment, and the mean ESS score decreased from 14.2 ± 2.5 before treatment to 11.1 ± 2.4 after treatment ($p < .0001$). The AHI decreased from 37.9 ± 19.1 before treatment to 28.8 ± 11.5 after treatment. Objective cure of OSAHS was achieved in only 2 of 29 patients (6.9%). In patients with OSAHS and physical findings suggestive of GERD, PPI therapy may be an important adjunct in the control of OSAHS symptoms. Also, pH monitoring may be a valuable ancillary test in evaluation and treatment of patients with OSAHS.

REFERENCES

1. Lipan MJ, Reidenberg JS, Laitman JT. Anatomy of reflux: a growing health problem affecting structures of the head and neck. *Anat Rec B New Anat* 2006;289:261-70.
2. Zanation AM, Senior BA. The relationship between extraesophageal reflux (EER) and obstructive sleep apnea (OSA). *Sleep Med Rev* 2005;9:453-8.
3. Green BT, Broughton WA, O'Connor JB. Marked improvement in nocturnal gastroesophageal reflux in a large cohort of patients with obstructive sleep apnea treated with continuous positive airway pressure. *Arch Intern Med* 2003;163:41-5.
4. Kerr P, Shoenut JP, Millar T, Buckle P, Kryger MH. Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome. *Chest* 1992;101:1539-44.
5. Wolf SM, Furman Y. Sleep apnea and gastroesophageal reflux disease. *Ann Intern Med* 2002;136:490-1.
6. Kerr P, Shoenut JP, Steens RD, Millar T, Micflikier AB, Kryger MH. Nasal continuous positive airway pressure. A new treatment for nocturnal gastroesophageal reflux? *J Clin Gastroenterol* 1993;17:276-80.
7. Steward DL. Pantoprazole for sleepiness associated with acid reflux and obstructive sleep disordered breathing. *Laryngoscope* 2004;114:1525-8.
8. Bortolotti M, Gentilini L, Morselli C, Giovannini M. Obstructive sleep apnoea is improved by a prolonged treatment of gastroesophageal reflux with omeprazole. *Dig Liver Dis* 2006;38:78-81.
9. Berg S, Hoffstein V, Gislason T. Acidification of distal esophagus and sleep-related breathing disturbances. *Chest* 2004;125:2101-6.
10. Demeter P, Pap A. The relationship between gastroesophageal reflux disease and obstructive sleep apnea. *J Gastroenterol* 2004;39:815-20.
11. Senior BA, Khan M, Schwimmer C, Rosenthal L, Benninger M. Gastroesophageal reflux and obstructive sleep apnea. *Laryngoscope* 2001;111:2144-6.
12. Chand N, Johnson DA, Tabangin M, Ware JC. Sleep dysfunction in patients with gastro-oesophageal reflux disease: prevalence and response to GERD therapy, a pilot study. *Aliment Pharmacol Ther* 2004;20:969-74.
13. Penzel T, Becker HF, Brandenburg U, Labunski T, Panikow W, Peter JH. Arousal in patients with gastro-oesophageal reflux and sleep apnoea. *Eur Respir J* 1999;14:1266-70.
14. Samelson CF. Gastroesophageal reflux and obstructive sleep apnea. *Sleep* 1989;12:475-6.
15. Friedman M, Schalch P, Vidyasagar R, Kakodkar KA, Mazloom N, Joseph NJ. Wireless upper esophageal monitoring for laryngopharyngeal reflux (LPR). *Otolaryngol Head Neck Surg* 2007;137:471-6.
16. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996;19:156-77.
17. Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. *Am J Dig Dis* 1976;21:935-6.
18. Sukanuma N, Shigedo Y, Adachi H, et al. Association of gastroesophageal reflux disease with weight gain and apnea, and their disturbance on sleep. *Psychiatry Clin Neurosci* 2001;55:255-6.
19. Guilleminault C. Obstructive sleep apnea. The clinical syndrome and historical perspective. *Med Clin North Am* 1985;69:1187-203.
20. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. *Chest* 1993;104:781-7.
21. Valipour A, Makker HK, Hardy R, Emegbo S, Toma T,

Spiro SG. Symptomatic gastroesophageal reflux in subjects with a breathing sleep disorder. *Chest* 2002;121:1748-53.

22. Close LG. Laryngopharyngeal manifestations of reflux: diagnosis and therapy. *Eur J Gastroenterol Hepatol* 2002;14 (suppl 1):S23-S27.

23. Koufman JA, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. *Otolaryngol Head Neck Surg* 2002;127:32-5.

24. Belafsky PC, Postma GN, Koufman JA. Laryngopharyngeal reflux symptoms improve before changes in physical find-

ings. *Laryngoscope* 2001;111:979-81.

25. Vakil N, Fennerty MB. Direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease. *Aliment Pharmacol Ther* 2003;18:559-68.

26. Reichel O, Keller J, Rasp G, Hagedorn H, Berghaus A. Efficacy of once-daily esomeprazole treatment in patients with laryngopharyngeal reflux evaluated by 24-hour pH monitoring. *Otolaryngol Head Neck Surg* 2007;136:205-10.

27. Joniau S, Bradshaw A, Esterman A, Carney AS. Reflux and laryngitis: a systematic review. *Otolaryngol Head Neck Surg* 2007;136:686-92.



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