ReviewArticle

Obstructive Sleep Apnea Syndrome and Gastroesophageal Reflux Disease

Prapaporn Pornsuriyasak, M.D.*, Paraya Assanasen, M.D., Choakchai Metheetrairut, M.D.****

**Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, **Department of Otolaryngology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

Siriraj Med J 2008;60:226-230
E-journal: http://www.sirirajmedj.com

Obstructive sleep apnea syndrome (OSAS) and gastroesophageal reflux disease (GERD) are common chronic diseases and share several similar risk factors. The prevalence of GERD in patients with OSAS is significantly higher than the general population. For example, 21 patients with sleep-disordered breathing were found to have GERD (33.3% of snorers, 64.3% of patients with OSAS). Twenty- three patients with sleep-disordered breathing had laryngopharyngeal reflux (LPR) (66.7% of snorers, 60.7% of patients with OSAS).[1] Furthermore, laryngeal inflammation assessed using the Reflux Finding Score was present in 26 out of 29 patients with OSAS (90%), with changes suggestive of LPR. There were significant correlations between laryngeal inflammation and severity of OSAS.[2] However, no temporal or causal relationship has ever been demonstrated between the two diseases.

This article focuses on the potential relationship between GERD and OSAS, which has been raised more recently. Because of the decrease of primary peristalsis and the reduced production of saliva, as well as the diminished acid and volume clearance of the esophagus, sleeping can be considered as a risk factor of the reflux event by itself. Moreover, it should also be taken into account that the transdiaphragmatic pressure increases in parallel with the growing intrathoracic pressure generated during obstructive apnea episodes. This has a non-negligible effect on the phrenoesophageal ligament, which is connected to the lower esophageal sphincter. Repetition of the pressure changes results in insufficiency of the cardia. While this pressure change produces a considerable suction effect, further reducing the clearing mechanism of the gastric volume, lower esophageal sphincter insufficiency can directly lead to reflux disease.

Basic sleep physiology

Sleep is composed of 2 phenomena: rapid-eye-movement (REM) sleep and non-REM sleep. Non-REM sleep is characterized by several electrophysiological manifestations that collectively demonstrate minimal physiologic alteration. In contrast, REM sleep is associated with remarkable physiological changes.[3] The cyclic alteration of REM and non-REM sleep in most individuals comprises a well-defined cycle of approximately 90 minutes, which may recur 4 to 6 times during the sleep cycle. REM sleep comprises approximately 25% of total sleep time. REM sleep is a state of consciousness associated with unique physiological changes.[3] The EEG shows a pattern of low-voltage mixed-frequency activity, reminiscent of waking, during a state of unequivocal sleep. The eyes show conjugate movements that are similar to those that occur in the waking state; although, these movements are accompanied by an associated skeletal muscle paralysis. In addition, REM sleep is associated with dreaming, a remarkable cognitive event. Respiratory control is markedly altered so much that there is very little response to increasing levels of carbon dioxide in the blood. Hypoxic responses are also diminished, but arousal occurs as a "fail-safe" response to diminished blood oxygen concentration. Temperature regulation shows quite profound alterations. Core body temperature tends to drift toward the ambient temperature, rather than invoking the typical measures to maintain homeostasis by conserving or dissipating heat.

Gastroesophageal reflux and sleeping—anatomy and physiology

The esophagus is a 20 to 25-cm-long hollow tube, with sphincter-like functions. The lower esophageal sphincter (LES) prevents the reflux of the gastric contents into the esophagus, while it also secures the passage of the swallowed food into the stomach when it is relaxed. The difference between the abdominal and the thoracic pressure, the compressive effect of the gastric bubble, the converged mucosal folds, and the transverse muscular fibers of the diaphragm contribute to the blocking function of the LES. The motor response of the esophagus to reflux events is peristalsis. Primary peristalsis is the most frequent response, which acts

Correspondence to: Paraya Assanasen
E-mail: paraya.assanasen@gmail.com

against the reflux through the stimulation of swallowing. This is the first reaction in 90% of the events. Secondary peristalsis is a rare but important phenomenon, which is carried out through distension of the esophagus. It is mainly important during sleep, when swallowing is impaired.[4] The esophagus clears away the regurgitated contents through its motor activity (volume clearance). The produced bicarbonate and saliva play a role in neutralizing the regurgitated acidic fluid (acid clearance). In addition, gravitational force also counteracts regurgitation.

Physiological effect of sleep on frequency and duration of gastroesophageal reflux

Studies have shown that gastroesophageal reflux does occur during sleep, but much less commonly than with arousal or during waking hours, particularly postprandially.[5] During sleep, gastroesophageal reflux occurs most commonly during the brief stages of arousal. When reflux episodes occur during sleep, they occur almost exclusively during non-REM sleep, and rarely during REM sleep. However, both REM and non-REM sleep are associated with the potential for increased esophageal acid contact times. Sleep is associated with a marked prolongation of acid clearance.[6] It is often imprecisely referred to as "nighttime reflux." Johnson and DeMeester[7] have demonstrated that, in normal individuals, the pattern of reflux is quite different during the sleep interval compared with the waking state. That is, in the daytime most reflux events are postprandial and are associated with rapid clearance. During sleep, episodes of gastroesophageal reflux, although less frequent than during waking, can produce long periods of continuous acid contact time. These results beg the question: What is occurring during sleep that leads to marked prolongation in acid clearance?

Prolonged acid contact time may lead to GERD, and normal sleep physiology makes some individuals more prone to this fate. A careful examination of responses to acid mucosal contact provides some clues as to how sleep can induce major alterations in the acid clearance process. Acid mucosal contact is associated with 4 responses in the waking state: heartburn (a conscious symptom that warns the individual of impending danger), salivation, swallowing and primary and secondary peristalsis. Combined, these events generally occur quite rapidly in response to acid mucosal contact, and provide mechanisms for both volume clearance and acid neutralization in the distal esophagus. All of these responses, except for secondary peristalsis, are significantly altered during sleep. Obviously, the warning symptom of heartburn is not experienced during sleep because it is a waking conscious response. Swallowing and primary peristalsis have been shown to be depressed during sleep,[8] and salivation is nearly nonexistent during sleep.[9] Taken together, these sleep-related changes produce an enhanced risk of abnormalities in acid clearance because the primary mechanisms for volume clearance (swallowing and peristalsis) and acid neutralization (salivation) are impaired.

Furthermore, respiration is not a static process. Both under healthy and pathological conditions, it influences the esophagus, which is located in the intrathoracic area. During inspiration, a pressure difference develops between the alveoli and the outer space: decompression is generated under inspiration, while compression occurs under expiration. Inspiration with a closed glottis (Müller maneuver) causes the intra pulmonary and consequently the intrathoracic pressure to fall below the atmospheric level by around 10 cm H_2O. On the other hand, exhalation with a closed glottis (Valsalva maneuver) results in an increase of the intrathoracic pressure significantly above the atmospheric level due to the work of the diaphragm and the abdominal and auxiliary respiratory muscles. The position of the body—lying on the back, or on one side, standing, or sitting—modifies the pressure conditions. In some respiratory diseases, the subatmospheric intrathoracic pressure rises with the volume increase produced by the increased resistance of the respiratory tract. This, in itself, predisposes to reflux of the gastric contents, especially in the relaxed state of the smooth muscle when the body is in the supine position.

The relationship between GERD, OSAS and obesity: overview and literature review

GERD and OSAS are often comorbid disorders.[10-12] OSAS is a condition marked by pharyngeal narrowing and upper airway obstruction during sleep that results in repeated episodes of decreased oxygen saturation and brief arousals. In one investigation of patients referred for an overnight sleep study, 74% reported GERD-related symptoms, including heartburn and /or acid regurgitation.[12] In an earlier study using a combination of polysomnography and distal esophageal pH monitoring, Ing and colleagues[13] found that patients with OSAS exhibited more frequent nocturnal refluxes than patients without OSAS. On average, patients with OSAS experienced > 100 reflux episodes during the 8-hour sleep period, compared with 23 reflux episodes in control subjects without OSAS. Esophageal acid clearance was also prolonged in patients with OSAS, with a significantly greater proportion of time, with an esophageal pH < 4.0, than in non-OSAS control subjects. While it is firmly established that GERD and OSAS co-occur, the nature and direction of the relationship between these two conditions are not yet fully understood. It has been proposed that OSAS may predispose patients to the development of nocturnal GERD, because apneic episodes are associated with increased arousal, movement, and transdiaphragmatic pressures, and low intrathoracic pressures.[14] Based on this model, apnea-related changes in the intrathoracic and diaphragmatic pressure would be expected to precede reflux events. Support for this model has not been observed. In the study by Ing and colleagues, only 23.7% of reflux events were preceded by or occurred simultaneously with apneic episodes.[13]

The pathophysiological mechanisms proposed to link GERD and OSAS are not mutually exclusive, and it seems possible that the two conditions may in fact interact, creating a kind of self-perpetuating positive feedback loop.[15] During the obstructive apnea period, the significant changes in transdiaphragmatic pressure facilitate the migration of the gastric contents toward the esophagus. On the other hand, the same repetitive pressure changes engender an irreversible destructuring of the phrenoesophageal ligament. This leads to LES insufficiency as an ultimate reason for the development of GERD. The large and repeated changes of the pressure gradient also, presumably, play a role in maintaining the duration of the refluxate clearance.[16] It is also

a plausible hypothesis that GERD contributes to the development of arousal from sleep, and consequently contributes to the changes in some cognitive functions as evidenced by reduced daytime vigilance. In addition, arousal from sleep could cause repetitive changes in the tone of the LES that would eventually result in daytime insufficiency in its work as well. Apart from this, the presence of a high pressure gradient in the lying position may facilitate a migrant reflux up to the pharyngeal region, which could eventually result in microaspiration, triggering asthmatic or coughing attacks and upper airway edema and narrowing. At the same time, the further narrowing of the pharyngeal region of the upper respiratory tract could lead to several forms of sleep-disordered breathing, such as OSAS or snoring. In support of this concept, higher numbers of apnea/hypopnea occurrences during REM sleep was found in children with nocturnal gastroesophageal reflux compared with children without nocturnal gastroesophageal reflux.[17] As a result of the depressed muscle control of the respiratory drive during sleep, there is considerable muscle tone relaxation in the pharyngeal region. Given that numerous receptors are located in the pharynx, the high reflux of either acid or gastric contents, added to this muscle relaxation, could lead to choking as a result of a delayed awakening from sleep.

The relationship of GERD and OSAS is also supported by evidence showing that treatment of GERD improves OSAS and vice versa. Studies show that treatment of GERD with continuous positive airway pressure (CPAP), a standard therapy for OSAS, improves GERD even in patients without OSAS.[11,13,14] In one of these studies to suggest such a clinical benefit, Kerr et al.[14] found a dramatic reduction in the frequency of reflux events in patients (n=6) complaining of regular nocturnal GERD who were treated with nasal CPAP. During one night in which nasal CPAP treatment was applied, continuous monitoring of esophageal pH showed that the percentage of time spent at esophageal pH < 4.0 decreased from 6.3% to 0.1% with nasal CPAP. Improvements in sleep-related (monitored via polysomnography) reflux with CPAP have also been seen in patients with OSAS.[11,13] In a large, open-treatment, long-term study of patients with OSAS (n=331), Green et al.[11] found that 62% of patients reported nocturnal reflux symptoms (heartburn, regurgitation and choking). Among those patients who used CPAP therapy, 75% reported reductions in the frequency of nocturnal GERD symptoms at follow-up, with a significant positive correlation observed between the degree of GERD symptom improvement and the CPAP pressure used. The authors have proposed that CPAP may improve GERD by increasing the mean esophageal pressure or by triggering reflex increases in lower esophageal sphincter tone.[14]

Conversely, some preliminary evidence indicates that treatment of GERD with an acid-suppressing agent also seems to help reduce OSAS.[18] In this small study of male patients (n =10) with OSAS and GERD confirmed via polysomnography and esophageal pH monitoring, omeprazole 20 mg twice daily was given for 30 days during which CPAP was not permitted. At the end of the 30-day treatment period, signs and symptoms of OSAS were reassessed. With omeprazole treatment, scores for apnea, hypopnea and respiratory distress were improved and a significant clinical response of OSAS to omeprazole was seen in 31% of the patients examined based on an improvement in the rate of occurrence of obstructive apnea. Although this was a very small, open-treatment clinical investigation, it provides the first evidence of a positive clinical effect on measures of apnea from acid-suppressing treatment for GERD.

It has been suggested that obesity may contribute to the risk of nocturnal GERD and OSAS by certain obesity-related alterations in gastrointestinal tract functioning, including slower esophageal transit, increased intra-abdominal pressure, and the development of hiatal hernia, which increases esophageal acid clearance times. With a reduction in body weight, symptoms of both apnea and GERD have been reported to improve.[15] The study of Gislason et al.[19] reported a rather challenging finding that 4.6% of the young population who complained of known symptoms of GERD tended to be associated with obesity.

Mechanisms of gastroesophageal reflux in patients with OSAS

Several mechanisms have been proposed to increase gastroesophageal reflux in patients with OSAS, including low negative intrathoracic pressures, arousals, movements, low esophageal sphincter tone, and an increase in the pressure gradient from the stomach to the lower esophagus. The most common mechanism proposed to cause GERD in patients with OSAS, with markedly negative intrathoracic pressure, has been evaluated in several studies. Graf and associates[20] attempted to determine if gastroesophageal reflux events were related to the severity of OSAS. They used the apnea index (AI) as a marker of severity and separated patients into two groups (AI 5 to 15, and AI > 15). The results suggest that a direct link between GERD and OSAS is unlikely; although, the authors did not account for the poor correlation between AI and OSAS severity. Heinemann and colleagues[21] found that 68% to 76% of patients with OSAS had significant GERD. The majority of these studies indicate that no direct association exists between obstructive respiratory events and the occurrence of gastroesophageal reflux events. Penzel and associates[22] attempted to correlate waking and sleeping events in patients with OSAS and found that the accumulated time with low esophageal pH readings was higher during the day than at night, but noted that 71% of the sleeping events were preceded by respiratory events. These data would suggest that OSAS is unlikely to cause gastroesophageal reflux events through alterations of intrathoracic pressures during respiratory events; although, these data should not be interpreted as meaning that there is no relationship between the two diseases or that they are independent. The increased incidence of GERD in OSAS suggests that an association exists, but it may be more complex than originally thought and would need to account for differences in sleep stage, respiratory effort, effects of age, and extent of GERD not related to OSAS.[23]

Treatment

Although the association between GERD and OSAS has been questioned by some, the high incidence (53% to 76%) of GERD in patients with OSA would suggest that some form of association between the two disorders exists and may affect treatment. The lack of an asso-

ciation between severity of OSAS and GERD[20] would suggest that therapy should not be tailored to the severity of OSAS, but rather to the severity and persistence of GERD symptoms. These factors should be addressed early in the course of treatment. Once GERD is identified, therapeutic interventions should not be delayed as the adverse effects on sleep may complicate the sleep study. In contrast, patients with previously diagnosed and treated OSAS must be evaluated to determine if previous or current intervention or both are effectively managing the patients' OSAS. In the setting in which therapy is found to be less than optimal, the clinician should consider alternative interventions to improve treatment efficacy. If the patient is not currently using positive airway pressure, then it should be strongly considered as it has been shown to decrease gastroesophageal reflux in OSAS.[24,25] These findings might suggest that a secondary effect of CPAP could be the reduction of gastroesophageal reflux and an improvement in symptoms. Whether an individual could be effectively treated with CPAP alone without the continuation of other modes of therapy has not been studied. On the basis of current knowledge, however, we would expect that patients with mild disease who responded completely without the use of medications or who could be withdrawn from medications without the recurrence of symptoms might be adequately treated in this manner. Patients with moderate to severe disease could be expected to require continuous therapy once their symptoms become stable.

In some patients, CPAP or bi-level positive airway pressure may be an ineffective therapy, although, lack of effectiveness is most commonly due to the patient's nonadherence to the regimen.[26] Thus, patients who are using CPAP or bi-level positive airway pressure should be monitored closely for adherence. Most positive airway pressure devices have some form of monitoring device to assess adherence. In recent years, these devices have added more sophisticated mechanisms for monitoring patients using computer technology, including the ability to monitor day-to-day use and adjust pressure settings. For patients with complicated illnesses, the enhanced monitoring capabilities of these devices are generally preferred.

Surgical interventions often does not provide effective control of OSAS, and frequently, these patients have never been reevaluated after their surgery. Patients who have not had follow-up polysomnography to verify effectiveness, those with continued symptoms, or those whose symptoms have returned should be sent for an evaluation. Recurrence of OSAS symptoms after surgery is known to occur in 40% to 50% of the patients who have an initial improvement. The recurrence usually occurs 3 to 5 years after the surgery. Other modes of therapy should be similarly evaluated. In addition, if the patient has gained weight or has had difficult-to-control cardiovascular disease,[27] polysomnography should also be repeated.

Because of the relatively high incidence of GERD in OSAS, the tendency would be to perform polysomnography on all patients with GERD. The routine application of this practice should be discouraged unless appropriate clinical indications exist. The majority of patients with GERD are not likely to have OSAS. For this reason, GERD does not serve as a good screening indicator of OSAS. Nonetheless, OSAS is a common disease and can complicate the therapy of GERD. Therefore, patients with GERD should be screened for symptoms that might suggest the presence of OSAS, and finding such symptoms should lead to the consideration of polysomnography. Medical therapy for GERD in patients with OSAS should be initiated by addressing several lifestyle changes in an attempt to reduce inciting factors. Many of these interventions have not been tested in clinical trials, but many patients find these changes reduce symptoms. In comparison to histamine H_2-receptor blockers, the degree of improvement achieved by elevating the head of the bed is similar. The next increment in therapy should be the addition of one or more medications from different classes. The major categories of medications that are effective include: histamine H_2-antagonists, proton pump inhibitors, antacids, and pro-kinetic agents.[28] Finally, several surgical alternatives have demonstrated effectiveness at controlling symptoms and reducing secondary disease.[29] The follow-up of the patient with GERD and OSAS is complicated by the efficacy of the intervention and patient's adherence to the treatment regimen. Symptoms for both disorders should be followed closely, and the treatment regimen should be altered to minimize these complaints. If less typical manifestations of the disease are present (such as cough, respiratory symptoms, recurrent respiratory illness), these manifestations should also be aggressively treated and followed.

CONCLUSION

In the light of the above reviewed lines of evidence, there is a strong reason to believe that GERD and OSAS potentially exhibit a two-way, mutually reinforcing relationship. During the obstructive apnea period, the significant changes in transdiaphragmatic pressure facilitate the migration of the gastric contents toward the esophagus. On the other hand, the same repetitive pressure changes engender an irreversible destructuring of the phrenoesophageal ligament. This leads to LES insufficiency as an ultimate reason for the development of GERD. The relationship of GERD and OSAS is particularly supported by the observation that treating either of the two conditions improves the other one as well. There is considerable evidence to link nighttime reflux with severe esophageal damage and respiratory complications. Sleep disturbances that occur with nocturnal reflux may have serious consequences on the general well being of patients. The implications for nocturnal gastroesophageal reflux and its impact on sleep have been overlooked by most clinicians. Given the high prevalence of both GERD and sleep disturbances, it is likely that there is substantial overlap in both prevalence and causality. Thus, the astute clinician must be aware of the sleep-related implications associated with nocturnal reflux in order to provide effective treatment.

REFERENCES

1. Wise SK, Wise JC, DelGaudio JM. Gastroesophageal reflux and laryngopharyngeal reflux in patients with sleep-disordered breathing. Otolaryngol Head Neck Surg 2006;135:253-7.
2. Payne RJ, Kost KM, Frenkiel S, Zeitouni AG, Sejean G, Sweet RC, et al. Laryngeal inflammation assessed using the reflux finding score in obstructive sleep apnea. Otolaryngol Head Neck Surg 2006;134:836-42.

3. Culebras A. Normal sleep. In: Lee-Chiong TL, Sateia MJ, Carskadon MA, eds. Sleep Medicine. Baltimore: Lippincott Williams & Wilkins, 2002:1-6.
4. Holloway RH. Esophageal body motor response to reflux events: secondary peristalsis. Am J Med 2000;108:S20-6.
5. Freidin N, Fisher MJ, Taylor W, Boyd D, Surratt P, McCallum RW, et al. Sleep and nocturnal acid reflux in normal subjects and patients with reflux oesophagitis. Gut 1991; 32:1275-9.
6. Orr WC, Johnson LF, Robinson MG. The effect of sleep on swallowing, esophageal peristalsis, and acid clearance. Gastroenterology 1984;86:814-9.
7. Johnson LF, DeMeester TR. Twenty-four hour pH monitoring of the distal esophagus. Am J Gastroenterol 1974;62:325-32.
8. Orr WC, Allen ML, Robinson M. The pattern of nocturnal and diurnal esophageal acid exposure in the pathogenesis of erosive mucosal damage. Am J Gastroenterol 1994;89: 509-12.
9. Schneyer LH, Pigman W, Hanahan L, Gilmore RW. Rate of flow of human parotid, sublingual, and submaxillary secretions during sleep. J Dent Res 1956;35:109-14.
10. Suganuma N, Shigedo Y, Adachi H, Watanabe T, Kumano-Go T, Terashima K, et al. Association of gastroesophageal reflux disease with weight gain and apnea, and their disturbance on sleep. Psychiatry Clin Neurosci 2001;55:255-6.
11. 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.
12. 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.
13. Ing AJ, Ngu MC, Breslin AB. Obstructive sleep apnea and gastroesophageal reflux. Am J Med 2000;108(Suppl 4a):120S-125S.
14. 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.
15. Orr WC, Heading R, Johnson LF, Kryger M. Sleep and its relationship to gastro-oesophageal reflux. Aliment Pharmacol Ther 2004;20(Suppl 9): 39-46.
16. Demeter P, Pap A. The relationship between gastroesophageal reflux disease and obstructive sleep apnea. J Gastroenterol 2004;39:815-20.
17. Wasilewska J, Kaczmarski M. Sleep-related breathing disorders in small children with nocturnal acid gastro-oesophageal reflux. Rocz Akad Med Bialymst 2004;49:98-102.
18. Senior BA, Khan M, Schwimmer C, Rosenthal L, Benninger M. Gastroesophageal reflux and obstructive sleep apnea. Laryngoscope 2001;111: 2144-6.
19. Gislason T, Janson C, Vermeire P, Plaschke P, Bjornsson E, Gislason D, et al. Respiratory symptoms and gastroesophageal reflux: a population based study of young adults in three European countries. Chest 2002;121: 158-63.
20. Graf KI, Karaus M, Heinemann S, Korber S, Dorow P, Hampel KE. Gastroesophageal reflux in patients with sleep apnea syndrome. Z Gastroenterol 1995;33:689-93.
21. Heinemann S, Graf KI, Karaus M, Dorow P. Occurrence of obstructive sleep related respiratory disorder in conjunction with gastroesophageal reflux. Pneumologie 1995; 49(Suppl 1):139-41.
22. Penzel T, Becker HF, Brandenburg U, Labunski T, Pankow W, Peter JH. Arousal in patients with gastroesophageal reflux and sleep apnea. Eur Respir J 1999;14:1266-70.
23. Foresman BH. Sleep-related gastroesophageal reflux. J Am Osteopath Assoc 2000;12(Suppl):S7-10.
24. 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.
25. Tawk M, Goodrich S, Kinasewitz G, Orr W. The effect of 1 week of continuous positive airway pressure treatment in obstructive sleep apnea patients with concomitant gastroesophageal reflux. Chest 2006;130:1003-8.
26. Weaver TE, Kribbs NB, Pack AI, Kline LR, Chugh DK, Maislin G, et al. Night-to-night variability in CPAP use over the first three months of treatment. Sleep 1997;20:278-83.
27. Foresman BH, Gwirtz PA, McMahon JP. Cardiovascular disease and obstructive sleep apnea: implications for physicians. J Am Osteopath Assoc 2000;100:360-69.
28. Pope CE. Acid-reflux disorders. N Engl J Med 1994;331:656-60.
29. Spechler SJ. Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. The Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group. N Engl J Med 1992;326:786-92.