GERD and Sleep

Ronnie Fass, MD

Professor, University of Arizona College of Medicine, Tucson, AZ USA

Introduction

Gastroesophageal reflux disease (GERD) is a chronic disorder and the most common disease that affects the esophagus. A population-based study estimated that 20% of the U.S. adult population experience GERD-related symptoms at least once a week (1). GERD can lead to esophageal mucosal injury in a subset of patients as well as bothersome symptoms, such as heartburn and acid regurgitation that may affect patients' reported quality of life.

The epidemiology of nocturnal gastroesophageal reflux is not well studied. According to a Gallup Poll from 1988 in which 1000 GERD patients completed a survey, 79% of the respondents reported nocturnal heartburn (2) In a study by Farup et al. 74% of the GERD subjects with frequent GERD symptoms reported nocturnal GERD symptoms (3). In contrast, Locke et al. found in a community-based survey that 47% and 34% of the GERD sufferers reported nocturnal heartburn and nocturnal acid regurgitation, respectively (1). Fass et al. in a large prospective, cohort study of subjects evaluated for sleep disturbances demonstrated that 24.9% reported heartburn during sleep (4)

Acid reflux episodes are divided into daytime reflux and nighttime reflux. However, because there is no clear definition of nighttime reflux some prefer the separation to reflux during awake period and reflux during sleep period. The latter division

underscores the impact of sleep physiology on gastroesophageal reflux. Acid reflux during awake time tends to be more frequent, but of shorter duration. In contrast, acid reflux during sleep is commonly less frequent, but of a significant longer duration (5).

Nocturnal gastroesophageal reflux has been demonstrated to be an important underlying mechanism for the development of complicated GERD and extra-esophageal manifestations of GERD. The latter may include oropharyngeal, laryngeal and pulmonary manifestations (6,7). The former may include erosive esophagitis, peptic stricture, esophageal ulcerations, Barrett's esophagus and adenocarcinoma of the esophagus. Furthermore, recent reports demonstrated that nocturnal GERD is associated with poor quality of sleep and a variety of sleep disturbances(8,9)

Nocturnal reflux is also associated with further decrease in health related quality of life (HRQL) as compared with the general population. In addition, patients with nighttime symptoms of GERD have a substantially diminished quality of life as compared with individuals without GERD symptoms during nighttime (3).

Definition of Nocturnal GERD

Presently, we are still devoid of an accepted definition for nocturnal GERD. Interestingly, studies that assessed either prevalence or therapeutic response of patients with nighttime heartburn, lacked clear definition of nocturnal GERD (1,2,10). Farup et al. offered the following definition of nighttime GERD: nocturnal awakening by GERD symptoms; nocturnal awakening caused by coughing or choking, regurgitation or fluid or food, and acidic/bitter taste; GERD symptoms while in the supine position; and morning awakening secondary to GERD symptoms (3). This is an inclusive definition that may include patients that experience GERD-related symptoms in the supine position while

still awake. In contrast, Fass et al. suggested that nighttime heartburn should be defined as heartburn that awakens patients from sleep during the night [Fass, NIH study, DDW 2003](4) . While this is a much more restrictive definition, it underscores the importance of having GERD-related symptoms during sleep physiology.

Pathophysiology of nocturnal GERD

Normal sleep physiology results in many changes of gastroesophageal function that contribute to the pathogenesis of GERD. Sleep may alter physiological mechanisms responsible for normal esophageal clearance, resulting in impairment of esophageal acid clearance. Rate of swallowing is reduced during sleep leading to decrease in primary peristalsis, a pivotal defense mechanism that is responsible for volume clearance of refluxate from the esophagus (11). Diminished salivary production during sleep as well as reduced delivery of saliva to the distal esophagus due to decreased primary peristalsis delay alkalization and thus normalization of esophageal pH after acid reflux has occurred. The upper esophageal sphincter basal pressure is significantly reduced, resulting in an increased risk for aspiration, which may lead to upper airways exposure to gastroesophageal reflux and consequently extra-esophageal manifestations. In addition, gastric acid secretion is increased and gastric emptying is delayed during nighttime. Moreover, there is less conscious awareness of gastroesophageal reflux during sleep, resulting in reduction in symptom perception and thus in alteration in conscious dependent defensive behavior against gastroesophageal reflux (antacid consumption, assuming the upright position, initiating a swallow, etc.) (12).

The overall weakening in esophageal defense mechanisms during sleep leads to prolonged esophageal acid exposure during nighttime, resulting in a more serious injury

to the esophageal mucosa. Several studies have demonstrated that nocturnal GERD is associated with increased risk of having severe gastroesophageal disease, such as erosive esophagitis, peptic stricture, Barrett's esophagus and even adenocarcinoma of the esophagus (13). DeMeester et al. (14) studied GERD manifestations in 100 patients with reflux-related symptoms and demonstrated that patients with supine reflux had a higher incidence of erosive esophagitis than those with predominantly upright reflux. Robertson et al. (15) compared pH testing results of patients with uncomplicated versus complicated GERD. The authors concluded that complicated GERD is associated with prolonged nocturnal acid exposure of the esophagus. They further stipulated that nocturnal acid exposure may be the cause of peptic stricture, esophageal ulceration or Barrett's metaplasia. Another study has demonstrated a significant nocturnal acid exposure in patients with Barrett's esophagus as compared to those with erosive esophagitis or non-erosive reflux disease (16). Furthermore, patients with long-segment Barrett's esophagus ($\geq$ 3 cm) demonstrated a significantly higher nighttime acid exposure as compared to those with short-segment Barrett's esophagus ($<$ 3 cm) (17,18). Overall, there was an increase in total as well as supine esophageal acid exposure, as documented by pH testing, from non-erosive reflux disease to erosive esophagitis and then to Barrett's esophagus (16).

Lastly, the risk of esophageal adenocarcinoma is eight times higher among patients with weekly reflux symptoms in comparison with asymptomatic subjects. The risk is even higher in patients reporting nocturnal heartburn (13).

GERD and sleep disturbances

There is some data supporting close association between nocturnal GERD and sleep disturbances. Sleep disturbances in patients with GERD are poorly recognized and rarely elicited during clinic visits. Despite the significant impact of these disturbances on patients' quality of life and, probably, on their perception of the severity of their disease. Sleep disturbance is not usually asked about in the routine history taken from patients with reflux disease. When 759 patients with endoscopy-negative reflux disease, who were enrolled in the esomeprazole (Nexium) clinical trial program, (19) were assessed by a quality of life tool for 'sleep disturbances for at least some of the time' (score ≤ 4), 50% reported that symptoms of GERD were responsible for difficulties in getting a good night's sleep. Other indicators of sleep disturbance were 'feeling tired/worn out due to lack of sleep' (42%), 'failure to wake up feeling fresh/rested' (41%), 'having trouble falling asleep' (40%), and 'heartburn/acid regurgitation waking the patient and preventing him/her from falling asleep' (35%) (19).

In a national survey of 1000 subjects with GERD, 75% of the participants reported that GERD symptoms affected their sleep, 63% believed that heartburn negatively affected their ability to sleep well (2). The prevalence of sleep disturbances among respondents increased with increase in frequency of the nighttime heartburn episodes during the week. Additionally, 42% could not sleep through the night and 39% took naps whenever possible. Green et al. reported, in an abstract form, that GERD patients that sleep less during the night are more likely to have symptoms that correlate with acid reflux events (20). Additionally, the extent of distal esophageal acid exposure has a significant effect on patients' reported sleep experience (8). The higher the acid exposure

the lower the overall reported quality of sleep (supine) and the higher the number of nocturnal awakenings (total and supine). Dekel et al. demonstrated that the frequency and severity of GERD symptoms were correlated with patients' quality of sleep. Patients with erosive esophagitis reported more nocturnal awakenings due to heartburn than those with non-erosive reflux disease, but otherwise reported similar sleep abnormalities and quality of sleep. Other investigators have demonstrated that nighttime gastroesophageal reflux may result in anamnestic short awakenings that lead to sleep fragmentation and feeling unrefreshed the next morning, dozing off and daytime sleepiness (9).

Obstructive sleep apnea (OSA) is a breathing disorder that occurs during sleep in which the patient experiences respiratory pauses lasting at least 10 seconds and occurring at least 5 times per hour of sleep (21). OSA is characterized by excessive daytime sleepiness, snoring, repeated episodes of upper airway obstruction during sleep, and nocturnal hypoxemia leading to memory problems, irritability, and depression. The exact association between OSA and GERD remains controversial. In one study, OSA was not influenced by severity of GERD. Additionally, objective measures of disordered sleep had stronger association with age, smoking and alcohol use than GERD in men and stronger association with age and body mass index than GERD in women (22). Kerr et al. have demonstrated that precipitous droops in pH were frequently preceded by arousal (98.4%), movement of the patient (71.9%), and swallowing (80.4%) (23). In this case, arousal is theorized to be caused by increased ventilatory effort (24). Arousal and movement may trigger gastroesophageal reflux by causing transient alteration in the pressure gradient across the lower esophageal sphincter (LES). Additionally, the lowered intrathoracic pressure that accompanies OSA may itself predispose the patient to

gastroesophageal reflux by exacerbating the LES pressure gradient. Treatment with nasal continuous positive airway pressure (CPAP) showed dramatic reduction in the frequency of gastroesophageal reflux by elevating intrathoracic pressure (23).

Investigators have suggested that GERD causes OSA, and OSA has been linked to GERD (22). Other studies could not demonstrate a causal relationship between OSA and GERD. In a study by Penzel et al. 37 of 52 reflux events that occurred during sleep, involving either apnea or hypopnea, were found prior to the reflux event (25). The sequence in time did not prove a causal relationship between the respiratory and reflux events. Patients subjectively report that the quality of sleep is affected by the severity of GERD; however, objective correlation between OSA and GERD is lacking, which may suggest that both are common entities sharing similar risk factors but may not to be causally linked (22) .

Diagnostic evaluation and initial treatment

Upper endoscopy should be performed in all patients with classic symptoms of GERD who also report alarm symptoms (dysphagia, odynophagia, weight loss, anorexia, evidence of gastrointestinal bleeding or iron deficiency anemia) (26). All patients with chronic symptoms of GERD, particularly those who are 50 years and older, are at increased risk for Barrett's esophagus and thus should undergo an upper endoscopy at least once during their lifetime to rule out the presence of Barrett's mucosa (27). Patients who are found to have Barrett's esophagus should undergo regular surveillance using a standard esophageal mucosal biopsy protocol.

Presently, the sole presence of nocturnal heartburn is not an indication for an upper endoscopy, unless alarm symptoms are also elicited. Similarly, pH testing should be

reserved only for individuals who are not responding to potent anti-reflux treatment (on therapy).

Patients with symptoms of nocturnal GERD may be treated with diet, lifestyle modifications and medications without prior endoscopic evaluation. A step-up approach may be adopted, starting with an H_2 receptor antagonist and upgrading to a proton pump inhibitor if nocturnal symptoms are not improved. Others may elect either a step-in or a step-down approach. The former suggests initiating and maintaining subjects on a proton pump inhibitor, while the latter proposes initiating patients on a proton pump inhibitor and then tapering them down to the least potent anti-reflux modality that can still control patients' symptoms.

References

1. Locke G, III, Talley NJ, Fett S, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112: 1448-1456.

2. Shaker R, Castell DO, Schoenfeld PS, et al. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: The results of a Gallup Survey conducted on behalf of the American Gastroenterological Association. Am J Gastroenterol 2003; 98: 1487-1493.

3. Farup C, Kleinman L, Sloan S, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. Arch Intern Med 2001; 161: 1448-1456.

4. Fass R, Quan SF, Howard BV, et al. Predictors of nocturnal heartburn in a large population-based study. Chest in press.

5. Orr WC, Johnson LF, Robinson MG. Effect of sleep on swallowing, esophageal peristalsis, and acid clearance. Gastroenterology 1984; 86: 814-819.

6. Cuttitta G, Cibella F, Visconti A, et al. Spontaneous gastroesophageal reflux and airway patency during the night in adult asthmatics. Am J Respir Crit Care Med 2000; 161: 177-181.

7. Jacob P, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with 'reflux laryngitis'. Gastroenterology 1991; 100: 305-310.

8. Green C, Dekel R, Quan S, et al. The relationship between the extent of esophageal acid exposure and reported quality of sleep [abstract]. Gastrointest Endosc 2003; 57: AB133, #M1749.

9. Dekel R, Green C, Quan S, et al. Abstract: The relationship between severity and frequency of symptoms and quality of sleep (QOS) in patients with gastroesophageal reflux disease (GERD). Gastroenterology 2003; 124: A-414, #M2093.

10. Castell DO, Richter JE, Robinson M, et al. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. The Lansoprazole Group. Am J Gastroenterol 1996; 1996: 9.

11. Schoeman MN, Holloway RH. Integrity and characteristics of secondary oesophageal peristalsis in patients with gastro-oesophageal reflux disease. Gut 1995; 36: 499-504.

12. Pasricha PJ. Effect of sleep on gastroesophageal physiology and airway protective mechanisms. Am J Med 2003; 18: Suppl 3A.

13. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825-831.

14. DeMeester TR, Johnson LF, Joseph GJ, et al. Patterns of gastroesophageal reflux in health and disease. Ann Surg 1976; 184: 459-470.

15. Robertson D, Aldersley M, Shepherd H, et al. Patterns of acid reflux in complicated oesophagitis. Gut 1987; 28: 1484-1488.

16. Martinez SD, Malagon IB, Garewal HS, et al. Nonerosive reflux disease (NERD) - acid reflux and symptom patterns. Aliment Pharmacol Ther 2003; 17: 537-545.

17. Fass R, Hell RW, Garewal HS, et al. Correlation of oesophageal acid exposure with Barrett's oesophagus length. Gut 2001; 48: 310-313.

18. Brandt MG, Darling GE, Miller L. Symptoms, acid exposure and motility in patients with Barrett's esophagus. Can J Surg 2004; 47: 47-51.

19. Fass R. Poorly recognized reflux-induced symptoms. Eur J Gastroenterol Hepatol 2001; 13: S32-S34.

20. Green C, Dekel R, Quan S, et al. The effect of sleep duration on symptoms perception of patients with gastroesophageal reflux disease (GERD) [abstract]. Gastroenterology 2003; 124: A-255, #S1729.

21. Farmer W, Yaffe J, Santiago T. Managing sleep disorders in military personnel. Federal Practitioner 2002; 19: 21-39.

22. Morse CA, Quan SF, Mays MZ, et al. Is there a relationship between obstructive sleep apnea and gastroesophageal reflux disease? Clin Gastroenterol Hepatol 2004; 2: 761-768.

23. Kerr P, Shoenut JP, Millar T, et al. Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome. Chest 1992; 101: 1539-1544.

24. Gleeson K, Zwillch CW, White DP. The influence of increasing ventilatory effort on arousal from sleep. Am Rev Respir Dis 1990; 142: 295-300.

25. Penzel T, Becker HF, Brandenburg U, et al. Arousal in patients with gastro-oesophageal reflux and sleep apnoea. Eur Respir J 1999; 14: 1266-1270.

26. The role of endoscopy in the management of GERD: guidelines for clinical application. From the ASGE. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc 1999; 49: 834-835.

27. Sampliner RE, Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol 2002; 97: 1888-1895.

Table 1: Extra-esophageal manifestations of GERD

Pulmonary

- Asthma
- Aspiration pneumonia
- Chronic bronchitis
- Bronchiectasis
- Interstitial pulmonary fibrosis

Oral

- Halitosis
- Dental caries
- Poor oral hygiene

Pharynogo-laryngeal

- Pharyngitis
- Vocal cord granuloma
- Subglottic stenosis
- Laryngitis
- Stridor
- Hoarseness
- Globus
- Laryngeal cancer
- Chronic cough

Sleep Apnea and Gastroesophageal Reflux Treatments Serve Dual Purpose

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By Jessica Ross for Reflux1

A team led by Dr. J. Barry O'Connor at Duke University Medical Center recently determined that continuous positive airway pressure (CPAP) treatment of obstructive sleep apnea (OSA) can also ease symptoms of gastroesophageal reflux disease (GERD).

While O'Connor and colleagues found that treating obstructive sleep apnea helped alleviate GERD, this is by no means the first indication that the two diseases are closely related. Some physicians believe that OSA results in pressure changes that encourage GERD, while others suggest that GERD's characteristic acid backup may result in vocal cord spasms, leading to OSA. Although the truth may lie on one side or the other, or even in between, it is becoming increasingly clear that when treating either OSA or GERD, both conditions often improve.

The American Sleep Apnea Association estimates that approximately twelve million Americans experience some symptoms of OSA. The condition is characterized by a relaxation of the soft tissue towards the back of the neck, resulting in closed or partially obstructed air passages. The resulting oxygen deprivation causes the patient to wake up frequently during the night, disrupting normal sleeping patterns.

Notably, two key risk factors for OSA, obesity and high alcohol consumption, have also been identified as contributors of GERD. Gastroesophageal reflux affects as many as 20% of Americans once a week or more, with heartburn as the most reported symptom. If left untreated, the acid back flow that accompanies this condition can also lead to more serious problems such as esophagitis, Barrett's esophagus, or even cancer.

A potential physiological link between OSA and GER has been further suggested by the work of O'Connor et al., indicating that CPAP devices treat OSA and heartburn simultaneously.

The Duke University Medical Center team began with the knowledge that nocturnal gastroesophageal reflux (nGER) is common in patients with OSA. Of 331 patients with OSA who were asked to grade their nGER symptoms on a scale from 1 (never) to 5 (always), a substantial 62% (204) reported symptoms of nGER. All the patients were started on a treatment program of continuous positive airway pressure to alleviate their OSA.

Significantly, follow-up studies showed that patients who continued with the program of CPAP treatment had an average decrease in score of nGER symptoms from 3.38 to 1.75, or 48%. On the contrary, patients who failed to follow the CPAP regimen showed no improvement in their nGER score. O'Connor and colleagues also found that patients using higher CPAP pressures showed the most improvement in their nGER scores.

The results of the O'Connor study seem to indicate that a CPAP device may treat both obstructive sleep apnea and gastroesophageal reflux disease. The device consists of a facemask connecting to a pump that acts to force air through the nose at pressures high enough to overcome any physical obstructions. According to O'Connor, the CPAP device "works by raising the pressure in the chest. CPAP elevates the pressure in the esophagus and keeps acid from coming up."

Short of surgery, many physicians consider CPAP the best means for treating sleep apnea, and this additional benefit makes it an even more attractive option.

Just as CPAP treatment of OSA seems to help reduce GERD, yet another study authored by Dr. M. Benninger has shown that antacid treatments of GERD can, in turn, alleviate apnea. Benninger and colleagues conducted a trial to determine how much GERD contributes to incidence of OSA. In their study, ten men ages 20 – 64 with confirmed OSA were treated for thirty days with omeprazole, a drug which acts to suppress acid production in the stomach. Significantly, the results showed a 31% decrease in the mean apnea index, as well as a 25% decrease in respiratory disturbances.

It is clear from the work of O'Connor, Benninger, and others that obstructive sleep apnea and gastroesophageal reflux share an underlying connection. Although the exact basis for their relationship is still unclear, treatments such as CPAP and omeprazole continue to show promise as a means for treating both problems concurrently.

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