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DIAGNOSTIC CHALLENGES

Differentiating Nighttime GERD

ISSUES FOR CLINICIANS

Stephen Brunton, MD ■ James McGuigan, MD

EDITOR'S NOTE

This article is meant to alert the reader to different symptomatology in GERD at night; therefore, treatment will not be discussed.

Prevalence estimates for gastroesophageal reflux disease (GERD) range from 8% to 40%, depending on the definition and diagnostic criteria.¹⁻⁴ While heartburn and regurgitation are considered the hallmark symptoms, GERD actually represents a spectrum of disorders that generally result from transient relaxations of the lower esophageal sphincter (LES), so that gastric refluxate comes into contact with the esophageal epithelium. Additionally, differences in rates of acid secretion and clearance and the time since food ingestion affect symptoms, potentially leading to differing presentations of GERD associated with daytime and nocturnal episodes. To facilitate accurate diagnosis of GERD, it may be helpful for clinicians to distinguish between the symptoms that occur during the day or in an upright position and those that occur at night or when a person is supine.⁴ This paper reviews the differences in symptoms and explains the pathophysiologic mechanisms involved.

Key points and recommendations

- Reflux episodes with nighttime GERD occur less frequently but are more prolonged than those with daytime GERD. **(SOR: B)**
- Esophageal complications are generally more severe and nonesophageal complications more common in nighttime than in daytime GERD. **(SOR: B)**
- Nighttime GERD-induced alterations in sleep cause significant patient morbidity and reduced quality of life and productivity. **(SOR: B)**
- Several factors are associated with nighttime GERD, including increased body mass index, carbonated soft drink consumption, hypertension, benzodiazepine use, obstructive sleep apnea, and asthma. **(SOR: B)**
- The history and physical examination generally provide the most useful information in making the diagnosis. **(SOR: C)**
- Sleep-induced physiologic alterations are thought to be important factors responsible for the more common and severe symptoms and complications in nighttime vs daytime GERD. **(SOR: C)**



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Stephen Brunton, MD

Director of Faculty Development
Cabarrus Family Medicine Residency Program
Charlotte, North Carolina

James McGuigan, MD

Division of Gastroenterology
University of Florida College of Medicine
Gainesville, Florida

Disclosures: Dr Brunton reports that he is a consultant to Ortho-McNeil Pharmaceuticals, Inc. and Wyeth Pharmaceuticals. Dr McGuigan reports that he is a consultant to Wyeth Pharmaceuticals.

TABLE 1

**Adjusted medical outcomes study
Short-Form 36 Health Survey scores**

Scale	Nocturnal GERD (n=945)	Non-nocturnal GERD (n=339)	Controls (n=268)
Physical functioning	63 [†]	68 [†]	69
Role limitations—physical	53 ^{*†}	64 [†]	67 [*]
Bodily pain	54 ^{*†}	63 [†]	69 [*]
General health	48 ^{*†}	53 ^{††}	59 ^{**}
Vitality	41 ^{*†}	47 ^{††}	54 ^{**}
Social functioning	70 ^{**†}	76 [†]	78 [*]
Role limitations—emotional	69 ^{*†}	80 [†]	81 [*]
Mental health	66 ^{*†}	71 [†]	74 [*]
Physical component summary	39 ^{*†}	42 [†]	43 [*]
Mental component summary	47 [†]	50 [†]	51

Analysis of covariance, adjusted for age, sex, and comorbidity.

* $P < .001$ nocturnal GERD vs controls; [†] $P < .001$ nocturnal vs non-nocturnal; ^{††} $P < .001$ non-nocturnal GERD vs controls.

Farup C, et al. *Arch Intern Med.* 2001;161:45-52.¹

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Issues of GERD and quality of life

Patients' quality of life and ability to function is negatively impacted by factors associated specifically with nocturnal episodes of GERD. Patients who experience GERD primarily at night may complain of sleep disturbances. Symptoms associated with nighttime GERD generally are more severe,⁵ and the complications more diverse and frequent,⁴ due to the prolonged length of nighttime reflux.⁶ For these reasons, determining if the underlying cause of a group of symptoms is nighttime episodes of GERD is an important treatment step.

Complications of reflux: associations with nighttime occurrences

Esophageal complications of GERD include erosive esophagitis, esophageal hemorrhage, ulceration, and strictures and appear to be more severe in patients with nighttime episodes of GERD than in those complaining of daytime reflux. An early study showed that patients who experience reflux only in the supine position have a higher incidence of esophagitis compared with patients who only refluxed in an upright position.⁷ Prolonged acid contact time increases the risk that esophagitis will become erosive. This was demonstrated in a study that concluded particularly that the presence of nocturnal reflux events lasting more than 5 minutes was a powerful predictor of erosive damage.⁶

Overall, approximately 7% to 12% of patients with chronic GERD develop Barrett's esophagus compared with fewer than 1% of those in the general population.⁸ Potentially, more severe nocturnal symptoms may be among the factors that increase the risk of Barrett's esophagus.^{9,10} Esophageal adenocarcinoma also is more likely in patients with nocturnal episodes of GERD: In a national, population-based, case-controlled trial, an 11-fold increased risk for esophageal adenocarcinoma was reported in patients who experienced once-weekly episodes of nighttime heartburn, regurgitation, or both. Overall, an 8-fold increased risk of esophageal adenocarcinoma was observed in all patients with GERD.¹¹

Impact of nighttime episodes on sleep

Not surprisingly, sleep is significantly affected by nighttime GERD episodes. A recent Internet-based survey of full-time working adults in the United States identified 1002 patients with symptomatic GERD.¹² Using the validated GERD Symptom and Medication Questionnaire, symptomatic GERD was defined as a score of 10 or greater for at least one episode of heartburn or acid regurgitation within the past 7 days. Symptomatic nighttime GERD was defined as at least 2 nights with symptoms during the past 7 days. GERD-related sleep problems were twice as frequent in patients with nighttime compared with daytime GERD. Patients with nighttime episodes of GERD experienced GERD-related sleep impairment an average of 1.6 to 1.9 nights per week compared with 0.3 to 0.4 nights per week for the daytime GERD group.

In both groups, the most commonly reported sleep problem was awakening due to symptoms (75% vs 37%, respectively). Sixty-five percent of nighttime and

TABLE 2

Mean medical outcomes study Short-Form 36 Health Survey scores

Scale	Nocturnal GERD (n=945)	Hypertension (n=2089)	Type 2 diabetes (n=541)	Congestive heart failure (n=216)	Clinical depression (n=502)	Angina (n=256)
Physical functioning	77	73	68*	48*	72*	63*
Role limitations—physical	69	62*	57*	34*	44*	44*
Bodily pain	62	72*	69*	63	59	62
General health	63	63	56*	47*	53*	52*
Vitality	49	58*	56*	44	40*	49
Social functioning	79	87*	82	71	57*	80
Role limitations—emotional	75	77	76	64*	39*	70
Mental health	71	78*	77*	75	46*	73
Physical component summary	45	44	42*	35*	45	39*
Mental component summary	48	52*	52*	50	35*	50

**P* < .001 vs nocturnal GERD. Norms for non-GERD disorders were obtained from the Short-Form 36 Health Survey: Manual and Interpretation Guide. Farup C, et al. *Arch Intern Med.* 2001;161:45-52.⁴ Copyright © 2001 American Medical Association. Reproduced with permission.

28% of daytime GERD patients indicated that GERD symptoms prevented them from feeling rested in the morning.¹² In addition, respondents with nighttime GERD experienced an additional 2.7 hours per week of lost work productivity when compared to those with daytime GERD.¹³ A similar survey also found that in those with nighttime GERD, the number of nights with sleep interference was associated with reduced work productivity.¹⁴

These results are consistent with 2 previous telephone surveys. In one survey, 13% of 1000 adults who experienced heartburn at least weekly had only nighttime episodes; 20% reported only daytime heartburn.¹⁵ Altogether, 79% of the heartburn sufferers reported experiencing heartburn at night. Of these, 75% reported that heartburn had a negative impact on sleep; 63% indicated that heartburn adversely affected their ability to sleep well; and 40% reported impaired functioning the next day. The prevalence of sleep disturbances increased directly with the incidence of nighttime heartburn.

The second telephone survey of persons with nighttime GERD had lower scores using the Short-Form 36 Health Survey (a measure of quality of life) than did

persons with daytime GERD or controls (**TABLE 1**).⁴ In another study, the greatest differences between groups occurred in terms of physical and emotional role functioning, vitality, and general health.¹⁶ A comparison with other major disorders affirmed the substantial impairment in health-related quality of life caused by nighttime GERD (**TABLE 2**).⁴

In summary, although heartburn and regurgitation are common in daytime and nighttime GERD, patients with nighttime GERD are more likely to experience impaired sleep, fatigue, reduced work productivity, and decreased quality of life.

Diagnosis: Evaluation of symptoms

Physicians should inquire specifically about GERD symptoms to ensure diagnosis, as the signs of GERD are often subtle, nonspecific, or judged to be trivial by patients. Symptoms of GERD may include esophageal or nonesophageal complaints, or both. Importantly, heartburn or regurgitation may be absent in many patients: One group of investigators reported that neither heartburn nor regurgitation was experienced by approximately half of all patients who had nonclassical symptoms of GERD.³

TABLE 3**Nonesophageal conditions associated with GERD**

■ Aspiration pneumonia
■ Asthma
■ Atelectasis
■ Atypical chest pain
■ Bronchiectasis
■ Carcinoma of the larynx
■ Chronic cough
■ Decreased vocal pitch
■ Exacerbation of reactive airway disease
■ Globus pharyngeus
■ Hemoptysis
■ Hoarseness
■ Laryngitis
■ Laryngospasm
■ Postnasal drip sensation
■ Pulmonary fibrosis
■ Sleep apnea
■ Throat clearing (excessive)

Fass R, et al. *Aliment Pharmacol Ther.* 2004;20(suppl 9):26-38.¹⁷

McGuigan JE, et al. *Aliment Pharmacol Ther.* 2004;20(suppl 9):57-72.¹⁸

Nonesophageal symptoms associated with GERD

Laryngitis, laryngospasm, chronic cough, hoarseness, excessive throat clearing, and globus pharyngeus are common nonesophageal symptoms in patients with GERD (**TABLE 3**).^{17,18} In a recent investigation, 86% and 77% of patients with nighttime and daytime episodes of GERD, respectively, reported one or more nonesophageal symptom. In patients experiencing GERD at night, the most common symptoms were sinusitis (52%), dry cough/throat clearing (49%), and snoring (47%). Symptom severity scores were significantly higher in the nighttime vs daytime GERD groups (2.42 vs 1.80, respectively).⁵

In a cross-sectional international population survey of 2202 randomly selected persons and 459 additional individuals with asthma, Gislason et al estimated the

possible association between reported symptoms of nighttime GERD, sleep-disordered breathing, respiratory symptoms, and asthma. The investigators reported a 2- to 3-fold increased prevalence of asthma and other respiratory symptoms (such as wheezing, chest tightness, breathlessness, and nighttime cough) in patients with nighttime reflux.¹⁹

Patient history

The patient's history is the primary focus of the diagnostic workup and the physician should explore patient risk factors for GERD. For patients with atypical symptoms of GERD, the history is especially important to determine the diagnosis.

The presence of at least one esophageal or non-esophageal sign and symptom should prompt consideration of GERD as the cause, and discussion with the patient may help classify GERD further. The symptoms of nighttime GERD range from mild to severe. Though they can be similar to the symptoms of daytime GERD, nocturnal symptoms may be exacerbated by lying down or may differ in their manifestation. Asking questions about a patient's quality of sleep, with input from the patient's sleep partner, if possible, is useful in assessing nighttime GERD (**TABLE 4**).

Predictors of nighttime reflux

A high body mass index (BMI) may lead to a reduction in LES pressure and is a risk factor for GERD.^{20,21} Social habits such as smoking and alcohol use are often cited as risk factors for GERD; however, data to confirm this premise are lacking.¹¹ Several other factors and the presence of some pulmonary disorders may be specific predictors and indications of nighttime GERD episodes.

A recent large prospective cohort study specifically evaluated predictors of heartburn during sleep. Symptoms of GERD were strongly associated with increased BMI, carbonated soft drink consumption (possibly due to low pH), snoring and daytime sleepiness, insomnia, hypertension, asthma, and usage of benzodiazepines (**TABLE 5**).²⁰ It was noted that the association of hypertension with nighttime heartburn likely is a reflection of factors associated with hypertension rather than hypertension itself. Possible factors of hypertension include antihypertensive medications, comorbidities, diet, and body habitus.²⁰

Several sleep-related and respiratory factors are associated with nighttime GERD. Among these, insomnia and sleepiness are probably consequences rather than causes of nighttime reflux. An association of

GERD with obstructive sleep apnea has been established, although causality has not been determined. Similarly, asthma is clearly associated with GERD, but the extent of causality remains unclear. Nonetheless, nighttime GERD should be suspected in patients who present with one of these sleep disturbances, particularly obstructive sleep apnea, or adult-onset or difficult-to-treat asthma.²⁰

Diagnostic tests for GERD

Various tests have been investigated for the diagnosis of all types of GERD, and there is no difference in the tests used when nighttime GERD is suspected. Endoscopy is an important diagnostic tool for either identifying or ruling out complications such as erosions or Barrett's esophagus. Esophageal pH monitoring can be helpful in diagnosis.

Pathophysiology: potential differences between daytime and nighttime GERD

Several mechanisms have been established to contribute to the development of GERD. Included are transient LES relaxations and, less frequently, sustained LES pressure abnormalities. Other factors that contribute to the pathophysiology of GERD include hiatal hernia, which reduces LES pressure and impairs acid clearance, and poor esophageal clearance.²²

Despite their similarities, important pathophysiologic differences between daytime and nighttime gastroesophageal reflux can be seen. Increased acid secretion and gastric volume are associated with food consumption, so daytime reflux and associated symptoms tend to occur after meals. Nighttime gastroesophageal reflux occurs less frequently, but the episodes are of longer duration than those of daytime reflux, as a result of delayed acid clearance from the esophagus at night.^{6,7,23}

Sleep-related mechanisms combined with impairment of the LES and the supine position help explain the more common and severe symptoms and wider range of complications seen in nighttime compared with daytime GERD.

Protective processes impaired during sleep

Differences between daytime and nighttime GERD are thought to be due to the sleep state rather than just to differences in posture (TABLE 6).^{24,25} Processes that occur normally during the day to facilitate refluxed acid clearance from the esophagus, such as swallowing and

TABLE 4

Key questions in the assessment of nighttime GERD

- Do you have trouble falling asleep?
- Are you restless?
- Do you wake up coughing?
- Do you snore?
- Do you awaken with an acid or bitter taste or food in your mouth?
- Do you experience daytime fatigue?

Note: Input should also be sought from the patient's sleep partner.
 Farup C, et al. *Arch Intern Med.* 2001;161:45-52.⁴

TABLE 5

Factors associated with nighttime GERD

- Increased body mass index
- Carbonated soft drink consumption
- Insomnia
- Sleepiness (daytime)
- Asthma
- Obstructive sleep apnea
- Hypertension
- Benzodiazepines

Lagergren J, et al. *N Engl J Med.* 1999;340:825-831.¹¹
 Fass R, et al. *Chest.* 2005;127:1658-1666.²⁰
 Fisher BL, et al. *Dig Dis Sci.* 1999;44:2290-2294.²¹

TABLE 6

Sleep-related mechanisms contributing to nighttime GERD

- Depressed perception of heartburn
- Depressed arousal
- Decreased saliva production
- Decreased swallowing
- Delayed gastric emptying
- Impaired esophageal clearance

Orr WC, et al. *Am J Gastroenterol.* 2000;95:37-42.²⁴
 Orr WC, et al. *Aliment Pharmacol Ther.* 2004;20(suppl 9):39-46.²⁵

acid neutralization (via bicarbonate-containing salivation), are suppressed during sleep.²⁵

Saliva, composed of mucus, bicarbonate, and epidermal growth factor, neutralizes refluxed acid and protects esophageal tissue. Saliva production is diminished during sleep, with implications for GERD symptoms.^{26,27} Swallowing is reduced during sleep and may not occur during deeper stages of sleep.²⁸ Absence of the voluntary swallow-initiated peristaltic wave of esophageal contractions during sleep also results in reduced volume clearance.²⁹

Delayed gastric emptying during sleep may result in increased gastric distention and contribute to the occurrence of nighttime reflux.^{25,30}

Effect of reduced consciousness

Reflux during sleep may be accompanied by a brief period of arousal, which helps to hasten esophageal clearance of refluxate and protect the airway against aspiration and acid exposure.²⁵ However, arousal does not occur in all reflux episodes, since the conscious perception of heartburn is absent during sleep. Consequently, the sleep-induced mechanisms are allowed to persist leading to prolonged periods of acid exposure.²⁵

Summary

For the purposes of understanding symptoms and facilitating diagnosis, GERD can be divided into daytime and nighttime GERD. Compared with daytime GERD, nighttime reflux episodes occur less frequently but are more prolonged. In addition, nighttime symptoms are more common and more severe, and esophageal and nonesophageal complications are more likely. The presence of severe symptoms or at least one esophageal and/or nonesophageal symptom should prompt an investigation of nighttime GERD. In doing so, the history and physical examination findings are the most helpful; laboratory values and other test results are generally less so. Physiologic alterations during sleep are thought to be the primary factors that contribute to nighttime symptoms. ■

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