

Nocturnal Gastroesophageal Reflux: Assessment and Clinical Implications

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Article: Nocturnal gastroesophageal reflux revisited by impedance-pH monitoring

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Nocturnal gastroesophageal reflux has been shown to be associated with the more severe forms of gastroesophageal reflux disease (GERD), particularly with atypical/extraesophageal manifestations as well as complications of mucosal damage, such as esophagitis and stricture, Barrett's esophagus and esophageal adenocarcinoma.^{1,2} Heartburn during sleep and sleep disturbances are common manifestations of nocturnal gastroesophageal reflux. In a population-based telephone interview survey of 1,000 adults, 13% of the respondents reported experiencing heartburn only during nighttime and 65% experienced heartburn on both day and night. Altogether 79% of heartburn sufferers reported nocturnal heartburn.³ Farup and colleagues⁴ reported that 74% of GERD patients had nocturnal reflux symptoms and 54% experienced heartburn that awakened them from sleep. In contrast, in a community-based study by Locke and colleagues,⁵ 47% and 34% of GERD sufferers reported nocturnal heartburn and nocturnal acid regurgitation, respectively. About one-quarter of subjects with sleep disturbances report heartburn during sleep.⁶ Thus, a better understanding of nocturnal gastroesophageal reflux is of significant diagnostic and management implications.

In the current issue of the Journal, Fornari et al re-assessed nocturnal gastroesophageal reflux using impedance-pH monitoring in order to elucidate the prevalence and characteristics of nocturnal reflux in healthy subjects and GERD patients. They found that GERD patients had more nocturnal reflux events than healthy subjects. Of nocturnal reflux events, 57% were weakly acidic reflux, which predominated in the last 3 hours of the night. In this study, they demonstrated that nocturnal reflux reached the proximal esophagus more often in GERD patients than in healthy subjects and described prolonged chemical clearance associated with less esophageal activity in GERD patients. Reflux episodes are divided into daytime and nighttime events. Nighttime gastroesophageal reflux is of clinical importance because it is associated with the development of complicated GERD, extraesophageal manifestations of GERD and a variety of sleep disturbances. In addition, patients with nocturnal GERD symptoms have a substantially diminished quality of life as compared with individuals without nocturnal GERD symptoms.⁴ Nocturnal gastroesophageal reflux is an underappreciated clinical challenge in many patients with GERD. Previous studies assessing

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nocturnal reflux have addressed on acid events. Conventional esophageal pH monitoring is not able to detect all gastroesophageal reflux events, particularly when little or no acid is present in the refluxate. Esophageal impedance-pH monitoring can detect non-acid reflux as well as acid reflux, and increase the sensitivity for detection of reflux episodes.⁷ Non-acid reflux includes weakly acidic and weakly alkaline reflux. The number of acid reflux events and the total percentage of esophageal pH < 4 are believed to be correlated to the degree of mucosal damage. However, the importance of non-acid reflux in the genesis of mucosal damage or symptoms has not been fully established. The results of the study by Fornari et al suggest possible involvement of weakly acidic reflux in the genesis of GERD symptoms or complications associated with nocturnal reflux. They showed that combined impedance-pH monitoring made it possible to identify more patients in whom gastroesophageal reflux was the cause of their nocturnal GERD symptoms. However, they did not evaluate the correlation of weakly acidic reflux with nocturnal symptoms, probably because of the difficulty in checking symptoms during sleep. The majority of reflux episodes during nighttime was weakly acidic in healthy subjects as well as in GERD patients. Thus, further investigation on the association of nocturnal symptoms with weakly acidic reflux events is warranted.

In the study from Fornari et al, 43% of reflux episodes in GERD patients off proton pump inhibitor (PPI) therapy was acidic and 57% was weakly acidic. In general, the majority of episodes was acidic off PPI, which caused the majority of symptoms. On PPI, the majority of reflux episodes was weakly acidic and these were responsible for reflux symptoms occurring during the PPI therapy.^{8,9} Weakly alkaline reflux was very rare.^{8,9} The high predominance of weakly acidic reflux during the night suggests that nocturnal GERD symptoms are not well controlled by PPI therapy. PPIs are the mainstay of anti-secretory therapy for daytime and nighttime gastroesophageal reflux disease, but their effectiveness for nocturnal reflux may be limited by the characteristics of nocturnal reflux events. Given that acid can sensitize the esophagus to subsequent reflux episodes, a high dose PPI or addition of a histamine H₂-receptor antagonist at bedtime to PPI therapy seems logical. However, if this is not helpful, the next choice is lacking. Drugs that effectively reduce the number of reflux episodes are not currently acceptable. Baclofen has unfavorable side effects and is not commonly used for the treatment of GERD. Anti-reflux surgery can reduce both acid and weakly acidic reflux episodes. However, it may also produce side effects such as dysphagia, the sensation of inability to belch, and severe

symptoms of bloating and abdominal discomfort. Development of effective treatments is required for reducing excessive weakly acidic reflux events, through which is expected to be able to decrease nocturnal reflux.

The majority of the refluxate from the stomach is cleared from the esophagus by either primary or secondary peristalsis. The residual hydrogen in the esophagus is neutralized by salivary bicarbonate.¹⁰ Since swallowing ceases during sleep, primary peristalsis is not induced. Accordingly, secondary peristalsis stimulated by the reflux of gastric contents plays a main role in clearing the refluxate from the esophagus. Fornari et al demonstrated that post-reflux poor esophageal motor activity and prolonged acid clearance were associated with nocturnal reflux in GERD patients. This observation is in keeping with the previous finding that the triggering mechanism of secondary peristalsis was deteriorated in GERD patients.¹¹ In addition, the effect of gravity in the recumbent position during sleep retards esophageal clearance. The cessation of swallowing during sleep also reduces esophageal clearance and impairs acid neutralization. Thus, nocturnal reflux is associated with prolonged acid contact with the mucosa, damaging to the esophageal mucosa. Furthermore, the reduced esophageal peristaltic activity may lead to proximal extent of the refluxate, which is also shown in the study from Fornari et al. This finding explains the association of atypical/extraesophageal manifestations with nocturnal reflux.

In conclusion, the study by Fornari et al has contributed to a better understanding of nocturnal gastroesophageal reflux by re-assessing nocturnal gastroesophageal reflux using esophageal impedance-pH monitoring in healthy subjects and GERD patients.

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