Objective  Gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA) often coexist. We sought to determine the presence and direction of any association between GERD and sleep events in patients with OSA.

Materials and methods  We conducted a case–crossover study among 18 patients with known OSA and GERD. All study patients underwent overnight simultaneous polysomnography and esophageal pH monitoring. A series of case–crossover analyses was conducted by defining each of the sleep (i.e. arousal, awakening, and apnea) and gastroesophageal reflux (GER) events as the outcome in turn. Respective control time points were randomly selected in all eligible control periods. When a sleep event was the outcome, the GER event was the exposure of interest. When GER was the outcome, each sleep event was assessed as the exposure individually. Conditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results  Both awakenings and arousals were significantly associated with the subsequent onset of a GER event. The OR for a GER event following an awakening was 5 (95% CI 3.6–6.9) and for a GER event following an arousal was 2.5 (95% CI 1.8–3.4). Apnea did not lead to GER (OR 1.0, 95% CI 0.8–1.4). GER was not more commonly observed before any of the sleep events compared with control periods without sleep events.

Conclusion  In patients with coexisting GERD and OSA, both awakening and arousal preceded GER events, but GER does not appear to precipitate sleep-related events. Eur J Gastroenterol Hepatol 25:1017–1023 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: case–crossover design, gastroesophageal reflux disease, obstructive sleep apnea

Introduction  The prevalence of gastroesophageal reflux disease (GERD) is as high as 20% in the Western world with up to 10% of people reporting symptoms of nocturnal reflux exclusively [1,2]. Obstructive sleep apnea (OSA) has been estimated to affect 4% of men and 2% of women in the USA and the rates continue to rise [3,4]. GERD and OSA frequently occur together. GERD has been shown to be prevalent in patients with OSA on the basis of studies recording symptoms and esophageal pH [5–8]. Patients with OSA are at a significant risk for nocturnal gastroesophageal reflux (GER) [9,10,7,11]. Despite the apparent epidemiologic link between these two common conditions, the exact nature of the relationship between GERD and OSA is complex and incompletely defined. Specifically, it is unclear whether the co-occurrence of these conditions represents a causal relationship or is simply a reflection of shared risk factors. Elucidating the causal relationship between these entities would have obvious implications on the management approach for both conditions. Therefore, we carried out the current study to determine both the presence and direction of any association between objective sleep events and GER events, which is an important first step toward understanding the causal relationship between these two entities.

Materials and methods  Study design  A case–crossover design was used to evaluate any association between GER and sleep events [12].

Study population  Consecutive patients between the ages of 18 and 75 years with comorbid OSA and GERD were recruited by one of the investigators (S.S.-R.) from the Penn Presbyterian Sleep Center at the University of Pennsylvania. The vast majority of those invited enrolled in the study. Therefore, the enrolled study patients were a representative sample of the underlying study population. The diagnosis of GERD was clinically based. Patients were required to have a history of GERD symptoms (e.g. heartburn and regurgitation) and receive medication for treatment of GERD (e.g. proton pump inhibitors and H2 receptor antagonists) for inclusion. At the time of recruitment, the patient was required to be under treatment for both
GERD and sleep apnea [i.e. continuous positive airway pressure (CPAP)]. All patients had been previously diagnosed with OSA on the basis of standard sleep criteria [13,14]. Patients were excluded if they had any unstable medical condition, dangerous hypersomnolence, previous history of acid reducing surgery, or other surgeries of the esophagus or upper gastrointestinal tract. Also excluded were patients with pyloric stenosis, gastroparesis, or any other gastrointestinal conditions that might affect pH measurement for GERD.

**Study procedures**

The study protocol was approved by the University of Pennsylvania's Institutional Review Board. All individuals provided informed consent to participate in the study.

All individuals underwent an 8-h polysomnography study overnight with simultaneous distal esophageal pH recording (described below) beginning at the onset of sleep. The polysomnography study was diagnostic in nature (i.e. without the use of CPAP). Before testing, individuals did not use CPAP for at least 3 nights and they all discontinued any GERD-related medications for at least 7 days. These medications included proton pump inhibitors, H2 receptor antagonists, metoclopramide, antacids, or any other medication affecting acid production and/or gastrointestinal motility. Individuals were required to abstain from eating for 3 h before the initiation of the study and during the study.

Before the initiation of the sleep study, individuals were asked to fill out a questionnaire assessing basic demographic information, as well as the Epworth Sleepiness Scale and the GERD Health-Related Quality-of-Life questionnaire. Basic measurements of height and weight were obtained. BMI was calculated using these values for each individual (BMI 25–29, overweight; ≥ 30, obese).

**Esophageal pH monitoring**

Distal esophageal pH was continuously monitored and recorded for the duration of the polysomnography study with an antimony multiuse pH catheter (Medtronic, Minneapolis, Minnesota, USA) and pH meter recording device (Medtronic). The catheters were calibrated in polyelectrolyte buffer solutions of pH 7 and 1 before use. The external reference electrode was placed on the chest, after which the catheter was placed while simultaneously monitoring pH values. Placement of the pH catheter was performed transnasally using the standard step-up technique in which the lower esophageal sphincter (LES) is identified by a rise in pH from the more acidic pH in the stomach. The catheter was then withdrawn 5 cm further, for placement of the recording probe 5 cm above the upper border of the LES, and the distance from the nares was recorded. The pH meter was connected and calibrated to the sleep monitoring computer so that all sleep and GER data could be recorded simultaneously.

**Polysomnography**

Overnight sleep testing was conducted under standard polysomnographic protocols, using the Sandman system (Natus Systems Inc., Broomfield, Colorado, USA) for collection and analysis. Polysomnographic evaluation included the following parameters: nasal and oral airflow [measured using Braebon transducers (Braebon Medical Corp., Ogdensburg, New York, USA) and Pro-Tect pressure transducers (Philips Respironics, Murrysville, Pennsylvania, USA)], respiratory and abdominal efforts (measured using Respitrace plethysmography bands; Respitrace Corp., Ardsley, New York, USA), oxyhemoglobin saturation by pulse oximetry [Nellcor (Covidien, Mansfield, Massachusetts, USA) and Omeda (GE Healthcare Technologies, Waukesha, Wisconsin, USA)], ECG, submental and leg electromyelograms, electrooculograms, body position, snoring (pressure transducers), and electroencephalograms (International 10–20 system). The Sandman recording system collected esophageal pH data and sleep data simultaneously. Sleep parameters were determined on the basis of standard scoring criteria (Rechtschaffen and Kales) by registered polysomnographic technologists and a board certified sleep physician without knowledge of the results of the questionnaire or esophageal pH. Sleep apnea events were identified and scored using American Academy of Sleep Medicine Task Force criteria [13]. All scoring was performed by only one sleep technician to have consistent scoring. The scoring was verified by the sleep coinvestigator (S.S.-R.) who is the Director of the Penn CPAP Program and is also the American Board of Sleep Medicine/American Academy of Sleep Medicine (AASM)-designated scoring specialist for all of the Penn Sleep Center laboratories. The AASM requires greater than 85% exact inter-reliability scoring for all AASM accredited sleep labs with the American Board of Sleep Medicine/AASM gold scorer. An apnea was defined as cessation in airflow for at least 10 s during sleep and a hypopnea as an abnormal respiratory event lasting for more than 10 s with greater than 50% reduction in airflow and oxygen desaturation. The apnea–hypopnea index (AHI) was defined as the number of respiratory events (apneas and hypopneas) per hour of total sleep time. OSA was defined as an AHI of at least 5/h (mild 5–14/h, moderate 15–29/h, severe ≥ 30/h). Arousals were defined as an abrupt change in electroencephalogram frequency lasting 3–14 s that was preceded by 10 s of sleep. Awakening was defined on the basis of electroencephalogram criteria.

**Statistical analysis**

GER events were defined as a drop in distal esophageal pH to less than 4 for at least 4 s and were combined into a single event if the conclusion and initiation of two
events were separated by 15 s or less (reflux aggregation criteria). Sleep events included apnea, arousal, and awakening and were scored on the basis of the criteria described above. All pH and sleep data used in this analysis were recorded simultaneously. Separate case–crossover analyses were carried out defining case periods by the occurrence of one of the following in turn: a GER event, apnea, arousal, or awakening. In instances in which the case event was a GER event, the exposure of interest included each of the three sleep events; for analyses in which sleep events were the case event, only a GER event was the exposure of interest. Control periods were defined by exclusion of the case periods plus periods within 5 min preceding or following the case periods to ensure a lack of relationship between the outcome event and exposure variable(s) during the control period (Fig. 1). A control index time point was randomly selected within each eligible control period. Exposure status was determined by searching for the exposure event of interest in a 60- s window preceding the start of the case event and the control index time point (Fig. 1).

Conditional logistic regression models, conditioning on individual patients, were used to assess the association between GER and sleep events. All analyses were carried out using SAS version 9.1 (SAS Institute, Cary, North Carolina, USA).

The primary analysis used an exposure window of 60 and 15 s to combine GER events. A series of one-way sensitivity analyses were carried out by varying the exposure window to 120 and 180 s and the reflux aggregation times to 5 and 30 s to confirm our baseline analysis.

**Results**

**Participants**

A total of 18 participants were enrolled in the study. One participant was intolerant to placement of the pH probe and withdrew during the sleep study. Characteristics of the study participants are summarized in Table 1. The mean age was 52.9 years. Of the 17 participants participating in the study, 12 met the BMI criteria for obesity and five were overweight. All 17 participants had sleep apnea: three with mild OSA, five with moderate OSA, and nine with severe disease. All 17 participants reported a history of GERD: 15 were taking proton pump inhibitors daily, one was taking histamine receptor antagonists daily, and one was using antacids daily before the study.

**Gastroesophageal reflux and obstructive sleep apnea measurements**

During the polysomnography study, 11 of the 17 participants (65%) were observed to have abnormal nocturnal GER (pH < 4 for >1.2% of study participants) [15]. In the 17 participants, the mean percentage of time with a distal esophageal pH of less than 4 was 4.7% [interquartile range (IQR): 0.5–16.4%]. The mean number of GER events per hour was 3.4 (IQR: 1.6–7.2). In addition, the mean duration of reflux events was 25 s (IQR: 8.1–68.6 s).

The mean AHI was 31.3 (IQR: 18.8–51.1). The mean arousal index was 27 (IQR: 12.6–38.8) and the mean percentage of time with an oxygen saturation of less than 90% was...
2.4 (IQR: 0.4–9.9). We also report the total number of apnea, arousal, awakening, and GER events in Table 2.

**Relationship between obstructive sleep apnea and gastroesophageal reflux**

Using the case–crossover methodology, the association between sleep and GER events during the polysomnography study was examined. Both awakenings and arousals were significantly associated with the subsequent onset of a GER event (Table 2). The odds ratio for a GER event following an awakening was 5 [95% confidence interval (CI) 3.6–6.9, \( P < 0.001 \)] and for a GER event following an arousal was 2.5 [95% CI 1.8–3.4, \( P < 0.001 \)]. Apnea did not lead to GER (odds ratio 1.0, 95% CI 0.8–1.4). GER events were not more commonly observed before any of the sleep events compared with control periods without sleep events (Table 3). These relationships remained unchanged across the sensitivity analyses with varying exposure windows and reflux aggregate criteria (Table 3).

**Discussion**

In this case–crossover study, we found that awakening and arousal, but not apnea, preceded GER events. In contrast, GER events did not lead to apnea, arousal, or awakening. These relationships remained unchanged in extensive sensitivity analyses.

Theoretically, apnea may be associated with negative intrathoracic and intraesophageal pressures, leading to GER. In addition, arousals may lead to transient LES relaxations precipitating reflux events. Numerous studies have demonstrated that sleep disturbances and GER often coexist [16–24]. Nevertheless, data in terms of the nature of the relationship between OSA and GERD remain very limited and conflicting. Symptoms of nocturnal GER were found to be present in 62% of OSA patients; however, other studies have failed to show a significant relationship between GERD and OSA [25,26]. Because of the cross-sectional nature of these reports, it is impossible to know whether these associations represent causal relationships or merely reflect shared risk factors (e.g. obesity) [27].

To better elucidate the link between sleep events and GER, several studies used simultaneous polysomnography and esophageal pH monitoring in patients with sleep disturbances or OSA. Some of these studies demonstrated a longer esophageal acid exposure time in patients with sleep disturbances [28] or OSA [7] than in controls. Others demonstrated that a high proportion of GER events followed sleep events [29,30]. However, it is difficult to interpret these results without a proper nonreflux control period because the high prevalence of sleep-related events throughout the night almost guaranteed that GER events would appear to follow sleep events.

Besides our study, few studies specifically investigated the temporal relationships between sleep events and GER events with a control period [11]. In a study pooling data collected from six patients, Kerr et al. [11] showed that GER events were more likely to be preceded by arousal, movement, and swallowing compared with what arbitrarily selected control time points 10 min before the GER events, whereas no significant association existed between apnea and subsequent GER events. Their study did not specifically address whether GER events preceded sleep events. Our study extended these findings. First, we examined whether GER events preceded sleep events, which was not addressed in prior studies. Our study also provided more definitive evidence that sleep disruptive events in OSA patients, specifically awakenings and arousals, play a direct role in precipitating GER. Notably, we analyzed three times as many patients as analyzed in the previous study. Further, the case–crossover design was well suited for elucidating complex relationships between recurrent outcome and exposure events within the same individual. It also allowed us to incorporate a more representative sample of control periods and to effectively control for measured and unmeasured within-person confounders that are relatively constant over time. In addition, we carried out extensive sensitivity analyses to enhance the validity of our findings.

Our study did not generate any data to allow us to speculate on why arousal and awakening might lead to GER, but presumably this is related to a change in the LES tone. The lack of association between apnea and GER observed by Kerr and colleagues and by us was somewhat counterintuitive. However, this observation is consistent with the finding of one recent study using simultaneous high resolution manometry and polysomnography [31]. It showed that the pressure of the upper esophageal sphincter and the gastroesophageal junction increased despite a drop in esophageal body pressure during apnea. Although apnea itself may not be directly temporally associated with GER, it may still be an indirect contributor of GER through its link with arousals and awakenings. Further studies are needed to resolve this issue.

If sleep disruptive events are causally associated with GER, then CPAP, which reduces sleep events such as arousal and awakening, should theoretically reduce

**Table 2 Number of sleep and gastroesophageal reflux events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea (n)</td>
<td>158 (93–334)</td>
</tr>
<tr>
<td>Arousal (n)</td>
<td>134 (84–269)</td>
</tr>
<tr>
<td>Awakening (n)</td>
<td>22 (15–35)</td>
</tr>
<tr>
<td>Reflux (n)</td>
<td>26 (13–48)</td>
</tr>
<tr>
<td>AHI [median]</td>
<td>31.3 (18.6–51.1)</td>
</tr>
<tr>
<td>AI [median]</td>
<td>27 (12.6–39.8)</td>
</tr>
</tbody>
</table>

AHI, apnea–hypopnea index; AI, arousal index; IQR, interquartile range.
nocturnal GER. Indeed, in a follow-up overnight therapeutic study with CPAP performed among the same study participants as those in our study, we observed a significant reduction both in sleep disruptive events and in fractional distal esophageal acid exposure time and mean reflux event duration (data not shown). In the study by Kerr et al. [11], CPAP not only led to a marked reduction in arousal and awakening events, but also a reduced GER frequency and duration. Ing et al. [7] also reported significant reduction in nocturnal acid exposure with CPAP in 14 male patients with OSA. Further, CPAP has been shown to significantly increase intraesophageal pressures and reduce GER in patients without OSA who suffer from GERD [32]. Therefore, the decrease in esophageal acid exposure in OSA patients using CPAP likely results from attenuating the physiologic changes associated with sleep events as well as creating increased esophageal pressures.

There has been a great deal of interest in the concept that GER impacts sleep and may worsen sleep quality in individuals with and without OSA. An early study by Orr et al. [33] demonstrated that introduction of exogenous acid into the esophagus may cause arousal. To exploit the potential role of GER in sleep-related disturbances, there have been attempts to improve sleep with antisecretory therapy. Studies using proton pump inhibitors in patients with OSA and/or GERD have demonstrated improvements in subjective measures of sleep quality and daily functioning, assessed through diaries or questionnaires [34–38]. However, there was no improvement in objective sleep measures on polysomnography despite acid suppression [37]. Our observation that GER events did not precipitate apnea, arousals, or awakenings provides an explanation for these earlier findings. The fact that subjective sleep measures are improved with antisecretory therapy without improving objective parameters suggests the presence of another mechanism by which these therapies affect sleep. There may be delayed onset of sleep and/or a delay in returning to sleep when an awakening or arousal episode is accompanied by GER. Alternatively, individuals may be more likely to remember these sleep events in the setting of GER.

There are several limitations to our study. There is no definitive biological basis to determine how closely related an exposure event must be to the outcome event to have an effect on the outcome event. Similarly, there is no consensus on a perfect reflux aggregation time. However, it is reassuring that our results are virtually unchanged when we varied these parameters extensively. Because of the widespread use of acid suppressants for GERD symptoms, we were only able to recruit patients with treated GERD symptoms. In addition, our study participants were limited to patients with treated OSA. Therefore, our results may not be generalizable to patients with untreated OSA or GERD. Further, manometric localization of LES is the reference standard. Although the pH step-up method was chosen to minimize participant discomfort (by avoiding a separate transnasal esophageal intubation), it might be unreliable in patients with free reflux because of large hiatal hernias. Among the nine study participants with a known hiatal hernia status, six did not have a hiatal hernia, two had a small hiatal hernia, and only one had a medium-sized hiatal hernia. The prevalence of medium-to-large hiatal hernias is unlikely to be higher among the other eight patients whose GERD symptoms did not warrant radiographic or endoscopic examination of the upper gastrointestinal tract. Therefore, a potential impact of using the step-up method as opposed to manometry for LES localization could be true but is likely limited. Finally, we did not measure impedance and therefore could have missed weakly acidic or nonacid reflux.

### Table 3 Gastroesophageal reflux and sleep event associations

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Baseline analysis [OR (95% CI)]</th>
<th>Sensitivity analysisb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P-valuea</td>
<td>Exposure window</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120 s</td>
</tr>
<tr>
<td>Awakening</td>
<td>Reflux</td>
<td>5.0 (3.6–6.9) P&lt;0.001</td>
<td>4.5 (3.3–6.2) P&lt;0.001</td>
</tr>
<tr>
<td>Apnea</td>
<td>Reflux</td>
<td>1.0 (0.8–1.4) P=0.28</td>
<td>1.2 (0.9–1.6) P&lt;0.001</td>
</tr>
<tr>
<td>Arousal</td>
<td>Reflux</td>
<td>2.5 (1.8–3.4) P&lt;0.001</td>
<td>2.7 (2.0–3.7) P&lt;0.001</td>
</tr>
<tr>
<td>Reflux</td>
<td>Awakening</td>
<td>0.7 (0.4–1.1) P=0.12</td>
<td>0.9 (0.6–1.4) P=0.12</td>
</tr>
<tr>
<td>Reflux</td>
<td>Apnea</td>
<td>1.2 (0.9–1.9) P=0.21</td>
<td>1.1 (0.7–1.5) P=0.12</td>
</tr>
<tr>
<td>Reflux</td>
<td>Arousal</td>
<td>1.4 (0.9–2.2) P=0.10</td>
<td>1.5 (1.0–2.2) P=0.05</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

*aBaseline analysis with an exposure window of 60 s and reflux aggregation of ≤ 15 s.
*bOne-way sensitivity analysis varying the exposure window (120 and 180 s) or reflux aggregation times (≤ 5 and ≤ 30 s).
Conclusion
This study demonstrates that both awakening and arousal preceded GER, but GER itself did not appear to precipitate sleep-related events in patients with OSA. These results support the role of CPAP in the treatment of both OSA and associated GERD. They might also offer a potential mechanistic explanation for why objective sleep parameters are not improved with antisecretory therapy in these patients. Further, these results may incentivize OSA patients with GERD to be more compliant with CPAP treatment. In addition, if apnea is a model for a sleep disorder that causes arousals and awakenings, and if CPAP decreases GERD by decreasing apnea-caused arousals and awakenings rather than those with mechanical etiologies, then, in theory, improving sleep continuity (e.g., sleeping pills or treatment of other arousal-causing sleep disorders) may improve nocturnal GERD.

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Conflicts of interest
David C. Metz, MD, has served as a consultant and speaker for and has received grant support from AstraZeneca, TAP Pharmaceuticals, Esai Pharmaceuticals, Novartis, and Tercica. For the remaining authors there are no conflicts of interest.

References


