Sleep Disturbances and GERD: Physiological and Behavioral Consequences

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Prevalence of Nocturnal GERD Symptoms

Among Patients With Weekly Heartburn—AGA Survey¹

- 79%
- 57% report waking up during sleep
- 40% report impact on ability to work the next day

Among Patients With GERD Symptoms—Farup et al²

- 74%
- 54% wake up from sleep

Nighttime Reflux Increases Risks of GERD Complications

**Esophageal Disease Progression**

- Erosive esophagitis

- Complicated erosive esophagitis
  - Ulceration
  - Strictures
  - Barrett’s esophagus

- Adenocarcinoma

**Atypical Manifestations**

- Asthma
- Aspiration pneumonia
- Chronic cough

**Other Symptoms**

- Sleep deprivation

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GI Symptom Score vs. Sleep Disturbance in a General Population

The symptom of nighttime heartburn is a reliable indication of sleep related GER
Figure 1. Number of Reflux Events After Sleep Onset by Group

Error bars represent +1 SE of the mean
* p<.01 vs. Daytime Heartburn and Normal Controls
** p<.05 vs. Normal Controls
GER and Insomnia


• Population survey of an entire county in Norway (population 92,808) assessed GERD symptoms and insomnia
  – 3153 cases with GERD symptoms (severe) and 40,210 with no GERD symptoms
  – Risk of reflux symptoms in insomnia was 3X greater than in those with no sleep complaints
  – The odds ratio showed a dose response with an increase with increasing frequency of complaint.

• This relationship may be a bidirectional relation with GERD sx contributing to insomnia and insomnia contributing to GERD sx.
Sleep related GER is not a new concept
**Brief Historical Overview of Nighttime Reflux**

1970: Atkinson and Van Gelder measured esophageal acidity during the 12-hour nocturnal period and “showed a significant correlation between the duration of nocturnal periods of high esophageal acidity and the severity of esophagitis.”

1978: Johnson evaluated whether reflux in the recumbent position resulted in prolonged exposure to acid and concluded that: “Recumbent acid exposure during sleep appears to be the most important exposure to control ...”

1981: First PSG study: “These data also emphasize the importance of actually identifying the patients who reflux during sleep since such patients would be considered more likely to develop severe esophagitis.”
Is Nighttime Reflux a Distinct Clinical Entity?

• Yes! But why???
• Sleep related GER shows distinct prolongation of acid clearance
• Patients with nighttime heartburn have a greater risk of developing esophagitis
• Patients with nighttime heartburn have a greater incidence of extra-esophageal symptoms (chest pain, cough etc.)
• Quality of life is significantly worse
• Symptoms can be resolved with aggressive PPI Rx
How is sleep different than waking?
Normal Defense Mechanisms Against Acid Load

- Heartburn (Warning)
- Acid Mucosal Contact
- Salivary Flow
- Swallowing (1° Peristalsis)
- Local Response (2° Peristalsis)
Acid-Mucosal Response

Sleep

- No Heartburn
- ↓ 1° Peristalsis
- ↓ Salivary Flow

Risk of Complications
How does sleep affect the pattern of GER?
Normal Postprandial Reflux
(in Normal Volunteer)
Sleep Reflux
Supine Sleep Condition
H⁺ Ion Movement and Duration of Acid Exposure

ACID CONTACT TIME AND DISEASE SEVERITY
(Frazzoni, et. al, Ail. Pharmacol. Ther 2003, 18:1091-1098)

% ACT

* P < 0.01 Complicated vs NERD
+ P < 0.05 Erosive vs Complicated & NERD
Percent Acid Exposure
24-hr pH Monitoring
(Orr et. al. Amer. J. Gastro. 1994: 89; 509-512)
Sleep Disturbance and GERD
The Relationship Between Intensity Rating Score and Sleep Deprivation During an Acid Perfusion Test

Schey R et al., Gastroenterology 2007; 133:1787-1795
Sleep/GERD Interaction

Respiratory Complications of Sleep Related GER
Respiratory Sx and Nighttime GER

( Gislason T. et.al. Chest 2002; 121: 158-163 )

• Population study of 2202 randomly selected subjects (structured interview and sleep questionnaire)

• Results:
  – 4.6% had nighttime heartburn
  – Compared to those without nighttime heartburn this group had significantly more sleep complaints
  – Nighttime heartburn subjects were more likely to report wheezing (OR=2.5) and nighttime SOB (OR 2.9)
  – Physician diagnosed asthma was 9% in those with nighttime heartburn compared to 4% in those without nighttime heartburn (P<.05)
Diagnosis And Treatment Of Atypical GERD

Pathophysiology Of GERD And Asthma

Reflux

Reflex

Proximal Migration

% Infusions

0 50 100

Wake
Sleep

Volume

1 mL
3 mL

Laryngitis and GER

- Reflux common (75%) in patients with posterior laryngitis, with longer mean acid clearance time\(^1\)
- Data concerning treatment are conflicting; results depend on patient population, dose of PPI, and treatment duration.
- Nocturnal proximal esophageal acidification found in >50% GERD patients (n=25) with persistent laryngeal symptoms; none in reflux controls (n=15) without laryngeal symptoms\(^2\)
- In dysphonia patients (n=20) and proven laryngitis treated with PPI tid:
  - response at 6 and 12 wk: 47% and 63%
- Symptoms and signs resolved in 50–80% chronic laryngitis patients after 8 weeks PPI therapy in another trial\(^4\)

\(^1\)ULRICH, OTOLARYNGOL HEAD NECK SURG 1999; 120: 672
\(^2\)JACOB, GASTROENTEROLOGY 1991; 100: 305
\(^3\)WILLIAMS, ANN J GASTROENTEROL 2004; 39: 777
\(^4\)KLOPSTICK, MED SCI MONIT 2004; 10: 118
GER and OSA: Is There An Association?
# OSA and GERD Clinical Observations

- OSA and GERD share risk factors—primarily obesity
- Increased negative pressure with airway obstruction predisposes to GER
- OSA patients seem to have an increased prevalence of the clinical complaint of heartburn
Relationship Between OSA and GER

- Two groups evaluated
  - >15 OSA per hr.
  - <5 OSA per hr.
- OSA patients had significantly greater acid contact
- 18% of reflux events were associated with an obstructive airway event
GER and OSA

• Tardif et al: Neurophysio Clin 1988;18:323-332:
  – Could not prove a temporal association between GER and apnea in 8 obese patients.

• Graf et al: Z Gastroenterol 1995;33:689-693
  – By visual analysis there was no obvious correlation between reflux periods and apnea periods.
OSA and GERD Clinical Data
(Shepherd et. al. J. Sleep Res. 2010; 1365-2869)

• Sleep related complaints of heartburn have been noted in over 60% of patients

• Assessed the prevalence of GERD related complaints in untreated OSA patients, OSA patients on CPAP and controls (population survey)
PREVALENCE OF NIGHTTIME GERD SYMPTOMS (OSA POPULATION)

- any nighttime Sx
- frequent nighttime Sx

* p<0.05 vs mild OSA
Responses to Treatment
CPAP Rx in Patients With OSA and GERD
(Green et. al. Arch Int Med 2003; 163: 41-45)

• Studied 331 patients having Dx of OSA

• At baseline patients graded the frequency of nighttime GER Sx from 1 (never) to 5 (always)

• All were treated with CPAP

• 62% noted nighttime GER Sx

• Patients compliant with CPAP had 48% improvement in GER Sx score

• Higher CPAP pressures were correlated with greater reduction in GER Sx score
Does upper airway acid exposure predispose to OSA?
Study by Orr et. al.  
(J. Clin. Sleep Med. 2009: 5; 330-33)

• Documented GER and mild OSA (AHI <15)
• All had laryngoscopy before and after Rx
• 8 wks of Rx with standard dose of PPI
• Marked reduction in sleep related GER
• No significant change in AHI
• Modest changes in upper airway anatomy
Table 3—24-Hour pH Monitoring Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatment (n = 25)</th>
<th>Posttreatment (n = 25)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total acid contact time, %</td>
<td>8.2 ± 3.1</td>
<td>1.9 ± 5.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Waking</td>
<td>8.7 ± 3.2*</td>
<td>1.8 ± 5.2*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sleep</td>
<td>8.0 ± 7.0</td>
<td>1.7 ± 5.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total number of events</td>
<td>172.3 ± 72.2</td>
<td>21.1 ± 33.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Waking</td>
<td>136.0 ± 63.8</td>
<td>17.6 ± 27.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sleep</td>
<td>35.4 ± 27.8</td>
<td>3.4 ± 8.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total long-duration (&gt; 5 min) events</td>
<td>5.5 ± 9.1</td>
<td>0.8 ± 1.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Waking</td>
<td>1.9 ± 2.5</td>
<td>0.4 ± 1.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sleep</td>
<td>4.3 ± 9.4</td>
<td>0.6 ± 1.6</td>
<td>&lt; 0.057</td>
</tr>
</tbody>
</table>
Table 4—Anatomic Changes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pretreatment (n = 15)</th>
<th>Posttreatment (n = 15)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior commissure hypertrophy</td>
<td>1.3 ± .9</td>
<td>0.7 ± 0.5</td>
<td>0.04*</td>
</tr>
<tr>
<td>Ventricular obliteration false cord obliteration</td>
<td>0.3 ± 0.7</td>
<td>0 ± 0</td>
<td>NS</td>
</tr>
<tr>
<td>Vocal fold edema</td>
<td>1.0 ± .9</td>
<td>0.5 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Erythema</td>
<td>0.8 ± 1.0</td>
<td>0.7 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Laryngeal edema</td>
<td>0.1 ± 0.5</td>
<td>0.0 ± 0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Subglottic edema</td>
<td>0.1 ± 0.5</td>
<td>0 ± 0</td>
<td>NS</td>
</tr>
<tr>
<td>Reflux Finding Score</td>
<td>3.6 ± 3.2</td>
<td>1.9 ± 1.4</td>
<td>0.07*</td>
</tr>
</tbody>
</table>

Data are shown as Mean ± SD. *p < 0.05
Improvement in Sleep Quality
(Johnson et. al. Amer. J. Gastro 2005: 100; 1914-1922)

- Eso 40mg (n=204)
- Eso 20mg (n=214)
- Placebo (n=214)

PSQI Baseline: 9.5 9.6 9.6
PSQI Week 4: 6 5.8 7.5

* p<0.0001 vs. placebo
Sleep Quality in PPI Rx

(Fass et. al. Amer. J. Gastro. 2011; 106: 421-431)
Conclusions

• Nighttime heartburn and associated sleep disorders are common among patients with GERD

• Physiological changes associated with sleep produce significant alterations in responses to acid mucosal contact

• Sleep related GER is a major factor in the pathogenesis of esophagitis and other extra-esophageal complications of GERD

• Clinicians should inquire about the presence of nighttime heartburn as well as its frequency and severity as an indication of more severe and complicated GERD
“The sleeping patient is still a patient, his disease goes on not only while he sleeps, but indeed may progress in an entirely differently fashion from it’s progression in the waking state.” Eugene Robin, 1958