

## Role of sleep in the pathogenesis of gastroesophageal reflux disease and its complications

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Gastroesophageal reflux (GER) is a common event, occurring primarily post-prandially, and usually associated with symptoms of heartburn or regurgitation. Numerous epidemiologic studies have recently noted that approximately 5% of the American population has heartburn nearly everyday<sup>[1]</sup>. Episodic heartburn is usually treated with over-the-counter medications such as antacids, and a recent survey has documented that about 13% of the American population takes antacids at least twice a week<sup>[2]</sup>. Although GER with heartburn has been noted to be relatively common, the long-term consequences and complications of this physiologic event have not been generally well recognized or appreciated by the practicing physician. The severity of GER is determined by its combined frequency and duration, or total acid contact time (ACT). Although ACT can accumulate via numerous short episodes of GER, or fewer longer episodes, there are data suggesting that the accumulation of ACT during sleep related episodes may be more damaging to the esophageal mucosa<sup>[3,4]</sup>. The advent of 24-h ambulatory esophageal pH monitoring has allowed an accurate correlation of the pattern of GER during daytime and nocturnal periods.

### THE PATTERN OF GER

Considerable attention has been focused on the differences in the pattern of GER during the daytime and during sleep in a study published by Johnson and Demeester<sup>[3]</sup>. By utilizing 24-h esophageal pH monitoring these investigators identified three different groups of patients with reflux esophagitis, and they noted that the more

severe forms of esophagitis were associated with an increase in supine or nocturnal GER. On the basis of these results, the authors suggested that reflux events occurring during the nocturnal interval were more likely to be associated with the development of complications of GER. Additional data from our laboratory provides support for this hypothesis is that we have shown that the single most effective marker in discriminating patients with and without erosive esophagitis was the number of sleep related reflux episodes lasting more than 5 min<sup>[5]</sup>. These data support work by Johnson and DeMeester which have identified different patterns of GER associated with daytime (predominantly upright position) and nighttime (predominantly supine position) esophageal pH monitoring<sup>[3]</sup>. In the upright position, episodes of GER tend to be more numerous, particularly post-prandially, but they are rapidly neutralized to a pH of 4 or above. In the supine position, predominantly during sleep, episodes of reflux are fewer, but acid clearance is more prolonged.

### PARAMETERS OF ACID CLEARANCE DURING SLEEP

Prolonged acid clearance during sleep has been identified as a risk factor in the development of esophagitis as noted above. We have identified a number of parameters concerning acid clearance during sleep which further delineate the mechanisms by which infused acid into the esophagus during sleep is cleared and subsequently neutralized to a pH of 4.0. For example, in normal volunteers our work has shown that the clearance of infused acid from the distal esophagus is specifically correlated with the percent of waking time during the acid clearance interval. That is, if individuals spend most of the acid clearing interval asleep as defined by polysomnography, the ACT is more prolonged than if the individual spends most of the acid clearing duration awake<sup>[6]</sup>. These data were also analyzed in terms of evaluating the swallowing rate subsequent to water infusion compared to acid infusion. The swallowing rate for the 10 min interval subsequent to the infusion of acid or water was compared to the swallowing rate in the 10 min interval preceding the infusion. The data revealed a marked and highly statistically significant increase in the swallowing rate associated with acid infusion. This identifies the fact that in this group of normal volunteers, they are quite differentially sensitive to acid when infused during sleep. All of these individuals had a negative acid perfusion test in the daytime which proved that they were unresponsive to acid infusion during the waking state. Obviously, the esophagus appears to be responding quite differently to the acid stimulus as a function of the state of consciousness (*i.e.* waking vs sleep).

In other studies we have documented differential effects of both volume and pH stimulation of the distal esophagus during waking and sleep. We have shown that infusing different volumes into the esophagus will produce quite differential arousal and swallowing

responses which are volume dependent. That is, larger volumes, which are presumably more likely to show longer acid clearance and greater proximal migration in the esophagus, reveal a shorter arousal latency<sup>[7]</sup>. In addition, the latency to the first swallow was compared in both the waking state and during sleep. This analysis revealed that in the waking state, different volumes did not produce any effect on the latency to the first swallow, while during sleep there was a clear decrease in the latency to the first swallow with increasing volume. This would suggest that in the sleeping state, where individuals are more vulnerable to the pulmonary aspiration of refluxed gastric contents, a protective response is in place in the form of enhanced responsiveness to larger volumes of acid.

In a similar study comparing different pH levels of the infused acid, lower pH levels have also shown shorter arousal latencies and first swallow latencies<sup>[8]</sup>. These data combine to suggest that both volume and the pH of reflux gastric contents can markedly affect that arousal latency, swallowing responses which suggest that intrinsic communication exists between the brain and the esophagus to provide protective mechanisms against the possibility of pulmonary aspiration.

## CONCLUSION

From the research conducted in our laboratory and others it would appear that prolonged esophageal acid contact time is associated with a greater risk to develop erosive esophagitis. In addition, sleep is a time of increased risk of not only esophageal acid contact, but

also proximal migration and aspiration of refluxed gastric contents. Our research suggests that there are afferent mechanisms producing higher cortical responses in the form of arousals from sleep and subsequent swallowing behaviors which serve to protect the organism against prolonged acid contact time and possible pulmonary aspiration.

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