The Effect of Esophageal Acid Volume on Arousals from Sleep and Acid Clearance*

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To assess the effect of different volumes of acid infused into the esophagus, seven normal volunteers were studied in the waking and sleep state. All subjects were studied for three nights in the sleep laboratory, which included complete polysomnographic monitoring and esophageal pH recording. Multiple infusions of either 5, 15, or 25 ml of 0.1 N HCL were administered each night. Similar infusions were also accomplished in the waking state. The results showed a significant (p<0.05) decrease in the arousal from sleep with 25-ml vs 5-ml infusions. During sleep, the latency to the first swallow was significantly (p<.05) shorter with the 25-ml infusion when compared with that of the 5-ml infusion. While awake, the infusion volume did not affect the latency to the first swallow. The acid clearance times were not significantly altered by the different volumes infused. It is concluded that the larger volumes of acid in the esophagus create an afferent "warning" signal to the central nervous system to produce a rapid arousal from sleep along with a shortened interval to the first swallow. These responses rapidly empty the larger acid volumes from the esophagus. (Chest 1991; 99:351-54)

LES = lower esophageal sphincter

An intriguing and persistent question regarding the pathogenesis of gastroesophageal reflux disease relates to the effect of the volume of acid refluxed on subsequent acid clearance. Studies by Helm et al. have suggested that acid clearance is a two-stage process of volume clearance and acid neutralization. Using scintigraphy to assess esophageal clearance, they demonstrated that peristalsis accounted for clearance of most of the acid volume from the esophageal lumen. However, the pH remained unchanged due to a persistent film of acid that coated the mucosa. The authors incidentally reported no effect of bolus volume on the acid clearance time in a subset of six subjects. However, the effects of varying volumes on the actual acid clearance time have not been formally investigated.

Using a constant volume of acid, previous studies from our laboratory have demonstrated a prolongation of the acid clearance time during sleep. In addition, arousal responses to a constant volume of infused acid were significantly different during wakefulness and sleep. More specifically, normal volunteers, who showed no subjective response to acid perfusion in the waking state, clearly showed an increase in the percentage of arousals from sleep associated with acid vs water infusion during sleep. This discrimination during sleep was also manifest by an increase in swallowing frequency for acid when compared with a comparable volume of water.

Thus, these data clearly showed that during sleep, normal individuals maintained a heightened awareness for the presence of intraluminal acid and had an effective mechanism to accomplish its clearance. That afferent input from the esophagus to the central nervous system (CNS) exists for acid during sleep suggests that the esophagus might also be differentially sensitive to changes in acid volume. The present study addresses the importance of volume in the acid clearance response during waking and sleeping by infusing three different volumes of acid during these different behavioral states in a group of normal asymptomatic volunteers.

METHODS

Subjects

Seven normal volunteers without complaints of heartburn or other gastrointestinal disease were studied. All subjects had a negative acid perfusion (Bernstein) test. The study was approved by the Institutional Review Board (IRB) of the University of Oklahoma Health Sciences Center.

Procedures

Subjects were studied for three nights in the sleep laboratory. Each night consisted of multiple infusions of a single volume of either 5, 15, or 25 ml of 0.1 N HCL. Sleep was polygraphically monitored by recording the electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG). On each study night, one infusion occurred during waking.
prior to sleep onset (5, 15, or 20 ml). At least two infusions were accomplished for each study night and the results of these data were averaged for infusions within each night for each specific volume.

Esophageal pH was monitored with an antimony tip pH probe placed transnasally into the esophagus 5 cm above the manometrically determined lower esophageal sphincter (LES).

**Esophageal and Arousal Parameters Analyzed**

The following parameters were measured as defined below: (1) esophageal acid clearance: this is defined as the time accumulated from a drop in the esophageal pH to below 4 to reestablishment of an esophageal pH of 4; (2) latency to the first swallow: this is defined as the interval of time from when the pH drops to below 4 until the first swallow occurs as defined by the submental EMG (a short diamond-shaped burst of EMG activity); (3) arousal latency: this is defined as the interval of time between the drop in the pH below 4 until the first polygraphically defined arousal (increase in the EMG tone, low voltage mixed frequency EEG) response.

All data were normalized by using a square root transformation. Standard t tests were applied and appropriate analyses of variance within-group comparisons were used in the analysis of these data. If the overall analysis of variance was significant, each within-group pair of means was compared using the Dunnett method.

**RESULTS**

The arousal latency for a 25-ml volume of acid was significantly shorter than that noted for 5 ml (Fig 1). The arousal latency for the 15-ml acid volume closely approximated that of the 25-ml volume, but it did not obtain statistical significance. While asleep, the latency to the first swallow was significantly (p<0.05) shorter for the 25-ml infusion than that noted for the 5-ml infusion (Fig 2). In fact, the latencies systematically decreased for infusions of 5, 15, and 25 ml of acid. While awake, the latency to the first swallow was comparably short for the 5-, 15-, and 25-ml acid infusions. For equal volumes of infused acid, the latency to the first swallow while asleep always significantly exceeded that noted while awake (Fig 2). Even though the mean latency to arousal shown in Figure 1 tended to be slightly longer than that to the first swallow shown in Figure 2, close examination of the raw data (polygraphic arousal responses and EMG responses identifying swallows) showed that the arousal response preceded the first swallow in most of the nocturnal infusions.

While asleep, the esophageal acid clearance times were comparable even though there was a fivefold increase in the volume of infused acid. Esophageal acid clearance times tended to increase with increasing volume while awake; however, this trend was not statistically significant.

**DISCUSSION**

Previous studies have documented that normal individuals are significantly more responsive to acid compared with sterile water when infused during sleep. The most logical clinical question arising from these observations would be whether different volumes of acid refluxed into the esophagus would be...
more likely to produce an arousal or “protective” response. The results of this study clearly indicate that large volumes of acid are more likely to produce an arousal response from sleep (Table 1).

Although not affecting the overall acid clearance time, the larger volume infusions during sleep (15 and 25 ml) both produced decreased arousal and first swallow latencies. That is, the larger esophageal volumes appear to rapidly initiate a “warning signal” to the CNS. This “warning” is manifest by shorter latencies for both the arousal from sleep and the first swallow. It is important to note that the swallow latencies are not significantly different during waking. These shorter latency responses to larger esophageal volumes would tend to protect against possible pulmonary aspiration.

Our previous studies2,3 have suggested that the clearance response is initiated by an arousal from sleep followed by the resumption of a higher rate of swallows. The present data suggest, however, that these are essentially simultaneous processes. While the arousal response may initiate the clearance process, the latency to the first swallow may be just as important, especially since the majority of the intraesophageal acid volume is cleared by the first swallow.1 Rapid volume clearance would be important in the prevention of pulmonary aspiration, since larger refluxed volumes would be more likely to result in aspiration.

Sleep appears to be associated with entirely different responses to esophageal acid contact.6 Although, as already mentioned, waking volunteers cannot distinguish water from acid infusions into the esophagus during sleep, acid infusions clearly produce an enhanced percentage of arousal responses.8 Similarly, in the present study, we have demonstrated that larger volumes of acid produce a decreased latency to the first swallow during sleep, a response not evident with identical infusions in the waking state. Moreover, this enhanced response to larger volumes of acid is consistent with the clinical observation that a comparable intragastric volume (≥40 ml) constitutes a risk for pulmonary aspiration. These observations strongly suggest that arousals from sleep, swallowing, and peristalsis are important protective mechanisms that prevent pulmonary aspiration of nocturnal gastroesophageal reflux. Larger volumes of gastroesophageal reflux would be expected to produce a more consistently short arousal and swallow latency response during sleep to protect the tracheobronchial tree from aspiration.

Although it is conceivable that larger volumes in the distal part of the esophagus would induce more secondary peristaltic contractions, the fact remains that the actual acid clearance times were similar. Thus, it is unlikely that there were appreciable differences in the motor responses of the esophagus to these different volumes of infusion. Helm et al.1 have shown volume to be a less important factor in acid clearance than had been previously believed. Their data show

![Figure 2. Mean latencies to the first swallow with infusions of 5, 15, and 25 ml during sleep and waking.](https://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21624/)
that one or two swallows will remove the vast majority of gastric contents refluxed into the esophagus. Salivary flow and swallowing appear to be more important variables in actually neutralizing the distal part of the esophagus. The present results are consistent with this model in that different volumes have not produced different clearance times, but clearly have resulted in a higher incidence of arousal responses with the larger volume. This could be interpreted as a "fail safe" mechanism to ensure that swallowing will occur with sufficient predictability and rapidity to prevent pulmonary aspiration.

It would appear from our data that an increase in the volume of a reflux event during sleep would not further aggravate the development of reflux esophagitis. This assumption is based on the observation that there was no significant difference in the esophageal acid clearance time for the sleep-related infusions of 5 vs 25 ml of acid. However, the data clearly suggest that even a small volume of reflux during sleep can result in prolonged acid mucosal contact time, which is an important determinant of reflux esophagitis.5,6 Thus, even trivial volumes of acid reflux during sleep pose a risk for the development of esophagitis.

In conclusion, we have demonstrated that the esophagus and CNS of asymptomatic volunteers during sleep maintain an awareness for the presence and volume of intraesophageal acid. The response time of this system is inversely related to acid volume. While a prompt response to a large intraesophageal acid volume may help to prevent tracheobronchial aspiration, the relative insensitivity of this system to a small volume of acid may actually contribute to the development of reflux esophagitis.

REFERENCES
2 Orr WC, Robinson MG, Johnson LF. Acid clearing during sleep in the pathogenesis of reflux esophagitis. Dig Dis Sci 1981; 26: 423

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