positive or were receiving corticosteroids or chemotherapy. Mortality (three deaths in IPF patients at 30 days) was greater in patients requiring mechanical ventilation at the time of surgery or in those who were immunosuppressed (the type of immunosuppression was not specified). Age, requirement for supplemental oxygen, and severity of pulmonary function impairment did not affect outcome. The authors concluded that patients with IPF tolerate surgical lung biopsy well, but those who are ventilator dependent or are immunosuppressed are at higher risk of surgical lung biopsy.

Utz and colleagues" of the Mayo Clinic reported a 30 day mortality of 17% after surgical lung biopsy in 60 patients who had the diagnosis of usual interstitial pneumonia (UIP)/IPF or UIP associated with connective tissue diseases. Of note, this small series" presented only a fraction of patients with UIP seen at the Mayo Clinic, and lung biopsies and thoracic CT scans were performed infrequently for the evaluation of IPF at the time of the study. Many of the 10 patients who died had an accelerated decline in respiratory status at the time the lung biopsy was done. Results of a more recent and larger series" from the same institution showed a much lower mortality rate in patients with interstitial lung disease following lung biopsies.

Caution is needed in interpreting the studies of Lettieri et al and Utz et al." The small number of deaths and potential sampling biases by including predominately sicker patients may have contributed the higher reported mortality rates. It is reassuring that when the high-risk patients were excluded from these two studies, the mortality rates were acceptably low. Multivariate analysis to define characteristics that predict increased risk is required on a larger population undergoing surgery. One large database that could be utilized, for example, is that from the clinical trials of interferon \( \gamma \)-1b in IPF." In the absence of more precise data for determining which patients with IPF are at greater risk of surgical lung biopsy, clinicians have to apply reasoned judgment to each patient by weighing the potential for harm against possible gain. The first decision is whether a surgical biopsy is necessary as dictated by the certainty of the diagnosis of IPF using radiographic and clinical criteria. The second decision concerns the risk of the contemplated biopsy. Based on available information, elements that indicate high risk include mechanical ventilation, marked impairment of lung function (FEV\(_1\) < 1 L), coagulopathy, immunosuppression, pulmonary hypertension, and severe hypoxia. A rapid deterioration of underlying lung disease can probably be added to this list based on the observations of Lettieri et al and Utz et al.""**

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REFERENCES


Heartburn
Another Danger in the Night?

Heartburn has long been largely trivialized in the medical community. It has had a bit of a Rodney Dangerfield reputation in that it “gets no respect!” Primary care physicians treat symptoms of heartburn quite readily with antacids and varying degrees of
acid-suppressing drugs ranging from H2 blockers to proton-pump inhibitors, depending on the severity and refractoriness of the symptom. The generally excellent clinical response to symptoms of daytime heartburn has contributed to a notable lack of interest in nighttime gastroesophageal reflux (GER). It is a common clinical observation that patients who have been successfully treated for heartburn complaints will spontaneously report that they are sleeping better. This observation has focused the attention of both researchers and clinicians on the relationship between GER and sleep, as well as on the importance of sleep in the patient’s quality of life. Despite this, and the burgeoning body of evidence suggesting that sleep-related GER is an important factor in both the esophageal and respiratory complications of GER, the role of sleep in the clinical presentation of GER has been largely ignored.

Considerable clinical attention has more recently been focused on the importance of the symptom of nighttime heartburn, and the concomitant occurrence of nighttime GER. For example, two epidemiologic studies have focused more attention on the occurrence of the symptom of nighttime heartburn. These studies showed remarkable similarity in that they both noted that symptoms of nighttime heartburn are common (about 75% of patients) and that nighttime heartburn was a more bothersome symptom. Furthermore, a portion of these patients reported that nighttime heartburn interfered with their sleep and daytime performance. Other epidemiologic data have shown a strong link between the occurrence of nighttime heartburn (i.e., two times a week or more) and respiratory symptoms and sleep disturbance.

The excellent study by Fass and colleagues in the current issue of CHEST (see page 1658) adds considerable support and credibility to the above-noted previous studies. The study included > 15,000 subjects who were participants in other large ongoing clinical trials. The subject pool in this study was several times larger than that of any of the previously cited studies. This alone adds considerable credence to their findings. To their credit, they framed questions concerning nighttime heartburn in a way that would create face validity for the occurrence of this phenomenon during sleep. That is, their question was phrased, “in the past year, how often, on average, have you been awakened during the night with heartburn or indigestion?” An affirmative response to this question would be more likely to reflect an episode of GER that did occur during sleep. In some studies, nighttime heartburn could include an interval of time when an individual may be lying in bed prior to sleep. This study clearly documented a strong relationship between nighttime heartburn and all variables associated with disturbed sleep. Specifically, complaints related to daytime sleepiness appeared to be significantly associated with nighttime heartburn. Also a strong relationship was noted between the symptoms of sleep apnea, such as snoring and daytime sleepiness, and nighttime heartburn. Not surprisingly, body mass index was also a significant predictor of nighttime heartburn. Other variables that have been reported to have a significant association with nighttime heartburn were both self-reported hypertension and asthma as well as the use of benzodiazepines. This is not particularly surprising in view of the now well-established relationship between asthma and GER, as well as among obstructive sleep apnea, GER, and hypertension.

Certainly, the logical conclusion that would be drawn from the increased use of benzodiazepines would be an effort to treat sleep disturbances, particularly insomnia.

These data, as well as the provocative and interesting study presented by Fass and colleagues, raise the question as to the clinical significance and importance of nighttime heartburn. The first, and perhaps most obvious, question pertains to whether heartburn is really different in the daytime vs the nighttime, or whether it is only a matter of timing. Data by Fass et al did not directly address the issue of whether the variables noted might also predict daytime heartburn. Thus, we are left with the question as to whether any of these variables uniquely predict nighttime heartburn. If indeed this were the case, a very strong argument would be made for the fact that nighttime heartburn is indeed a different entity. Certainly, there are abundant physiologic data to demonstrate that sleep-related GER is responded to physiologically quite differently than daytime GER, although the sensation and experience of heartburn is not notably different. For example, the pattern of daytime GER is quite different from that occurring during sleep. The pattern of GER in the daytime is noted to be primarily postprandial and associated with episodes of short duration, while the pattern associated with sleep-related GER is one of fewer episodes with a marked prolongation in the acid clearance time.

This pattern of reflux, most notably the supine or nighttime GER events, has been shown to be associated with more severe forms of esophagitis and the complications of GER. These associated complications appear to be the result of several features of the esophageal acid mucosal response that are associated with sleep. Three key elements of the waking response to acid mucosal contact are quite clearly altered during sleep. First, there is no “warning signal” since heartburn is a waking conscious phenomenon. The swallowing rate is quite markedly diminished during sleep, and the production of saliva, which is essential for acid neutralization, is also markedly suppressed during sleep. Also, the prolongation of acid mucosal contact associated with sleep-related GER is associated with greater a back-diffusion of hydrogen ions.
into the esophageal mucosa.\textsuperscript{12} It would seem clear from the available data that sleep-related GER is a much more “malignant” form of reflux.

Unfortunately, the occurrence of sleep-related GER is not always associated with the symptom of nighttime heartburn. Thus, the occurrence of nighttime heartburn would appear to be a fairly sensitive, but not a very specific, symptom. The reason for this has to do with the phenomenology of sleep itself. Events that occur in and around brief arousals from sleep are poorly recalled. Thus, an individual patient who reports nighttime heartburn perhaps once a week may indeed be experiencing sleep-related GER and its attendant complications much more frequently.

Given the fact that relying on the symptom and frequency of nighttime heartburn may not provide a totally accurate reflection of the occurrence of sleep-related GER, what other symptoms or clinical clues may be present to more accurately predict the frequency and clinical significance of nighttime heartburn? As has been noted above, nighttime heartburn has significant associations with other symptoms such as wheezing or coughing, and sleep disturbances. Patients who complain of bothersome daytime heartburn who deny nighttime heartburn should be further queried as to the presence of other possibly sleep-related symptoms. These would include awakening from sleep with coughing or an acidic taste in the mouth, as well as frequent arousals from sleep and unrefreshed sleep. In fact, it is not unreasonable to postulate that GER could be a cause of sleep disturbance in individuals with sleep complaints without other obvious causes such as obstructive sleep apnea.

The study by Fass and colleagues has given further credence to the notion that the occurrence of nighttime heartburn is a particularly important clinical manifestation of GER. The perspicacious clinician should be aware that nighttime heartburn, when occurring with a frequency of once a week or more, is an important clue to the existence of a malignant form of GER, as well as of the possibility that GER may be causing other symptoms such as cough, sleep disturbance, and the exacerbation of asthmatic symptoms.

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References

Finding Haystacks Full of Needles
From Opus to Osler

When we compose medical school curricula, we choose what to stress to our students based on how common or how instructive the disease is. What are the common plagues of our society? Vascular disease, trauma, and some infectious diseases affect a large percentage of our population and rightfully assume an important place at the curriculum table. However, most diseases affect < 1% of the population. Based on what their pathophysiologic, mechanistic, or basic science processes can teach us, these uncommon diseases assume a role in our curriculum that is greater then their frequency would seem to warrant. Many genetic diseases and cancers fall into this category. Other diseases such as rabies or necrotizing fasciitis are so terrible that even though most