Apneic events result in brief, but striking surges in sympathetic nervous system activity,\(^5\) vasoconstriction, and transient systemic hypertension. Intermittent bradycardia,\(^6\) pulmonary vasoconstriction, and major decrements in stroke volume\(^7\) have been recorded during apneas. These transient alterations in cardiovascular function lend increased credibility to findings of retrospective studies, which suggest that untreated apnea leads to a greater risk of myocardial infarction,\(^8\) stroke,\(^9\) and excessive mortality among patients with OSA.\(^{10}\) The fact that sustained hypertension\(^2\) and elevated sympathetic activity\(^5\) while awake are found in patients with untreated apnea further implicates apnea as a risk factor for cardiovascular morbidity and mortality. However, this hypothesis remains unproven and is being investigated by a National Institutes of Health (NIH)-sponsored multicenter trial (Sleep Heart Health Study) where a well-characterized cohort of 6,000 individuals will be followed prospectively to determine if those with untreated and predominantly asymptomatic apnea demonstrate increased cardiovascular morbidity or mortality.

The application of nasal-continuous positive airway pressure (N-CPAP) is highly effective in maintaining pharyngeal patency during sleep in OSA, thereby eliminating apneas, transient cardiovascular events, abnormal sleep architecture, and daytime hypersomnia. However, 3 recently published prospective studies evaluating CPAP compliance show strikingly similar findings: objectively measured mean duration of nightly use is less than 5 h,\(^{11-13}\) and this interval is routinely overestimated by 1 h by apparently cooperative patients. In addition, of the less than 5-h interval when CPAP is used each night, the prescribed mask pressures are maintained about 90% of the time. Accordingly, it is now recognized that many CPAP-treated patients are exposed to apneic events and probable cardiovascular sequelae for 2 to 3 h/night. What is the clinical impact of continued apneic events during years of CPAP therapy?

A prospective trial evaluating the morbidity and mortality associated with suboptimal OSA treatment would be of great interest. A study of this type would be a large undertaking but would be justified if the NIH Sleep Heart Health Study demonstrates increased cardiovascular sequelae in untreated mild OSA. In the meantime, it is likely to be in our patients' best interest to determine if nightly CPAP use can be enhanced so that apneic events are minimized. I favor prospective studies designed to determine if suboptimal nightly CPAP use once detected, can be improved. A positive study would stimulate dialogue among sleep clinicians, CPAP manufacturers, and insurers regarding the need for improved monitoring devices, possible intervention, and long-term follow-up. It is possible that successfully enhancing CPAP compliance would be cost-effective by significantly decreasing long-term cardiovascular morbidity and mortality among the hundreds of thousands of partial CPAP users in the United States today.

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REFERENCES


Picking Up the Pieces

The Consequences of Sleep Fragmentation

Obstructive sleep apnea (OSA) is undoubtedly a multifaceted sleep disorder when one tries to explain its pathogenic importance. It is undisputed among sleep researchers that OSA plays an important role in the increased cardiovascular morbidity\(^2\,\,3\) and
It is also very well accepted that sleep-disordered breathing can significantly impair brain functions which guarantee physiologic levels of daytime alertness.

The search for individual factors responsible for the pathophysiologic importance of sleep apnea has prompted sleep researchers to take a closer look at the bits and pieces of mechanisms potentially responsible for the increased cardiovascular morbidity and mortality. These include the systemic blood pressure changes, effects on pulmonary artery pressure, and metabolic changes to name a few.

Less attention has been paid to the effects of the frequent sleep disruption associated with repetitive apneas during sleep. Experimental paradigms using frequent sleep disruption have shown that sleep fragmentation may play a far more important role regarding the cardiovascular changes which are observed in sleep apnea and that sleep architecture itself can be significantly altered as a function of sleep fragmentation.

The investigation by Berry and coworkers published in this issue of CHEST (see page 1490) utilized an experimental paradigm to expose individuals to apneic stimuli over 3 days. The study was designed as an experiment to take a look at the impact of sleep apneas modulating arousability during sleep. They found that the event duration and the maximum esophageal pressure deflection were increased after three nights of exposure to recurring OSA, suggesting a blunted arousal response.

While in this investigation the authors have not tried to investigate individual factors responsible for this phenomenon, it is suggested that sleep fragmentation per se may play an important role. Thus, undisturbed sleep appears to be a prerequisite for a functioning linkage between brain systems involved in central nervous activating systems.

Previously collected data on arousal responses under frequent sleep fragmentation support the findings documented in this report. Phillips et al. have demonstrated in dogs that the arousal response to potentially detrimental stimuli such as hypoxemia, hypoxia, and mechanical stimulation is impaired by sleep fragmentation.

On the other hand, data from Guilleminault et al. suggests that the redistribution of specific sleep stages and states under conditions of sleep fragmentation may play an important role in the arousal response to obstructed breathing during sleep. Guilleminault et al. have shown in this investigation that individuals may present different arousal responses to obstructed breathing during sleep and that the occurrence of arousal is linked to specific stages of sleep. Individuals presenting stable stage 3-4 NREM sleep can have a different arousal response than during lighter sleep stages. This is also supported by a recent study using an experimental paradigm of sleep fragmentation mimicking arousal pattern commonly found in patients with sleep apnea. These investigations show that sleep fragmentation is commonly associated with a decrease in slow wave sleep (SWS) and that SWS is an important determinant of sleepiness under conditions of sleep fragmentation. These data suggest that the arousal response to obstructed breathing during sleep may be more dependent on the sleep stage (SWS vs stage 1-2 NREM sleep) than on biochemical stimuli.

We have also recently documented a significant difference in the amount of inspiratory negative pressure necessary to induce arousal in stage 2 NREM sleep vs the amount necessary in stage 4 NREM sleep.

Biochemical stimuli or redistribution of sleep stages and states did not play an important role in the investigation presented by Berry et al. in this issue. Comparative data sets were similar as far as these variables were concerned.

The practical implications of the data presented by Berry and coworkers in this issue of CHEST point in the same direction of data previously published by Kribbs et al. They have demonstrated that withdrawal of continuous positive airway pressure for one night is already associated with a reappearance of significant sleepiness.

Sleepiness per se caused by the frequent sleep fragmentation under conditions of recurrent sleep apnea may thus be the link in the systems which are involved in the physiologic response to detrimental respiratory stimuli.

With their investigation, Berry and coworkers have resumed some of the discussion from the late 70s and early 80s.

Sleep apnea leads to sleep fragmentation and sleep fragmentation leads to sleepiness. But what is the role of sleepiness on the arousal response? There is undoubtedly a much greater impact of sleepiness at the beginning of the night, if we acknowledge the homeostatic function of sleep. At the beginning of the night, we should find a lower arousal threshold than at the end of the night, given similar sleep stages. The sleep disruption, which can be seen during the night, should present a different pattern based on the role of the homeostatic function and the circadian distribution of sleep. This may explain why Guilleminault et al. found that much less apneas and a maintained stage 3-4 NREM were seen at the beginning of the night when the tracheostomy was closed after 2 years of treatment than later periods of the night.

Thus, future studies should take a closer look at the interaction between delta sleep, or even better delta power, and the appearance and the duration of apnea,
arousal threshold, or better alpha power threshold and sleep fragmentation.

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REFERENCES

Transudate vs Exudate: Genug!

In 1972, Light et al developed criteria for the diagnostic separation of transudates and exudates. The authors developed three criteria, with a pleural effusion categorized as exudative if it met one or more of them: (1) a pleural fluid:serum protein ratio >0.5; (2) a pleural fluid:serum lactic dehydrogenase (LDH) ratio >0.6; or (3) a pleural fluid LDH >200. The upper limits of normal for serum LDH in their laboratory was 300, so a pleural fluid LDH >200 was also greater than two thirds the upper limit of normal for the laboratory.

In this issue of CHEST (see page 1503), Vives and colleagues report on the pleural fluid characteristics of 195 patients with pleural effusion of known etiology. The purpose of their study was to compare the accuracy of the criteria of Light and colleagues for categorizing a pleural effusion as an exudate with several alternative criteria. The authors come to the conclusion that the criteria of Light et al remain the most clinically useful and accurate diagnostic standard available.

The study by Vives et al in this issue of CHEST is one in a long series of attempts to improve upon the criteria of Light and coworkers. Different authors have looked at the pleural fluid cholesterol and pleural fluid:serum cholesterol ratio,2,4 pleural fluid:serum bilirubin ratio,5 serum-pleural fluid albumin gradient,6 and different manipulations of pleural fluid protein and LDH levels.4 When the dust has settled, it appears that none have been superior to the criteria of Light et al.

The fact that the criteria of Light et al have held up so well is not surprising. There are several reasons why they have stood the test of time. First, the criteria were developed and then modified by looking at diagnostic variables in a group of 150 patients with pleural effusions in whom the etiology of the effusion had been definitively determined. Second, protein and LDH each has separate physiologic import. The pleural protein concentration reflects increased “leakage” into the pleural space or decreased clearance, and the pleural fluidLDH reflects pleural inflammation. Third, the criteria as used by Vives and colleagues (using an LDH level greater than two thirds of the upper limit of normal rather than an absolute pleural fluid LDH level ≥200) avoid all absolute values. As pointed out by the authors, this use of ratios eliminates much of the between-lab variability that would otherwise occur; a lab whose protein determinations run high and a lab whose protein determinations run low will each have different absolute values for all determinations, but both will have almost identical pleural fluid:serum protein ratios. Finally, when one looks at sensitivity and specificity, the criteria of Light et al maximize sensitivity over specificity in the diagnosis of an exudative effusion. This is consistent with the concept that it is better to occasionally misdiagnose a transudate as an exudate than it is to mistakenly characterize an exudate as a transudate.

Only one important sophistication has been added to the criteria of Light et al over the years. Following diuresis, the characteristics of a transudative effusion, particularly from congestive heart failure, may be altered enough for pleural fluid chemistries to shift