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Sleep, Circadian Rhythms, and Critical Illness

Commentary on Gehlbach et al. Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. SLEEP 2012;35:1105-1114.

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Annually, an estimated 21 million patient-days are spent by critically ill patients in intensive care units (ICUs), and they cost the US Healthcare System an estimated $82 billion in 2005.[1] We know that sleep in such critically ill patients is severely disrupted, with derangements of circadian rhythms and altered electroencephalography (EEG) during both sleep and wakefulness.[2-8] While derangements of sleep and circadian rhythm have been implicated in causing significant morbidity and mortality in ambulatory patients, whether the wealth of sleep and circadian science can be extrapolated to critically ill patients is unclear.[9] Conceivably, critically ill patients are more susceptible to such adverse physiological effects of sleep and circadian rhythm derangements than ambulatory patients. In contrast to ambulatory patients, the study of sleep and circadian rhythms in critically ill patients is still in its infancy and is confronted by the challenges of studying the intersection of three complex fields—sleep, circadian rhythms, and critical illness.

In this issue of *SLEEP,* Gehlbach and colleagues[10] assessed sleep and circadian rhythmicity simultaneously in critically ill patients who were receiving intravenous sedatives and mechanical ventilation, and they should be commended for an arduous and well-done study in such a challenging population. While circadian rhythms have been measured in critically ill septic patients in the past and sleep (or lack thereof) has been measured in such patients, prior to the report of Gehlbach et al. there have not been studies that simultaneously examined sleep EEG and circadian rhythms in critically ill patients.[11-13] The authors report no change in spectral power-derived measures of sleep (spectral edge frequency 95% [SEF95]) between night and day, whereas the circadian rhythmicity as measured by urinary 6-sulfatoxymelatonin (6SMT)—albeit delayed—was present in a majority of these patients. They conclude that the circadian rhythms and PSG of critically ill patients exhibit pronounced temporal disorganization and suggest that the circadian pacemaker may be free running.[10]

The finding that a majority of the critically ill patients have preserved circadian rhythmicity as measured by urinary 6SMT is new. This finding is in contrast to prior studies that reported that the majority of critically ill patients lacked a circadian rhythm.[2,14,15] However, such prior reports suggesting the abolishment of circadian rhythmicity in critically ill patients may have been attributable to methodological and patient-related factors. Such factors include greater acuity of illness; administration of norepinephrine and other pressor agents with sympathomimetic activity that could increase melatonin production and constantly elevate melatonin levels; less frequent sampling of urinary 6SMT levels; lack of normalization of melatonin levels to account for inter-individual variability; presence of brain injury; and perhaps even differences in ICU lighting or other zeitgebers between these studies.[2,14,15] Conversely, it is tempting to wonder whether the daily sedation interruption practices of the modern ICUs may have facilitated the occurrence and therefore the detection of circadian rhythmicity in the study of Gehlbach et al.,[10] as opposed to earlier reports that may pre-date such practice.

The finding that circadian rhythms exist in critically ill patients may be of clinical utility. We know that loss of circadian rhythmicity due to environmental desynchronization may lead to lack of immune system coordination, and to particular vulnerabilities to infection.[16] Therefore, the identification and correction of phase delay in the circadian pacemaker may conceivably augment immune function—but this possible benefit is purely speculative on our part.[16,17] In the Gehlbach study, exposure to continuous low level light may have led to the uncoupling of sleep and circadian rhythm, but their study also indicates that implementing such light interventions to entrain circadian rhythms may be an obstacle.[10] Additionally, the finding that circadian rhythmicity in urinary 6-SMT levels were present would encourage us to consider melatonin therapy in such critically ill patients to entrain their circadian rhythm. While there are some preliminary studies[18] that favor the improvement of sleep efficiency in critically ill patients receiving melatonin therapy, circadian rhythmicity was not measured in such studies, and there is a clear need for larger and more definitive studies in this area. Also, critically ill patients manifest very little to no REM sleep.[19] Such REM sleep deprivation in association with circadian rhythm disturbances may contribute to delirium.[5,20] In order to test whether all such described associations are causal, we need to develop effective interventions aimed at improving sleep and circadian rhythms in critically ill patients.

The study by Gehlbach et al.[10] has additional value from a methodological standpoint. We previously reported that the conventional qualitative Rechtschaffen and Kales methodology for sleep scoring had poor inter-observer reliability for all stages of sleep and wakefulness except for REM sleep in critically ill patients.[6] In keeping with our findings, Gehlbach et al.

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found similar lack of reliability of the manual Rechtschaffen and Kales scoring for sleep stages, excepting for REM sleep.[10] Moreover, we suggested that for assessment of sleep in critically ill patients the use of quantitative measures (such as spectral analysis), or other more reliable qualitative measures such as sleep-wakefulness organization state or REM sleep alone, may be preferred over the conventional Rechtschaffen and Kales methodology.[6] Gehlbach et al. successfully adopted the quantitative analysis of sleep EEG using SEF95 and improved upon it by simultaneous meticulous measurements of circadian rhythmicity (with urinary 6-SMT levels) and thereby demonstrated the uncoupling of the circadian timing system from the sleep-wakefulness cycle.[10] Such findings would favor the use of quantitative and reproducible methodologies for sleep EEG measurements in critically ill patients. Other investigators have made valid arguments for measuring and scoring qualitative EEG features that can be characterized as "atypical sleep" and "atypical wakefulness" based upon observed behavioral state of patients.[5] However, such supplementation of qualitative EEG recordings with behavioral state assessments of sleep or wakefulness performed at the bedside or through video-based assessments awaits rigorous study. Such rigorous study is needed, considering that investigators have demonstrated lack of reliability of such bedside assessments of sleep or wakefulness assessments in critically ill patients.[21]

All of the above underscores the complexity of this area of study, and the need for large, well-coordinated, multicenter studies with sufficient sample size to improve our understanding of sleep and circadian rhythm in critically ill patients relative to clinical outcomes. Our wish list also includes an accepted outcomes-based sleep scoring system and effective interventions that can manipulate and improve sleep and circadian rhythms in critically ill patients. The individually highly complex areas of sleep, circadian rhythms, and critical illness collide every day in our ICUs. Our lack of understanding on how to optimize the clinical benefits of healthy sleep and circadian rhythmicity in critically ill patients in ICUs is likely perpetuating the suffering of these patients. Gehlbach et al.[10] have improved our understanding of this complex area of study, but there are miles to go before we sleep.

CITATION

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